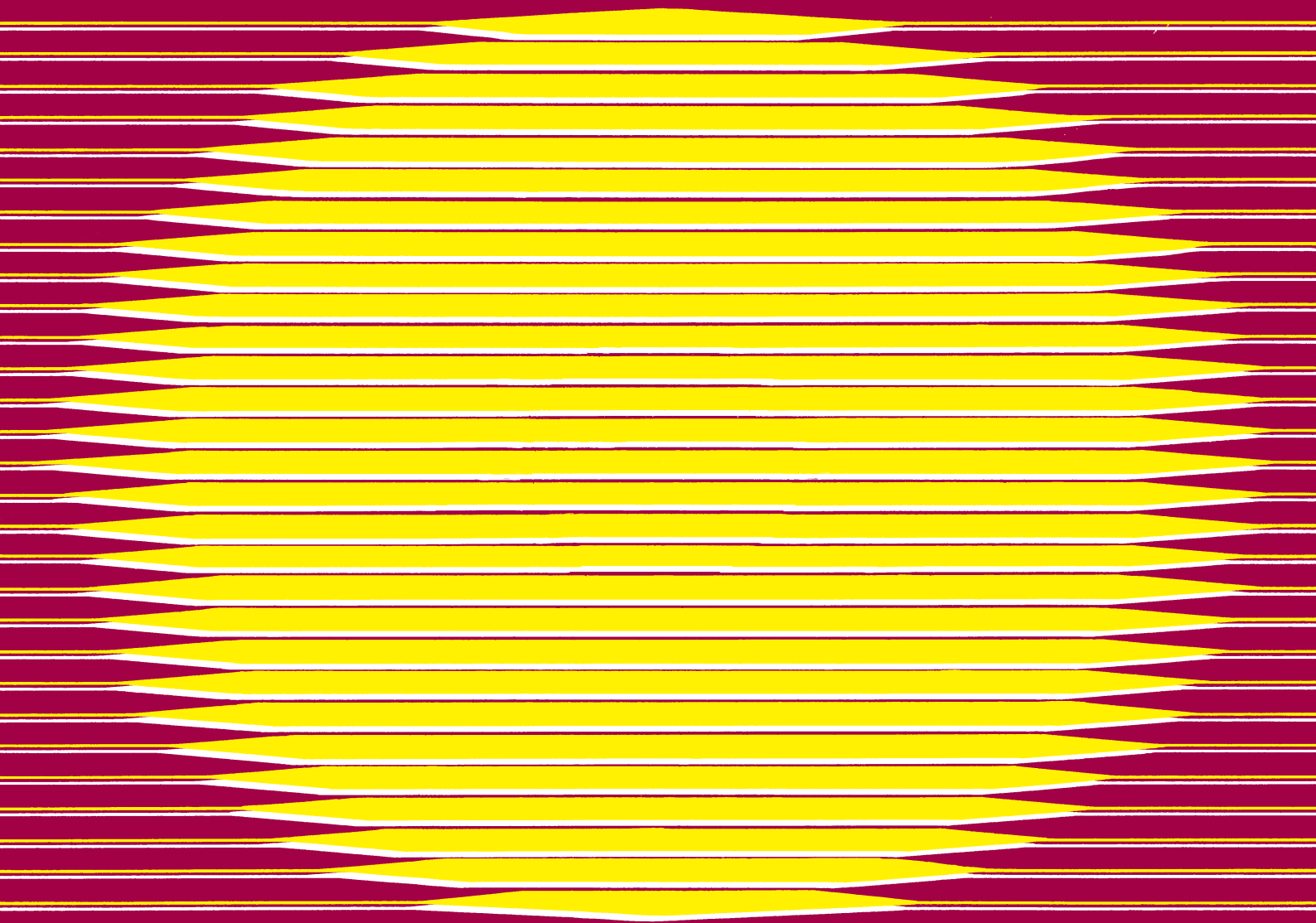
IONIZING RADIATION: SOURCES AND BIOLOGICAL EFFECTS

United Nations Scientific Committee on the Effects of Atomic Radiation
1982 Report to the General Assembly, with annexes



UNITED NATIONS

UNITED NATIONS SCIENTIFIC COMMITTEE ON THE EFFECTS OF ATOMIC RADIATION

1982 REPORT

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United Nations Scientific Committee
on the Effects of Atomic Radiation

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UNITED NATIONS
New York, 1982

NOTE

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Report of the United Nations Scientific Committee on the Effects of Atomic Radiation to the General Assembly

CONTENTS

I. INTRODUCTION

1. Since its establishment in 1955 the United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR)[1] has reported yearly to the General Assembly and at irregular intervals has submitted more comprehensive reports with detailed scientific annexes. This is the eighth in the series of such substantive reports.[2] It consists of a summary and a main text outlining the conclusions reached in the Committee's discussions and twelve scientific annexes reviewing in considerable detail the procedures and the scientific information on which such conclusions rest.

2. Although the Committee has attempted some systematic coverage of the issues entrusted to its attention, not all sources of radiation exposure and radiation effects have been included in this report. In the light of previous work, this report deals specifically with subjects that were felt to be in need of consideration because of the development of relevant scientific knowledge. Thus, some annexes have simply been updated from the 1977 report; others have largely been reassessed after many years of development; other matters are essentially considered for the first time.

3. Following past practice, only the summary and the main text of the report are submitted to the General Assembly. The full report with scientific annexes is being made available at the same time as a separate publication[3] for wide circulation to the scientific community, which has received past reports of UNSCEAR as authoritative sources of independent information and evaluation. The Committee wishes to draw the attention of the General Assembly to the fact that separation of the main text of the report from its scientific annexes is simply for reasons of convenience. The documentary evidence given in the annexes as a basis for the Committee's conclusions is of major importance.

4. Preparation of this report took place during the twenty-seventh to the thirty-first sessions of UNSCEAR. M. Klímek (Czechoslovakia), F.E. Stieve (Federal Republic of Germany) and K. Sundaram (India) served as chairman, vice-chairman and rapporteur, respectively, at the twenty-seventh session. The same functions were performed by F.E. Stieve (Federal Republic of Germany), Z. Jaworowski (Poland) and D. Beninson (Argentina) at the twenty-eighth and twenty-ninth sessions. Finally, Z. Jaworowski (Poland), D. Beninson (Argentina) and T. Kumatori (Japan) acted as chairman, vice-chairman and rapporteur, respectively, in the course of the thirtieth and thirty-first sessions. All these sessions were held in Vienna.

5. The work of the Committee was carried out in meetings of specialist scientists who, in their capacity as official representatives or scientific advisers of national delegations, considered, discussed and amended working papers prepared by the Secretariat at the Committee's request. The names of those specialists who attended one or more of the sessions during the preparation of the report are listed in Appendix I.

6. The Committee was assisted in its work by a small scientific staff and by expert consultants appointed by the Secretary-General. While in approving the present report the Committee itself assumes full responsibility for its content, it wishes to acknowledge the assistance given by those scientists who were responsible for the preliminary review and analysis of the data. The names of those scientists and consultants are listed in Appendix II. The Committee owes much to their collaboration and technical advice.

7. Information received between 13 April 1977 and 26 March 1982 at the Committee's Secretariat from State Members of the United Nations, members of specialized agencies and of the International Atomic Energy Agency, as well as from these agencies themselves, is given in Appendix III. Information received previously has been listed in earlier reports to

[1] The Scientific Committee was established by the General Assembly at its tenth session. The terms of reference of the Committee are set out in resolution 913 (X). The Committee was originally composed of the following Member States: Argentina, Australia, Belgium, Brazil, Canada, Czechoslovakia, Egypt, France, India, Japan, Mexico, Sweden, the Union of Soviet Socialist Republics, the United Kingdom of Great Britain and Northern Ireland and the United States of America. The membership of the Committee was subsequently enlarged by General Assembly resolution 3154 C (XXVIII) to include the following other States: Germany, Federal Republic of, Indonesia, Peru, Poland and Sudan.

[2] Previous substantive reports of the Scientific Committee to the General Assembly are to be found in: *Official Records of the General Assembly, Thirteenth Session, Supplement No. 17* (A/3838); *ibid., Seventeenth Session, Supplement No. 16* (A/5216); *ibid., Nineteenth Session Supplement No. 14* (A/5814); *ibid., Twenty-first Session, Supplement No. 14* (A/6314 and Corr. 1); *ibid., Twenty-fourth Session, Supplement No. 13* (A/7613 and Corr. 1); *ibid., Twenty-seventh Session, Supplement No. 25* (A/8725 and Corr. 1); *ibid., Thirty-second Session, Supplement No. 40* (A/32/40). These documents will be referred to in this context as the 1958, 1962, 1964, 1966, 1969, 1972 and 1977 reports, respectively. The 1972 report with appendices and scientific annexes was also made available as: *Ionizing Radiation: Levels and Effects, Volume I: Levels* (United Nations Publication, Sales No. E.72.IX.17) and *Volume II: Effects* (United Nations Publication, Sales No. E.72.IX.18). The 1977 report with appendices and scientific annexes appeared as: *Sources and Effects of Ionizing Radiation* (United Nations Publication, Sales No. E.77.IX.1).

[3] United Nations Publication, Sales No. E.82.IX.8.

the General Assembly. All these data were obtained officially by the Committee and were supplemented by, and interpreted in the light of, a large amount of information published in the open scientific literature. In a very few instances, unpublished contributions by individual scientists were also utilized or information was made available by individuals or organizations in response to specific requests by the Committee. These contributions are acknowledged with appreciation.

8. Representatives of the International Atomic Energy Agency (IAEA), the World Health Organization (WHO), the United Nations Environment Programme (UNEP), the International Commission on Radiological Protection (ICRP) and the International Commission on Radiation Units and Measurements (ICRU) attended the sessions of the Committee during the period under review. Their contribution to the discussions for the preparation of this report is gratefully acknowledged.

9. In compliance with its mandate, the Committee has formulated plans to continue its review of the radiation levels to which the world population is at present, or may in the future become, exposed and of the effects and risks that could derive from such exposures. The Committee proposes to keep under close scrutiny those areas which will emerge as meriting special attention for their scientific relevance or their practical significance. The Committee believes that such studies will also provide a significant contribution to the activities of the United Nations Environment Programme with which the Committee intends to maintain close functional relationships.

10. In the sections to follow the Committee summarizes the main conclusions reached in the present report in the light of previous substantive reports and then examines in detail the outcome of the studies that were conducted in specific areas in both the physical and biological fields.

II. SUMMARY OF THE MAIN CONCLUSIONS

11. This report has been structured in such a way that it may be read at various levels of detail and complexity. The present chapter summarizes the most important conclusions of the extensive surveys carried out in the different fields, particularly in the light of previous reports submitted to the General Assembly. The text aims at highlighting the main trends that have become apparent throughout the years in the form of overall comprehensive evaluations.

A. ASSESSMENTS OF RADIATION LEVELS AND DOSES

12. In this report, as in previous ones, the Committee has systematically reviewed all the sources of ionizing radiation that give rise to human exposure, namely, natural sources, nuclear explosions, nuclear power production, use of radiation for medical, industrial and research purposes, and radiation-emitting consumer products. Both occupational exposures (that is, the exposures incurred during the course of work) and non-occupational exposures have been considered. For each source of ionizing radiation, the results are expressed in two ways. On the one hand, results are given in terms of individual doses, which from an individual point of view show the relative importance of the type of work, the place of residence, or particular habits. On the other hand, collective doses have also been used. As these are the sum of the individual doses resulting from a given source, they provide an index of the total health impact of that source. The use of collective doses permits comparison of the impact from a wide range of dissimilar sources or practices giving rise to ionizing radiation.

13. A basic assumption was adopted by the Committee for the purpose of dose assessments at the start of its activity and is still in use at present. This is the hypothesis of direct proportionality between doses and probability of occurrence of effects (cancers or genetic disease) for the relatively low levels of dose and dose rate that are generally considered in this report. The hypothesis is meant to apply to large populations comprising individuals of both sexes and of various ages, and not to a single individual. This hypothesis is not contradicted by the large body of experimental and epidemiological data. There are reasons to believe that it does not underestimate the risk at the low doses and dose rates of interest to the Committee, and it may in fact overestimate this risk.

14. This report differs from previous reports in one important aspect. Instead of estimating the absorbed doses to only a limited number of important tissues (for example, gonads, lungs and bone marrow) the Committee now combines the doses in all organs and tissues in an expression of dose called the "effective dose equivalent" (see paragraphs 66–69) which the Committee believes to better represent the whole risk incurred by the exposed populations. As a consequence, the present assessment of the relative importance of some radioactive substances has changed in certain cases in comparison with the previous reports of the Committee.

1. Natural sources

15. The major contribution to the annual average doses received by mankind comes from natural radiation sources, which include external sources, such as cosmic rays and radioactive substances in the ground and in building materials, and internal sources resulting from the inhalation and ingestion of naturally occurring radioactive substances in air and in diet. Inhalation is now recognized to be the most important pathway, followed by external irradiation and ingestion. Most of the effective dose equivalent from inhalation is due to radon which is a radioactive noble gas often present in relatively high concentrations in indoor air.

16. Distinctive characteristics of natural irradiation are that it involves the whole population of the world and that it is and has been experienced at a relatively constant rate over a very long period of time. For these reasons, it may be used as a reference level for comparison with man-made sources of ionizing radiation.

17. The dose from natural sources of radiation received by a given individual depends upon a number of conditions, including the place of residence, the type of dwelling and the altitude. For most of the world's population, however, the range of individual doses from natural sources is considered to be rather narrow, as it probably extends only between one-half to two times the average value.

18. Nevertheless, when a separate component of the dose from natural sources is considered, it is generally found that some individuals are exposed to levels much higher than the average. Examples of such individuals are those who live in areas where the soils and rocks are rich in natural radioactive substances, those who live in buildings with high radon concentrations, those who live at high altitudes above sea level, and those who eat foodstuffs containing unusually high concentrations of radioactive substances.

19. The Committee has previously reviewed the exposures from natural sources of radiation in its 1958, 1962, 1966, 1972 and 1977 reports. Because of an increasing number of measurements, dose assessments have become increasingly accurate, particularly with respect to external irradiation. In the present report, expressing dose in terms of effective dose equivalent emphasizes the importance of the inhalation pathway; on average, about one-half the effective dose equivalent from natural sources of radiation is now calculated to be due to the presence of radon in the air inside buildings.

2. Man-made sources

20. Exposures to natural sources of radiation vary little from year to year and involve the whole population of the world to about the same extent. On

the contrary, man-made sources may vary significantly with time and the resulting exposures may differ substantially from one population group to another.

(a) Medical irradiation

21. At present medical irradiation ranks first in amount among the man-made sources of human exposure. Radiation is used in medicine for diagnostic purposes (e.g., x-ray or nuclear medicine examinations) and for the treatment of diseases, mainly cancers. The doses received by patients are extremely variable: from very small, as in many diagnostic examinations, to very high, such as those delivered in clinical radiotherapy. As medical exposures usually involve irradiation of limited regions of the body, it has been difficult in the past to compare them with other types of exposure. The use in this report of the effective dose equivalent is intended to diminish that difficulty.

22. Annual individual doses vary from zero, for the non-exposed patient receiving no diagnostic or therapeutic exposure, up to several tens of thousand times the annual average dose from natural sources, delivered to the treatment volume of patients undergoing radiotherapy. Under these conditions average doses are not very meaningful, although collective doses may give some indication of the impact of medical sources. In industrialized countries, the annual collective effective dose equivalents from x rays and nuclear medicine diagnostic irradiation may be in the region of one-half of the annual collective dose from natural sources. The contribution from exposure of patients for therapeutic purposes has not been estimated by the Committee. However, this component would need to be assessed differently, since it applies generally to people in later life who have a low probability of long-term or latent radiation-induced consequences due to their more limited life expectancy.

23. Data from developing countries are only now becoming available, in part as a result of collaboration with the World Health Organization. These data indicate an examination frequency about ten times lower than that in industrialized countries. Consequently, the annual collective effective dose equivalent applying to medical exposure throughout the world may be about one-fifth of the annual collective effective dose equivalent from natural sources of radiation. Although the individual doses received by workers involved with medical uses of radiation may be significant, the overall occupational contribution to the collective dose is insignificant compared with that from the irradiation of patients, because of the relatively small number of workers to be considered.

24. The Committee has previously presented data on medical irradiation in its reports issued in 1958, 1962, 1972 and 1977. However, in view of the limited information available and of the uncertainties attached to the dose estimates, trends in the collective dose over the years cannot be easily assessed. In industrialized countries an increasing number of examinations has taken place over the years; on the other hand, continuing improvement in the equipment that has occurred during this period should have resulted in a lower dose per examination. These two trends may have balanced out to some extent. For the purposes of the comparisons made in this report, the Committee has assumed a roughly constant annual collective dose from medical exposure.

(b) Nuclear explosions

25. Artificial radioactive material from nuclear weapons tests in the atmosphere was the cause of widespread contamination of the environment. Much of this material was initially injected into the upper atmosphere, from which it transferred slowly to the lower atmosphere and then to earth in a process usually referred to as fallout. The radionuclides occurring in fallout give rise to exposure by inhalation while they are present in ground level air, or by external irradiation and ingestion when they are deposited onto plants or in the soil.

26. Nuclear explosions have been conducted since 1945. Intensive nuclear test programmes in the atmosphere took place during 1954–1958 and 1961–1962. Since 1964, additional atmospheric explosions have occurred, the latest one in October 1980. Underground nuclear explosions have been, and still are being, conducted but the resulting environmental contamination is relatively minor. As in all its previous reports, the Committee has assessed the exposures to which the population of the world has been subjected as a result of the atmospheric nuclear tests. Although several hundred radionuclides are produced by nuclear explosions, only a few contribute significantly to human exposure, since most of them decay within a short time or are produced in very small amounts. The Committee, in this report, has considered 21 radionuclides, including iodine-131, strontium-90, caesium-137 and carbon-14. Because of the wide range of decay times, the doses resulting from a nuclear test are delivered at a varying rate after the explosion. For example, the doses from iodine-131 are delivered in a matter of weeks, those from strontium-90 and caesium-137 are completed in a few decades, while doses from carbon-14 will be delivered over thousands of years.

27. At any given time, the doses depend also on the location being considered. There is a latitudinal variation in fallout which has caused the doses in the southern hemisphere to be generally lower than in the northern hemisphere by a factor of about four. In addition, local fallout (in the vicinity of a test site) has occasionally given rise to higher individual doses for small groups of population.

28. The annual collective doses expressed as percentage of the average exposure to natural background provide an illustration of the yearly trend of the exposure from nuclear tests. The long-term trend, derived from data contained in this report and in the previous reports of the Committee, is illustrated in Figure I(a). There was a sharp increase of the annual collective doses in the early 1960s leading to a peak in 1963, corresponding to about 7% of the average exposure to natural sources. In 1966 the annual dose had decreased to approximately 2% of the annual average exposure to natural sources and it is at present less than 1%. Assuming no further atmospheric explosions, the future annual doses will become smaller and smaller until they vanish out completely.

29. The average annual collective doses received by the world population at any given time shown in Figure I(a) are the result of all the explosions that have taken place up to that time. It is also of interest to study the trend of the collective doses that were committed until complete decay of the radionuclides released by each year of testing. This is done in Figure I(b) which shows that explosions in the years 1961–1962 were the major

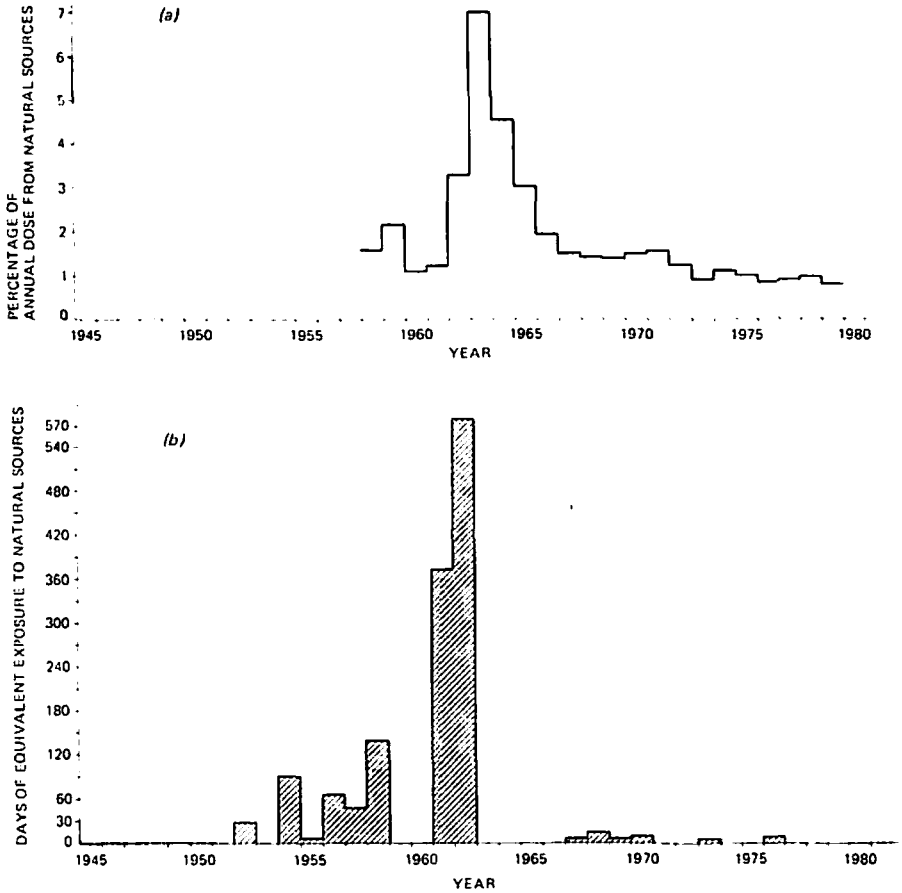

Figure I. Trends with time of collective doses from nuclear explosions in the atmosphere. (a) Average annual collective doses received in 1958–1979; (b) Collective doses committed for the future by explosions carried out between 1945 and 1980

contributors to the total impact of fallout from weapons testing carried out so far.

30. In Figure I(b) collective doses are expressed in terms of the number of days of exposure of the world population to natural radiation which would cause the same impact. If the doses received by the world's population could have been delivered at a constant rate equal to that of the average exposure to natural radiation sources, instead of at a low and irregular rate over more than thousands of years, then the total collective dose would equal that currently received from natural sources in about 4 years. It can thus be said that the impact from fallout corresponds to about 4 years of average natural background. The collective doses delivered so far can be derived from Figure I(a) and amount to about 0.4 year of exposure to natural sources. The rest, that is, about 3.3 years of natural background, corresponds to doses from fallout which will be delivered until complete decay of the radionuclides released. Fifty per cent of the impact from fallout will be delivered at a small rate in the next 2000 to 3000 years.

(c) Nuclear power production

31. The number of nuclear reactors in operation has increased since the previous report of the Committee to include, in 1979, 235 reactors with a total installed nuclear generating capacity of about 120 gigawatt (GW). The production of electrical energy by nuclear reactors presupposes the existence of a fuel cycle which involves many steps. They are: mining and milling of uranium ores; conversion to various chemical forms; enrichment of the isotopic content of uranium-235 (in some cases); fabrication of the fuel elements; production of power in nuclear reactors; reprocessing of irradiated fuel (in some cases); transportation of materials between the various installations and, finally, disposal of radioactive waste. For each major step of the nuclear fuel cycle the Committee has evaluated the doses to workers as well as the doses to members of the public.

32. With respect to the latter doses, it should be realized that at any given time a source such as a nuclear power plant will deliver doses to individuals which are strongly dependent on their distance from the source. Also, for any given location of an individual, the dose due to the releases from the plant will change with time, including the time after the practice is terminated, owing to the radionuclides that remain in the environment. It is therefore difficult to give a value of the individual doses that might be representative of that source, although the total impact may be assessed by adding all the individual doses in space and time and over all individuals in the present and in the future. Indications concerning the individual doses can, however, be expressed in different ways.

33. For example, one could choose to give a value referring to the individual (present or future) who has received (or will receive) the highest dose from the operation of a given source. However, the actual individual doses will range between zero and that highest value. Alternatively, one could give, for any given year, the annual dose averaged over all people in the world, in other words the per caput annual dose.

None of the above estimates will provide a complete representation of the real situation, although each of them might be of some interest for special purposes.

34. In spite of all the above conceptual difficulties, it is nevertheless interesting for the exposed individuals to have some estimate of individual doses. For example, the maximum individual doses may provide some indication of the upper bound of risk that might be incurred on account of a given source. In an analysis of trends in time the average annual dose over the population of the world at a given time may give useful guidance. However, it should be stressed again that such values are indicative averages and may not be taken to refer to the actual exposure of any given individual.

35. Almost all the radioactive material associated with the nuclear industry remains in the reactor sites or in special storage facilities; but, at most steps of the operations, environmental releases of small quantities of radioactive material occur. Most of the radionuclides released are of local relevance only, because they decay rapidly. However some radionuclides, which have a longer life or are more rapidly dispersed, become globally distributed and contribute to the exposure of the entire population of the world, now and, in some cases, well into the future.

36. By rough approximations, the short-term annual collective effective dose equivalents to members of the public from these sources can be calculated to have increased from 0.0001% of the corresponding values from natural sources in 1960 to about 0.01% in 1980. The increase in dose is directly related to the expansion of nuclear power production in the same time. The annual doses to individual members of the public vary widely around the average value, the highest doses usually being received by population groups living in the vicinity of nuclear installations. Typical values around nuclear reactors are reported between a fraction of one percent to a few percent of the average annual effective dose equivalent from natural sources. In addition, radiation workers involved in the nuclear power industry receive annual effective dose equivalents which are typically of the order of the corresponding average value from natural sources.

37. The long-term component of radiation impact arises from releases of long-lived radionuclides during the operation of the plant and from effluents from mill tailings or from high-level waste disposal. The long-term component corresponding to a period of 500 years following the release has been crudely assessed. For one year of nuclear power production at the 1980 level, the impact of this long-term component on members of the public may represent about 2 hours of exposure to natural background, whereas the radiation impact of the short-term component is estimated to amount to about 30 minutes of exposure to natural radiation sources. Most of the effective dose equivalent from the long-term component stems from releases from mill tailings which may emanate radon over extremely long periods of time. The rate of emanation can be modified by improvements in management practices, which could result in decreases by orders of magnitude. In the far future (thousands to millions of years) the releases from mill tailings or from waste repositories will be influenced by geological and climatological changes, which are very difficult to predict. The dose estimates from those releases also depend on living habits in the far future, which might be very different from present ones.

38. On the assumption that the production of nuclear power by fission reactors may continue for 500 years at the present rate, the Committee estimates that the maximum annual collective effective dose equivalent may amount to a fraction of one percent of the corresponding dose received annually from natural sources of radiation. It must be emphasized that this long-term forecast is based on existing technologies and is therefore subject to change. It is likely that changes in present technologies such as the introduction of fast reactors or other advanced fuel cycle technology, or the containment of long-lived radionuclides may further reduce the long-term impact of future practices.

39. The contribution of occupational exposures to the impact from nuclear power production is much easier to assess as most radiation workers are individually monitored. At the present level of nuclear power production, the annual collective effective dose equivalent resulting from occupational exposure amounts to about 0.03% of the corresponding value from natural radiation sources.

B. NEW DEVELOPMENTS IN RADIOBIOLOGY

40. Radiation induces biological effects essentially through the deposition of energy in the cells of the irradiated individual. Two classes of cells may be visualized in this respect: the somatic cells, which do not survive beyond the life span of the individual; and the germinal cells, whose function is to transmit genetic information to new individuals. The somatic effects of irradiation take place in the somatic cells and they must become apparent, by definition, within the life of the irradiated person. On the other hand, hereditary effects occurring in the second class of cells become apparent in the descendants of the irradiated persons within the first, or in some later, generation.

41. In general terms, the radiobiologically important effects interfere with the division of somatic cells in one of two possible ways: they may either cause the irradiated cell to stop dividing and eventually to die; or they may confer upon the cell a capacity for unrestrained division which is characteristic of cancer. A distinction is usually made between early and late effects of irradiation, according to the time at which such effects become manifest: a few hours to a few weeks in the first case; many months to many years in the latter.

42. It has been past policy of the Committee not to attempt to cover all biological effects in animals and man in any one report, but rather to review selected areas, depending on the amount of information accumulating and on the need to survey all fields at some interval of time. This report was compiled in the light of the same general policy. Among somatic effects, some non-cancerous consequences of irradiation administered to the whole body or to selected tissues are considered. Information on genetic effects is updated and assessed for the purpose of risk estimation.

1. Genetic effects

43. In the field of genetic effects, important conclusions were reached on the basis of recent publications. These have increased the Committee's confidence that

earlier assumptions and risk estimates remain essentially valid. These estimates have been compared with spontaneously-arising hereditary defects which affect, with different grades of severity, roughly 10% of all liveborn children. Physical agents such as ionizing radiation, as well as some noxious chemicals, may interact with the genetic material of the germinal cells in the testes or in the ovary by altering the genes, the elementary units of heredity (thus causing gene mutations), or with the structure or number of chromosomes on which the genes are carried (thus causing chromosomal aberrations). Changes in the genetic material may be associated with a variety of hereditary defects, some of which have severe clinical consequences.

44. Using gene mutations and chromosomal aberrations as end-points of experimental observations, data on dose-effect relationships have been compared in a variety of organisms. These comparisons have strengthened the assumption that one may expect a proportionality between the rates of spontaneous and of induced mutations of particular genes. This basic assumption has been applied in the indirect method of risk estimation.

45. Using the indirect method, the Committee estimated in 1977 that when a population is continuously exposed to low doses of low-LET radiation at a rate of 0.01 Gy per generation (1 generation = 30 years), 63 new cases of hereditary diseases per million first generation progeny would be expected. A substantial part of the hereditary diseases included in this estimate is related to those arising from numerical anomalies of chromosomes. However, data on experimental animals and man point to the possibility that the estimate for diseases falling under the category of chromosomal diseases may be lower than previously estimated. In view of this, the Committee has now estimated that when a population is exposed under the conditions specified above, the increment in genetic diseases is likely to be of the order of 20 (instead of 63) cases per million births in the first generation and about 150 (instead of 185) cases per million births at equilibrium (or about 2000 and 15 000 cases in the first generation and at equilibrium, respectively, when the exposure is at a rate of 1 Gy per generation).

46. As in the 1977 report, an estimate of risk for hereditary disorders has also been made using the direct method. The estimated values using these two different methods (i.e., indirect and direct methods) are in reasonable agreement.

47. The risk from the induction of a particular type of chromosomal effect of radiation (reciprocal translocations) has been re-evaluated on the basis of results from studies in marmosets, rhesus monkeys and man. However, the health consequences to the individuals carrying such translocations cannot be reliably assessed at present.

48. Further advances have been made in our knowledge of the dose-response relationships and other aspects of some of the more important types of genetic changes which can be induced by radiation in experimental mammals. Extensive use of experimental data for genetic risk assessment is still considered essential in the absence of significant results with respect to hereditary effects after human exposures. Suggestions have also been formulated for more detailed analyses of genetic effects with respect to detriment.

2. Somatic effects

49. One of the conclusions of the present report is that at low doses and dose rates the induction of non-neoplastic effects is not observed. This conclusion holds true for both whole-body and specific organ irradiation. At comparable doses and dose rates cancer induction may be the only somatic consequence of irradiation in animals and man.

50. In its 1977 report the Committee discussed factors which make any accurate assessment of risk of cancer induction in man very difficult. In spite of such difficulties, the Committee provided at that time an analysis of the human data and of the risk estimates to be derived therefrom, to be used as a necessary starting point for decisions of practical value, particularly as scientific criteria for radiation protection policies.

51. In view of the limited amount of new epidemiological evidence, there would have been no merit in repeating the same analysis in a short time interval. The Committee undertook instead to review whatever information might be of interest, in experimental animals and in man, in the light of some basic models of tumour induction. The scope was to assess the possible errors that might affect the estimates if one or another model of radiation action applied. Such a study might be regarded as an indirect way of estimating risk ranges at the low doses and dose rates where direct evidence is not available.

52. The Committee decided, however, to postpone the publication of a document based on this study when it became known that revisions had been proposed to the dosimetric estimates for the survivors of the atomic bombs at Hiroshima and Nagasaki on which some of the Committee's analyses had been based. Not only the total doses received by the exposed populations, but also the relative contributions of the neutron and gamma-ray components in the presently used T65D (Tentative 1965 Dose) were called into question. The effect of the proposed revisions is to reduce the neutron dose component at both cities and to increase the gamma component at Hiroshima substantially, while reducing the gamma component at Nagasaki slightly. In addition, many more factors must be examined and taken into account before reliable revised estimates of individual organ doses can be determined for the survivors. This matter is technically complex, and it appears unlikely that the proposed revisions can be thoroughly investigated and agreed upon within a short time.

53. The Committee awaits with interest the results of further studies in this field, as they would form one of the bases on which radiation risk estimates in man must be founded. In the meantime the Committee wishes to emphasize that it does not expect a significant impact of these revisions on the risk estimates contained in the 1977 report of the Committee, namely, that the risk of fatal cancer induction for x and gamma rays is of the order of $2\ 10^{-5}$ for an effective dose equivalent corresponding to one year of natural background, as an average for both sexes and all ages. This is so for two reasons. First, while it is impossible yet to say exactly what influence the revisions, if accepted, will have on the risk estimates, it is unlikely that this influence will exceed a factor of 2. Indeed, improved agreement between data from Hiroshima and Nagasaki may tend ultimately to strengthen confidence in the estimates. Secondly, the information derived from the survivors of

the atomic bombs in the two cities is only one of the sources of human exposure that the Committee has used in arriving at its estimates.

54. While little change is therefore expected to result in regard to estimates for cancer induction in man by x and gamma rays, an important presumed source of information for whole-body neutron irradiation will no longer be available if these dose revisions are indeed substantiated. The calculation of the doses to the atomic bomb survivors of Hiroshima and Nagasaki will be kept under close scrutiny and the Committee will continue to study dose-effect relationships.

55. A large amount of information has been available on the effects in man of irradiating selected organs and tissues for radiotherapy of various types of disease, mostly cancer. There was a need to review these data and to verify their consistency with information obtained for different purposes in experimental animals. The Committee's study considered: the nature of the early and late non-stochastic damage (see Annex J) induced by radiation on normal tissues; the dose thresholds at which specific forms of early damage may become apparent in various animal species, and particularly in man; the effect of some important variables of exposure (radiation quality, fractionation of treatment) on these thresholds.

56. Two unifying concepts emerged. First, tissue damage depends primarily on the loss of reproductive capacity of some of the constituent cells; second, the structure and function of each tissue determines to a large extent the time and magnitude of its observed response. It was necessary to derive, from experience collected mostly at high doses and dose rates, information applicable at low doses and dose rates, which are the irradiation conditions of most interest in practice. Finally, it was necessary to rely on experience derived from exposure of normal human tissues during radiotherapy.

57. The study was useful for the great amount of information it provided in respect to each particular tissue. The most general conclusions to be drawn from such a complex analysis are that non-stochastic tissue effects are generally characterized by non-linear relationships with dose and apparent thresholds at low doses. These conditions are of paramount importance for any consideration of non-stochastic tissue damage. Although the magnitude of the threshold may vary for each tissue and for each specific effect, the mechanisms producing the effects make it unlikely that thresholds will be abolished at low doses and dose rates. Thus, if a non-threshold response applies or is assumed to apply for induction of cancer, it follows that this latter might be induced at the low doses where the threshold would prevent expression of the non-stochastic damage to be seen. In this respect the induction of cancer may in general be regarded as the most important effect at low doses and dose rates for planning of radiation protection.

58. In cases of partial-body irradiation it is, in principle, easier to attribute the resulting damage to target cells in organs and tissues than in the case of whole-body irradiation, where effects and symptoms may be of doubtful significance and of uncertain pathogenesis. A typical example is to be found in an effect of whole-body irradiation which is commonly, and incorrectly, referred to as "aging" or "non-specific life span shortening". The Committee has carried out an analysis of the experimental findings regarding radiation-induced aging in animals and man. Since the biological mechanisms of natural aging are essentially unknown, there appears to be insufficient ground to postulate a possible effect of irradiation in the absence of convincing experimental data; this possibility may not, however, definitely be ruled out. The study was therefore limited to the radiation-induced shortening of life.

59. Although the length of the life span is usually taken as a measure of aging, it represents simply the actuarial aspect of it, and ignores the complex interplay of factors leading to death. It is well known that, on the average, the life span of irradiated animal and human populations tends to be shorter than the life span of suitably matched controls. However, to ascertain the causes of death may be an exceedingly difficult task, though the only reasonable means to attribute death to specific causes and thus to decide on the reality of possible non-specific mechanisms. An overwhelming body of literature shows that at low doses and dose rates life shortening is essentially caused by the occurrence of cancers at above the spontaneous rate. When the contribution to life shortening by these cancers is subtracted from the total life shortening effect, there is no evidence of other non-specific mechanisms being responsible for additional shortening. This conclusion is well documented and it applies in humans and in other mammals. There is indeed some conflicting evidence but this does not, in the Committee's opinion, carry sufficient weight to invalidate the conclusion. Further study on this point may be required.

60. It is essential that risk estimates be formulated with a wide perspective of possible applications. In this connection it is important to ascertain if the effects of ionizing radiation, a ubiquitous agent in nature, could be modified by the interaction with other agents (physical, chemical or biological) having a widespread distribution in the environment and therefore apt to affect large numbers of people and, possibly, to cause changes of the risk estimates.

61. Although the possibility of such interactions has often been suggested, the amount of positive information, particularly regarding effects that are significant for risk estimates in humans (induction of cancer, hereditary effects, developmental abnormalities), is rather scanty and inconsistent. The analysis of the Committee was therefore of necessity mostly theoretical, with illustrations drawn from published work. It has, however, demonstrated the complexities of a thorough scientific treatment of this matter because the nature of the interacting agents, the variable mechanisms of action, the doses, the order and the schedules of administration allow a variety of possible interactions.

62. The study reviewed some agents which are important under specific conditions, mostly occupational, among which the best documented is the interaction of tobacco smoke and alpha-irradiation by radon daughters for lung tumour induction in uranium miners. Although this finding is certainly applicable to specific occupational situations (and may be relevant to actions by local authorities) the review of the Committee indicates that it does not decrease the general validity of the broad use of radiation risk estimates. There is a need for more research to be directed towards these problems, with coherent strategies and sensible choices of the agents to be investigated. The Committee has made recommendations in this respect.

III. MAIN TEXT OF THE REPORT

63. After an initial section outlining the concepts and quantities used by the Committee in its assessments, this chapter systematically covers, for the various fields of interest, specific conclusions to be drawn from the Committee's studies since the presentation of the last substantive report. Each section is preceded by a paragraph which summarizes the content of the section. The data and the analyses on which the Committee's conclusions are founded are given in the scientific Annexes A to L.

A. QUANTITIES AND UNITS

64. In studies of radiation effects it is customary to correlate the probability of the response or the magnitude of the effects with estimates of the exposure to radiation. The primary quantity used for this purpose is the energy absorbed per unit mass of the irradiated biological object, which is called the absorbed dose.

65. For risk assessment it may be desirable to weight the contribution of different radiations in order to account for their different biological effectiveness. One weighted quantity defined by ICRP for the purposes of radiation protection is the dose equivalent, which is derived by weighting the dose of a given radiation with the quality factor based upon a range of experimental observations. The dose equivalent, H, is thus the product of the absorbed dose, D, and of the quality factor, Q, together with any other relevant factor recommended by the ICRP.

66. An important development for the purpose of risk assessment that has taken place recently and is used in this report is the definition of effective dose equivalent. This stems from the need for both uniform and partial irradiations of the body to be taken into account for risk evaluations. To this end it is necessary that the weight to be assigned to irradiation of a given part of the body should be in proportion to the risk of developing stochastic effects, by comparison with effects expected from whole-body irradiation with the same dose equivalent. For example, if, for the same dose equivalent, irradiation of an organ results in 10 times less effects than would be expected to result from irradiation of the whole body, it would be necessary, in order to maintain equality of the risk when summing exposures of different organs, to assign 10 times less weight to the organ than to the whole-body dose equivalent. A list of weighting factors applying to various organs has been provided by the ICRP for the purposes of radiation protection and these same factors have been used throughout this report.

67. The effective dose equivalent, as defined by ICRP, was not designed for risk estimates, but was introduced as a suitable dosimetric quantity for comparison with administrative dose limits. Since the organ weighting factors are average values for all ages and both sexes, the effective dose equivalent is not well suited to reflect the probability of radiation-induced cancer and severe hereditary harm from exposures of single individuals but will indicate the average risk for a heterogeneous population of both sexes and all ages.

68. For such populations, the expectation of harm from low doses of radiation is postulated to be proportional to the collective dose, which is the average individual dose multiplied by the number of individuals exposed. The radiological impact of a given source of radiation can therefore be assessed by summing individual contributions to the collective dose over space and time. When related to the particular practice that is assumed to cause these present and future exposures, this sum is called the collective dose commitment from that practice.

69. In conclusion, weighting of absorbed doses to derive dose equivalents makes allowance for the biological efficiency of different types of radiation. Use of the effective dose equivalent takes into account the relative risk of exposures of different organs of the body. The collective dose permits an estimate of the expectation of harm in an exposed population. The commitment concept relates the total future expectation of harm to the practice that causes the exposure. In spite of their apparent complexity, these concepts facilitate assessments and intercomparisons of doses and risks from different sources of radiation.

70. In considering the radiation spontaneously emitted from a radioactive material it is convenient to characterize such emissions in terms of activity (of the radionuclide). Activity is the number of nuclear transitions of the radionuclide per unit time. The SI unit is reciprocal second (s^{-1}). The special name for reciprocal second, when used for activity of radionuclides, is becquerel (Bq). Thus

$$1\ s^{-1} \equiv 1\ Bq \text{ (for activity)}$$

The SI unit for both absorbed dose and dose equivalent is joule per kilogramme ($J\ kg^{-1}$). The special name for $J\ kg^{-1}$, when used for absorbed dose, is gray (Gy). Thus

$$1\ J\ kg^{-1} \equiv 1\ Gy \text{ (for absorbed dose)}$$

The special name for $J\ kg^{-1}$, when used for dose equivalent, is sievert (Sv). Thus

$$1\ J\ kg^{-1} \equiv 1\ Sv \text{ (for dose equivalent).}$$

B. RADIATION LEVELS AND DOSES

1. Dose assessment models[4]

71. To calculate the dose delivered by radiation sources to exposed populations it is necessary to use models linking the measured or calculated amounts of radioactive materials that are released by the source or that are present in the environment, with the resulting dose in the exposed subjects. Environmental transport models and dosimetric models are used for this purpose. As background information for the assessments which follow, this section provides a description of the main models used by the Committee.

[4] This subject is reviewed extensively in Annex A "Dose assessment models".

72. The Committee reviews the information on human radiation exposure for several purposes. One purpose is to assess the levels of exposure to which individuals are subjected, another is to assess the levels of exposure to population groups, a third is to provide basic data. The relationship between the level of exposure of an individual and the probability of induction of health effects which are presumed to result is extremely complex. At the present state of knowledge it is reasonable to assume that an increased exposure carries with it an increased risk of harmful effects. The principal assumption underlying, implicitly or explicitly, the Committee's evaluations is that the probability of occurrence of stochastic effects in a given tissue is linearly proportional to the dose equivalent in that tissue, down to the lowest doses and with a proportionality factor which is different for various tissues. The importance of this basic model cannot be overemphasized because, in the absence of linearity, it is not permissible to add doses to give a measure of the total risk, nor to calculate collective doses as expressions of the total detriment to exposed populations.

73. When individuals at work are being considered, it is usually possible to evaluate the level of exposure from direct measurement. The doses resulting from such exposures over a given period of time (e.g., one year, the working life, the whole life time) provide an indication of the presumed level of risk incurred. When assessing exposures to members of the public, considered either individually or collectively, the level of exposure cannot be measured directly and must be assessed by indirect means. This is accomplished by the use of models linking the measured or calculated amounts of activity that are released by a source or that are present in the environment, with the resulting doses in the exposed individuals. Models of this sort fall into two broad categories: environmental and dosimetric. Environmental models describe the movement of radionuclides from the point of release through various sectors of the environment. Dosimetric models include those for predicting the behaviour of radionuclides inside the human body after their intake and those for providing estimates of the resulting doses to organs from radionuclides in the body or from external sources.

74. If it is possible to measure the absorbed dose rate in air from radionuclides in the air or deposited on the ground at a sufficient number of places and over a sufficient time, then the absorbed doses to individuals and populations from external irradiation can be assessed without the need for environmental transfer models to describe the manner in which the airborne contamination or deposition resulted from the source of radionuclides. Similarly, if the activity concentrations in organs or tissues of the radionuclides concerned can be measured in a sufficient number of people, the absorbed doses from incorporated radionuclides can be assessed using only dosimetric models and without the need for environmental transfer models. In many situations, especially for naturally-occurring radionuclides and for those produced from nuclear explosions, sufficient measurements have been carried out in different places and over long enough periods of time to enable the Committee to estimate doses directly from them.

75. Slightly less direct estimates of internal doses can be made from measurements of activity concentrations of radionuclides in the air or in foodstuffs. In this case the additional information required is the intake rates of the radionuclides from air or from the foodstuff concerned, and the appropriate dosimetric models to provide the absorbed doses in organs and tissues following intake. These less direct methods are used for some radionuclides from nuclear explosions, often to supplement a more limited measurement programme on people. They are also used in assessing absorbed doses to critical groups of the population exposed as a result of deliberate releases of radionuclides from nuclear installations, for a limited number of radionuclides. A difficulty in placing too much reliance on such measurements is that there has to be a great deal of preliminary effort to ensure that the foodstuff being monitored is the only, or the major, route of intake of the radionuclide concerned. When dealing with a mixed diet and a large number of radionuclides this becomes extremely laborious. For radionuclides which are not evenly distributed in the environment it is not a feasible method to establish the collective dose.

76. Sometimes direct measurements may not be practicable. This may be due to technical difficulties in measuring the activity concentration of the radionuclide concerned in an appropriate medium, or to the difficulty of obtaining samples, or to the number of radionuclides and pathways being too large. Direct measurements may also be impracticable because predictions of dose rates are required, for example to derive collective dose commitments, rather than measurements which have to be carried out after or during the delivery of the dose. In these cases models are necessary in order to derive doses and dose distributions from data on the quantities of radionuclides released into the environment and the rates of release. The relationship between doses and releases will depend on many factors, such as the conditions of the release, the physico-chemical form of the radionuclide, whether the release is into the atmosphere, a water body or the ground, and the characteristics of the receiving environment. In general, the environmental models with which the Committee is concerned are simplified mathematical representations of actual transfer processes. Some of those processes are well understood and can be described reasonably precisely by mathematical models which are very closely based on measurements. The transfer of fallout radionuclides such as strontium-90 through food chains is an example. Other processes may only be partially known and the time scales or other aspects may render it very difficult to verify the models by measurement, as in the case of the long-term stability of sorption of actinides on soils or sediment particles.

77. Annex A reviews the models used by the Committee but a detailed account of all these is beyond the purpose of this chapter. Suffice it to say that the Committee describes, in that Annex, the atmospheric (local, regional and global), the aquatic (rivers, lakes, oceans) and the terrestrial transport models used throughout all other Annexes. It also reviews the bases of the models and the detailed pathways for various modes of irradiation. This material is regarded as necessary background information for the dose assessments in all cases involving environmental dispersion of radioactive substances.

2. *Exposure to natural radiation, including the technologically modified sources, and to radiation-emitting consumer products*

78. The main conclusion to be drawn from the work of the Committee in this area is that the dominant contri-

bution to the collective dose from natural sources may be attributed to the decay products of a noble gas, radon. New studies have investigated a number of radon sources such as building materials, radon released from ground, from tap water and from natural gas. A number of parameters are also being studied (emanating power, building technology and, particularly, ventilation) which may greatly influence the contribution of this source. The realization of the importance of these factors coincides with technological developments which increase the radon concentration indoors. Exposures to other natural sources, to enhanced natural radiation or to various consumer products, have not been found to depart substantially from previous assessments.

79. The Committee has reported frequently on natural sources of human exposure because they are at present (and are likely to represent also in the foreseeable future) the largest part of the collective dose received by the population of the world. Their ubiquitous nature and the very low and fairly constant rate of delivery during the whole of man's life time are the main characteristics of these sources. Improvements in knowledge of natural exposure, with the exception of the exposure to the decay products of radon, have not been very substantial since the 1977 report. The present treatment is therefore essentially an updating. However, some new information on technologically modified exposures to natural radiation and to consumer products has resulted in a better assessment of the sources and of the doses therefrom.

80. Any form of life on earth is unavoidably associated with exposure to radiation from natural sources. These may be of two different kinds: sources in the extraterrestrial environment (i.e., cosmic rays) and terrestrial sources (i.e., the radioactive substances in the earth's crust). These irradiate the human body from outside. There arises also, however, from both types of sources, internal exposure from naturally occurring nuclides which are taken up into the body through normal physiological pathways. When living in a natural environment man is exposed to all these sources.

81. There are circumstances, related mostly to technological developments, in which human exposure to these natural sources can be modified. Air travel, the use of natural gas for heating purposes, and living in the vicinity of power plants burning fossil fuel, are examples of conditions giving rise to enhanced exposure to natural radiation. These exposures would not occur if the related technologies (not expressly designed to produce radiation) had not been available. In this report these exposures are referred to as "technologically modified natural exposures" and are treated separately from the truly natural ones.

82. Since it is known from previous analyses of the Committee that a substantial part of the dose received by internal exposure is due to inhaled radon, thoron and their decay products, a comprehensive study of these radionuclides was undertaken for the present report. The study relates to the levels of these nuclides in the living and working environments, to the extent and causes of their variability in nature, and to the conditions affecting the dose delivered by these nuclides in the course of human exposure, particularly of the lung. The results of this study will be discussed separately (see paragraphs 108–116).

83. Finally, there are exposures to widely used consumer products, arising either because radioactive materials are deliberately incorporated in them, or because radiation is produced in the course of their normal function. Exposure to consumer products is similar in a way to exposure to technologically modified sources; their joint treatment with the technologically modified sources is, however, essentially a matter of convenience.

(a) Natural sources[5]

84. With regard to external exposure, the Committee has evaluated the doses from cosmic rays (both the ionizing and neutron components) separately from the doses due to terrestrial irradiation produced by potassium-40, uranium-238, thorium-232 and their decay products. The cosmic ray component is usually very stable at the earth's surface, but it does vary with the geomagnetic latitude and, to a greater extent, it increases with the altitude above sea level. Thus, population groups living at high altitudes receive substantially higher doses than others living on low land or at sea level. The external dose equivalent received from cosmic rays by populations living at sea level is about 0.3 millisievert per year.

85. The terrestrial component of the natural background is dependent on the composition of the soils and rocks in which natural radionuclides are contained. There is sufficient information concerning the outdoor terrestrial radiation doses over large areas of the world to state that the majority of the population residing in these areas receives of the order of 0.35 millisievert per year, with a standard deviation of the order of 25% of this average value. This figure is derived from knowledge that exposure rates indoors are on the average about 20% higher than outdoors and from the assumption that people spend 80% of their time indoors. This population weighted average may reasonably be thought to represent the "normal" level of terrestrial radiation to which mankind is exposed. Based on averages applying to large numbers of adult subjects living in areas of normal background, the external dose received from terrestrial irradiation is slightly higher than that from cosmic rays.

86. There are regions of the world where external exposure from natural terrestrial sources may substantially exceed the normal variability ranges. Such areas have been identified (and in some cases rather carefully mapped) in Brazil, India, Iran, Italy and other countries. In some of these locations the yearly dose received by the inhabitants may be more than 10 times greater than that received by people living in areas of normal background. The relevance of these high background areas to the global collective dose from external exposure has not yet been ascertained with great accuracy. Current estimates are that this contribution does not exceed 10% of the global collective dose.

87. Internal exposure resulting from radionuclides entering the body through ingestion or inhalation has also been assessed by the Committee. These radionuclides are either cosmogenic (i.e., produced by the interaction of cosmic rays with atoms in the upper atmosphere) or primordial, in the sense that they have existed in the earth's crust throughout its history. Very little of the dose from natural background is contributed by the first class of nuclides. Tritium (hydrogen-3), beryllium-7, carbon-14 and sodium-22 are the only

[5] This subject is reviewed extensively in Annex B "Exposures to natural radiation sources".

components adding significantly to the dose. Of the latter class, the short-lived decay products of radon-222 are by far the most important contributors. Then follow potassium-40, the decay products of thoron (radon-220) and polonium-210. The effective dose equivalent from internal sources of natural radiation may be estimated to be about two times that from external exposure. However, groups of people living under special housing conditions may be exposed to considerably elevated internal absorbed doses.

88. Table 1 summarizes data relating to various sources of natural exposure in terms of effective dose equivalent. The per caput global annual effective dose equivalent resulting from natural sources of radiation is estimated to be 2 millisievert, about half of which is due to indoor inhalation of the short-lived decay products of radon-222 and radon-220 which are part of the uranium-238 series and of the thorium-232 series, respectively. The relative importance of the contribution from the short-lived decay products of radon-222 and radon-220 stems from the use of the new concept of effective dose equivalent. This implies the multiplication of the absorbed dose in lung by a quality factor of 20 for alpha particles to calculate the dose equivalent in lung, and a multiplication by a factor of 0.12 which is the organ weighting factor for the lung in the derivation of the effective dose equivalent. The overall conversion coefficient from absorbed dose in lung to effective dose equivalent is thus 2.4 sievert per gray. As the corresponding overall conversion coefficients for the other significant contributors to the exposures from natural sources are equal to one or less

TABLE 1. ESTIMATED ANNUAL EFFECTIVE DOSE EQUIVALENTS FROM NATURAL SOURCES OF RADIATION IN AREAS OF "NORMAL" BACKGROUND

	Annual effective dose equivalent (millisievert)		
Source	*External irradiation*	*Internal irradiation*	*Total*
Cosmic rays			
Ionizing component	0.28		0.28
Neutron component	0.02		0.02
Cosmogenic nuclides		0.015	0.015
Primordial nuclides			
Potassium-40	0.12	0.18	0.30
Rubidium-87		0.006	0.006
Uranium-238 series	0.09	0.95	1.04
Thorium-232 series	0.14	0.19	0.33
TOTAL (rounded)	0.65	1.34	2.0

than one sievert per gray, the effective dose equivalent from the decay products of radon-222 and radon-220 is given a higher prominence. The average indoor concentrations of radon-222 and radon-220 are expected to vary from one region of the world to another according to the rate of ventilation and to the type of dwelling. It is estimated in this report that, by comparison with the average global value, the exposure from the decay products of radon-222 and radon-220 are about 25 per cent higher in the temperate latitudes and about 70 per cent lower in the tropical latitudes, resulting in average annual effective dose equivalents from natural radiation sources of 2.2 and 1.3 millisievert in temperate and tropical latitudes, respectively. The global average value of 2 millisievert in a year is reasonably consistent with the estimates presented in the 1977 Committee's report in terms of absorbed dose. The annual global collective effective dose equivalent is thought at present to be about 10^7 man sievert.

(b) Technologically modified natural sources[6]

89. The following subsection summarizes the characteristics of sources previously defined as "technologically modified" (see paragraphs 81–83).

90. *Coal fired power plants.* Coal contains trace levels of natural radionuclides and its combustion results in their release to the environment. Their redistribution from deep in the earth crust to the environment may significantly modify ambient radiation fields and population exposure. New information has become available on activity measurements in coal and on the behaviour of the radionuclides in and around power plants. Some estimate of doses arising from this source of exposure may now, therefore, be carried out.

91. When coal is burned, the mineral matter is fused into vitrified ash. Most of this is retained in the power plant as slag-ash but the lighter portion, the fly-ash, is carried with the hot gases to the stack of the plant from where, depending on the efficiency of the collecting devices, some fraction is released into the atmosphere. An estimate of the average releases of radionuclides in the atmosphere has been obtained from reported discharges and measured concentrations in coal and ash. The estimated discharges are thought to be representative of the current situation world-wide.

92. The main pathways of exposure of the population living around the power plants to the radionuclides emitted are considered to be the following: inhalation during the passage of the plume, external exposure, and inhalation and ingestion resulting from the radionuclides deposited on the ground. Doses to the various parts of the body may reasonably be calculated and dose commitments estimated for the various nuclides.

93. In terms of the collective effective dose equivalent commitments, each of the three pathways mentioned is found to contribute significantly. The predominant components are the isotopes of thorium (for inhalation during the passage of the cloud) and the isotopes of radon (for internal exposure resulting from the activity deposited). Assuming that 70% of the coal mined throughout the world is used for power production and that one gigawatt year of energy produced requires the burning of 3 million tonnes of coal, the collective effective dose equivalent commitment resulting from the use of coal in 1979 is calculated, world-wide, to be about 2000 man sievert. The combustion of coal for other uses will add a somewhat larger amount.

94. *Use of phosphate rock.* Phosphate rock is extensively used as a source of phosphorus for fertilizers. It contains trace amounts of uranium-238, radium-226, thorium-232 and potassium-40, which are redistributed to the environment in the course of the rock's industrial processing and use. This comes about through effluent discharges, the agricultural use of fertilizers, and the utilization of by-products and waste material for other purposes.

95. Industrial effluents give rise to variable concentrations of the relevant radionuclides in airborne or liquid discharges. The type and amount of radionuclides released depend very strongly on the technology used for the rock processing. Inhalation during passage of the cloud, and the uptake of activity deposited onto

[6] This subject is reviewed extensively in Annex C "Technologically modified exposures to natural radiation".

soil, are the main mechanisms of irradiation; for each of them very approximate dose assessments can be provided and are discussed in Annex C.

96. Dose assessments are also possible for the radionuclides contained in the fertilizers. From knowledge of the world production of fertilizers, of the radionuclide content of these substances, of their distribution and use, of the radionuclide levels in the treated food crops, etc., approximate estimates of dose may be obtained. These doses are delivered to people occupationally exposed to the fertilizers, and to members of the public by various mechanisms of external or internal exposure.

97. The main by-product of the processing of phosphate rock is phosphogypsum in wet-process plants. In thermal-process plants calcium silicate slag is the main end-product. Phosphogypsum is used instead of natural gypsum in prefabricated building elements, calcium silicate in railroad and concrete constructions. Both these materials may contain much higher concentrations of radium-226 than most natural products. Radiation exposure of members of the public results from the above-mentioned uses and in view of the nuclide composition and of the conditions of irradiation, exposure would be expected to be significant, e.g., up to 30% higher, for persons living in houses built using phosphogypsum.

98. The Committee assessed the radiation exposures that might result from the full cycle of exploitation of phosphate rock, using reasonable simplifying assumptions and considering the most important radionuclides. Under the assumption that 10% of the phosphogypsum produced may be used in houses, the Committee came to the conclusion that by far the most important contribution to the collective dose resulting from the exploitation of phosphate rock would be derived from that source. If that use could be avoided, the rest of the dose commitment would only amount to about two thousandths of the potential dose.

99. *Use of special building materials.* Other materials have been found to deliver high doses to the inhabitants of dwellings built with them. They include: pumice stone, alum-shale concrete, lithoid tuff, granite, and tailings from uranium mills. The doses are due to high concentrations of potassium-40, radium-226 and thorium-232. In some countries, sampling of many building materials revealed, in certain cases, excessive concentrations of the above nuclides. However, the average absorbed dose rates measured in buildings containing such materials is often much lower than might be expected from the radioactive content of the materials considered, because usually less active materials are also used in the same buildings.

100. *Enhanced exposure to cosmic radiation.* During flight, passengers are exposed to higher dose rates from the cosmic component, which increases appreciably as a function of altitude. For example, an increase by a factor of 20 in the dose rate is observed between the altitudes of 4 and 12 kilometres. It has been estimated that the collective effective dose equivalent to the world population due to commercial flight in 1978 amounted to about 2000 man sievert. Similar evaluations have been performed specifically for the case of supersonic air transport. In spite of the fact that, due to altitude, radiation of solar origin does add to the galactic component and that during occasional intense solar flare radiation levels may increase substantially, these sources of exposure do not at present contribute significantly to the natural radiation exposure of the world population. Individual doses received by persons such as airline crew members are not however negligible.

101. The examples of technologically modified exposures brought to the attention of the Committee are likely to be incomplete. From the assessments performed, the Committee concludes that these exposures do not add significantly to the collective dose received by mankind on a world scale. However, in localized areas or for population groups exposed under extreme conditions, appreciable increases in individual doses from natural radiation may occur. The present state of knowledge does not allow very accurate estimates of the collective doses incurred from these sources. Further research is required to this end.

(c) Radiation-emitting consumer products[7]

102. *Luminous timepieces.* The energy emitted during the radioactive decay of radium-226, promethium-147 and tritium may be converted into light by a scintillator. This phenomenon has been used extensively in the dial painting industry for the illumination of timepieces and other scientific devices. Recently tritium has been used instead of radium, because its radiation is less penetrating than that accompanying the decay of radium and of its daughters, thus causing less external exposure of the users. With the advent of liquid-crystal display, the use of gaseous tritium light sources to illuminate digital watches is becoming increasingly common. The annual collective dose equivalent arising from radioluminous timepieces employing different radionuclides has been assessed in a number of countries. When projected to the world population this dose is of the order of 2000 man sievert.

103. *Electronic and electrical devices.* They include starters for fluorescent lamps, trigger tubes in electrical appliances, and excess voltage protection devices. Radionuclides incorporated into this equipment for better, faster and more reliable operation include krypton-85, promethium-147 and thorium-232. In spite of the very high number of these devices in operation, and the significant amounts of activity involved, the resulting doses are expected to be very low. They may however become appreciable in the event of accidental breakage and careless disposal.

104. *Antistatic devices.* These are used in industry and, in some countries, in domestic appliances to reduce the build-up of electric charge in certain materials. Polonium-210 is mainly used in these devices to ionize the air. Under normal conditions of use, the only significant hazard would result from external irradiation due to the very small gamma component emitted. Under extreme stress conditions (e.g., impact or fire) the integrity of the component parts may however be altered and a significant potential for doses arising from internal irradiation may ensue.

105. *Smoke detectors.* These appliances usually contain americium-241. In many countries they have a very large market in industrial, public, commercial and private buildings because fire experts recognize their value for the protection of life and property. Assuming a useful life of ten years for the many millions of units

[7] This subject is reviewed extensively in Annex C "Technologically modified exposures to natural radiation".

now installed, and assuming that they may be disposed of by sanitary land-fill or by incineration, the resulting collective effective dose equivalent commitment resulting from the 1978 production is found to be about 10 man sievert. Most of it results from external exposure during the useful life of the smoke detectors.

106. *Products containing uranium and thorium.* Uranium is used primarily as a pigment in ceramic and glassware. Thorium is used in incandescent mantles and in some optical products. The principal hazard posed by the utilization of these substances under normal conditions is the dose from the beta-emitting decay products, and, under special circumstances, high doses could be delivered to specific tissues. For example, fairly high doses to the lens of the eye could be delivered from optical lenses containing high percentages of thorium. Also, the dose to the oral epithelium from uranium incorporated into the porcelain used in prosthetic dentistry to simulate the fluorescence of natural teeth could be high.

107. *Television sets.* During normal operation, television sets give rise to soft x rays from which external exposure may result. However, the x-ray emission from recently built colour television receivers is negligible under conditions of normal operation and appropriate servicing.

(d) Radon and its decay products[8]

108. It has become increasingly evident that a very important contribution to exposure from natural sources results from radon-222 (usually called radon) and its decay products. Another naturally-occurring radioactive isotope, radon-220 (usually called thoron), also contributes some dose. These facts prompted the Committee to investigate in depth the exposure to these gases and to examine the most important physical and physiological variables influencing the exposure.

109. Radon and thoron are naturally-occurring radioactive gases, products of the uranium and thorium decay series, respectively. Uranium and thorium occur in nature as primordial elements in rocks. By diffusion, a small proportion of the radon and thoron produced leaks out of these materials and is dispersed in ground water and in air where these radionuclides may be found in varying concentrations. Radon and thoron decay to their numerous daughters until the uranium and thorium series are completed by stable isotopes of lead.

110. The Committee has considered the mechanisms of radon and thoron release from their natural sources and the variables influencing this release (particle size of the rocks, porosity, humidity); the mechanisms of diffusion of these gases to the surrounding water and air; the transfers of radon and thoron through soil and their exhalation to air; the dispersion in air of these gases and their decay products; and the influence of the vertical temperature gradient, the wind strength and the turbulence of air on such dispersion. Because of the short half-life of thoron (about one minute), this gas is only to be found within a few tens of metres above the ground, while radon, with a half-life of approximately four days, reaches an altitude of several kilometres. The geographical location and the prevailing meteorological conditions affect the concentration of these nuclides at ground level, with pronounced seasonal variations. Usually air masses above continental regions have the highest concentrations, while air masses above the oceans or the artic regions have the lowest concentrations. Mean annual values of radon concentration in outdoor air at ground level vary between 0.1 and 10 becquerel per cubic metre. A typical value in populated areas is 3 becquerel per cubic metre.

111. Because of the rapid diffusion of radon in the atmosphere, the activity concentration of the radon daughters in ground level air shows in general a deficiency in comparison with the radon concentration. The equilibrium factor between radon and thoron and their daughter products is a measure of this deficiency. The equilibrium factor depends on many other conditions, such as the decay constants of the various daughters, the concentration and size distribution of the aerosol particles in the air, the deposition of these aerosols on the surrounding surfaces and the air exchange rate. All these conditions may be investigated experimentally. For practical purposes it is important to point out that low ventilation rate in confined spaces may result in high exposure to radon and thoron decay products.

112. The concentration of radon in water may vary from practically zero to values of up to about 100 megabecquerel per cubic metre in some waters. The radiation doses caused by radon in drinking water are due partly to ingestion but mostly to inhalation of the radon daughters produced by decay of radon released from the water. Approximate calculations of the relative doses resulting from a given radon concentration in drinking water are possible. However, owing to the fact that reported measurements were often carried out in areas known for their high content of uranium or radium, such values cannot readily be considered representative of mean values applying to a whole region or to an entire country. Available information shows that the dose of radiation delivered by radon in drinking water is not usually a major problem for exposure of the general population, except for some cases in which, owing to special geological conditions, the radon content is particularly high.

113. Since most of the radiation dose from radon is received by man while living indoors, the Committee has reviewed a large body of data on the measured concentrations of radon and thoron and their decay products in houses in different parts of the world. These concentrations, normally of the order of 20 becquerel per cubic metre, are higher than for outdoor air. Very high indoor concentrations may result from low rates of ventilation, or from elevated radon levels due to high radium content in the building materials or in the soil under the house, or from the use of radium-rich water. Under adverse conditions peak values of 10 000 becquerel per cubic metre of air, or more, may be found.

114. Radon daughters give rise to exposures in mines. The review of the Committee has considered measurements in many different mines and countries. It has shown that, depending on the type of rock and on the conditions of ventilation, concentrations to be found in uranium mines are usually less than 1000 becquerel per cubic metre of air. However, in some unventilated sections of the mines concentrations of up to 1000 times higher may occur. In non-uranium mines average concentrations are about the same but ventilation requirements to achieve such values are less stringent.

[8] This subject is reviewed extensively in Annex D "Exposures to radon and thoron and their decay products".

115. Irradiation from radon and thoron decay products arises from inhalation and takes place in the respiratory tract. The actual dose delivered to the various anatomical structures depends on the relative fraction of attached and free daughter products, on the size of the aerosol particles to which they are attached and on pulmonary function. On the average, the dose from radon daughter products to the bronchial basal cell layer is a factor of 5 to 8 times higher than the dose to the pulmonary region. Using weighting factors for the regional distribution of the lung dose and the mean lung dose, the relevant effective dose equivalent may be calculated. Global averages of the annual effective dose equivalents caused by inhalation of radon and thoron and their decay products are given in Table 2. Values in temperate and tropical regions are estimated to be about 25% higher and 70% lower, respectively, than these global averages. It should be pointed out that, in temperate latitudes, the dose indoors is about 15 times higher than outdoors, both because concentrations of the radioactive gases are higher inside the houses and because people usually spend more time inside than outside.

TABLE 2. GLOBAL AVERAGES OF THE ANNUAL EFFECTIVE DOSE EQUIVALENTS (MILLISIEVERT) CAUSED BY EXPOSURE TO RADON AND THORON DAUGHTERS THROUGH INHALATION UNDER VARIOUS CONDITIONS

Condition	*Radon daughters*	*Thoron daughters*[a]
Outdoors[b]	0.06	0.02
Indoors[b]	0.7	0.15
Uranium mines[c]	~15	

[a] Based on limited data.
[b] The occupancy factor was taken to be 0.8 indoors and 0.2 outdoors.
[c] Applies to years 1977–1979.

116. In view of the importance attached to the development of energy conservation programmes, the Committee has outlined some general considerations on the possible increase in effective dose equivalent due to radon daughter inhalation that may arise as a consequence of such programmes. Decreased ventilation in factories, and particularly in mines, could enhance substantially the values of the collective effective dose equivalent of workers. In houses, decreased ventilation would also lead to a dose increase—and therefore presumably to health consequences—depending on the type of house, its location, the type of heating, ventilation and other factors. The Committee has outlined the basic principles for the assessment of the radiological impact of such energy conservation measures.

3. Exposures resulting from nuclear explosions[9]

117. Although nuclear explosions in the atmosphere have diminished from the intensity of 1954 to 1958 and 1961 to 1962, occasional testing in the atmosphere still occurs. All these explosions are the cause of a continuing exposure of the world population to radioactive fallout. It is estimated that the exposures from all nuclear tests conducted through 1980 is equivalent to about four years of additional exposure of the present world population to the natural radiation background. Much of the exposure from fallout activity will be delivered at low rates for years into the future. Each new atmospheric test commits present and future generations of mankind to some radiation exposure.

118. The Committee has continued to assess the exposures to which the population of the world has been subjected from the release to the environment of radioactive materials produced in nuclear explosions. Such explosions have been carried out in the atmosphere since 1945. Intensive nuclear testing programmes were conducted in the years 1954 to 1958 and 1961 to 1962. Further explosions occurred to the end of 1980, although no tests were conducted in 1979 and 1981. The Committee has not reviewed exposures from any small emissions which might be associated with underground tests.

119. Radioactive debris from nuclear explosions enter the tropospheric and stratospheric regions of the atmosphere, the partitioning depending on the location and yield of the explosion. The Committee has presented estimates of the amount of radioactive materials produced in atmospheric nuclear testing, the dispersion in atmospheric regions and the deposition of the debris onto the earth's surface. The pathways leading to irradiation of man, including inhalation of contaminants in air, ingestion of radionuclides in diet, and external irradiation from activity in soil, have been considered in evaluating exposures.

120. The 1977 report of the Committee contained estimates of the dose commitments to the world population from nuclear tests conducted prior to 1976. This report updates such estimates to the end of 1981. The Committee has evaluated separately the dose commitments to the populations of the northern and southern hemisphere and the average value for the world. Dose estimates are higher for the northern than for the southern hemisphere, since most of the testing and thus most of the deposition took place in the northern hemisphere.

121. A summary of the Committee's findings is given in Table 3, which presents the effective dose equivalent commitments from nuclear testing to the populations living in the north and south temperate zones and in the whole world. The most significant pathway is through ingestion, largely due to carbon-14, caesium-137 and strontium-90, followed by external irradiation due to caesium-137 and several other short-lived radionuclides. The collective effective dose equivalent commitment due to the tests conducted in the atmosphere up to the end of 1981 is 3 10^7 man sievert. This value, which takes into account an estimated future growth of the population of the world, is equivalent to about 4 years of present exposure of the population to natural sources. Most of the collective effective dose equivalent commitment can be attributed to the test

TABLE 3. SUMMARY OF EFFECTIVE DOSE EQUIVALENT COMMITMENTS AND PATHWAY CONTRIBUTIONS FROM NUCLEAR EXPLOSIONS IN THE ATMOSPHERE CONDUCTED TO THE END OF 1981

Location	*Effective dose equivalent commitment (millisievert)*	*Pathway contribution (%)*		
		Ingestion	*External irradiation*	*Inhalation*
North temperate zone	4.5	71	24	5
South temperate zone	3.1	90	8	2
World	3.8	79	18	3

[9] This subject is reviewed extensively in Annex E "Exposures resulting from nuclear explosions".

programme that took place in 1961 and 1962 (580 days and 370 days of present exposure of the world population to natural sources, respectively). The per caput annual dose reached a peak in 1963 corresponding to about 7% of the average annual exposure to natural sources; in 1966, this figure had decreased to about 2% and it is at present less than 1%.

122. Twenty-one radionuclides were considered by the Committee in these evaluations. Of these, only 4 contribute more than 1% to the collective effective dose equivalent commitment of the world population. In decreasing order of importance these nuclides are: carbon-14, caesium-137, zirconium-95, strontium-90. For zirconium-95, its contribution to the global population dose committed by tests up to 1981 is already largely completed. For caesium-137 and strontium-90, a large part of the dose commitments will have been delivered by the end of this century. Only carbon-14 will continue to contribute doses into the far future, though at low dose rates, due to its long decay half-life. The long-lived decay products of the actinides may also have to be taken into consideration in the long term, but preliminary indications are that they deliver at very low rates an additional contribution of the order of 0.1% to the total effective dose equivalent commitment.

123. The assessments of doses due to radioactive fallout contained in this report are only marginally different from those reported in the past, because of the relatively small amounts of activity released from the fewer nuclear explosions in recent years. The present dose assessments are however more complete, as additional nuclides and other possible transfer pathways have been considered, the transfer factors have been re-evaluated, and the dose estimates extended to more recent measurements of radioactive fallout. There are still some uncertainties concerning both the measurements and the modelling. It can be reasonably expected that further knowledge may lead in the future to minor adjustments and improvements in the Committee's assessments.

4. Exposures due to nuclear power production[10]

124. The collective dose commitment arising from environmental contamination due to reactor operation provides a relatively minor contribution to the total radiological impact of the nuclear fuel cycle. Uranium mining and milling, through the emanation of radon and its daughter products from the tailings of the mills, is one important contributor to the collective dose commitment. The dose commitment from nuclear power, assuming present technology, would be expected to increase with the increase in installed nuclear capacity. The utilization of plutonium in either recycling or fast breeding reactors or other advanced fuel cycle technologies would substantially decrease the collective dose commitment per unit energy generated.

125. The number of nuclear reactors in operation for the generation of electric power has increased since the previous report of the Committee to include, in 1979, 235 reactors in 22 countries, with a total installed nuclear generating capacity of about 120 gigawatt of electrical energy [GW(e)]: this represents a doubling of installed nuclear plants over the period 1975 to 1979 covered by the Committee's report. Projections to the year 2000 are somewhat uncertain but they are at present within a range of 1000–1600 GW(e), which is about two-thirds of the capacity projected in the previous report for the same year. Revised estimates in many countries confirm that the increase in generating capacity will be smaller than previously predicted.

126. The nuclear fuel cycle includes many steps, as follows: mining and milling of uranium ores; conversion to various chemical forms; enrichment of the isotopic content of uranium-235 (in some cases); fabrication of the fuel elements; production of power in the nuclear reactors; reprocessing of irradiated fuel and recycling of fissile and fertile nuclides recovered (in some cases); transportation of nuclear materials between installations at various steps of the fuel cycle; and, finally, disposal of radioactive wastes. Although almost all of the artificial activity associated with the production of nuclear power is present in the irradiated nuclear fuel, at each of the above steps of the cycle, releases of small amounts of radioactive materials to the environment occur. Most of these releases, in view of the short half life of the radionuclides and of their limited environmental mobility, are only of local or regional concern. However, some radionuclides having very long half-lives or rapid environmental dispersal, are distributed globally and may contribute to the irradiation of man and the environment on a world-wide scale.

127. For each step of the nuclear fuel cycle the Committee has evaluated the doses to members of the public resulting from releases of radioactive materials. The Committee's assessments have been derived in terms of collective absorbed dose commitments per unit energy generated, that is in terms of man gray per GW(e) year. The models through which absorbed dose commitment to various body organs or tissues may be converted to effective dose equivalent commitment per unit electricity generated have been extensively discussed in Annex A.

128. Because environmental releases from nuclear installations are subject to technical control, doses to individual members of the public are usually kept well below the recommended limits. There are four groups of people exposed to these types of sources: those irradiated on account of their work in the plants; the local population residing within a few hundred kilometres of the plants; the regional population within a few thousand kilometres; and, finally, the whole world population. Only the last three groups are examined here, since the occupationally exposed individuals are treated separately in Annex H.

129. Since the concentrations of the effluents from the nuclear installations are low at the point of release and extremely low in the surrounding environment, models must be used to estimate the doses to populations over long distances from the plants and over long periods of time. The values of the transfer parameters of the various radionuclides in these models are derived from environmental monitoring results and from experiments of various types. The most important starting point of these models is the amount and type of radioactive material released from various nuclear installations. This information was available to the Committee essentially up to the year 1979 and was converted to average releases per GW(e) generated between 1975 and 1979. Such average values do not apply to any particular installation and they reflect

[10] This subject is reviewed extensively in Annex F "Exposure resulting from nuclear power production".

differences in reactor design and changes in the rates of release between new and old reactors. Although normalized release rates are deemed to be representative of the current situation for nuclear power production around the world, they should not be extrapolated to future practices or to particular plants without great caution and appropriate corrections.

130. In order to estimate collective dose commitments corresponding to the above-mentioned normalized releases, the Committee used for its assessments hypothetical sites whose location characteristics are broadly representative of each major stage of the fuel cycle, namely, mining and milling, fuel fabrication, reactor operation and reprocessing. The Committee also assumed that the environment receiving the releases from each model plant would be a hypothetical environment containing the main features of existing sites and enabling calculations of dose to be made for the most common pathways of transfer to man of the released radionuclides. It should be stressed that such broad generalizations intended to produce estimates on the overall impact of nuclear installation around the world are not representative of any one site. Site-specific calculations would need data on the specific releases, the local and regional environmental characteristics and the actual pathways of radionuclide transfer to man.

131. Calculations of the collective dose commitment require that the instantaneous dose rate absorbed in any organ or tissue be summed over the whole period of exposure. This operation may be difficult and the Committee made use of approximations concerning the size of the world population and the dietary and other habits of the exposed individuals which were assumed to be stable over the period during which the summing operation was carried out. Using these major assumptions, the Committee reviewed the various steps of the nuclear fuel cycle and calculated the dose contributions to the public from the various nuclides and irradiation pathways applicable to each source of exposure.

132. Finally, the Committee made an attempt to estimate the collective effective dose equivalent commitment to the public from nuclear power production. As outlined in Annex A, these figures are indicative of the overall health detriment incurred by mankind from this source of exposures, under the assumptions specified. In Table 4, the values of this quantity are normalized to one GW year of electrical energy produced. Within the next 100 years the total will be about 20 man sievert per GW year, although additional exposures at low annual rates will occur over very long periods of time. Table 4 indicates how the collective doses committed per GW year accumulate with time up to 10 000 years.

TABLE 4. ESTIMATES OF THE COLLECTIVE EFFECTIVE DOSE EQUIVALENT COMMITMENT (MAN SIEVERT) TO THE PUBLIC FROM THE PRODUCTION OF NUCLEAR POWER, NORMALIZED TO ONE GW YEAR OF ELECTRICAL ENERGY PRODUCED, AND THEIR ACCUMULATION WITH TIME

	Fuel cycle operation (excluding tailings and waste disposal)			
Years	*Local and regional*	*Global*	*Mill tailings*	*High-level waste disposal*
10^2	6	12	< 3	0
10^4	6	70	<500	0

133. No estimates are given in Table 4 for periods exceeding 10 000 years, when radon emanating from mill tailings and iodine-129 from reprocessing plants or spent fuel repositories are likely to be the dominating sources. For such periods the Committee's conservative methods of calculation would have led to higher values of collective dose equivalent commitment, not exceeding a few thousand man sievert per GW(e) year under the headings "global" and "mill tailings" combined, and not higher than a few tens of man sievert per GW(e) year under the heading "high-level waste disposal". However, the uncertainties associated with assessments of dose in the far future and the limited usefulness of those assessments are not easily summarized. The reader is referred to Annex F, especially paragraphs 194–201 and paragraphs 207–212 of that Annex, for further discussion.

134. The local and regional contribution from fuel cycle operations is estimated to be 5.7 man sievert per GW(e) year; of this 0.5 is due to mining, milling and fuel fabrication, 4.2 to the reactor operation, and 1.0 to fuel reprocessing. Ninety per cent of this dose commitment is delivered in the year following discharge and the remainder over the next few years. For those nuclides which become globally dispersed, the collective dose commitment is 670 man sievert per GW(e) year, 90% being delivered in the period between 10^4 and 10^8 years from discharge. For all of these future estimates the figures are uncertain. This applies especially to mill tailings, because different management practices or climatological changes could reduce the values by several orders of magnitude. Also, the introduction of fast breeder reactors may reduce uranium ore requirements by two orders of magnitude, which would affect the dose commitment from tailings by the same factor. Other advanced fuel cycle technologies could achieve substantial reductions.

135. Available studies on the dose commitment resulting from the disposal of high-level radioactive wastes in deep geological formations indicate that up to several thousands of years this contribution is negligible, by comparison with the other sources. For periods in excess of ten thousand years the relevant dose may only reach about 0.1–1% of the total normalized dose commitment from nuclear power production.

136. In order to estimate the maximum per caput or average annual dose in the future as a result of nuclear power production, an incomplete collective dose commitment must be used which is here taken at 500 years. The releases during the operational stage of the nuclear fuel cycle lead to a local and regional collective effective dose equivalent commitment which is all received in this period. For those nuclides which become globally dispersed, the incomplete collective dose commitment to 500 years is 18 man sievert per GW(e) year. The choice of 500 years as a mean duration of the practice of producing power by nuclear fission implies the use of breeder reactors which would decrease the rate of mining. The incomplete collective dose commitment from mining and milling, based on the present fuel cycle, is therefore taken to 100 years and is likely to be due only to radon releases, giving 2.5 man sievert per GW(e) year. Thus, on the pessimistic assumptions that no technological improvements are made and current levels of discharge continue for 500 years, the maximum annual collective dose would be about 25 man sievert per GW(e) year. The annual collective and per caput doses for a notional nuclear

programme to the year 2500 are shown in Table 5, again assuming that present release levels are not reduced and that the generation of electric power reaches some 10^4 GW(e) year in 2500. It can be seen that even with the maximising assumptions made here, the level of the annual per caput dose due to effluent releases would rise to the equivalent of 1% of the average exposure to natural background radiation. After the end of the practice, the per caput doses would reduce to about 1% of the final values after 100 years.

TABLE 5. ANNUAL PER CAPUT DOSES FROM THE CONTINUED GENERATION OF NUCLEAR ELECTRIC POWER TO THE YEAR 2500

	Year			
Item	*1980*	*2000*	*2100*	*2500*
Annual projected nuclear generation (GW[e]a)	80	1 000	10 000	10 000
Annual collective effective dose (man sievert)	500	10 000	200 000	250 000
World population (billion people)	4	10	10	10
Annual per caput dose (microsievert)	0.1	1	20	25
Percentage of average exposure to natural sources of radiation (%)	0.005	0.05	1	1

137. Attention should again be drawn to the fact that extrapolation into the future is very uncertain and to a large extent speculative: for example, over the last decade the development of new concepts in radiation protection, better design criteria for the new plants, and technological improvements in the old plants, have resulted in a decrease of the releases to the environment, in spite of an increased electrical output of the plants.

138. The Committee carried out a first attempt to evaluate the collective dose commitment arising from the accidental release of radioactive materials, on the basis of two major accidents for which data on the irradiation of the public and the environment were available. It proved impossible, on the basis of these two accidents, to evaluate retrospectively the component of the collective dose commitment due to accidental release of radioactivity in nuclear power programmes.

5. Occupational exposures[11]

139. The Committee revised its estimates of average doses to various groups of workers and the collective doses from various occupations. The methodology developed in the previous report for extracting parameters from dose distributions useful for comparisons has been refined. Through this analysis the Committee was able to assess collective doses from a number of occupations and identify several groups of workers for whom the average exposures are higher than for other groups. The absolute value of these doses may vary from one installation to another and between workers performing similar operations in different countries. However, for routine operations, the difference in dose levels is generally no more than 50 per cent of the authorized dose limits.

140. As in the past, the Committee updated and analysed the existing information on the radiation exposure of various categories of workers, incurred as a result of their occupation. Knowledge of data on occupational exposure, both individual and collective, is required to evaluate trends in the doses delivered by various practices; to assess the level of individual risks for radiation workers for comparisons with the risks of other occupations; and to assess the total radiological impact per unit practice on the population from different sources. Differences in general methods for monitoring exposed workers in various countries, as well as technical difficulties, contribute to the inhomogeneity of the data available and limit their usefulness to some extent. However, the Committee believes that a judicious analysis of the existing information may still be very valuable, and at least may provide some objective preliminary background for the above needs.

141. In the previous report the Committee suggested certain parameters of a dose distribution which would be useful for comparison and proposed a reference distribution solely for the purpose of intercomparison. The log-normal form of the distribution was meant to reflect the fact that in many occupations involving radiation exposure the majority of workers receive low doses and only a few are exposed to relatively high doses. Such a reference distribution has attracted inappropriate attention, so that the Committee has now revised its techniques of analysis to permit direct comparisons of dose distributions with a standard range of values. The parameters selected for intercomparison are the annual collective dose; the average dose, which depends on the number of workers included; and the proportion of the collective dose delivered at annual individual doses exceeding a certain level, taken as 15 milligray. The increasingly wide acceptance of this method of analysis is evidence of its usefulness and the Committee would like to stress the need to report doses in a manner which might improve such analyses.

142. The work of the Committee covered several different classes of occupational exposure. In relation to the nuclear fuel cycle, systematic consideration was given to the workers exposed in mining and milling operations, in fuel manufacture, in various operations with nuclear power reactors, in fuel reprocessing, and in reactor research and development. An increasing amount of information is becoming available on these subjects and higher doses to large groups of individuals are to those involved in uranium mining. It is also possible to calculate the radiation doses per unit practice. Thus, the total annual collective dose equivalent for workers in all the above operations is calculated to be about 30 man sievert per GW year: the more detailed breakdown in Table 6 shows that reactor operation and fuel reprocessing contribute by far the largest proportions of the occupational doses. On the whole, the data show no striking departure from previous assessments of the Committee. However, it is difficult to separate out the research which is specifically directed to the nuclear fuel cycle and therefore a precise evaluation of this component is not possible; the indications are that it represents lower doses per unit practice than reported earlier. Taking the energy generated by nuclear power in 1979 to be 70 GW year, the occupational collective dose in that year is about 2000 man sievert.

143. Other classes of occupational exposure examined were those involving medical and industrial uses, and

[11] This subject is reviewed extensively in Annex H "Occupational exposures".

TABLE 6. SUMMARY OF COLLECTIVE EFFECTIVE DOSE EQUIVALENTS PER UNIT ENERGY GENERATED DELIVERED TO WORKERS ENGAGED IN DIFFERENT PARTS OF THE NUCLEAR FUEL CYCLE

Operations	*Collective effective dose equivalents per unit energy generated (man sievert per GW[e] year)*
Mining and milling	1
Fuel fabrication	1
Reactor operation	10
Fuel reprocessing	10
Nuclear research	5
TOTAL	~30

research and development using radiation and radionuclides. Although the individual doses received by medical workers may be significant, the overall contribution is relatively small. An indication of this may be derived from the annual collective dose equivalent per million population; this varies from country to country, but a reasonable value for countries with a high standard of medical care is of the order of 1 man sievert per million people. Some situations have been identified in industrial uses of radiation where more information is needed, especially for industrial radiographers. Other large groups exposed are aircrew and non-uranium miners. The total impact of all these uses, together with non-nuclear power research, is about 1.5 man sievert per million people.

144. The Committee collated and analysed information brought to its attention on the subject of accidental irradiation of occupationally exposed people. The data showed consistently that industrial radiographers, particularly those handling mobile sources, were the category most exposed to accidents. Mishandling of sources and equipment, coupled with a high incidence of equipment failure, inadequate training and human errors appeared to be among the most common causes for these accidents. Some criticality accidents resulting in several fatalities were reported in the early days of nuclear power development. The overall number of incidents and accidents reported appears very small considering the number of people using radiation or radioactivity in their work, but the distribution of accidents between different types of work is highly non-uniform.

145. The Committee has made a number of recommendations concerning areas where more analysis of data is required to extract pertinent information; particularly with regard to the pattern of accumulation of dose over a working lifetime, this could most usefully be done by those gathering the data. If these recommendations are acted upon there should be a much clearer indication of the overall occupational exposure situation in all areas of work within a few years.

6. Medical exposures[12]

146. Medical exposures are characterized by high dose rates and very uneven distributions of dose. The latter fact makes the use of concepts such as the effective dose equivalent helpful, but this concept has substantial shortcomings when applied to patients. Nevertheless, a cautious application of effective dose equivalent indicates that the relative detriment from various types of medical examinations could be different from that given in previous reports where the main emphasis was on the genetically significant and the mean marrow doses. Preliminary information concerning radiological practices in some developing countries points to the conclusion that two-thirds of the world population live in countries where the frequency of radiological examinations appears to be an order of magnitude lower than in developed societies.

147. An important contribution to the global collective dose takes place in the course of radiological procedures. Medical exposure gives the largest man-made contribution to the radiation doses received by the population and in some industrialized countries this contribution approaches the doses received from natural sources. The main difference between this and other sources of exposure is that the individuals receiving the doses are usually the same individuals who are expected to benefit directly from the procedures involving irradiation.

148. Radiation is used in medicine for diagnostic purposes or for the treatment of diseases, particularly cancer. The doses received by the patients are extremely variable: from very low, as in many diagnostic examinations, to very high, as in radiotherapy. Although all individual doses contribute to the collective dose received by the population at large, the bulk of this collective dose comes from the small doses involving many individuals, rather than from the high doses delivered to relatively few radiotherapy patients.

149. The scope of the Committee's analysis of exposure levels in the course of medical examinations or treatments is very wide. First, the Committee considers that knowledge of individual and collective medical exposures is necessary to place these into the appropriate perspective with respect to the other sources of human radiation exposure. Secondly, there is a need for analyses of the doses to individual organs—and of the range of their variability—for various types of radiological examinations, in order to know and compare the risk of selected practices. Finally, it might be possible from such a review to identify groups of patients exposed to high doses that could be followed in the future through epidemiological studies for improved assessments of the incidence of unwanted radiological sequelae.

150. In view of the magnitude of the medical exposure component, and of the great potentiality for its significant reduction, the Committee has repeatedly reviewed the relevant information in order to monitor the trend closely. The earlier reports were particularly focused on the doses delivered to the gonads, to derive assessments of the possible genetic risk of exposures through the so-called genetically significant dose. More recently, the doses received by other organs were also given increasing attention, in order to identify the medical procedures resulting in particularly high organ doses. The Committee followed this same trend in the present report.

151. The Committee reviewed available information on the total frequency of diagnostic x-ray examinations, indicating that their rate may vary between 300 and 900 examinations per thousand inhabitants per year in industrialized countries, excluding mass surveys and dental examinations. Examinations of skeleton and

[12] This subject is reviewed extensively in Annex G "Medical exposures".

thorax were seen to be the most frequent in many countries. A special effort was made to survey the state of diagnostic radiology in developing countries, with the collaboration of the World Health Organization, by collating information on the population coverage of radiological services. It was found that equipment was scarce and unevenly distributed in these countries, with the rural population having limited access to the existing facilities. In industrialized countries a pronounced tendency in a reduction of the individual exposures was documented for some types of examinations such as dental radiography and mammography.

152. Absorbed doses in various organs and tissues of interest to the Committee were in the range of less than 0.01 to 50 milligray per examination, considering all types of radiodiagnostic examinations. Special attention was given to certain x-ray examinations, for various reasons: either because they are very common and could contribute therefore substantially to the collective dose (e.g., dental examinations); or because they involve exposure of tissues of known high susceptibility to cancer induction by radiation (e.g., mammography). In both of these cases a trend towards a decrease of the doses delivered in the course of a single examination was documented, due to the improved technical conditions of exposure.

153. In two developed countries the collective effective dose equivalent for diagnostic radiology has been reported as about 600 and 1800 man sievert per million people. In the absence of any other data, the Committee has tentatively, for the purpose of this report, used the round number of 1000 man sievert per million population as the annual collective effective dose equivalent for developed countries, which corresponds to about 50 per cent of the exposure to the natural radiation sources. The corresponding value for developing countries may be an order of magnitude lower, so that a weighted figure for the whole world could be in the region of 400 man sievert, or about 20 per cent of the average exposure to natural sources.

154. Nuclear medicine examinations contribute, on the whole, relatively little to the exposure of the population from medical sources, by comparison with x-ray diagnostic procedures. The value of the collective effective dose equivalent would, however, be expected to be highly variable owing to the differences in radiological practice in various countries and to the variable spectrum of diseases of the different populations. For radiotherapeutic exposures, the Committee analysed data collected by IAEA and WHO on the availability and use of radiotherapy equipment in many countries. They show, at the same time, a general tendency towards an increase in the services and a very unequal distribution between developed and developing countries.

155. With regard to the genetically significant dose equivalent, the Committee believes that a rough estimate that may apply to developed countries for which some information is available is about 0.1–0.2 millisievert per year, all components of the dose received in the course of medical practices being taken into account. The corresponding figures for developing countries would be about an order of magnitude lower.

156. The Committee would like to express the wish that statistics for medical irradiation may in the future be reported in such a way to allow a more precise evaluation of the above quantities.

7. Summary and conclusions

157. In this report, the Committee used various quantities to evaluate the exposures from the radiation sources it has reviewed. The individual effective dose equivalent rates have been used to show the variability of the individual exposures according to location, occupation, time or other factors. By adding all the individual effective dose equivalent rates, the collective effective dose equivalent rates have also been obtained, which express for a given time the radiation impact resulting from a given source or practice.

158. It is of interest to study the variation in time of the collective effective dose equivalent rates over the last few decades. Figure II(a) presents the contributions of the exposures from medical uses of radiation, nuclear explosions in the atmosphere and nuclear power production, expressed as a percentage of the average exposure to natural sources. The values for medical irradiation and nuclear power production include the exposures of the workers as well as those of members of the public. It is estimated that the contribution of medical exposure has not changed appreciably over the years, while the contribution of nuclear explosions has followed a discontinuous trend but has mostly decreased since 1963, with small variations due to more recent explosions. The annual collective effective dose equivalent attributable to the production of electrical energy by nuclear means has been increasing continuously, due to the expansion of nuclear power programmes, although its contribution is at a substantially lower order of magnitude.

159. In spite of the many uncertainties, most of the values in Figure II(a) are unlikely to be in error by orders of magnitude and therefore lend themselves to some general considerations. Among the various sources of radiation, the natural sources with an average annual effective dose equivalent of 2.0 millisievert are by far the most important.

160. With respect to the man-made sources, the highest contribution comes from the medical uses of radiation, particularly for diagnostic purposes. The average annual effective dose equivalent from medical uses of radiation throughout the world is taken to be about 0.4 millisievert, which corresponds to approximately 20% of the average annual exposure to natural background. The Committee believes that there is a good potential for dose reduction, compatible with the objective of the practices. Since this dose is relatively high, the corresponding gain would be expected to be great.

161. Summing the collective effective dose equivalent rates over time leads to the collective effective dose equivalent commitments which are assumed to be proportional to the total health impact from a given source or practice. The sources or practices could be, for example, the nuclear explosions in the atmosphere conducted so far; or one year of power production by nuclear fission at the present time; or the extraction of one tonne of phosphate ore. The global collective effective dose equivalent commitments are the most convenient quantities in order to compare the expected detriment from the exposure to different radiation sources.

162. In the 1977 report the Committee adopted a table to summarize its global dose estimates in which the whole-body dose commitments from different sources

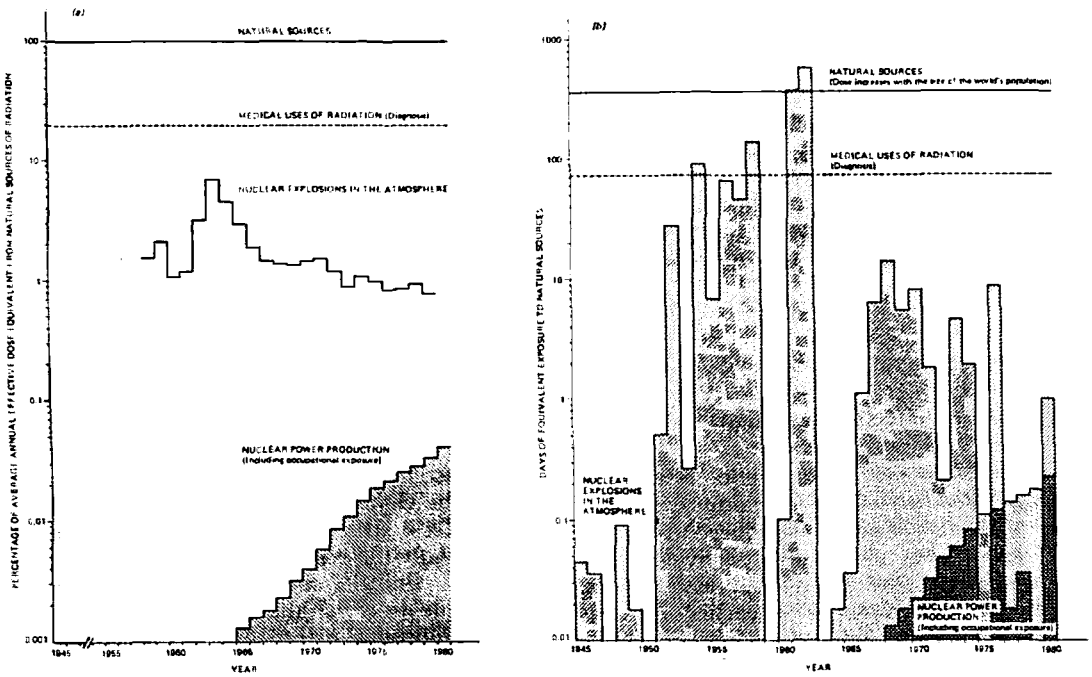

Figure II. Trends with time of doses from different sources of radiation. (a) Annual effective dose equivalents, expressed as percentage of the average exposure to natural sources; (b) Collective effective dose equivalent commitments per year of practice, expressed as days of equivalent exposure to natural sources

were expressed in terms of the duration of exposure to natural radiation of the world population which would cause the same dose commitment. This format of presentation received widespread attention because it allows comparison of the different sources on an easily appreciable scale of time. The Committee has therefore updated some of the relevant estimates, comparing the global collective effective dose equivalent commitments, expressed in days of exposure to natural sources. Figure II(b) presents, on a semi-logarithmic scale, estimates of such collective effective doses that were committed by the use of radiation for medical diagnostic purposes, by nuclear test explosions and by the production of nuclear power in each year from 1945 to 1980. These collective dose commitments are expressed as the number of days of exposure to natural background that would give the same dose. The doses from natural and medical irradiation are assumed by the Committee to have remained constant.

163. The collective effective dose equivalent commitments per year of atmospheric tests reached a peak in 1962 corresponding to about 1.6 year of natural background; since that time the annual commitments have been substantially lower. The collective effective dose equivalent commitments per year of nuclear power production have been steadily increasing up to the present time.

164. Two considerations should be stressed to avoid possible misconceptions about the content of Figure II(b). Firstly, the presentation of the exposures from the various sources in the same graph is simply to be regarded as one way of representing the relative contribution to the global effective dose equivalent commitment. It does not imply any judgement from the Committee as to the justification of the various sources or practices on ethical, social or economic grounds. Secondly, such presentation would be misleading if the many qualifications discussed in the preceding paragraphs of this report and in all its scientific Annexes were not taken into account.

165. The collective effective dose equivalent commitment resulting from all nuclear explosions that have taken place up to the end of 1980 corresponds to about 4 years of natural radiation exposure (Figure II(b)). About 10% of the collective effective dose equivalent commitment has already been delivered; the remaining fraction, mostly due to carbon-14, will be delivered in the next ten thousand years or so.

166. Averaged over the whole world, the collective effective dose equivalent commitment (truncated to 500 years) due to one year's production of nuclear power at the 1980 level of installed capacity of 140 GW(e) corresponds to approximately 5 hours of natural radiation exposure (Figure II(b)). This estimate includes the exposure of the workers as well as that of the public. While the long-term component of the global dose to members of the public may to a first approximation be regarded as uniformly distributed within the time of delivery of the dose, the short-term component is spread non-uniformly around nuclear installations. The Committee has analysed the extent of such non-uniformity and has thus indirectly pointed out the conditions for further improvement of the present situation through national or international actions. On the assumption that there would be no change in the collective dose commitment per unit practice, one year of energy production, at the projected installed nuclear capacity of 1000 to 1600 GW(e) by the year 2000, would result in a global dose equivalent commitment (truncated to 500 years) of about 2 days of background radiation exposure, including the occupational component. This assumption could however be unrealistic because of technological developments and the evolution of regulatory actions.

167. The total collective effective dose equivalent commitment due to the production up to the present time of electrical energy by nuclear fission is roughly estimated to correspond to 1 day of average exposure to natural background (Figure II(b)). This value is truncated to 500 years and includes the exposure of workers and of the general public.

168. Other sources of radiation give rise to much lower collective effective dose equivalent commitments and require no special comment.

169. The situation depicted calls for further review at appropriate intervals of time, in order to keep the trends under surveillance, to ascertain possible deviations of the predicted values, and to refine the estimates further. Detailed studies on selected subjects rather than comprehensive assessments may be particularly appropriate for the time being.

C. RADIATION EFFECTS

1. Genetic effects of radiation[13]

170. New experiments on the genetic effects of radiation have provided further scientific information for the assessment of the risk of radiation-induced hereditary diseases in man. They have also increased the Committee's confidence that the general assumptions, and the estimation procedures used earlier for this purpose, remain valid in the light of current knowledge. They have not led to any substantial change in the previous estimates of genetic risk.

171. It is well established that a significant proportion of all conceptions is genetically abnormal, i.e., carries a spontaneously-arising hereditary defect. The most severe changes in the genetic make-up are incompatible with life and lead to abortions. It has been estimated that about one-half of all clinically diagnosed spontaneous abortions have an abnormal genetic constitution. Some genetic changes are however compatible with life, but the individuals carrying these show abnormalities (ranging from severely handicapping diseases and disabilities to fairly mild conditions) at some stage of their life after birth. Surveys of populations have shown that roughly 10% of all live-born children carry some type of genetic or partially genetic defect of different grades of severity.

172. It is also well known that many toxic agents, and ionizing radiation in particular, are capable of increasing the incidence of inherited harmful conditions. When radiation interacts with the genetic material of the germinal cells in the testis or in the ovary, damage to this material may ensue. If this damage is then transmitted to the descendants of the irradiated person, it may give rise to a variety of clinical conditions which, as in the case of the spontaneously-occurring ones, may cause considerable hardship to the affected persons, their family or society in general. It is therefore very important to assess the degree to which the spontaneously-occurring genetic defects may be increased through exposure to radiation.

173. Arbitrarily, radiation effects on the genetic material may be grouped according to their nature into two different classes, gene mutations and chromosomal aberrations. Gene mutations are heritable alterations of the elementary units of heredity, which are called genes. These are further operationally classified into dominant mutations, when their effects are expressed in the immediate offspring of the individuals in whose germ cells they arose or were induced; and recessive mutations, which may not manifest themselves in the immediate progeny and are expressed only when an individual receives the same mutated gene from both the parents. In humans, as in all outbreeding species, the probability of such an event is small, except when parents are related. Thus, recessive mutations will be transmitted unnoticed from generation to generation and will persist in the population until, by chance, two individuals carrying the same mutated gene will produce progeny and the recessive mutations that arose (or were induced) earlier will become manifest. Most gene mutations do not fit precisely into one or the other of the above two categories; in fact, where it has been possible to study effects in detail, mutations of all grades ranging from fully dominant to fully recessive have been found.

174. Chromosomal aberrations can be divided into those involving changes in the normal number of chromosomes (numerical aberrations) and those involving changes in the structure of the chromosomes themselves (structural aberrations). Numerical aberrations involving loss or gain of whole chromosomes have severe clinical consequences, such as Turner's syndrome, in which the female individual has only one X chromosome instead of the normal two, or Down's syndrome, in which the individual has one extra chromosome 21. When chromosomes are broken and rejoined into new configurations which may lead to loss or gain of parts of chromosomes (deletions or duplications) the individuals receiving these may also be abnormal.

175. The Committee reviewed all data that have become available since the publication of its 1977 report and classified the new data in four groups, as follows:

(a) Those that confirm and further document previous conclusions;
(b) Those that extend the data base on which certain assumptions for risk evaluations were made in the past;
(c) Those that may be relevant for certain qualitative inferences, but not for quantitative assessments;
(d) Those which may be regarded as potentially useful to improve our evaluations of the genetic hazard posed by exposure to ionizing radiation.

176. Confirmatory data have come from studies on experimental animals. These data have extended our previous knowledge to a wider range of radiation doses and irradiation conditions (internal and external irradiation, various dose rates), to several mammalian species, many germ cell stages and genetic end-points. On the whole, these new results have strengthened our understanding of the form of the dose-response relationships in the germ cells of male and female animals, on which estimates of induction of genetic defects by radiation must be based. They have also provided more confidence in the necessary inferences from animal data to the evaluation of genetic effects in humans.

177. In humans, new data have provided a firmer basis to our estimates of the spontaneous incidence of various genetic defects; however, information on radiation-induced changes in the progeny of irradiated parents continues to be limited. Technical advances may allow direct estimates of some types of damage in the genetic material of irradiated persons. The probable genetic basis of certain somatic defects has continued to remain an area of intensive research; the results show that a number of genetic diseases in humans is associated with increased radiosensitivity and with familial proneness to neoplasia.

[13] This subject is reviewed extensively in Annex I "Genetic effects of radiation".

178. Further data have become available concerning some assumptions used in risk evaluations. Thus, for instance, new results with bacteria and the fruitfly are consistent with one of the basic assumptions involved in the indirect method of risk evaluation, namely, that there is proportionality between the rates of spontaneous and of induced mutations of particular genes. New data have also confirmed that, for irradiation conditions applicable to humans, the female germ cells are mutationally less sensitive than are male germ cells.

179. Advances have also been reported which may have a bearing on genetic risk estimates in humans, at least in a qualitative sense. These pertain to findings of increased frequencies of chromosomal aberrations in somatic cells of:

(a) Population groups living under conditions of high natural background irradiation;
(b) Groups occupationally exposed;
(c) The survivors of the A-bombs in Hiroshima and Nagasaki.

Other data concern the possible clinical significance of spontaneous chromosomal abnormalities (balanced translocations, for example), a topic to which previously little attention has been paid. Finally, detailed cytogenetic studies of the chromosomal evolution in primates point to the potential use of evolutionary similarities for making inferences on the nature and effects of certain chromosomal changes inducible by radiation or other toxic environmental agents. The problem of the contribution of recessive mutations, both spontaneous and induced, to the human genetic burden has been, and continues to be, one to which it is difficult at present to provide reliable quantitative answers.

180. Although genetic risk estimates are expressed as a certain number of cases of serious genetic defects per unit radiation dose to the population, this way of expressing risk does not adequately reflect the degree of detriment or the impact of these diseases on the affected individual, his family, the health-care facilities and society in general. In this report a preliminary attempt is made to derive an index of harm for spontaneously-occurring and radiation-induced genetic diseases. To this end the Committee used certain measurable criteria such as the length of life lost or impaired. Although recognizing that the above criteria are still inadequate, the Committee regards the attempt as one possible way to refine risk in socially meaningful terms.

181. The main objective of the Committee's review has been the assessment of possible genetic risks of radiation in humans. Direct human data, particularly at low doses and dose rates, are, however, still very limited and the assessments must of necessity continue to be based on data obtained in the mouse and, to some extent, in the non-human primates. In using such experimental data to estimate the expected effects in humans a number of assumptions are required. The most important are that

(a) Unless there is evidence to the contrary, the amount of genetic damage induced by a given type of radiation under a given set of conditions is the same in the germ cells of the test species and in those of humans;
(b) Physical and biological factors affect the magnitude of damage in similar ways and to similar extents in humans as in the test species.

The Committee stresses again the uncertainties and limitations of the extrapolation procedure and its assumptions.

182. As on previous occasions, two methods were used to obtain genetic risk estimates. With the direct method the amount of a given type (or types) of genetic damage is estimated for the test species. This estimate, with suitable correction factors, is then expressed in terms of effects expected in the progeny of exposed human individuals. With the indirect, or doubling dose method, an assessment is first made of the amount of radiation that will produce as many mutations as occurring spontaneously in the test species. An average of the estimates for the different categories of damage is the "doubling dose" for the species in question. Under the assumption that the doubling dose so estimated is applicable to man, and taking into account the current incidence of genetic diseases in humans, the expected increase of diseases per unit radiation dose is finally calculated.

183. Using the direct method, the Committee estimated in 1977 that the risk of induction of mutational damage in the first generation following irradiation of males (low dose, low dose rate, low-LET radiation) would be of the order of 2000 cases of serious genetic disorders per Gy per million progeny. The basis for this calculation had come from studies on the production of dominant skeletal mutations in male mice. No new data on skeletal mutations have been obtained that might warrant a change in this estimate. The Committee has now made another independent estimate based on the induction of dominant mutations causing cataract of the eye following irradiation of male mice. The new estimate of 1000 cases per million per Gy of paternal exposure is in reasonable agreement with that of 2000 per million per Gy based on skeletal mutations.

184. The agreement between the figures lends support to the view that the estimates are probably of the right order of magnitude. It should, however, be stressed that such estimates, however close, rest on a number of assumptions and might be subject to revisions with further advancement of scientific knowledge. Estimates of risk to the offspring of irradiated females cannot be obtained by the same approach, owing to the lack of relevant experimental data. Inferences from other data, however, point to a lower, and probably to a much lower, sensitivity of the female germ cells, as compared with those of the males for low dose, low dose rate, low-LET irradiation conditions.

185. The Committee has also been able to reassess risk from induction of reciprocal translocations, on the basis of new data from studies with the rhesus monkey, as well as of previous data on marmosets and men. This risk is now estimated to lie between about 30 and about 1000 cases of congenitally malformed children per million conceptions per Gy of paternal irradiation (low dose, low dose rate, low-LET irradiation). These cases would derive from the unbalanced products of radiation-induced balanced reciprocal translocations. However, in the absence of sufficient data on the effect of such translocations on the carriers themselves, the contribution of balanced reciprocal translocations as such to human ill-health cannot be reliably assessed. As to the risk from the induction of reciprocal translocations in females, no new data have appeared. Again, inferences from data support the Committee's view, expressed in the 1977 report, that the risk is likely to be low. The same conclusion would apply to structural

aberrations of chromosomes, other than those specifically mentioned above.

186. Using the indirect, or doubling dose method, the Committee estimated in 1977 that when the population is continuously exposed to low doses of low-LET radiation at the rate of 0.01 Gy per generation (1 generation = 30 years), 63 new cases of genetic diseases per million first generation progeny would be expected (20 from the induction of dominant and X-linked ones, 38 from chromosomal ones, 5 with complex aetiology). At equilibrium (which would be reached after different numbers of generations, depending on the category of genetic disease) this number would increase to 185 cases per million progeny (100 from the induction of dominant and X-linked diseases, 40 from chromosomal ones, and 45 from those with a complex aetiology).

187. Recent analyses have permitted some refinement of these estimates. Firstly, it has been shown that, for dominant and X-linked diseases, the first-generation increment is likely to be about 15% of that at equilibrium (i.e., for low-LET, low dose radiation exposures at the rate of 0.01 Gy per generation, 15 cases per million births, the equilibrium frequency being the same as before, namely, 100 cases per million births; or, for an exposure at the rate of 1 Gy per generation, 1500 cases per million births in the first generation and 10 000 cases per million births at equilibrium). Secondly, most of the diseases included under the category of chromosome anomalies are numerical ones. In 1977, the increment (due to radiation under the stated conditions) for this class of diseases was estimated on the assumption of a doubling dose of 1 Gy, as for other categories of genetic damage. However, data on experimental animals and man point to the possibility that a doubling dose of 1 Gy may be inappropriate for numerical chromosomal diseases. The Committee has therefore used the above doubling dose only for those chromosomal diseases stemming from structural aberrations of chromosomes and has arrived at estimates of 240 and 400 cases per million progeny in the first generation and at equilibrium, respectively, when the population is exposed to 1 Gy per generation under the stated conditions. There has been no change in the estimates with respect to diseases of complex aetiology (i.e., the figures of 450 and of 4500 per million progeny in the first generation and at equilibrium, respectively, remain valid for a radiation exposure of 1 Gy per generation under the stated conditions).

188. In summary, using the doubling dose method, the Committee now estimates that, when a population is exposed to low-LET irradiation at low doses at a rate of 1 Gy per generation, the expected increase in the incidence of genetic diseases will be about 2200 cases per million progeny in the first generation (i.e., 1500 + 240 + 450 ≈ 2200) and of about 15 000 cases per million progeny at equilibrium (i.e., 10 000 + 400 + 4500 ≈ 15 000).

2. Non-stochastic effects of irradiation on normal tissues[14]

189. When radiation kills a sufficiently large number of cells, it causes anatomical and functional tissue damage. Doses below a given threshold, which is variable for various effects and tissues, may produce detectable changes but relatively higher doses are generally required to induce pathological effects. For single whole-body doses in excess of the threshold, bone marrow is the critical tissue for survival. However, the large capacity for repopulation of the marrow enables it to withstand much larger doses if administered over a long time. With protracted or fractionated irradiation the loss of function of other tissues (for example, the testis or the lens of the eye) may appear at lower doses. The review of the Committee examines, for all important tissues, the dose-time relationships under which the various effects become critical. It also discusses the relative importance of other physical or biological variables.

190. No systematic analysis of the morphological and functional changes in irradiated normal tissues had been undertaken by the Committee since 1962. The objectives of the present review were firstly to identify for each tissue and for various modalities of irradiation, the effects and the doses that may become critical for the function of that tissue; and, secondly, to analyse the main physical and biological factors which modify these doses and effects. These objectives required a complex study of the dose-time relationships in each tissue, based both on animal data and on clinical effects in man.

191. The study was confined to non-stochastic effects. These effects arise when a large proportion of cells in a tissue are inactivated by radiation, thus giving rise to anatomical or functional tissue damage. In general, non-stochastic effects require that a minimum dose, called the threshold dose, be delivered before they can be detected. The clinical severity of the injury increases with increasing dose. The time of appearance of tissue damage is very variable, ranging from a few hours or days to many years after exposure, depending on the type of effect and on the characteristics of the particular tissue.

192. The concept of dose threshold is difficult to define and must be discussed in relation to each tissue and effect because it depends to a large extent on the sensitivity of detection. There is also a need to distinguish between the threshold of detection of any effect, however small or trivial, and the threshold of appearance of clinical changes with clear pathological connotations. While recognizing that these concepts have important practical implications, the Committee felt that a thorough discussion of tissue pathology was beyond the scope of this study, which was primarily aimed at an assessment of the effects as reported, rather than their significance for practical purposes.

193. The information available on these subjects is very large and an interpretative, rather than a comprehensive, treatment was therefore necessary. This was facilitated by the significant advance in knowledge of the basic mechanisms of cell and tissue response to irradiation. The premise of the Committee's review is that the non-stochastic response of a given tissue to radiation depends primarily on the level of killing of the component cells and that the degree and timing of damage are related to the special way in which each given tissue is organized and functions. Therefore some discussion of basic radiobiological concepts was first required, to outline the effects of radiation on cells and tissues, the repair phenomena, the functional structure of tissues and the changes induced by radiation therein. All this was intended as a unifying frame of reference for the specialized and systematic analysis of effects in various tissues.

[14] This subject is reviewed extensively in Annex J "Non-stochastic effects of irradiation".

194. Although the Committee has considered human data separately from other animal data, for the purpose of the present report the similarities between the observed effects warrant a common treatment of the subject matter, with the necessary qualifications to point out discrepancies. Doses quoted in this subsection are absorbed doses in gray (Gy) from x or gamma rays administered in conventional fractionated radiotherapy, unless otherwise specified.

195. In skin radiation reactions range from a temporary reddening and loss of hair, to atrophy, permanent epilation, colour changes, anatomical changes of the blood vessels, ulceration and necrosis. In order to produce observable changes in animal skin by external x or gamma irradiation, acute doses of the order of 7 to 10 Gy must normally be administered. However, as this tissue has a very large capacity for repair, up to 5 times more dose may be tolerated when radiation is delivered over weeks or months. Observations on patients following radiotherapy generally confirm these findings. With single treatments temporary loss of hair is seen after 3 to 5 Gy and mild reversible skin changes normally occur after 1 or 2 Gy. However, human skin may receive up to 50 or 60 Gy spread out during 6 weeks, without severe consequences developing. The area and depth of skin irradiated is important, with more severe changes appearing for irradiation of larger areas and deeper layers. Other biological variables are also known to influence the level of the threshold dose: among these are the anatomical location of the skin, the age of the irradiated person, and the normal skin colour. Mucous membranes exhibit changes analogous to those seen in the skin at similar doses.

196. In experimental animals, blood-forming tissues are particularly sensitive. Lymphocytes and stem cells are largely inactivated by single doses of a fraction of a Gy. These tissues have, however, a remarkable capacity for regeneration. In man the haemopoietic system is also one of the most sensitive tissues. Responses may be observed after 0.5 to 1 Gy, whether given in a single exposure or as a series of small fractions. With this tissue, as with many others, the volume irradiated is very important in determining the level of response. If depression of the peripheral blood cells is too severe, infection or haemorrhage may occur. These are the major symptoms of the so-called haematopoietic syndrome, which may lead to death.

197. External irradiation of the gastro-intestinal system results in a variety of symptoms and lesions ranging from dyspepsia and diarrhoea with loss of fluid and blood, to localized ulcers and, later, to bowel strictures and obstructions. The various sections of the gastro-intestinal tract must be treated separately since they are not uniformly sensitive. Considering the early forms of radiation injury, the stomach in man may tolerate up to 40 Gy of long-term fractionated treatment. The small intestine may also withstand doses of the order of 30 to 40 Gy over a few weeks. The large intestine is even more resistant and shows only transient symptoms at similar doses, while the oesophagus appears to tolerate fractionated irradiation up to 60 Gy. The late consequences of these large doses (particularly those given to large volumes) are little known and difficult to quantify. The liver is a relatively radioresistant organ. In animals, single doses of over 10 Gy are necessary to induce permanent changes in liver and these doses may be increased up to six times upon extended fractionation. In man, the liver is known to tolerate 40 to 50 Gy in 30 days given to parts of the organ, the threshold for measurable effects being around 30 Gy of conventional fractionated radiotherapy.

198. Moderate doses of radiation to the lungs may result in pneumonitis which leads eventually, through a complex chain of pathological reactions, to fibrosis and loss of function. The sensitivity of the lung with respect to long courses of irradiation is moderate. Doses of over 20 Gy given in a few weeks may lead to an appreciably increased incidence of complications. Among other thoracic organs, the heart is regarded as being rather radioresistant in experimental animals where it shows only microscopic changes in the muscle cells and blood vessels after moderate doses. In man, a high incidence of cardiac complications, consisting mainly of pericarditis and eventually fibrosis, is seen after long fractionation courses to total doses in excess of 60 Gy.

199. There is a wide range of sensitivities among the various structures of the urinary system: the kidney is believed to be the most vulnerable, followed by the bladder and the ureters. Acute and chronic nephritis followed by hypertension and proteinuria usually result from high radiation doses to the kidney. In experimental animals, changes have been reported after acute irradiation with threshold doses between 5 and 12 Gy. With conventional fractionation these doses might be increased by a factor of at least 3. In man, a dose of 20 to 24 Gy in 3–4 weeks results in alterations in kidney function, so that the tolerance dose in radiotherapy is normally regarded to be around 23 Gy in five weeks. In both humans and experimental animals the kidney appears to be more sensitive at around the time of birth. The tolerance dose to the urinary bladder is taken to be 55 to 60 Gy delivered over 3–4 weeks.

200. The testis and ovary are particularly sensitive. Irradiation of the testis may cause either temporary or complete sterility, depending on the dose. The testis appears to be unique, in that fractionated irradiation causes more, rather than less, non-stochastic damage than single treatments. In man, single doses as low as 0.1 Gy have been reported to cause temporary sterility, although doses in excess of 2 Gy are needed to produce permanent aspermia. Many years may sometimes be necessary for complete functional recovery after severely damaging doses. The adult ovary is more resistant than the testis, because, by the time of birth, the oogonial cells have all progressed to the more resistant oocytes. However, if irradiation is delivered to the developing ovary, fractionated treatments to a total of 2 Gy cause severe damage in dogs and monkeys. Permanent sterility is caused in women by single doses in excess of about 3 Gy, or higher fractionated doses.

201. The threshold doses for the central nervous system differ for different structures. The lesions consist in alterations of the glial structure, loss of myelin, encephalitis and necrosis. The more severe damage is believed to result, at least in part, from primary lesions of the blood vessels, and it is irreversible. The central nervous system has limited capacity for regeneration. Data in animals show that structural damage to the glial cells may occur after doses of 1 to 6 Gy, which may produce cellular degeneration some months after treatment. Higher doses will cause earlier effects. In man the radiotherapy tolerance dose for the whole brain is around 55 Gy delivered in 5 to 6 weeks, but morphological changes are seen after 10 Gy of fractionated treatment. Threshold doses for the spinal

cord are lower, in the region of 35 Gy in 4 weeks. Fractionation effects are particularly important for brain and cord.

202. Irradiation of growing cartilage leads to disturbances in the process of bone formation, with resulting deformities. Growing cartilage is very sensitive and the threshold dose to cause growth stunting is probably small and possibly zero. In the young animal, about 3% stunting per Gy has been reported. In children, total doses of 10 Gy or more given in daily fractions over a few weeks are sufficient to cause some degree of reduced growth. The younger the child, the more severe the degree of stunting. Mature cartilage, on the other hand, may tolerate much higher doses. In general, adult bone is considered to be fairly resistant and total doses of 65 Gy given in 6–8 weeks do not normally cause necrosis: there may be however predisposition to fracture, depending on the mechanical stress normally exerted on the bone.

203. Of the many tissues in the region of the eye (lacrimal glands, conjunctiva, cornea, sclera, retina) the lens is the most sensitive to radiation, with production of lens opacifications or clinical cataract. Initial effects are seen in man after 2 Gy of acute exposure. In some animals such as the mouse, much lower doses are usually required to cause early cataract. For the lens the increase in threshold dose with increasing fractionation may be rather less than for many other tissues. Regarding the endocrine organs, in the adult the pituitary is regarded as radioresistant. The thyroid is a slowly proliferating tissue in which radiation effects may become apparent after many years. Doses of the order of 10 Gy in a single treatment are necessary to cause morphological damage to thyroid cells and evidence of malfunction.

204. The time sequence between changes in the blood vessels and in parenchymal tissues suggests that vascular injury may play an important role in pathological changes (cell loss, fibrosis) following high doses of radiation, although it is difficult to assess the reaction of vascular and parenchymal components separately. Morphological damage is known to occur in the blood vessels of irradiated organs, and long after exposure these changes may lead to disturbances of vascular function. Threshold doses for relatively subtle changes tend to be lower than for more marked functional injuries. Blood vessels located in different tissues may have different thresholds of reaction.

205. The Committee reviewed systematically the effects produced by fast neutrons that are known to produce, dose for dose, a higher degree of biological effects than x or gamma rays. For acute doses causing detectable injury, the effectiveness of neutrons is normally between 1 and 5 times that of x or gamma rays. Neutrons are even more effective in the course of fractionated treatments as the dose per fraction decreases.

206. The non-stochastic effects produced by beta- or gamma-emitting radionuclides administered internally are usually consistent in type and degree with those caused by comparable mean tissue doses of external irradiation given at low dose rate. The tissues affected by treatment with a given nuclide depend on the particular distribution of that nuclide in the body; the amount of injury depends on the radiation characteristics and on the temporal distribution of the energy delivered. Models to relate the temporal distribution of absorbed doses from a radionuclide to that of fractionated external irradiation on the basis of equal effects have not yet been fully explored. There are also uncertainties concerning the microdistribution of the radionuclide energy in the cellular targets, and they affect the assignment of precise values of relative biological effectiveness (RBE) to non-penetrating radiations, such as alpha particles and low-energy Auger electrons emitted by the radionuclides.

3. Radiation-induced life shortening[15]

207. Although shortening of life span is a real consequence of irradiation, a very large body of evidence in experimental animals indicates that this effect is essentially due, at low to intermediate doses and dose rates, to the induction of specific neoplastic diseases. The epidemiological data collected on the survivors of Hiroshima and Nagasaki point to the same conclusion in man.

208. Since the 1958 and 1962 reports, the Committee had not reviewed systematically the data on the non-specific effect of shortening of life that has often been claimed to occur over and above more specific (essentially carcinogenic) consequences of irradiation. The main objectives of the present Committee's review of the subject were: to examine the existence of such an effect and its relationship to natural or, possibly, radiation-induced aging; to investigate the range of doses, dose rates and irradiation conditions at which it may become apparent; to determine the influence of other biological variables (genetic constitution, age, sex) on such an effect.

209. It has repeatedly been noted in the past that animals surviving the short-term effects of irradiation showed symptoms typical of senescence (greying of the fur, appearance of cataract, loss of reproductive capacity). These animals tended to die sooner than non-irradiated controls, with an apparent shift to earlier times of diseases characteristic of late ages. Taken together, without any deep knowledge of the biology of senescence or of the radiation-induced changes themselves, these observations led to the conclusion that radiation, in addition to shortening life span, could also lead to accelerated aging. Much research was carried out in the past in an effort to substantiate this notion.

210. The Committee briefly reviewed the theories of physiological aging and the possible mechanisms that might underlie senescence. It appears that too little is known at present about the biological phenomena themselves to warrant any more extended discussion of their possible modifications by radiation. It is thought, on the contrary, that the actuarial aspects of senescence, that is the life shortening itself, could be profitably explored in respect to irradiation. In this context it is also legitimate to ask whether radiation-induced life shortening could be attributed to specific conditions or diseases or whether, and to what an extent, it may be sustained by non-specific diffuse causes.

211. There is usually little difficulty in establishing precisely the time of death and in analysing the derived statistics (mean and median survival times, age-specific mortality rates, etc.). These are, however, the end-points

[15] This subject is reviewed extensively in Annex K "Radiation-induced life shortening".

of a multiplicity of underlying phenomena. Any meaningful answer to the problems outlined in the preceding paragraph requires the ascertainment of the causes of death by careful pathological investigations, an objective which is in itself difficult, particularly in old subjects, owing to the presence of multiple and interacting diseases. Yet, such data are crucial for assessing whether irradiation has such a specific action. In principle, the Committee believes that unless it can be shown that radiation advances the time of death without modifying the spectrum and the relative incidence of diseases normally occurring in a non-irradiated population, the notion of non-specificity of life shortening is untenable. In practice, the Committee notes that a convincing experimental demonstration of non-specific life shortening has never been produced, particularly in the light of refined statistical analyses accounting for the effects of age-specific and competing diseases.

212. On the contrary, the vast majority of the data obtained in experimental animals, at doses and dose rates where short-term radiation damage is not detectable, lend no support to the views that radiation may cause premature or accelerated aging or that the induction of extra cancers, which may become evident under these conditions, is only one aspect of a more general effect of hastening the onset of aging. This is not in conflict with other observations that, at doses or dose rates high enough to cause short-term death of a sizeable fraction of the irradiated animals, non-specific damage to the blood vessels, to the connective tissues, or non-stochastic effects to other tissues, might be responsible for more diffuse non-cancerous modes of death that become apparent. Exposure to such high doses would be of relevance only under exceptional circumstances.

213. The Committee analysed the information on life shortening caused in many species and strains of experimental animals by x and gamma rays or by fast neutrons given in single doses. Single-dose irradiation is uncommon in practice but it is useful to establish an upper boundary to the effect. Although in each given experimental series the life shortening induced by the x or gamma rays follows different linear or curvilinear relationships with dose, a linear or linear-quadratic non-threshold relationship was shown to have a good fit to the pooled data from many available series in the mouse. For a linear relationship, the average life-shortening effect amounts to about 5% for a dose of 1 Gy, with differences in one or the other direction depending on the strain of the animals and their biological characteristics. In the same animal species, and for single doses of fast neutrons, a convex upward relationship of life shortening to dose seems to apply; here too the variability between strains is quite pronounced.

214. The condition of irradiation which is most relevant for practical purposes is one where animals are exposed at low rate for the entire duration of their life. Dose rates many orders of magnitude higher than the normal background rate must of course be used to elicit significant effects. Under continuous irradiation the efficacy of the x- or gamma-ray doses could be up to an order of magnitude lower than that of single doses. For x and gamma rays, irradiation at low dose rate spread over the whole lifetime defines approximately a lower boundary of effectiveness in experimental work. Under life-long conditions of exposure it is very difficult to distinguish between the dose and time variables and to analyse them separately, because the former accrues as a function of the latter. Thus, depending on the life span of the animals, on their susceptibility to life shortening, and on the actual values of the exposure rate, different shapes of dose-response relationships may actually be generated over a wide range of doses, but for low doses and dose rates essentially linear shapes are normally found.

215. The Committee examined all the available data concerning the effect that changing the rate of exposure or the pattern of dose fractionation has on life shortening. It concludes that, within a large range of these variables, the change of effectiveness is modest for x or gamma rays and is doubtful for neutrons. Other data were obtained by exposing animals to a protracted treatment and by terminating this treatment some time before death, which might ensure more precise evaluations of the time-dose relationships. These data are, in reality, very difficult to interpret, probably because the animal susceptibility to life shortening changes during irradiation as a result of repair phenomena stimulated by the radiation treatment itself. In general, however, the life-shortening response following such treatments is found to be intermediate between that of the very high dose rate and that of the very extended low dose rate modalities.

216. In cases of internal irradiation by injected or ingested radionuclides conditions of selected exposure of particular organs or tissues usually apply, owing to the concentration of the various radionuclides in different parts of the body. It has been shown that under these conditions the life shortening that is seen may be explained by the induction or acceleration of cancers in the irradiated body sites, except at the very high doses where non-stochastic early damage may become detectable.

217. The effectiveness of neutrons up to 14 MeV in producing life shortening compared with the effectiveness of x or gamma rays has also been examined. In single experimental series, fairly high doses of neutrons are 3 to 10 times more effective in causing distinct life shortening. Higher RBE values apply at lower doses and dose rates.

218. The Committee reviewed the biological variables affecting life shortening. Among them, the genetic characteristics of species and strains, the sex, and the animal's age, both before and after birth, were considered. Also, the modifications of the life-shortening effect brought about by various physical, chemical or biological treatments were examined. In view of the fact that life shortening depends so much on the pathological characteristics of various species, the Committee believes that quantitative projections of data from experimental animals to man under conditions of practical significance would be unwarranted in the light of present knowledge.

219. In occupationally exposed people, radiologists in particular, radiation-induced diseases such as leukaemia and cancer of the skin occurred in the early days after x rays and radium were discovered. Some life-span reduction over and above that attributable to these conditions may have been present in pioneer radiologists exposed over a long period of time to unknown but probably high doses, as shown by some, but by no means all, data. However, life shortening not associated with cancer was reported to have disappeared in radiologists who began to be exposed after radiation protection practices came into operation. It

should logically follow that up to the range recommended as "permissible" at the times when these exposures took place (that is, at dose limits up to ten times higher than those presently accepted) no reduction of life span could be expected and any residual prevalence of leukaemia and cancer induced by radiation would be insufficient to cause a statistically detectable shortening of life in the human species, within the sample sizes usually analyzed.

220. The data obtained from groups of radiotherapy patients show no evidence of life shortening. This statement is limited by the nature of the underlying data and particularly by two considerations. Firstly, the fact that only a part of the body was irradiated in these patients and under these conditions there would be less reason to expect much unspecific shortening of life; secondly, the size of the groups examined is usually smaller than that of the occupationally-exposed individuals and very much smaller than in the cases of the A-bomb survivors.

221. The appearance of cases of leukaemia and cancer in excess of the average spontaneous rate of induction did produce some shortening of life among the survivors of the A-bomb explosions in Japan. The magnitude of such an effect can be accounted for entirely by these malignancies and a non-specific cause need not be postulated. The very large sample size on which these observations have been made, and the fact that they have been confirmed during more than thirty years, even though applying only to the oldest cohort of the population, make this conclusion reasonably sound.

4. Biological effects of radiation in combination with other agents[16]

222. The combined effects of radiation and of other physical, chemical and biological agents are potentially of great importance but the relevant data are scattered and inconsistent. Therefore the emphasis of this review has been mainly theoretical, with illustrative examples of the complexities of the subject drawn from experimental and epidemiological reports. Except for the case of tobacco smoke, which may act synergistically with radiation in producing lung cancers under some working conditions, this study has been unable to document in man any clear case of interaction, at least of the kind which may result in substantial modifications of the estimates of risk for significant sections of the population. The Committee has outlined the main directions along which future work might be usefully pursued since data on combined effects are at present inadequate.

223. The joint effects of ionizing radiation and other physical, chemical or biological agents are of potentially great importance because radiation is ubiquitous in nature and in modern life many situations could be envisaged which might lead to some form of interaction.

224. In spite of many reports claiming or showing some kind of interaction, the Committee believes that the results of these studies are, on the whole, inconclusive, for a number of reasons. First, when considered comprehensively in the light of the Committee's objectives, these reports appeared to involve exposure levels much higher than the environmental levels of practical significance, and to involve single, rather than protracted, exposures. Secondly, there was a lack of any systematic treatment of each case of interaction in regard to the dosage of the interacting agents and to the interaction mechanisms. Thirdly, many of the reports made little use of appropriate methodologies of analysis, although these had long been available in other fields of the biological sciences. Finally, the absence of sound conceptual bases about the possible nature of the interaction made it impossible to define this notion to even a moderate degree of refinement.

225. Given the above situation, the Committee assumed that a preliminary theoretical treatment of the field in an attempt to suggest definitions, to identify methodologies of analysis, and to exemplify the complex nature of the problems with practical examples, would be more appropriate than a systematic review of literature reports. The Committee considered two possible types of interactions. In the first type both ionizing radiation and the other interacting agent may each produce some effect: here, additivity, synergism and antagonism are seen as the three possible conditions of interaction. The second type is that between ionizing radiation and any other agent which is by itself inactive when administered alone: protection and sensitization are here the terms describing the reduction or the enhancement, respectively, of the effects of radiation acting alone. Such a classification is not an absolute one because the doses of the interacting agents and the types of effect may influence profoundly the nature and degree of the interaction. Cancer-promoting substances were examined as a special case.

226. The concepts of exposure, dose and response as applicable to the special case of combined actions were first discussed. The Committee then reviewed the existing methodologies of analysis, which might allow an assessment, at least qualitative, of the results of combined treatments. A more detailed probabilistic discussion of this subject was also provided leading, under certain conditions, to a precise description of the interaction factors. Attention was given to the applicability of these basic but rather abstract concepts to practical situations in the presence of complex biological effects.

227. In order to produce meaningful answers, the biological effects under study must be well defined and explored for the full range of doses of the interacting agents, applied both separately and jointly. The temporal pattern of the exposure (contemporaneous or sequential, single or fractionated) and the order of administration of the agents are often of decisive importance in respect to the production of a given type and degree of effect. A detailed knowledge of the mechanisms is also a prerequisite for the assessment of the conditions and the level of interaction. However, in much of the work examined these basic requirements were not met or were only imperfectly explored; also, the statistical significance of the results was often so low as to make any assessment of interaction at best suggestive.

228. Regarding the interaction of radiation and other physical agents, the available information was mostly on interactions between different types of ionizing radiation or between ionizing radiation, on the one hand, and ultraviolet radiation, microwaves and heat, on the other. Some synergistic action was apparently

[16] This subject is reviewed extensively in Annex L "Biological effects of radiation in combination with other physical, chemical and biological agents".

reported in workers in the radiotechnical industry exposed jointly to ionizing radiation and microwaves. Functional disturbances of the autonomic nervous system and subjective symptoms of discomfort were the effects under study. A critical analysis of the data showed that the nature of the symptoms, the difficulty with their quantification, the insufficiently controlled conditions of exposure and the incomplete statistics were all reasons to regard these reports with some reservation. Fewer data were available on the combined action of radiation with high altitude, physical stress, mechanical damage and ultrasound, and the results seemed on the whole inconclusive.

229. Many different classes of chemical compounds have been examined for their possible interaction with radiation. Inorganic compounds containing lead, cadmium, chlorine, beryllium and platinum may be of importance under special conditions of work and the very limited experience available could profitably be enlarged for more definitive conclusions. Data on various types of dust were thought to be very uncertain because additive, synergistic and inhibitory effects were described, to a degree not exceeding a factor of four under the worst possible circumstances, compared with the effects induced by radiation alone. Antibiotics, chemotherapeutic substances and other pharmacological agents appeared to be of more significance under special clinical situations than for the population at large.

230. The possible combined action of radiation with compounds known for their carcinogenic properties was the object of special attention. Although the information reviewed concerned a variety of initiators and promoters, the data available for each of these substances were very incomplete and the evidence conflicting. No final statement could be offered in regard to any substance or to any class of tumour unless the dose, the dosage schedule and the treatment modalities of the combined treatments had been analysed to a greater depth. The experience on benzo(a)pyrene, diethylnitrosamine, various types of dust and oil exhaust fumes might be enlarged for firmer conclusions, in view of the widespread environmental presence of these substances.

231. It appears that in man tobacco smoke may act by shortening the time of appearance of lung cancer induced by alpha particles of radon daughters. It is not yet clear whether such an action might result from promotion by some specific component of tobacco smoke, or might be ascribed to other non-specific effects on the respiratory tissues. The precise evaluation of the interaction factor may depend critically on the length of the observation period, as well as on the age structure and exposure history of the persons at risk.

232. In animals, there is evidence that some hormones may affect the time or rate of appearance of radiation-induced tumours, particularly of the mammary gland. This type of synergism is mainly expressed through a shortening of the time necessary for tumour induction. There is, however, a large variability of the synergistic effect with the strain of the animals, such that the same treatment schedule will produce synergism in some strains and antagonism in others. There is also variability in relation to tumour type. In man direct information is lacking. Other biological agents such as viruses and bacteria, or changes in diet, when applied in conjunction with radiation, have produced equivocal or negative results.

5. Summary and conclusions

233. The studies carried out by the Committee in the area of biological effects of ionizing radiation have not resulted in major revisions of the current thinking about the genetic risk estimates or the somatic effects analyzed. They have however focussed on some important new developments and have led to refinements of previous knowledge. On the whole, these new studies have strengthened the Committee's belief that the mechanisms of some radiation effects are becoming reasonably well understood. This applies particularly to non-stochastic effects.

234. For other effects, such as those depending on the neoplastic transformation of the irradiated cells, present knowledge of mechanisms is still largely incomplete. A further analysis of cancer induction mechanisms will be undertaken when the dosimetry in Hiroshima and Nagasaki survivors is clarified. The Committee will continue its surveillance and reviewing of the whole field of radiation carcinogenesis, including the theoretical foundations and the actual risk estimates of cancer induction in man.

235. With regard to hereditary effects, the Committee notes that further advances have been made in our knowledge of the dose-response kinetics and other aspects of some of the more important types of genetic change which can be induced by radiation in experimental mammals. Extensive use of experimental data for genetic risk assessment is still considered essential in the absence of significant positive results with respect to hereditary effects after human exposures. A new method has been developed for assessing the magnitude of first-generation risks from harmful dominant mutations. This approach and other methods for estimating genetic risks in the progeny of those exposed to low radiation doses have yielded very similar results. However, many important problems remain. For instance, human female germ-cells are considered to be less sensitive than male ones for the induction of genetic damage from low-level radiation, but the actual magnitude of this difference is still uncertain. Further work will also be needed on the extent to which recessive mutations lead to genetic damage over many generations after the first. However, advances in human genetics and new methods of comparing mutation rates in human and animal cells should help to solve some of these outstanding problems.

Appendix I

LIST OF MEMBERS OF NATIONAL DELEGATIONS

The specialist scientists who took part in the preparation of this report while attending sessions of the Committee as members of national delegations are listed below.

ARGENTINA

D. Beninson (Representative), A. J. Gonzalez (Representative)

AUSTRALIA

K. Lokan (Representative), J. R. Moroney (Representative)

BELGIUM

M. Errera (Representative), F. H. Sobels (Representative), B. T. Aten, J. Maisin

BRAZIL

E. Penna Franca (Representative)

CANADA

G. Butler (Representative), E. G. Letourneau (Representative), A. M. Marko (Representative), W. R. Bush, E. Muller, D. K. Myers, F. Prantl, H. Rothschild

CZECHOSLOVAKIA

M. Klimek (Representative)

EGYPT

M. El-Kharadly (Representative)

FRANCE

H. Jammet (Representative), A. Bouville, R. Coulon, B. Dutrillaux, J. Lafuma, P. Pellerin

GERMANY, FEDERAL REPUBLIC OF

F. E. Stieve (Representative), U. Ehling, W. Jacobi, A. Kaul, H. Kriegel, L. Rausch, C. Streffer

INDIA

V. A. Shah (Representative), S. D. Soman (Representative), K. Sundaram (Representative)

INDONESIA

A. Baiquni (Representative), O. Iskandar

JAPAN

T. Kumatori (Representative), K. Misono (Representative), R. Ichikawa, A. Kasai, Y. Kishimoto, S. Kobayashi, S. Nakai

MEXICO

J. R. Ortiz-Magana (Representative), J. R. Telich (Representative)

PERU

C. Guzman-Acevedo (Representative), M. Zaharia (Representative)

POLAND

Z. Jaworowski (Representative)

SUDAN

A. Hidayatalla (Representative)

SWEDEN

B. Lindell (Representative), K. Edvarson, K. G. Lüning, J. O. Snihs, G. Walinder

UNION OF SOVIET SOCIALIST REPUBLICS

A. Guskowa (Representative), A. M. Kuzin (Representative), R. M. Alexakhin, A. Moiseev, V. V. Redkin, V. A. Shevchenko, A. I. Vichrov

UNITED KINGDOM OF GREAT BRITAIN AND NORTHERN IRELAND

E. Pochin (Representative), C. O. Carter, K. E. Halnan, F. Morley, A. G. Searle

UNITED STATES OF AMERICA

R. D. Moseley (Representative), W. K. Sinclair (Representative), R. E. Anderson, R. Baker, A. M. Brues, C. Edington, J. H. Harley, F. A. Mettler, W. L. Russell, J. B. Storer, J. C. Villforth, H. O. Wyckoff

Appendix II

LIST OF SCIENTIFIC STAFF AND CONSULTANTS WHO HAVE CO-OPERATED WITH THE COMMITTEE IN THE PREPARATION OF THIS REPORT

D. Beninson
B. G. Bennett
A. Bouville
R. H. Clarke
M. Coppola
M. F. Cottrall
S. B. Field
B. Lindell
J. Liniecki
V. Lyscov
R. B. Persson
K. Sankaranarayanan
G. Silini
J. O. Snihs
F. D. Sowby
F. Taylor
G. A. M. Webb

Appendix III

LIST OF REPORTS RECEIVED BY THE COMMITTEE

1. Listed below are reports received by the Committee from Governments between 13 April 1977 and 26 March 1982.

2. Reports received by the Committee before 13 April 1977 were listed in earlier reports of the Committee to the General Assembly.

Document No.	*Country*	*Title*
A/AC.82/G/L.		
1561	United States of America	Health and Safety Laboratory: Environmental Quarterly, HASL-318, April 1, 1977
1562	France	Surveillance de la radioactivité en 1976
1563	United Kingdom of Great Britain and Northern Ireland	Radioactive fallout in air and rain: results to the end of 1976
1564	Germany, Federal Republic of	Environmental radioactivity and radiation levels in the year 1975
1565	United States of America	Health and Safety Laboratory: Environmental Quarterly, HASL-321, July 1, 1977
1566	United Kingdom of Great Britain and Northern Ireland	Radioactivity in human diet in the United Kingdom, 1976
1567	Japan	Radioactivity Survey Data in Japan, Number 41, November 1976
1568	Japan	Radioactivity Survey Data in Japan, Number 42, April 1977
1569	United States of America	Health and Safety Laboratory: Environmental Quarterly, HASL-328, October 1, 1977
1570	United States of America	Health and Safety Laboratory: Final tabulation of monthly strontium-90 fallout data: 1954–1976. HASL-329, October 1, 1977
1571	Switzerland	20th Report of the Federal Commission on Radioactivity for the year 1976
1572	Germany, Federal Republic of	The content of radioiodine in air, rain, grass, cowmilk and goatmilk following the Chinese nuclear test explosion on 26 September 1976
1573	United States of America	Environmental Measurements Laboratory: Environmental Quarterly, EML-334, January 1, 1978
1574	United Kingdom of Great Britain and Northern Ireland	Fallaout in rainwater and airborne dust — levels in the UK during 1976
1575	Germany, Federal Republic of	Environmental radioactivity and radiation levels in the year 1976
1576	Japan	Radioactivity Survey Data in Japan, Number 43, November 1977
1577	United Kingdom of Great Britain and Northern Ireland	Radioactive fallout in air and rain: results to the end of 1977
1578	United States of America	Environmental Measurements Laboratory: Environmental Quarterly, EML-339, April 1, 1978
1579	United States of America	Environmental Measurements Laboratory: Environmental Quarterly, EML-342, July 1, 1978
1580	United Kingdom of Great Britain and Northern Ireland	Radioactivity in human diet
1581	United States of America	Environmental Measurements Laboratory: Environmental Quarterly, EML-344, October 1, 1978
1582	United States of America	Environmental Measurements Laboratory: Index to Environmental Quarterly, EML-345

Document No.	*Country*	*Title*
1583	United States of America	Environmental Measurements Laboratory: Regional Baseline Station, Chester, NJ; EML-347
1584	United Kingdom of Great Britain and Northern Ireland	Calculation of dose rate and air ionisation from radioactive fallout deposited at Chilton, 1951 to 1977
1585	Switzerland	21st Report of the Federal Commission on Radioactivity for the year 1977
1586	Switzerland	Radiation levels and dosimetry of the persons occupationally exposed in Switzerland in 1977
1587	Germany, Federal Republic of	Environmental radioactivity and radiation levels, annual report 1975
1588	Germany, Federal Republic of	Environmental radioactivity and radiation levels, annual report 1976
1589	Germany, Federal Republic of	External radiation exposure from natural radioactivity outside and in housings, with special reference to the influence of building materials
1590	United States of America	Environmental Measurements Laboratory: Environmental Quarterly, EML-349, January 1, 1979
1591	United Kingdom of Great Britain and Northern Ireland	Fallout in rainwater and airbrone dust — levels in the UK during 1977
1592	United Kingdom of Great Britain and Northern Ireland	Radiation exposure of the UK population
1593	Japan	Radioactivity Survey Data in Japan, Number 46, September 1978
1594	Japan	Radioactivity Survey Data in Japan, Number 47, December 1978
1595	Germany, Federal Republic of	Stochastic late effects after partial body irradiation in diagnostic radiology
1596	Union of Soviet Socialist Republics	Accumulation of radiostrontium by agricultural plants from soil in different soil and climatic conditions
1597	Union of Soviet Socialist Republics	Some peculiarities of the extra-radical pollution of agricultural plants in different soil-climatic zones of the country
1598	Union of Soviet Socialist Republics	Collective dose for the USSR population as a result of the use of the sources of ionizing radiation for medical purposes
1599	Union of Soviet Socialist Republics	Late effects expressed as a yield of the mammary tumours after iodine-131 incorporation in conditions of combined action
1600	Union of Soviet Socialist Republics	The biological danger of iodine-129
1601	Union of Soviet Socialist Republics	The distribution of strontium-90 in the soils of the Azerbaijanian SSR
1602	Union of Soviet Socialist Republics	The significance of iodine radionuclides in the toxicity of nuclear fission products
1603	Union of Soviet Socialist Republics	The content of strontium-90 and caesium-137 of global origin in the food of the USSR population 1974–1975
1604	Union of Soviet Socialist Republics	Resorption and metabolism of iodine-131 after its accumulation through grass
1605	Union of Soviet Socialist Republics	The mechanism of the influence of lime and peat on the transfer of strontium-90 to the plants
1606	Union of Soviet Socialist Republics	The model of vertical migration of ^{137}Cs in soils and prognostication of the exposure
1607	Union of Soviet Socialist Republics	The content of strontium-90 in bones of the USSR population in 1974–1975
1608	Union of Soviet Socialist Republics	Regularities in the behaviours of iodine radionuclides in the environment
1609	United States of America	Environmental Measurements Laboratory: Environmental Quarterly, EML-353, April 1, 1979
1610	United States of America	Environmental Measurements Laboratory: Environmental Quarterly, EML-356, July 1, 1979
1611	Japan	Radioactivity Survey Data in Japan, Number 48, March 1979
1612	United Kingdom of Great Britain and Northern Ireland	Radioactive fallout in air and rain: results to the end of 1978

Document No.	*Country*	*Title*
1613	Argentina	^{90}Sr and ^{137}Cs from fallout in Argentina: monitoring results to the end of 1978
1614	Germany, Federal Republic of	Radiation levels in occupationally exposed persons
1615	Germany, Ferderal Republic of	Radiation exposure in the Federal Republic of Germany in 1976 due to nuclear facilities
1616	United States of America	Environmental Measurements Laboratory: Environmental Quarterly, EML-363, October 1, 1979
1617	United States of America	Environmental Measurements Laboratory: Regional Baseline Station, Chester, NJ; EML-367
1618	Union of Soviet Socialist Republics	The application of radioactive admixtures for studies of the transport of compounds injected to the stratosphere
1619	Union of Soviet Socialist Republics	The assessment of repair parameters and the effective dose after single internal contamination of the organism with radionuclides
1620	Union of Soviet Socialist Republics	The possibility to use dogs' bones to indicate the content of strontium-90 in the human skeleton
1621	Switzerland	22nd report of the Federal Commission on Radioactivity for the year 1978
1622	United States of America	Environmental Measurements Laboratory: Environmental Quarterly, EML-370, January 1, 1980
1623	Germany, Federal Republic of	Environmental radioactivity and radiation levels, annual report 1977
1624	Germany, Federal Republic of	Report of the Federal Government on environmental radioactivity and radiation levels in the year 1977
1625	Germany, Federal Republic of	Methods and results of surveillance of radionuclides released from nuclear power plants
1626	United Kingdom of Great Britain and Northern Ireland	Radioactivity in human diet
1627	United Kingdom of Great Britain and Northern Ireland	Fallout in rainwater and airborne dust—levels in the UK during 1978
1628	United States of America	Environmental Measurements Laboratory: Environmental Quarterly, EML-371, April 1, 1980
1629	Union of Soviet Socialist Republics	Photon radiation of natural radionuclides
1630	Union of Soviet Socialist Republics	Ratio of ^{210}Po to ^{210}Pb in the bones of humans and animals
1631	Union of Soviet Socialist Republics	The content of ^{90}Sr and ^{137}Cs in food products of the Estonian SSR 1966–1975
1632	United States of America	Environmental Measurements Laboratory: Environmental Quarterly, EML-374, July 1, 1980
1633	France	Surveillance de la radioactivité en 1977
1634	France	Surveillance de la radioactivité en 1978
1635	Germany, Federal Republic of	Environmental radioactivity and radiation levels in the year 1978
1636	United States of America	Environmental Measurements Laboratory: Environmental Quarterly, EML-381, October 1, 1980
1637	Japan	Radioactivity Survey Data in Japan, Number 50, September 1979
1638	Union of Soviet Socialist Republics	Genetic effects in populations after the action of ionizing radiation
1639	Japan	Radioactivity Survey Data in Japan, Number 49, June 1979
1640	Switzerland	23rd Report of the Federal Commission on Radioactivity for the year 1979
1641	United States of America	Environmental Measurements Laboratory: Regional Baseline Station, Chester, N. J.
1642	Union of Soviet Socialist Republics	Caesium-137 and strontium-90 in the biosphere of polar regions of the USSR
1643	Union of Soviet Socialist Republics	Strontium-90 in bone tissue of the USSR population for the period 1973–1978
1644	United Kingdom of Great Britain and Northern Ireland	Radioactive fallout in air and rain: results to the end of 1979

Document No.	Country	Title
1645	Belgium	Radioactivity measured at Mol 1972
1646	Belgium	Radioactivity measured at Mol 1973
1647	Belgium	Radioactivity measured at Mol 1974
1648	France	Surveillance de la radioactivité en 1979
1649	Japan	Radioactivity Survey Data in Japan, Number 51, December 1979
1650	United States of America	Environmental Measurements Laboratory: Environmental Quarterly, EML-390, May 1, 1981
1651	Germany, Federal Republic of	Environmental radioactivity and radiation levels, annual report 1978
1652	Argentina	Radiological impact of radioactive waste management
1653	Argentina	Levels of ^{137}Cs and ^{90}Sr in environmental samples in Argentina 1960–1980
1654	Argentina	Exposure of the public related to the operation of the nuclear power plant in Atucha
1655	Argentina	Doses from occupational exposure at the Comisión Nacional de Energía Atómica during 1977–1980
1656	Argentina	Determination of absorbed doses in a computerized tomography scanner
1657	Union of Soviet Socialist Republics	Questions concerning the metabolism of carbon-14
1658	United Kingdom of Great Britain and Northern Ireland	Fallout in rainwater and airborne dust—levels in the UK during 1979
1659	United Kingdom of Great Britain and Northern Ireland	Radioactive fallout in air and rain: results to the end of 1980
1660	Japan	Radioactivity Survey Data in Japan, Number 52, March 1980
1661	Japan	Radioactivity Survey Data in Japan, Number 53, June 1980
1662	Union of Soviet Socialist Republics	The formation of effective dose during chronic intake of various radionuclides in the body
1663	Union of Soviet Socialist Republics	Isotopes of the uranium and thorium series in fertilizers containing phosphorus, arable soils and agricultural plants
1664	Union of Soviet Socialist Republics	The combined effect on the body of ionizing and non-ionizing radiation and certain other factors
1665	Japan	Radioactivity Survey Data in Japan, Number 54, September 1980
1666	Japan	Radioactivity Survey Data in Japan, Number 55, December 1980
1667	Japan	Radioactivity Survey Data in Japan, Number 56, March 1981
1668	New Zealand	Environmental Radioactivity Annual Report 1980
1669	France	Surveillance de la radioactivité en 1980
1670	United States of America	Environmental Measurements Laboratory: Environmental Report, EML-395, November 1, 1981
1671	United Kingdom of Great Britain and Northern Ireland	Environmental radioactivity surveillance programme: results for the UK for 1980
1672	Switzerland	24th Report of the Federal Commission on Radioactivity for the year 1980

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Scientific Annexes

ANNEX A

Dose assessment models

CONTENTS

Introduction

1. As stated in the main text of the UNSCEAR 1977 report [U1], the Committee reviews data on human exposure to radiation for several purposes. One purpose is to assess the levels of exposure to which individuals are subjected, another is to assess the levels of exposure to populations resulting from identified sources of radiation, a third is to provide basic data.

2. The relationship between the levels of exposure to an individual and the probability of induction of a health effect which is presumed to result from the exposure is a matter of great complexity. There are certain effects which occur above some threshold dose and for which the clinical severity is dependent on dose. These effects have been called "non-stochastic" by the ICRP [12]. For another class of effects there seems to be no evidence of a threshold dose and no relationship between dose and clinical severity, such as cancer induction. These effects have been called "stochastic" by the ICRP [12]. At the present state of

knowledge a reasonable presumption is that increased exposure to radiation carries an increased probability of subsequent "stochastic" health effects. Therefore, for an individual, the level of exposure can give an indication of the presumed probability of occurrence of a stochastic health effect. Such indication may be found by consulting the appropriate dose-response relationship for the health effect being considered. This will be true irrespective of the form of the dose-response relationship, although the actual response will depend on other factors including the dose rate. If the relationship is not a simple proportionality, then the overall probability of occurrence of the health effect being considered will be determined by the total dose and cannot strictly be obtained by summing the probabilities corresponding to each component of the dose. This is illustrated in Figure I which shows two assumed dose-response relationships for the induction of a parti-

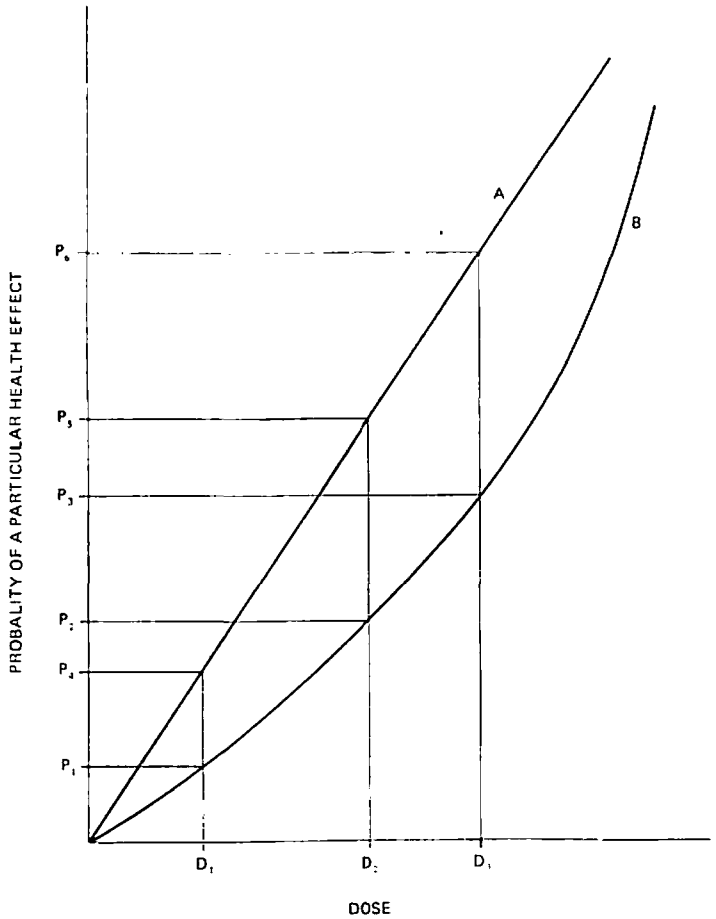

Figure I. Two assumed examples of dose-response relationships for the induction of a particular stochastic health effect

cular health effect; one relationship shown by the straight line A is simple proportionality, the other shown by the curve B is curvilinear, both are without threshold. Other curves might be postulated with different relationships between dose and response; the two curves presented in Figure I are merely examples. If an individual is exposed to two doses D_1 and D_2 such that $D_1 + D_2 = D_3$ and the relationship is given by curve B, then P_3 will not be equal to the sum of P_1 and P_2; however, if the relationship is given by curve A, P_6 will be equal to the sum of P_4 and P_5. Similarly for incremental doses, the incremental probability of a health effect corresponding to a small incremental dose will, for the curvilinear case, depend on the previous level of dose, whereas for the proportional case it is independent of other doses.

3. For the situation in which doses are delivered in addition to a reasonably constant pre-existing dose, such as that from natural radiation, and the additional doses are not large in comparison with the pre-existing dose, it is reasonable to approximate the relevant portion of the curvilinear response by a linear relationship; although in this case the straight line may not, when extrapolated, pass through the origin. If this approximation is made then small additional doses can be treated independently of the pre-existing dose and of each other. This is the basis which underlies the use of risk factors to relate the incremental probability of a health effect to the incremental dose, which are independent of the absolute level of dose. Clearly this approximation may not hold if both large and small additional doses are involved, as for example in the case of an individual who has received a large dose for medical purposes and is then exposed to smaller doses from environmental sources.

4. Because the above procedure relies to some extent on an approximation, the Committee presents its basic data in terms of absorbed dose in organs or tissues wherever possible. Other dosimetric quantities which combine absorbed doses weighted in various ways have been developed by ICRP in the context of radiation protection. Although the purposes of the Committee are different, it is possible in many cases to use the ICRP quantities rather than defining new, but simi-

lar, quantities. To avoid confusion, therefore, the ICRP quantities have been adopted by the Committee for use in the appropriate circumstances. These other dosimetric quantities contain further assumptions; for example, dose equivalent includes assumptions as to the relative risk factors for different types of radiation, and takes the risk factors as constants for a given organ; effective dose equivalent introduces further assumptions as to the relative risk factors for irradiation of different organs or tissues.

5. When assessing exposures to populations, although in principle these may be expressed as the distribution of individual doses, it is necessary in practice to carry out some procedure such as totalling or averaging to convey these exposures in a manageable way. If there are not many individuals in the population who receive very high doses from medical treatments, and the other doses are comparable with or less than the dose from natural radiation, then the conditions for the approximation referred to earlier hold and the collective dose obtained by summing individual incremental doses from any source can be related to the mathematically expected number of health effects using the appropriate constant risk factor. This relationship will hold irrespective of the distribution of individual doses; indeed in many cases the procedure may be carried out without knowledge of the individual dose distribution.

6. In a few cases in which individuals are being considered it may be possible to estimate the levels of exposure from direct measurements. This is normally the situation for occupational exposure to external and to some forms of internal irradiation. In most other cases involving exposure to members of the public, whether considered as individuals or collectively, it will be necessary to estimate the levels of exposure indirectly, using models to connect the known or measured quantity of activity released or in the environment with the level of exposure to humans. The purpose of this Annex is to collect together and explain the dosimetric and environmental transport models used by the Committee in this report.

7. The models used have been separated into two general categories: environmental transport models which describe the movement of radioactive materials through all sectors of the environment after their release, and dosimetric models to calculate the absorbed dose following an intake of radioactive materials or exposure to external irradiation. Dosimetric models for intakes obtain the absorbed dose from calculations of the residence of radionuclides in the body after intake. In the later Annexes environmental transport models are used first to assess the radionuclide distributions which then form the input to dosimetric models. In this Annex, however, since the quantities involved in the dosimetric models contain many basic ideas and definitions, the order is reversed. The dosimetric models are presented in chapter II, followed by the environmental models in chapters III to VI.

8. A specialized model which does not fall into either of the above categories is used in Annex H (Occupational exposures). This is based on the observation that the distribution of annual occupational doses appears to be log-normal in a number of cases. Dose distributions on which there are insufficient data for direct calculations are then analysed using the assumption that the distribution is log-normal. Other specialized models, often tailored to particular irradiation conditions, are used in Annex G (Medical exposures).

9. To introduce some consistency into the use of symbols and terms for defined quantities, the Committee has used the SI system [P4], but additionally based its terminology in this report on the recommendations of the International Commission on Radiation Units and Measurements [I9] and of the International Commission on Radiological Protection [I2] where appropriate. Standard terminology used in areas other than radiation dosimetry has been retained where possible [I13]. In some cases, however, it has been necessary for consistency to use unfamiliar symbols. For this reason the quantity name, quantity symbol, unit name and unit symbol for most of the quantities used in the physical Annexes are given in Tables 1 and 2 of this Annex. Table 1 gives the basic and derived units for some of the quantities of interest in this report; Table 2 gives derived units for some other quantities, along with the quantity and unit symbols. Symbols are also given in Table 2 for terms used as designators or indices. There are a few terms indicated by multiple letter symbols that are included because they are generally recognized acronyms. The symbols used in Table 2 are those selected for use by the Committee in the physical Annexes (A to H) of this report; some may be used for different purposes by other bodies. The biological Annexes (I to L) did not lend themselves to such a consistent treatment as the physical ones, since many references are made to nomenclature introduced by different authors, which may be inconsistent with each other. The terms "radioactivity", "activity" and "radioactive material" are often confused and interchanged although they are not synonymous. "Radioactivity" is the phenomenon of spontaneous decay, while "activity" is the number of nuclear transitions per unit time. Some of the confusion arises because the activity of a sample used to be a measure of the "quantity" of that sample. It was then permissible to refer to the "release of activity", etc. However, with the present definitions by the ICRU [I9], this is no longer correct. The Committee has therefore tried to avoid the use of "activity" as a synonym for "radioactive material"; some unintentional misuse may have been carried on because of previous practices.

I. THE PURPOSE OF DOSE ASSESSMENTS

A. INDIVIDUAL-RELATED ASSESSMENTS

10. The important quantities to assess when considering individuals are the absorbed doses associated with exposure during a year or over a lifetime. The magnitudes of both these quantities may be used to assess the probability of harmful consequences to the health of individuals exposed to radiation in a given year or over a lifetime.

11. Considerations of external irradiation are relatively simple as the absorbed dose is delivered at the time of the irradiation. Thus there is no problem of protraction of dose beyond the period of exposure.

12. Internal irradiation following an intake of radioactive materials whether by inhalation, ingestion or other means is, however, protracted to some extent and the absorbed dose in the organs or tissues of any individual after an intake will depend on conditions particular to the individual such as metabolism, age and life expectancy as well as on more general determinants

such as the half-life of the radionuclide. While it is possible to make estimates for particular individuals, and this may be done for medical purposes, the Committee assesses the mean absorbed dose in each organ or tissue, usually taking representative values for the various conditions, either for complete populations or for particular subgroups in the population.

B. SOURCE-RELATED ASSESSMENTS

13. The source-related assessments carried out by the Committee estimate the total human irradiation resulting from the source, practice or event. This total human irradiation is obtained by considering all the population groups exposed to radiation in different geographical locations and at different times. This is generally obtained by integrating in an appropriate fashion to cover the spatial and temporal distributions of radiation or radionuclides from the source. The parameters used in the calculations and the models are generally applicable to representative characteristics of large population groups. Source-related assessments are used by the Committee for comparisons of sources in terms of their presumed total health impact.

II. DOSIMETRIC MODELS

14. For the reasons given in the Introduction (paragraph 7), dosimetric models are described before environmental transport models, although in practical calculations the order is reversed. Dosimetric models are used by the Committee to assess the absorbed doses and weighted absorbed doses resulting from exposure to radiations of different types or from intakes of radioactive materials. The models include those for predicting the behaviour of radioactive materials in the body after intake and those making an allowance for the risk of induction of particular health effects after exposure to radiation. In some cases the model is not described explicitly but is part of the background underlying the choice of a particular quantity for use in characterizing the impact of radiation exposure of man. For the quantities used here to quantify the effect of irradiation of people, it is assumed that there is proportionality between the absorbed dose to an individual and the probability of occurrence of stochastic health effects, as discussed in the Introduction (paragraph 3). Other possible assumptions are discussed in Annexes I, J, K and L (Genetic effects of radiation, Non-stochastic effects of irradiation, Radiation-induced life shortening, and Biological effects of radiation in combination with other physical, chemical and biological agents, respectively).

15. The fundamental quantitative assumption describing the interaction of radiation with matter is that the relevant measure of the interaction is the mean energy deposited per unit mass. This energy deposition can result from all types of radiation and the quantity used to measure it is the absorbed dose, D, defined by [19] as $D = \frac{d\varepsilon}{dm}$ where $d\varepsilon$ is the mean energy imparted by ionizing radiation to matter of mass dm.

16. It soon becomes apparent that the biological effects do not depend solely on the energy deposition per unit mass, or absorbed dose, but also on other factors, notably the type of radiation. The additional factor needed to relate the observed effects to the absorbed dose is known as the relative biological effectiveness (RBE). This is the ratio of the absorbed dose of the radiation being studied needed to produce a specified biological effect to the absorbed dose of the reference radiation which produces the same number of the same effect. This reference radiation is usually penetrating x- or gamma-radiation. The RBE depends on the radiation type, the energy and all the circumstances of radiation delivery, which should be quoted. The RBE is thus obtained experimentally. If the dose-response relationship is linear with no threshold, the probability of occurrence of a given biological effect after exposure to radiation may be obtained from the absorbed dose multiplied by the RBE appropriate to the circumstances of the irradiation. As the RBE is a relative number, any change in the observed number of effects of a given type produced by a given absorbed dose of the reference radiation will cause a change in the RBE for that effect for all other radiation types. If the dose-response relationship for either radiation is non-linear, or if there is a threshold dose below which effects do not occur, a single value of RBE cannot be used as a weighting factor for biological response.

17. For many purposes there is a need for a well defined quantitative relationship between the radiation dose and the presumed number of resultant biological effects. The RBE is an experimentally determined quantity, and the best estimate of it for any particular radiation will change from time to time as better data are obtained. The amount of data on which RBE can be determined is limited and no functional relationships with dose are established. In radiological protection proportionality between absorbed dose and effect has been assumed for small values of absorbed dose and dose rates for all radiation types and energies. Given this assumption, the ICRP has defined the quantity dose equivalent, H, which is intended to indicate for radiation protection purposes the biological implications of the radiation exposure at the low levels of absorbed dose encountered. H is defined by $H = DQN$, where Q is the quality factor and N is the product of all other modifying factors specified by the ICRP. For the present the ICRP has assigned a value of unity to N. The quality factor is defined as a function of the collision stopping power for radiation at the point of interest, increasing from 1 for collision stopping powers of less than 3.5 keV μm^{-1} to 20 at collision stopping powers exceeding 175 keV μm^{-1}. When the precise distribution of collision stopping powers throughout the mass of interest is unknown or unimportant because the values of dose equivalent are small, it is permissible for radiation protection purposes to use approximate values of the quality factor related to the various types of primary radiation. The ICRP has recommended the following approximate values of Q for both external and internal radiation:

x rays, gamma rays and electrons	1
Neutrons and protons of unknown energy	10
α-particles and other multiply charged particles of unknown energy	20

These values of Q and hence values of H are intended only for use at levels of exposure within or near dose equivalent limits as defined by the ICRP. The values are independent of the effect, the organ or tissue exposed or other variables. For the general purposes of comparison between sources and assessment of individual dose equivalent levels, these approximate values are appropriate for use by the Committee for most radiation types. However, since they may not be

appropriate for other purposes, the Committee is presenting its basic data in terms of absorbed dose. For some special cases, such as the assessment of dose equivalents from cosmic radiation, the Committee has used other values of quality factors based on specific calculations.

18. It is assumed in the dosimetric model that the probability of occurrence of a stochastic effect in a particular organ or tissue is proportional to the mean dose equivalent in the organ or tissue. The constant of proportionality differs for the various organs or tissues of the body. If the dose equivalents are sensibly uniform for all organs or tissues of the body, then a single overall risk factor can be used to describe the probability of induction of health effects for the individual. Assessments and comparisons can then be made solely on the basis of the dose equivalent to the whole body. However, if different organs or tissues are irradiated to different dose equivalent levels, then a further procedure is necessary to evaluate the overall probability.

19. The ICRP has recommended a system which allows for the different probabilities of mortality associated with the same dose equivalent delivered to different organs or tissues and the probability of hereditary effects in the first two generations. This system uses the effective dose equivalent: $H_{eff} = \sum_T w_T H_T$ where w_T is a weighting factor representing the proportion of the probability of stochastic effects resulting from irradiation of organ or tissue T to the probability when the whole body is irradiated uniformly and H_T is the mean dose equivalent in organ or tissue T.

20. The values of reference risk coefficients and corresponding weighting factors recommended by the ICRP [I2] are shown in Table 3. They are averaged over age and sex and are therefore considered by the Commission to be appropriate for protection of individuals of all ages and both sexes. The value for gonads includes an allowance for serious hereditary effects expressed in the first two generations (i.e., the children and grandchildren of a pair of individuals). Numerically equivalent reference risk coefficients per unit collective dose equivalent can also be used to assess the expected number of the same health effects in populations.

21. The effective dose equivalent therefore is an indicator of the probability of occurrence of a health effect, which is either death from somatic effects or the induction of serious hereditary effects in the first two generations, assumed to result from any irradiation, whether uniform or non-uniform, from both external and internal sources. The effective dose equivalent does not include hereditary effects in generations after the first two, nor any allowance for non-fatal somatic effects such as in most cases of thyroid or skin cancer; to this extent it will underestimate the overall probability of induction of all health effects. Where appropriate, therefore, the dose equivalents in the tissues of interest can be used directly to give an indication of the likely incidence of non-fatal tumours. The risk coefficients to be used to give the probability of induction of non-fatal tumours, which exclude the probability of induction of fatal tumours in the same organ or tissues, are 0.15 10^{-2} Sv^{-1} for breast, and 10^{-2} Sv^{-1} for both thyroid and skin [U9]. The figures for the latter are a sufficient approximation whether the fatal tumours are included or not.

22. It is possible to define different sets of weighting factors which include some or all of these additional health effects or which deal separately with each health effect [C3]. For the present the Committee has decided to carry out comparisons in terms of the quantities defined in this chapter.

A. INDIVIDUAL-RELATED ASSESSMENTS

1. External irradiation

23. The primary assessment of radiation exposure of individuals should be carried out in terms of absorbed dose. Conceptually, the assessment of the distribution of absorbed doses in body tissues from external irradiation requires knowledge of the energy and angular distribution of the fluence rate of each component of the electromagnetic and charged particle radiation field. These differential distributions can be obtained by spectrometric measurements, but in general only calculated values, for known source distributions, are available. In practice most assessments of absorbed doses from external irradiation are based on simpler measurements.

24. Most measurements describe the field in the absence of an exposed person in "receptor-free" conditions. The absorbed dose rate in air $\dot{D}_a$ is used to describe environmental exposure situations resulting from gamma-emitting nuclides, and it is unambiguously specified if full secondary electron equilibrium exists in air. From the environmental quantity, the absorbed dose in the human organ or tissue of interest can be assessed. This involves a number of assumptions about factors which affect the results of depth dose calculations and about the periods of time during which the person is exposed to the various radiation fields. The latter factor is discussed further in section V.A.

25. When the receptor is located in the region of interest, the assessment of absorbed doses in tissues based on absorbed dose in air involves knowledge of the following parameters: the mass energy absorption, the depth transmission, the backscatter and the degree of isotropy. The mass energy absorption factor is the ratio of the mass energy absorption coefficients for tissue and for air. A value of 1.10 was used in Annex A of the 1977 report [U1] and is retained in this report. The other factors are to some extent interrelated. Backscattered radiation may increase the dose rate at the surface, but the body will also act as a shield and reduce the dose rate to deeper tissues. The overall effect will depend on the location of the tissue of interest, and the energy and angular distribution of the radiation.

26. Except for the rare case where the radiation field is monodirectional and the irradiated person is not moving, the apparent depth of an organ or tissue is determined from the weighted average absorption through the body that would be experienced by rays entering from different directions. The difference between monodirectional and isotropic fields will also be expressed in terms of a difference in absorbed dose rate at any depth for fields which produce the same absorbed dose rate in air under receptor-free conditions. The ratio of the absorbed dose rates cannot exceed 2 for points near the surface of the body, and it approaches 1 near the centre of the body. These problems have been discussed in detail by Kramer [K3] and by Kramer and Drexler [K4, K5] who have applied a Monte-Carlo method to a mathematical represen-

tation of ICRP Reference Man [I6] to calculate conversion ratios for a range of tissues, photon energies and irradiation geometries.

27. In Annex A of the 1977 report [U1], the Committee has adopted a value of 0.82, which includes all the factors mentioned, for the ratio between the absorbed dose rate in the body and the absorbed dose rate in air outdoors [U1, U2] based on the work of Bennett [B1] and a value of 0.69 indoors based on Spiers and Overton [S1]. A value of about 0.7 Sv Gy^{-1} has also been derived as the quotient of effective dose equivalent to absorbed dose in air [N1] based on calculations for clouds of gamma emitters of about 1 MeV [C1, P1]. This is compatible with the values derived by Kramer and Drexler [K4]. The values for individual organs are more sensitive to energy and to the field characteristics; for example, the ratio of absorbed dose in gonads to absorbed dose in air is about 0.6 for a semi-infinite cloud [C1, P1], 0.7 for an isotropic field [O1, O2, S1] and 0.8 for a normal field [B1, J1]. It now appears that the most appropriate average value of the quotient of effective dose equivalent rate to absorbed dose rate in air for males and females for use in this report is 0.7 Sv Gy^{-1} for environmental exposures to gamma rays. For medical exposures, specific conversion factors are discussed in Annex G (Medical exposures).

28. Another quantity which can be used to describe receptor-free conditions is the absorbed dose index, D_I. This has been defined by ICRU [I9] as the maximum absorbed dose that can occur in a 30-cm diameter tissue equivalent sphere located with its centre at the point of interest. This quantity is used, for example, to describe irradiation due to cosmic radiation. It is assumed that the absorbed dose index represents, sufficiently well, the absorbed dose in tissue at the location of interest.

2. Internal irradiation

29. For internal irradiation, the mean absorbed doses in the organs or tissues of interest of a given individual may be estimated from one or more of the following:

(a) Measurements of activity concentrations in the environment and in diet components, leading to estimates of the intake and, by use of appropriate metabolic models, to estimates of the uptake and residence time of the radionuclide in the organs or tissues of interest;
(b) Assessments of the activity concentrations in the relevant organs or tissues, by measurement of the radiation emitted from the body or of the activity concentration in tissue samples;
(c) Measurements of the activity concentrations in excreta or exhaled air leading, by the use of appropriate metabolic models, to estimates of the activity concentration in the relevant organs or tissues of the body.

30. The use of this information to calculate absorbed doses in organs or tissues requires models to describe the transfer of radionuclides between tissues and their eventual elimination from the body as a function of time. It is also necessary, given the radionuclide distribution between the various tissues as a function of time, to have further models to calculate the dose rate in any tissue of interest from the activity in any tissue, including the tissue of interest. The general concept of the mean absorbed dose per unit of time integrated activity is that used by MIRD [L1, B2], by ICRP [I4] and by ICRU [I10].

31. The general equation for absorbed dose calculations from internally deposited radionuclides is

$$\overline{D}(V_q) = \sum_k \sum_i \int_{t_1}^{t_2} A_k(t)\, dt\, \overline{E}_i\, \Phi_i(V_q \leftarrow V_k) \qquad (1)$$

where $\overline{D}(V_q)$ is the mean absorbed dose in a target volume V_q; $A_k(t)$ is the activity of the radionuclide considered in source tissue, k, as a function of time. $\overline{E}_i$ is the mean energy emitted per unit of time integral of activity through ionizing particles of type, i; $\Phi_i(V_q \leftarrow V_k)$ is the specific absorbed fraction, i.e., for the type of radiation i, the energy imparted to a target volume V_q from a source volume V_k divided by the energy emitted by source volume V_k and the mass of the target volume. It should be noted that, for the general calculation, the biological parameters are assumed to be independent of age.

32. Usually approximations to obtain the activity in an organ or tissue as a function of time A(t) are made; the most common is a sum of exponential terms:

$$A(t) = \sum_m A(m) \exp(-(\lambda + \lambda_b[m])\, t) \qquad (2)$$

where A(m) is the value of the mth exponential component at time $t = 0$; λ is the physical decay constant of the radionuclide; $\lambda_b(m)$ is the biological elimination rate constant for the mth exponential component.

33. The function A(t) is sometimes determined empirically from retention measurements; it can also be derived from compartment models in which the activity contents of the compartments are described in terms of rate constants for transfers between compartments and in terms of input functions. These methods are used for example by ICRP in calculating the integrated activities in body tissues following ingestion or inhalation of material [I4, I11].

34. For some radionuclides such as ^{3}H or ^{14}C which are continuously produced naturally or which have been uniformly distributed in the environment after release it is possible to use a simplified procedure based on the assumption that the activity concentration of the nuclide in tissue is constant. Activity concentration in tissue may also be assumed, under many circumstances, to be equal to the activity concentration in an appropriate environmental material such as water. Under these circumstances the formulation given in equation (1) can be replaced by a time independent expression using constant quotients to relate the absorbed dose rate in any organ or tissue directly to the activity concentration in that organ or tissue. This procedure is used for these radionuclides in Annex B (Exposures to natural radiation sources) and in Annex E (Exposures resulting from nuclear explosions).

35. In general, the Committee has not found it necessary to calculate directly the matrices of values of A(t) and Φ_i which are needed for assessment of absorbed doses in tissues. The absorbed dose rate in an organ or tissue is related as shown above to the activity concentrations in all organs or tissues in the body. This absorbed dose rate may be integrated over various

times for various purposes. An integration time of 50 years has been used by ICRP [I2] to derive the committed dose equivalent H_{50}. This is relevant in the control of internal doses to workers as the annual dose equivalent at the end of the period at work, taken to be 50 years, cannot exceed the maximum annual committed dose equivalent. Detailed tabulations of the committed dose equivalent per unit activity intake of all radionuclides of interest to the Committee have been published by ICRP [I4, I11].

36. In calculating the dose equivalent from intakes by populations, the Committee requires an appropriate average relationship. The relationships will be different for infants, young children and adults because of differences in metabolism and dosimetry. Nonetheless, when developing an appropriate average, it is necessary to recognize that most individuals in a population will be adults or older children for whom adult values are a very close approximation. Since a population contains individuals of all ages, the appropriate time over which to integrate the dose equivalent following an intake is the average remaining life expectancy which is just under 50 years. In the same way, for continuing intakes by an average individual with an anticipated lifetime of 70 to 80 years the appropriate integration time will decrease from 70 to 80 years for intakes in infancy and early childhood to a few years for intakes in the last years of life; again the appropriate average over a lifetime is less than 50 years. The Committee therefore considers it appropriate for populations in both situations to use the conveniently tabulated ICRP values of committed dose equivalent per unit activity intake based on a 50-year integration period. The dose equivalent commitment from intakes by a population can then be obtained from the infinite time integral of the rate of activity intake by an average individual in the population multiplied by the committed dose equivalent per unit activity intake.

37. As indicated earlier, the Committee feels it is reasonable to use the dose equivalent for comparison purposes, modifying the absorbed dose by the appropriate quality factor. For individuals the effective dose equivalent is also regarded as a reasonable approximation, implying use of further modifying factors as needed. These modifications will be made in some cases at a late stage in the calculations; in other cases it is more orderly to carry the modifications out at an early stage. In the latter cases it will be reasonable to use tabulations of effective dose equivalent per unit of activity intake such as those produced by ICRP [I4] or by Adams [A1], together with such additional calculations as may be needed for specific purposes; similar procedures have been carried out in Annex G (Medical exposures).

38. There are special problems connected with the dosimetric models for certain radionuclides which are dealt with in detail in the appropriate Annexes. An example is the dosimetry of radon and its daughters for the activity concentrations of which a special quantity, C_{pot}, has been defined as the potential alpha energy concentration in air of any combination of the short-lived radon daughters. This particular quantity is defined to allow for situations where the daughters are not in equilibrium. It can of course be expressed in units of J m^{-3}, but use is still made of the empirically determined unit, the working level, WL, which corresponds to a potential alpha energy concentration of 1.3 10^5 MeV per litre of air. Further problems concerning the dosimetry of radon and a discussion of the more complex models of the lung which have been developed mainly for use in the dosimetry of radon are covered in Annex D (Exposures to radon and thoron and their decay products).

39. In previous reports of the Committee, for absorbed dose rate assessments from maintained activity concentrations in the body, calculations have been carried out using a similar procedure to that underlying the formulation in equation (1). The details of these calculations, given in Annex B (Natural sources of radiation) of the 1977 report [U1], will not be repeated here. It should be noted that certain of the parameters used in the calculations and aspects of the models differed from those used by ICRP in the most recent reports on this subject [I4, I11], although the principles are the same. In its previous reports, the Committee has estimated, on the basis of measurements, the average activity intakes of radionuclides and the average activity concentrations of these radionuclides in tissue. On the other hand, ICRP [I4] provides a series of models which give the dose equivalent in tissue per unit intake of activity of a radionuclide as a function of the aerosol size and of the chemical forms of the radionuclide considered. Another part of the series of models enables the dose equivalent rate in tissue to be calculated per unit activity concentration in tissue.

40. The major differences between the ICRP and the Committee occurred in the calculation of dose equivalent in bone tissues. Both the Committee and ICRP calculated dose equivalents in the same tissues, namely red bone marrow and bone lining cells in a 10-μm layer on the surface. For the purposes of the calculations, radionuclides were considered to be either uniformly distributed throughout each bone tissue or distributed on the bone surface. The difference between the calculational methods used by the Committee and ICRP stemmed mainly from which components of bone were considered to be source regions. A comparison of the two methods is outlined in Table 4 for α-emitters from which it can be seen that the Committee generally calculated in its 1977 report [U1] the dose equivalent in the target region from activity in trabecular bone and red bone marrow based on the treatment of Spiers [S14], whereas ICRP ignored activity in red bone marrow but included activity in cortical bone in the calculation of dose in bone lining cells [I4]. A further difference was that the coefficient used by the Committee in assessing the dose equivalent from activity in trabecular bone was in most cases a function of energy. However, this only led to differences in that component of the calculation of a factor of from 0.5 to 2 for α-energies from 4 to 8 MeV. The differences resulting from inclusion of the other source regions depend on the radionuclide under consideration and the relative distribution of activity between the bone tissues.

41. In all cases the calculational methods used by the Committee in 1977 gave higher estimates than ICRP of dose equivalent in red bone marrow from a given activity concentration of an α-emitter. This difference was generally about a factor of 2, for example the ratio of the results of the Committee to ICRP dose equivalent calculation for the nuclides in the ^{238}U and ^{232}Th series varied from 1.1 to 3. For bone lining cells the ICRP method gives the average dose equivalent in cells on trabecular and cortical bone, whereas the earlier Committee method obtained the dose equivalent only in cells on trabecular bone surfaces, but included the

effect of red bone marrow as a source region. In this case either calculation may give the higher result, depending on the distribution of activity between the bone tissues. For example, the Committee model gave dose equivalents higher than ICRP by factors from 1.1 to 1.7 for the nuclides in the ^{232}Th series and dose equivalents lower than ICRP by factors of from 0.7 to 0.9 for the nuclides in the ^{238}U series (with the exception of ^{230}Th for which the factor is 1.7).

42. In this report, the Committee has modified its previous treatment to include the source regions used by ICRP and the red bone marrow, as shown in Table 4. The doses to the bone tissues are then calculated using the ICRP conversion factors. The only difference arises from the calculation by the Committee of the contribution due to the activity present in red bone marrow; for most radionuclides, that contribution to the total dose in bone tissues is very small.

43. Another aspect of the comparison between the treatments used by the Committee and by ICRP occurs when assessments of doses are based on estimates of intake and transfer through the body of radionuclides, rather than on measured activity concentrations in tissues. In general, the Committee has based its assessments of doses from naturally-occurring radionuclides and of doses arising from atmospheric weapons testing on measurements of activity concentrations in tissues. However, in assessing dose equivalents from radionuclides released from nuclear power establishments, this is not usually possible. Thus calculations are based on assessed intakes and make use of ICRP methods. Further differences are introduced between these two situations which can be traced to the additional assumptions needed about the transfer of activity from lung or through the gut wall and on its subsequent distribution in tissues. These differences depend on the radionuclide under consideration and on its physical and chemical form; they are thus specific to the circumstances considered.

44. The results of individual-related assessments may be expressed as the risk to an average individual. This risk is the probability of occurrence of a health effect and may be obtained using the appropriate reference risk coefficients from Table 3 if the organ or tissue dose equivalents are known. Otherwise the probability of induction of a fatal tumour or an hereditary effect in the first two generations is obtained by applying the overall reference risk coefficient of $1.65\ 10^{-2}\ Sv^{-1}$ to the effective dose equivalent.

B. SOURCE-RELATED ASSESSMENTS

45. Although, as explained in paragraph 13, for source-related assessments the emphasis is on the expected number of radiation-induced effects rather than on the probability of effects for each individual, nonetheless the basic information will still be expressed in terms of average absorbed doses in the organs and tissues of the individuals making up the irradiated population. For reasons expressed in paragraph 17, the Committee finds it reasonable to modify the absorbed dose by means of the quality factor and thus to give the irradiation in terms of dose equivalent.

46. As discussed in the Introduction to this Annex (paragraph 2), there is considerable uncertainty in the dose-response relationship for radiation-induced tumours. This matter has recently been reviewed in detail [N4]. Although accepting the uncertainty, the Committee nevertheless needs quantities which can be used to derive the number of radiation-induced health effects which may be expected from radiation sources that give a wide range of doses in large numbers of people. For intercomparisons it would be too cumbersome to deal always with the distribution of absorbed doses or dose equivalents in the irradiated populations. The Committee has therefore decided to express this summation in terms of collective quantities which are weighted sums of the absorbed doses in each irradiated individual. Implicit in most uses of these collective quantities is the assumption that the dose-response relationships are linear for additional doses which are not large in comparison with pre-existing doses for irradiation of any tissue with radiation of any type.

47. The collective dose equivalent rate, $\dot{S}$, is defined as the integral of the product of the dose equivalent rate resulting from the source and the number of individuals in the exposed population receiving that dose equivalent. It is defined by $\dot{S} = \int \dot{H}\, N(\dot{H})\, d\dot{H}$ where $N(\dot{H})\, d\dot{H}$ is the number of individuals receiving a dose equivalent rate between $\dot{H}$ and $\dot{H}+d\dot{H}$. The integral expression can often be approximated in practice by a summation over population subgroups receiving dose equivalent rates that can be sensibly averaged.

48. The collective dose equivalent rate can be integrated as a function of time. The integration may be continued to infinity. The quantity resulting has been called the collective dose equivalent commitment from the source, S_k^c, defined by: $S_k^c = \int_0^\infty \dot{S}_k(t)\, dt$. This is always related to a specific source, k. It is also often useful to present the pattern of accumulation of the collective dose equivalent commitment with time. This pattern may be presented graphically or by giving stages in the integration. It is also possible to define a truncated or incomplete integral in which the integration is terminated at time τ. The main purpose of truncation is to derive the maximum future dose equivalent rate from a practice which is assumed to continue for a time period τ.

49. Average or per caput quantities can be defined by dividing the collective quantity by the population size such that

$$\bar{\dot{H}}(t) = \frac{\dot{S}(t)}{N(t)} \qquad (3)$$

where $\bar{\dot{H}}(t)$ is the per caput dose equivalent rate and N(t) is the population size at time t. It may be more convenient under some circumstances to evaluate per caput quantities rather than collective quantities. The dose equivalent commitment, H^c, is defined as the infinite time integral of the per caput dose equivalent rate.

50. These average quantities are sometimes used to refer to individuals in the per caput sense. Insofar as these are not real individuals and the dose equivalents are usually assessed on the basis of the effect of a particular source, it is considered that these are more properly treated as source-related quantities. The quantity related to a source, k, will be the dose equivalent commitment H_k^c. There is however one instance in which information on individuals can be derived. This is because the annual dose equivalent to an average individual in the future from one year of release of a radionuclide into the environment does not exceed the

dose equivalent commitment resulting from that release. Thus a calculation of the dose equivalent commitment per unit practice enables at least a rough estimate to be made of the maximum future annual average dose equivalent per unit practice.

51. Where the collective effective dose equivalent is used for populations, care must be taken that the circumstances of the irradiation are not such that the omission of certain portions of the total health effects can lead to a substantially erroneous estimate of the expected number of health effects. This can occur, for example, if the irradiation were confined to specific organs such as skin or thyroid and it is felt that the total incidence of malignancies is relevant, even though the majority will not prove fatal. As stated earlier, the effective dose equivalent as defined by ICRP does not take into account hereditary effects after the first two generations, nor does it include non-fatal somatic effects. Although these omissions may not be sufficiently serious to affect the general level of probability of occurrence of a health effect for an individual, when considering irradiation of populations in a source-related manner, it seems to the Committee necessary to give further consideration to these effects. Clearly the various effects are not of equivalent importance; attempts have been made to assess the relative importance of each type of health effect with respect to the others [15]. However, the Committee has decided not to attempt such analyses now but to separate and compare the somatic and hereditary health effects in populations. This requires the assignment of the appropriate sets of weighting factors for the irradiation of particular organs or tissues in a manner analogous to those used in the definition of effective dose equivalent. The Committee has chosen to follow the format of its earlier definition of genetically significant dose equivalent for consistency with earlier reports.

52. The genetically significant dose equivalent, GSD, is defined as the per caput gonad dose equivalent which, if given uniformly to the irradiated population, would result in the same number of hereditary effects as those from the actual distribution of dose equivalents in the population. It is thus the gonad dose equivalent distribution modified by those factors which affect the outcome, namely the age and sex distribution of the irradiated population. The formal definition is

$$GSD = \frac{\sum_{l}\sum_{s} H_{l,s}\, N_{l,s}\, v_s}{\sum_{s} N_s\, v_s} \qquad (4)$$

where $N_{l,s}$ is the number of people of age/sex class s, irradiated within dose equivalent band l to an average gonad dose equivalent level of $H_{l,s}$; v_s is the expected number of children for an individual of age/sex class s; N_s is the number of people of age/sex class s.

53. From the above definition, the information needed to compute the GSD is the distribution of gonad dose equivalent in the population as a function of age and sex. This information, together with the child expectancy as a function of age and sex which is readily available in most countries, can be obtained by observation or by statistical methods. It is therefore practically possible in a large number of cases to carry through the computation of GSD based on the formal definition. The total number of hereditary effects is then obtained by multiplying the GSD by the population size and the appropriate collective risk coefficient, taken as 0.8 10^{-2} (man Sv)$^{-1}$, to include effects in all subsequent generations.

54. By analogy with the GSD, it is possible to define a somatically significant dose equivalent, SSD. This is the per caput whole-body dose equivalent which, if given uniformly to the irradiated population, would result in the same number of fatal tumours as those from the actual distribution of dose equivalents in the tissues of the irradiated population. The formal definition is

$$SSD = \frac{\sum_{l}\sum_{s}\sum_{T} H_{l,s,T}\, N_{l,s}\, w_{s,T}}{\sum_{s}\sum_{T} N_s\, w_{s,T}} \qquad (5)$$

where $N_{l,s}$ is the number of people of age/sex class s, whose tissue, T, is irradiated within a dose equivalent band l to an average tissue dose equivalent level of $H_{l,s,T}$; $w_{s,T}$ is the number of fatal tumours per unit dose equivalent for irradiation of tissue T in a subgroup of age/sex class s; N_s is the number of people of age/sex class s. Although the total number of fatal tumours predicted will be the same for the SSD as for the actual distribution of dose equivalent, the tissues in which they are predicted and the type of tumour will not necessarily be the same.

55. The information needed to compute the SSD includes the distribution of dose equivalents in the tissues of the population as a function of age and sex, which together with the incidence of fatal tumours for irradiation of a particular tissue at a particular age for each sex, is in principle obtainable by observation or by statistical methods. This incidence should include allowance for the induction rate of tumours which may vary with age and sex, together with a further allowance for the expression of the effect which will also depend on age and sex, taking into account the latent period of the effect. This information is not in general available at present in the detail required for computation of SSD based on the formal definition.

56. An approximation to SSD can be made using weighting factors for the incidence of somatic effects which are averaged over the age and sex distribution of a normal population. This approximation is so close to the definition of effective dose equivalent derived by ICRP that it does not seem useful to derive a separate set of weighting factors. The per caput effective dose equivalent, although containing a genetic component, may be taken as a reasonable approximation to the SSD, using the weighting factors in Table 3. The total number of health effects (fatal tumours and genetic effects in the first two generations) is then obtained by multiplying by the population size and by the appropriate collective risk coefficient, taken as 1.65 10^{-2} (man Sv)$^{-1}$ [12].

III. ENVIRONMENTAL MODELS

A. GENERAL

57. If it is possible to measure the absorbed dose rate in air from radionuclides in the air or deposited on the ground at a sufficient number of places and over a sufficient time, then the absorbed doses to individuals and populations from external radiation can be assessed without the need for environmental transfer

models to describe the manner in which the airborne contamination or deposition resulted from the source of radionuclides. Similarly, if the activity concentrations in organs or tissues of the radionuclides concerned can be measured in a sufficient number of people, the absorbed doses from incorporated radionuclides can be assessed using only dosimetric models and without the need for environmental transfer models. In many situations, especially for naturally-occurring radionuclides and for those produced from nuclear explosions, such measurements have been carried out in sufficient numbers, in different places and over long enough periods of time to enable the Committee to estimate doses directly from them.

58. Slightly less direct estimates of internal doses can be made from measurements of activity concentrations of radionuclides in the air or in foodstuffs. In this case the additional information required is of the intake rates of the radionuclides from air or from the foodstuff concerned and the appropriate dosimetric models to calculate the absorbed doses in organs and tissues following intake. These less direct methods are used for some radionuclides from nuclear explosions, often to supplement a more limited measurement programme on people. They are also used in assessing absorbed doses to critical groups of the population exposed as a result of deliberate releases of radionuclides from nuclear installations, for a limited number of radionuclides. A difficulty in placing too much reliance on such measurements is that there has to be a great deal of preliminary effort to ensure that the foodstuff being monitored is the only, or the major, route of intake of the radionuclide concerned. When dealing with a mixed diet and a large number of radionuclides this becomes extremely laborious. For radionuclides which are not evenly distributed in the environment, it is not a feasible method to establish the collective dose.

59. Sometimes direct measurements may not be practicable. This may be due to technical difficulties in measuring the activity concentration of the radionuclide concerned in an appropriate medium, or to the difficulty of obtaining samples, or to the number of radionuclides and pathways being too large. Direct measurements may also be impracticable because predictions of dose rates are required, for example to derive collective dose commitments, whereas measurements have to be carried out after or during the delivery of the dose. In these cases models are required in order to derive doses and dose distributions from data on the quantities of radionuclides released into the environment and the rates of release. The relationship will depend on other factors such as the conditions of the release, the physicochemical form of the radionuclide, whether the release is into the atmosphere, a water body or the ground and the characteristics of the receiving environment. In general, the environmental models with which the Committee is concerned are simplified mathematical representations of actual transfer processes. Some of those processes are well understood and can be described reasonably precisely by mathematical models which are based upon detailed measurements. The transfer of fallout radionuclides such as ^{90}Sr through food chains is an example. Other processes may be only partially known and the time scales or other aspects may render the models very difficult to check directly by measurement, as in the case of the long-term stability of sorption of actinides on soils or sediment particles. It is not the intention to review all types of transfer models but to concentrate on those used by the Committee in this report.

60. The type of model used depends on the information required, on the characteristics of the radionuclide concerned and on its mode of introduction into the environment. Of particular importance is whether the radionuclide can be considered as uniformly distributed and whether the activity concentration is approximately constant with time. If both these conditions are satisfied, as they are for certain naturally-occurring radionuclides, then the simplest form of environmental model is adequate to assess the collective absorbed dose rate in the world population. This model relates directly the assumed activity concentration in body organs or tissues with the measured activity concentration in a suitable environmental medium, such as the circulating waters of the hemisphere or the air of the troposphere. It is often referred to as a "specific activity model". If the activity concentrations in the environment result from continuous production, as for natural tritium and ^{14}C, an empirical relationship can be developed between the production rate and the activity concentrations. Very simple models of this type are used in Annex B (Exposures to natural radiation sources) for assessment of collective absorbed dose rates from natural radionuclides and in Annex E (Exposures resulting from nuclear explosions) for the same radionuclides which are widely distributed as a result of production in the atmosphere by nuclear explosions. The results of such models are compared with more complex time varying environmental models for appropriate radionuclides in Annex F (Exposures resulting from nuclear power production).

61. The information required by the Committee in the past has varied but has generally been directed towards assessment of the dose commitment, particularly in the treatment of the doses from fallout of debris from nuclear explosions in the atmosphere. The Committee developed a procedure for dealing with these calculations which was based on the idea of time-independent transfer coefficients [U2, U3]. These transfer coefficients have been defined in Annex A (Concepts and quantities in the assessment of human exposures) of the 1977 report [U1] in terms of the quotients of the infinite time integral of the appropriate quantity in compartment n of a sequence to the infinite time integral of the appropriate quantity in the preceding compartment m. For example:

$$P_{mn} = \int_{-\infty}^{\infty} C_n(t)\,dt \Big/ \int_{-\infty}^{\infty} C_m(t)\,dt \qquad (6)$$

where P_{mn} is the transfer coefficient from compartment m (diet) to compartment n (bone); $C_m(t)$ and $C_n(t)$ are the appropriate activity concentrations in diet and bone, respectively, at time t. The models were developed in a form which was appropriate to the results required and are used again in Annex E (Exposures resulting from nuclear explosions).

62. These transfer models are examples of the type of model in which the chain of events is represented by a series of compartments and the transfer processes occur between compartments: these will be called "compartment models". In some cases the compartments have some physical attribute such as representing a given volume of water but this is not an essential requirement of the technique. Other examples of such models are food chain models and some oceanic models. Some compartment models are better suited to predicting time-independent results although many give dynamic results.

63. A simple example of a compartment model is one which has been used to estimate the global dispersion of ^{85}Kr introduced into the northern hemisphere [N1]. Two compartments are assumed, corresponding to the tropospheres of the northern and southern hemispheres. Exchange takes place between the two compartments with a transfer coefficient in each direction of 0.5 a^{-1}. Input is into the northern hemisphere compartment which is assumed to be instantaneously uniformly mixed; the results are expressed in terms of the activity concentration in air as a function of time after the start of a continuous input. The transfer of material between the compartments is described by a set of two equations

$$\frac{d\chi_N}{dt} = \frac{\dot{A}_{o,N}}{V_N} - k_{NS}\chi_N + k_{SN}\chi_S - \lambda\chi_N$$
$$\frac{d\chi_S}{dt} = k_{NS}\chi_N - k_{SN}\chi_S - \lambda\chi_S \qquad (7)$$

where $\dot{A}_{o,N}$ is the rate of input of activity of the radionuclide into the northern hemisphere compartment; V_N is the volume of the northern hemisphere compartment; χ_N and χ_S are the instantaneous activity concentrations of the radionuclides in air at time t after the start of the input; λ is the physical decay constant; k_{NS} is the transfer coefficient from the northern to the southern hemisphere compartment; and k_{SN} is the reverse transfer coefficient between the two compartments.

64. The general solution of compartment models of this type depends on the assumption that the transfer rate of materials between compartments is proportional to the inventory of material in the source compartment and that the rate is governed by a transfer coefficient specific to the two compartments being considered. These relationships can be expressed by the sets of equations

$$\frac{dA_m}{dt} = \sum_{n=1}^{p} k_{nm} A_n - \left(\sum_{n=1}^{p} k_{mn}\right) A_m - \lambda_m A_m + \dot{A}_{o,m} \qquad (8)$$

which apply for two or more compartments; where A_m, A_n are the instantaneous activities in compartments m,n at time t; k_{mn} is the transfer coefficient from compartment m to n; λ_m is an effective transfer coefficient out of the system from compartment m which is used to describe loss of material, e.g., by radioactive decay or transfer to a stable sink; $\dot{A}_{o,m}$ is the rate of input of activity into compartment m; and p is the total number of compartments connected directly to m. These equations can be solved analytically for simple systems or numerically for larger systems.

65. Another type of model is that in which an attempt is made to represent the physics of a real transfer process. Examples of such models are diffusion and advection models in the seas, sediment transfer models in rivers, and trajectory models for airborne dispersion. Although these models are often used to produce results for an eventual equilibrium situation, many of them are inherently capable of producing time-varying outputs.

66. In general the model used should be the simplest type which will produce the required answer and is appropriate to the radionuclide, its mode of release and its environmental behaviour. For natural radionuclides in equilibrium in the environment, where the answer required is the collective absorbed dose rate, then the specific activity model is adequate. For mixtures of artificial radionuclides released to atmosphere and water from nuclear installations, answers are required on maximum absorbed doses to individuals resulting from the combination of all the radionuclides via all the pathways, together with collective absorbed dose rates in different groups of the population and integration of these collective dose rates over both space and time. In that case quite complex models may be needed which are capable of accepting time-varying inputs and giving dose distributions as a function of space and time. It is requirements such as this and the need to predict results well into the future which have led to the recent development of more complex and comprehensive models.

67. In principle all models are based on experimental observations and should be subject to experimental verification, if not of the model form at least of the parameter values. The conclusions of a workshop on the evaluation of models [H1] are that complex models may, because of the descriptive detail incorporated, be accepted as being more realistic and thus more defensible than simpler models. However, without adequate validation, there is no assurance that the predictions of these complex models are any closer to the real situation than those produced by simpler ones.

68. Since the purpose of models is to provide a simulation of reality and the real environment may be conveniently separated into sectors, the various types of models appropriate to each sector of the environment will be described together. In each case the models used by the Committee are described. The sectors of the environment considered are the atmosphere, the land and the waters. These are not isolated because, for example, a discharge into the atmosphere will, for many radionuclides, lead to an eventual input to both other sectors.

69. A problem in reviewing models is the large number of computer programmes in use. A survey by Hoffman et al. in 1977 [H2] identified 83 programmes for the assessment of accidental or routine releases of radionuclides to the environment from nuclear power facilities. Most of the programmes appear to have been developed in relative isolation and only in recent years have there been compilations which attempt to take into account all sectors of the environment. Examples of such compilations are the United States Nuclear Regulatory Commission guides [U4, U5, U6] which are very formal sets of general equations; the models used in the Federal Republic of Germany [F1]; and the comprehensive reports by Killough and McKay [K1] and by the National Radiological Protection Board of the United Kingdom in cooperation with the Commissariat à l'Energie Atomique of France [N1].

B. UNCERTAINTY OF PREDICTIONS FROM MODELS

70. All models are based on knowledge of the real systems being simulated and where possible use data determined empirically. The reliance to be placed on the predictions emerging from models depends on the knowledge of the system and the reliability of *data* used. Both of these aspects are felt by the Committee to be reasonably satisfactory for modelling of radionuclide behaviour. It is because these models for the

transport of radionuclides in the environment are developed more fully than those for other potential contaminants that it is possible to try to determine the uncertainty in their predictions. In simple situations direct verification of model predictions may be possible, but in many cases this will only be practicable for some portions of the model output and for some of the radionuclides being studied. Under these circumstances two techniques are available to investigate the variability of the results. These techniques consist of changing the form of model used and evaluating the differences in predicted results; or varying the input data over a range and evaluating the resultant changes in the prediction. The first technique can only be employed for particular problems where alternative ways of describing the situation can be found; it is not described further here. The second technique can and should be applied to all predictive models and has been insufficiently utilized up to now. This can be used to establish the inherent uncertainty in a prediction based on the model using the empirically determined ranges of input data and to identify those portions of the input data for which variations have the largest effect on the prediction and which therefore should be studied further if there is a need to reduce the overall uncertainty.

71. A particular method of carrying out sensitivity analyses of this type has been developed as part of a general assessment of models [H8, H9, M3, S12]. This technique can be applied to simple multiplicative chain models such as those used by the United States Nuclear Regulatory Commission [U4] and relies on the observation that the central part of the distribution of observed values for many environmental variables follows a log-normal form. In this case the log-normal statistics can be simply propagated through the model [S13]. The results of such studies cannot usually be expressed in a simple form; in general they indicate the probability that actual values will exceed the predictions based on a particular set of data [H9]. The most common method, and the simplest, of carrying out sensitivity analysis is to change the value of one input variable while holding all others constant [H10]. This procedure will not, however, give a complete range of variation in the output from the entire model and requires a very large number of individual calculations for complex models. Methods have been suggested for carrying out analyses in which several variables are changed together; see for example the suggestions by McKay and Bruckner [M4], which rely on some method of sampling output while changing all input variables simultaneously. The results from all such studies are useful in assessing the overall reliability of the model system predictions in comparison with direct observations.

72. In order to assess the collective dose equivalent rate as a function of time after the initiating event it is necessary to make a number of assumptions. Some of these assumptions are of parameters which are predictable with more or less precision depending on the present state of knowledge; an example is the long-term behaviour of radionuclides in the environment. Other assumptions are in principle unknowable and unpredictable as they depend on the presence and on the habits of human populations in the future; examples of such assumptions are population distributions and the uses made of flora and fauna as foodstuffs. Accordingly, the uncertainty of predictive calculations of collective dose equivalent rates in future populations will increase with the length of the time over which the predictions are made.

73. A further source of uncertainty is the relationship between the calculated collective dose rate in the future and the number and severity of health effects presumed to result. It is unlikely that the state of medical knowledge will remain constant and future populations may well have the ability to prevent or at least cure radiation-induced tumours which now prove fatal. This comment may also apply to radiation-induced hereditary effects. For these reasons predictions over tens, hundreds or even thousands of years may be useful guides as to the consequences of present actions but predictions over hundreds of thousands or millions of years are of very little use, except possibly by sensitivity analysis to indicate the range of potential consequences.

74. Although there has been no systematic effort to assess the accuracy of the models used by the Committee, some aspects of certain models have been studied. For example, the atmospheric dispersion model has been assessed by comparison with observed ground level concentrations after releases from elevated sources [C2]. The emphasis was on the accuracy of the prediction of mean values and it was concluded that typically the ratio of the standard deviation of concentrations about the mean, for a given dispersion category, to the overall mean lies in the range of 0.5 to 0.7. The larger ratio refers to conditions dominated by convection and the smaller one to conditions dominated by mechanical turbulence. It was concluded that the most likely error in calculations of the overall mean would come from an incorrect choice of wind speed and stability conditions. Under these circumstances a simple measure of the likely spread in results could be obtained by carrying out calculations for adjacent categories.

75. The models used for assessment of contamination from nuclear explosions are firmly based on observed data and have largely been derived through successive approximations to measurements obtained over a period of decades. These models therefore can be expected to give good predictions of the results of such contamination. There will sometimes be substantial uncertainties in the models for aspects of the environmental transport, especially close to the source, but if these local aspects make only a small contribution to the collective dose commitment the overall prediction will still be reliable. A similar comment applies to globally dispersed radionuclides from nuclear power such as ^{85}Kr.

76. The dietary transfer models described in chapter V are more difficult to verify, are more variable in time and space and have a more tenuous link with direct measurements. Sensitivity analyses of these models are being carried out but are not yet available. Some comparisons of portions of the model with observed values have been reported, for example the comparison of the predictions of the soil migration model with measurements of the migration of single deposits of plutonium in various soils [N1]. The results of this limited comparison showed agreement within a factor of two.

77. The models used for aquatic dispersion are all very much simplified even for restricted systems such as rivers. The general tendency of physical processes in aquatic systems is towards the well mixed average concentration, which is the same tendency as exhibited by the models. The major departures are in the processes which tend to perturb this situation and parti-

cularly affect the radionuclide transfer to man, such as sorption onto sediments or bioconcentration.

78. There has been a tendency to accept the values generated by complex modelling techniques uncritically and ascribe more accuracy to the predictions than is justified. This is now being challenged and the Committee recommends that wherever possible some suitable technique should be used to assess the overall uncertainty associated with predicted results from all types of models and that this uncertainty be reported together with the prediction.

IV. ATMOSPHERIC TRANSPORT MODELS

79. The transport of radioactive material released into the atmosphere is controlled by the normal atmospheric mixing processes. If the material is in the form of large particles which fall rapidly under gravity then most will settle close to the production point; small particles will move with the air masses, as will gases. The major mixing and transport processes which are incorporated into mathematical models are diffusion and advection. These large-scale mixing processes give rise to the distribution in the atmosphere of naturally-occurring cosmogenic radionuclides and of radionuclides released by atmospheric nuclear explosions. They are described briefly in Annex E (Exposures resulting from nuclear explosions).

80. For releases from positions near ground level models have been developed using two main approaches: trajectory tracing, in which discrete releases are followed along the wind direction; and statistical models, in which the activity concentration in the airborne plume containing the radionuclides released is described as a function of distance in the direction of the wind. While the trajectory models such as those in which successive very short duration releases are individually traced through a time-varying wind velocity field [H3, S3] are capable of treating complex situations and even operating in real time, the main concern of the Committee is with the relatively long-term average results of routine releases to the atmosphere. For these calculations the statistical models are adequate. As the plume containing the radionuclides travels downwind, the population will be exposed to direct radiation from the plume and to intake of radionuclides by inhalation. For radioactive materials other than gases both wet and dry deposition processes will result in radionuclides being deposited on the ground and on vegetation. These deposited radionuclides will cause external irradiation, enter food and drinking water supplies and become resuspended to cause a further airborne hazard. Comprehensive models need to take account of all these routes, which are described in chapter V.

A. MODELS FOR LOCAL AND REGIONAL TRANSPORT FROM A DEFINED POINT OF RELEASE

81. There are some circumstances in which it is necessary to assess the local transport of radionuclides released into the atmosphere from a defined point. This occurs in particular when dealing with releases from known nuclear sites such as reactors or reprocessing plants of which there are only a small number.

82. It is sometimes possible to derive an empirical relationship between the average or integrated activity concentration in air at particular locations and the discharge rates or total discharges in a given time of radionuclides. These relationships are sometimes referred to as empirically determined dispersion coefficients and are used for some well-characterized nuclear sites. This procedure is used, for example, in deriving doses to local populations around the Pickering reactor in Canada, referred to in Annex F (Exposures resulting from nuclear power production).

83. The dispersion of materials released into the atmosphere is controlled by atmospheric diffusion, a process that depends on the state of the atmospheric turbulence over any area and at the relevant time. It has been found useful in practice to develop empirically based turbulence classification schemes using easily observed quantities for characterization such as cloud cover, wind speed and insolation. The most widely used systems are based on the one proposed by Pasquill [P2, P3] in which seven weather categories, A to G, are defined in order of increasing atmospheric stability, as shown in Table 5. Category A represents the most unstable conditions, B and C less unstable, D neutral, E and F stable, and G very stable. Rainfall is only considered possible in categories C and D. The results of the dispersion calculations described later in this section are normally generated for a series of release heights, for each stability category and for the situations C + rain and D + rain. These results are then combined in the appropriate frequencies observed at the place of interest. Many other methods for determining the category or defining stability categories have been proposed and are in use; these are reviewed, for example, by Gifford [G1] and by Hoffman [H1].

84. The most useful and commonly used statistical model is the Gaussian plume equation initially proposed by Sutton [S4]. This is based on an analytical solution of the diffusion equation under the assumptions of constant wind speed and direction, no wind shear, flat topography and Fickian diffusion. The basic equation in a generalized form, taking into account the reflection from the ground, can be expressed as [N1]:

$$\chi_a(x, y, z) = \frac{\dot{A}_o}{2\pi\sigma_y\sigma_z\bar{v}} \exp\left(\frac{-y^2}{2\sigma_y^2}\right) \left[\exp\frac{-(z-h)^2}{2\sigma_z^2} + \exp\frac{-(z+h)^2}{2\sigma_z^2}\right] \qquad (9)$$

for the activity concentration corresponding to a given release rate; the integrated activity concentration from a release is obtained by substituting $\tilde{\chi}_a$ for χ_a and A_o for $\dot{A}_o$ in equation (9), where $\chi_a(x,y,z)$ and $\tilde{\chi}_a(x,y,z)$ are the activity concentration and the time integrated activity concentration per unit volume of air at the point (x,y,z); σ_y and σ_z are the standard deviations of the plume horizontally and vertically; A_o is the activity released; $\bar{v}$ is the average wind velocity at 10 m above the ground; h is the effective height of release; x is the downwind distance; and z is the height above the ground of the sampling position. The origin of the co-ordinate system is at ground level beneath the discharge point. In the derivation of equation (9) it is assumed that diffusion in the x-direction can be ignored compared with transport

by the wind for releases lasting a finite time. The standard deviations σ_y and σ_z are not defined by the mathematical assumptions but are determined from the atmospheric stability category as functions of the downwind distance. There are many ways of obtaining these values, and Vogt [V1] has produced a useful set of comparisons.

85. For prolonged releases there will be fluctuations in wind direction which lead to a more uniform activity concentration across the plume. In this situation the cross-wind Gaussian shape of the activity concentration distribution is replaced by a uniform distribution. Taking the angle subtended by the sector at the point of release as ϑ the activity concentration is given by

$$\chi_a(x, z, \vartheta) = \frac{A_o}{\sqrt{2\pi}\,\sigma_z\,\vartheta\,x\bar{v}} \left[\exp\frac{-(z-h)^2}{2\sigma_z^2} + \exp\frac{-(z+h)^2}{2\sigma_z^2}\right] \qquad (10)$$

and as before the integrated activity concentration is obtained by substituting $\tilde{\chi}_a$ for χ_a and A_o for $\dot{A}_o$ in equation (10), where $\chi_a(x,z,\vartheta)$ and $\tilde{\chi}_a(x,z,\vartheta)$ are the activity concentration and the time integrated activity concentration per unit volume of air at the points (x,z) across the sector of angular width ϑ. In many situations only the ground level activity concentration is required; this is obtained by setting $z = 0$ in equation (10). Equations (9) and (10) apply for a single stability category.

86. The accuracy of calculations based on equations similar to (9) and (10) has been assessed by Hoffman et al. [H1], and it was pointed out that they are generally based on measurements at distances less than a few tens of kilometres from the source so that extrapolations to greater distances must be made cautiously. In addition, the calculations are based on assumptions such as steady meteorological conditions and flat terrain. However, the calculated results are probably accurate within a factor of ten for relatively simple situations. Improvements to the basic formulation given in equations (9) and (10) can be made to achieve a closer approximation to the complexities of actual terrain. Many of these are discussed by the United States Nuclear Regulatory Commission [U4, U5, U6], by a joint study of the National Radiological Protection Board of the United Kingdom and the Commissariat à l'Energie Atomique of France [N1] and by a United Kingdom working group [C2].

87. When material is discharged from an elevated source, the plume will eventually reach the ground. Thereafter the plume is reflected so that the radionuclides in it are dispersed back up into the air. Where an inversion or boundary layer exists, the dispersed radionuclides are trapped between that and the ground. Reflections will in this case occur both at the ground and at the boundary layer. In the absence of reflections the plume would spread in the vertical plane to a size determined solely by σ_z at the distance of interest. The effect of introducing reflections is that the airborne activity concentration must be obtained by summation of contributions from many points over the unreflected radionuclide distribution across the plume. These may be represented by a series of virtual sources and the mean time integrated activity concentraction is obtained by summation. In most cases this series converges rapidly and can be summed to any desired mathematical accuracy, although the results are subject to the uncertainties inherent in this modelling approach.

88. The activity concentrations derived from equations (9) and (10) apply to the dispersion of radionuclides which are not removed from the plume as it travels downwind. A number of processes may act to remove the airborne radionuclides, in particular radioactive decay and dry or wet deposition. The equations given above need to be modified to take these processes into account. This is most simply achieved by modifying the initial source activity A_o to allow for depletion. This is simple for radioactive decay, except where the daughter radionuclide concentration is being considered but more complex for the deposition processes.

89. Radionuclides are removed from the plume by rain falling through it. Precipitation is intermittent and the true interaction with rain is very complex. The simplifying assumption made is either that there is no rain or that it rains for the duration of the dispersion; in the latter case the effects of rain are estimated by the use of a washout coefficient. As washout removes any particulate radionuclide equally throughout the entire vertical extent of the plume, the removal rate at any distance from the source depends only upon the radionuclide concerned and the total activity reaching that distance and not upon the vertical distribution of the radionuclide in the cloud.

90. Radionuclides are also removed from the plume by many other processes; these include impaction with the underlying surface or obstacles such as vegetation on it, absorption from the air by plants and chemical reactions with surfaces. The rate at which radionuclides are transferred from the plume to the ground or vegetation surface can be modelled using the concept of a deposition velocity. The deposition velocity, v_d, is defined as the quotient of the activity of the radionuclide deposited on the surface per unit area and unit time to the concentration of activity in air per unit volume above the surface. Removal by this process therefore depends on the activity concentration in air immediately above the surface. This idealized mathematical description is a poor representation of the actual, very complex processes and it cannot easily be correlated with experiments in which the concentration of activity in air has to be measured some distance above the surface and in which the activity deposited on the surface has to be averaged over a finite depth during measurement even for a flat surface. The description for complex surfaces such as vegetation is even less satisfactory.

91. The calculation of activity concentrations in air by the methods outlined above is moderately complex but the complexity is necessary in a general methodology for dealing with the many different radionuclides emitted from installations such as nuclear reactors or nuclear fuel reprocessing plants. In some circumstances where only single gaseous radionuclides are involved for average weather conditions and no account need be taken of the height of release, deposition, radioactive

decay or weather conditions it is possible to use a simple approximation such as

$$\tilde{\chi}_a(x) = A_o f \left(\frac{x}{x_1}\right)^{-p} \qquad (11)$$

where $\tilde{\chi}_a(x)$ is the time integrated activity concentration of the radionuclide in air at a distance x from the release point; $x_1 = 10^3$ m, is a normalization distance; A_o is the source activity; f is a coefficient with dimensions s m^{-3}; and p is a numerical exponent. For most weather categories and release heights this approximation, taking f as 3 10^{-6} s m^{-3} and p as 1.5, is within a factor of ten of the more rigorous plume calculation for moderate release heights and distances out to about 100 km. A comparison is shown in Figure II with the results

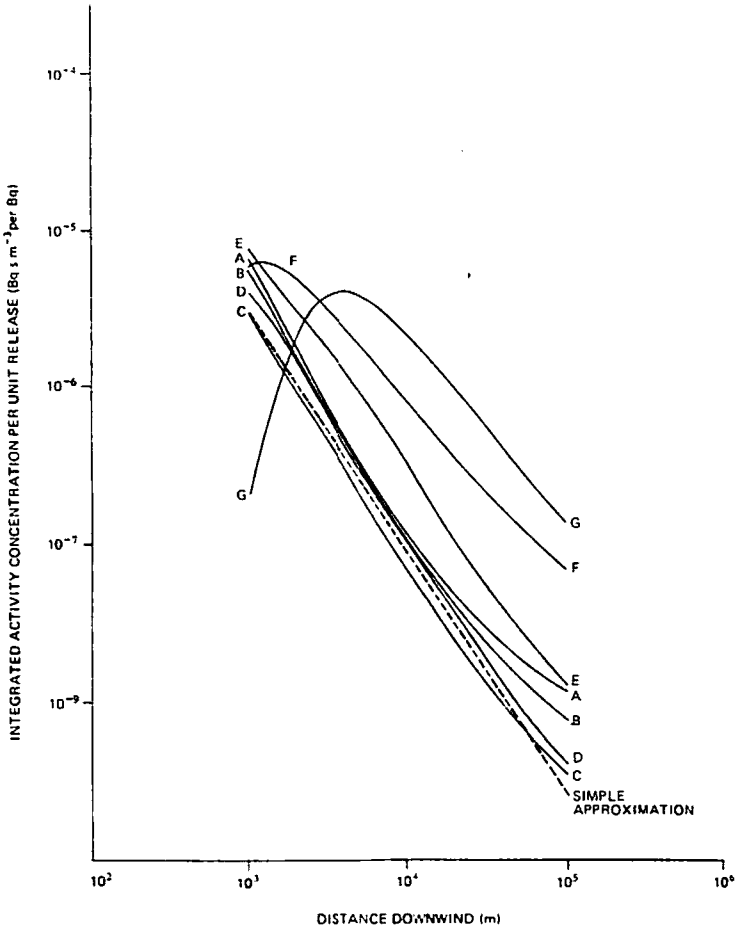

Figure II. Ground level integrated activity concentration per unit release as a function of distance downwind for uniform horizontal dispersion into a sector of angular width π/6 for a 30 m height of release in various weather categories [C2] compared with the simple approximate dispersion model taking f = 3 10^{-6} s m^{-3}, $x_1 = 10^3$ m, and p = 1.5

of calculations of the on-axis integrated activity concentrations for uniform horizontal dispersion into a sector of angular width π/6 in each weather category from an effective release height of 30 m [C2]. The stack height of 30 m is only chosen for illustration. The choice of height will have little effect on collective dose estimates but will considerably affect estimates of the maximum individual doses close to the discharge point. In comparisons with calculations of average integrated activity concentrations for dispersion in all directions a value of f = 3 10^{-7} s m^{-3} is more appropriate; this value is used in the calculations for Table 6 which compares the time integrated activity concentrations in air predicted by the dispersion model for various distances, with those predicted by simple global models. A better approximation for continuous release would be obtained by changing the exponent p from 1.5 to 1.2 in equation (11); however a value of 1.5 is often used.

92. For many purposes the annual integrated activity concentration in air is needed as a function of distance from the discharge point. The expression for this is given in polar coordinates by [N1]

$$\tilde{\chi}_a(x, \vartheta) = N A_o \sum_P \tilde{\chi}_o(P, x, \vartheta) f(\vartheta, P) \qquad (12)$$

where $\tilde{\chi}_a(x, \vartheta)$ is the annual integrated activity concentration in air at a distance x in a sector in the direction ϑ; $\tilde{\chi}_o(P,x,\vartheta)$ is the integrated concentration of the radionuclide per unit release in a dispersion category, P; $f(\vartheta,P)$ is the fraction of time a particular stability category, P, exists with the wind in the sector with direction ϑ and of width $2\pi/N$; N is the number of sectors in the windrose.

93. The atmospheric dispersion models described in this section apply to the behaviour of the radioactive

plume immediately after release and as it travels downwind. The model forms and parameters are most reliable for distances up to a few tens of kilometres although they are commonly used for distances up to 100 km. There are as yet no suitable general models which describe the behaviour of released radionuclides in the atmosphere at distances from the release point of thousands of kilometres. This is a distance at which calculations based on dispersion of plumes are likely to be increasingly in error but where the activity concentrations may not have approximated to the levels given by the global dispersion model discussed in the next section. For many relatively short-lived radionuclides or those with sufficiently large deposition velocities, this is of little consequence as the activity in the plume will be depleted to relatively very low percentages of the initial activity by distances of the order of 1000 km. For example, it has been shown that for long-lived radionuclides with a deposition velocity of 5 10^{-3} m s^{-1} at most 4% of the material remains in the plume after 3000 km in category D conditions assuming no rain [N1], while under all other conditions whether or not rain is assumed essentially none will remain at that distance.

B. GLOBAL MODELS

94. The radionuclides released from ground level point sources whose atmospheric dispersion need to be considered on a global basis are the noble gases with half-lives longer than a few days, of which ^{85}Kr is the most important example, and long-lived radionuclides with very low deposition velocities such as certain organic forms of ^{129}I . Other radionuclides which remain in the environment such as ^{3}H and ^{14}C and the bulk of the ^{129}I reside principally in the aquatic and terrestrial compartments and the models for these are described in the appropriate chapters. Radionuclides introduced into the atmosphere by nuclear explosions are widely distributed as a result of their mode of introduction and thus have also to be modelled on a global basis.

95. As has been described in chapter III (paragraph 57), for many purposes the Committee uses direct measurements of activity concentrations to obtain estimates of collective doses from globally distributed radionuclides from natural sources or fallout from nuclear explosions. For some nuclides such as ^{239}Pu insufficient direct measurements are available and therefore estimates are based on observed ratios of the radionuclide concentration in air to that of other radionuclides, especially to ^{90}Sr. Nonetheless comparisons are made with more complex models of the atmosphere such as the 12-compartment model developed by Bennett [B10] and this model was used directly to estimate the activity concentrations of ^{241}Am in surface air.

96. Some radionuclides such as ^{85}Kr will remain in the atmosphere and for the present there seems no alternative, for the purpose of estimating doses from the dispersion of such materials, to extending the models described out to distances of about a thousand kilometres and then making an abrupt transition to a global model. That this results in few difficulties is apparent from Table 6 in which typical time integrals of the activity concentrations in air at distances of 10, 100 and 1000 km for uniform dispersion in all directions from the dispersion models [C2] are compared with the predictions of simple global mixing models. The uncertainty in the prediction of collective dose commitments is less than might be thought since the results in, for example, Annex F (Exposures resulting from nuclear power production), show that the local and regional component contributes only about 10% of the collective dose commitment per unit discharge of ^{85}Kr.

97. If the simple two-compartment model described in chapter III (paragraph 63) is used with input into the northern hemisphere compartment and transfer coefficients of 0.5 a^{-1} then ^{85}Kr becomes uniformly dispersed within a few years. This model is used in Annex F (Exposures resulting from nuclear power production) for ^{85}Kr inputs from nuclear power production but in Annex E (Exposures resulting from nuclear explosions) the simpler approximation of instantaneous uniform dispersion is again used, as it was in Annex C (Radioactive contamination due to nuclear explosions) of the 1977 report [U1]. The time integrals of the activity concentrations in air from the two models per unit activity input are 1.0 10^{-10} and 1.2 10^{-10} Bq s m^{-3}/Bq from Annexes F (Exposures resulting from nuclear power production) and E (Exposures resulting from nuclear explosions), respectively.

C. DOSE CALCULATION

98. Given the concentrations of radionuclides in air as predicted by the various models, then a number of pathways exist through which man can be exposed. The major pathways are direct irradiation from the cloud of radioactive material, direct inhalation from the cloud, inhalation of resuspended material, and ingestion via terrestrial or aquatic food chains. The first three will be considered here, the last two are more conveniently discussed in the chapters on the terrestrial and aquatic environment in sections V.B and VI.D, respectively.

99. If the specific activity model referred to in section III.A is used, then no direct account is taken of the actual pathways by which activity enters the body. It is merely assumed that the activity concentration per unit mass of the stable element in the relevant organs or tissues are equal to the corresponding activity concentration in an environmental material, in this case air, and the absorbed dose rates are obtained from these activity concentrations.

1. Direct irradiation from the cloud

100. Several systems of equations and nuclear data are available to perform these calculations, as for example those used by the United States Nuclear Regulatory Commission [U4] or by the National Radiological Protection Board and the Commissariat à l'Energie Atomique [N1]. Provided that care is used in selecting the data and avoiding inappropriate models, such as the semi-infinite cloud at short distances, only slightly different results will be obtained from different calculation systems.

101. When the radionuclide is uniformly distributed in the atmosphere or the photon energy is sufficiently low that this is a reasonable approximation over the volume of a plume, then the simplest calculational method is the semi-infinite cloud model. This is based on the radiation from the cloud being in electronic equilibrium so that the energy absorbed by a given volume element equals that emitted by the same

element. For a point located at ground level only half the space contributes to the dose, so that the energy absorbed is divided by two. The absorbed dose rate in air is then given by

$$\dot{D}_a = 0.5 \frac{k}{\rho_a} \bar{\chi}_a \sum_{i=1}^{n} F_i E_i \qquad (13)$$

where $\dot{D}_a$ is the absorbed dose rate in air; $\bar{\chi}_a$ is the average value of activity concentration of the radionuclide in the cloud; ρ_a is the mass density of air; F_i is the fraction of photons of initial energy E_i emitted per disintegration; and k is a conversion coefficient from energy deposition per unit mass and unit time to absorbed dose rate, which although strictly not needed if the energy is expressed in joules, is sometimes given as Gy h^{-1}(MeV kg^{-1} s^{-1})$^{-1}$. A modified version of this model is used for beta irradiation of the skin.

102. If the distribution of the activity concentration in the plume is sufficiently non-uniform to invalidate the above approach, then a finite cloud model must be used. This involves simulating the cloud by a number of small volume sources and integrating over these sources. The calculation proceeds by finding the photon flux density, scattered and unscattered, for a particular decay energy, summing over all the decay energies for the radionuclide of interest and then carrying out a conversion to absorbed dose. The basic expression for the photon fluence due to the fraction F_i of photons of energy E_i emitted per disintegration is [N1]

$$\Phi_i = \int_V \frac{X_V F_i B_{en}(E_i, \mu_i x) \exp(-\mu_i x)}{4\pi x^2} dV \qquad (14)$$

where Φ_i is the photon fluence; X_V is the concentration of the atoms of each radionuclide in volume element dV; μ_i is the linear attenuation coefficient; x is the distance from the volume element dV; $B_{en}(E_i,\mu_i x)$ is the energy absorption build-up factor at a distance, x, for a radiation of initial energy, E_i, having an attenuation coefficient, μ_i. The integration is carried out over all space. The integral is evaluated numerically, the calculations in Annex F (Exposures resulting from nuclear power production) being based on the computer code developed by Jones [J3].

103. The conversion from absorbed dose in air to dose equivalent in tissue has already been discussed in general terms in section II.A.1. When the absorbed dose in air is the result of a calculation such as described in this section, then there are sufficient data on the photon energy spectrum to use more precise conversions. These conversion coefficients have been derived for adults [N1] from the work of Poston and Snyder [P1] based on a semi-infinite cloud model and are given in Table 7. Similar conversion coefficients for electrons emitted by the radionuclides of interest have been derived assuming an inert layer thickness on the surface of the body of 70 μm and are given in Table 8. The imprecise nature of the estimation of the dose in skin from electrons must be stressed. This imprecision arises from theoretical difficulties associated with the estimation of electron absorption in the epidermis and also from practical considerations such as absorption by clothing or nearby objects [N1].

2. Direct inhalation from the cloud

104. Calculation of doses from direct inhalation from the cloud only depend upon data concerning the integrated activity concentration in air over the period of exposure, the breathing rate and the committed absorbed dose per unit activity inhaled. The first depends on the circumstances (i.e., whether the exposure is to an isolated plume or to an annual average concentration) and is assessed as described earlier in this chapter. The breathing rates chosen by the Committee are normally taken to be similar to those specified by the ICRP [I6]; for example, a mean adult breathing rate B of 20 m^3 d^{-1} is taken in Annex F (Exposures resulting from nuclear power production). The committed absorbed dose per unit activity inhaled is generally obtained from the tabulations given by ICRP [I4, I11].

105. A 'very simple model is used in Annex C (Technologically modified exposures to natural radiation) to estimate the contribution of the inhalation pathways to the collective dose commitments resulting from the atmospheric release of a given radionuclide. The relationship between the activity A_o associated with the release of the radionuclide concerned and the collective dose commitment M_q^c in organ or tissue q is given by the expression

$$M_q^c = \frac{A_o}{v_d S} S\delta_N B \frac{D_q}{I_{ih}} \qquad (15)$$

where A_o/v_dS is the integrated activity concentration of the radionuclide in ground level air, obtained simply as the activity released divided by the area of the deposition region S and by the deposition velocity v_d; $S\delta_N$ is the population affected, which is the product of the area of the deposition region S and of the population density δ_N. The areal dependence is removed by the product of the quantities A_o/v_dS and $S\delta_N$; B is the individual adult breathing rate; D_q/I_{ih} is the committed absorbed dose in organ or tissue q per unit activity inhaled.

3. Direct inhalation from resuspended material

106. The resuspension of materials from surfaces depends on many conditions such as the physical characteristics of the surface, the age of the deposit, the strength of the wind and other disturbances. For a given radionuclide, the real relationship between the activity concentration in air per unit volume and the activity per unit surface area is extremely complex and many models of varying degree of complexity have been proposed. The simplest of them is the model implicit in the use of the "resuspension factor" which is defined as the quotient of the resuspended activity concentration in air per unit volume to the activity per unit area in the surface layer. If this factor is taken as a constant, it implies a time-independent relationship between those two quantities irrespective of the other parameters referred to earlier or that the model is only valid at one specific time; it further implies that the concentration of activity in air results only from the activity on the surface in the immediate neighbourhood. The problems involved in using this model have been reviewed by Linsley [L2].

107. As the deposited material weathers, it becomes more closely associated with the soil and the activity concentration profile gradually extends down into the soil. Only the top layers of soil are available to be resuspended and the net effect is that the activity concentration in air from resuspension falls off with time following a given deposition event. Such behaviour can be represented mathematically by a time-dependent resuspension factor, which then has to be defined in terms of the instantaneous values of the relevant quantities. This approach has been used with some success [A2, U7] in models which assume different initial resuspension factors in the range from 10^{-4} to 10^{-6} m^{-1}, but all converge to a value of the order of 10^{-8} to 10^{-9} m^{-1} for times longer than about 20 years after deposition. Healy [H4] has suggested that the activity concentration in air declines at a slower rate and to a lesser extent than the previously cited models would imply, but this suggestion appears to be based on very conservative interpretations of the observed results. Comparison of models with observations is complicated by inconsistency of those reporting data in assessing the depth of soil over which the contamination is averaged and which is assumed to be available for resuspension.

108. The Committee has decided that the most appropriate model at present is a time-dependent resuspension factor and has applied this in Annex F (Exposures resulting from nuclear power production). The value of the resuspension factor immediately after deposition is uncertain and will depend on the precise conditions of the land surface, whether it is desert or pasture, wet or dry, etc.; a value intermediate in the reported range of 10^{-5} m^{-1} is adopted. This initial resuspension factor is assumed to decline exponentially over about 2 years to a value typical of an aged deposit of 10^{-9} m^{-1}. Direct observations of the time dependence of resuspension factors are limited to about a 20-year period after deposition and therefore any estimates of the subsequent behaviour must be tentative. Nonetheless it seems likely that there will be some further decline in availability and a second exponential decrease with a half-life of about 100 years is assumed. The resuspension model is therefore given by

$$\kappa(t) = \kappa_1 \exp[-(\lambda_1 + \lambda_2 + \lambda)\,t] + \\ + \kappa_2 \exp[-(\lambda_2 + \lambda)\,t] \qquad (16)$$

where $\kappa(t)$ is the resuspension factor defined as the quotient of the activity concentration in air to the activity concentration in the top 1 cm of soil at time t; κ_1 and κ_2 are the initial and intermediate values of the resuspension factors taken as 10^{-5} and 10^{-9} m^{-1}, respectively; λ_1 and λ_2 are the decay constants for the initial and longer term decline in the resuspension factor; λ is the physical decay constant of the radionuclide of interest. The values taken for λ_1 and λ_2 are $1.46\ 10^{-7}$ s^{-1} (4.6 a^{-1}) and $2.2\ 10^{-10}$ s^{-1} (0.007 a^{-1}), respectively. More complex models have been developed which take into account such factors as the size of the contaminated area, the surface roughness and the wind speed [H5, H6]. At present, however, they can only be applied if there is site-specific information while no generally applicable model taking account of such factors is yet available.

109. Another simple approach to the modelling of resuspension is to assume that particulates in air and surface soil contain the same proportion of the contaminant. Then, given a knowledge of the average particulate content of the air and the specific activity of the surface soil, the concentration of activity per unit mass or volume of air can be derived [A2, U8]. The main problem with this model is the assumption that the contaminant and the soil are resuspended equally. This is almost certainly untrue for fresh deposits and even for aged deposits requires empirical correction factors [U8]. However, for material which is uniformly mixed in the surface soil, such as long-lived naturally-occurring radionuclides, these problems do not arise, therefore the model is used in Annex B (Exposures to natural radiation sources) for natural radionuclides such as uranium. The particulate content of air is taken as 50 $\mu g\ m^{-3}$; this is a representative global value for ground level air and corresponds to a resuspension factor of about $3\ 10^{-9}$ m^{-1}. There may, however, be some enrichment of the activity concentration of certain radionuclides in resuspended material; this should be taken into account if it is found to occur. Subsequent calculations of doses are carried out as in section IV.C.2 for direct inhalation from the cloud.

4. Population distribution models

110. To calculate the distribution of individual doses from radionuclides dispersed in the air it is necessary to know or to assume the population density as a function of position or distance from the source. If the distribution of individual doses is not needed, and only the collective dose is required without any indication of its distribution among the exposed population then it may be calculated directly from the total deposition, assuming some fraction of it is inhaled or ingested by the total exposed population. The simplest assumption which can be made of the population distribution is that it is uniform and a population density of 100 km^{-2} has been taken for some purposes in Annex C (Technologically modified exposures to natural radiation).

111. Population distribution weighting has also been used to modify the physical distribution of radionuclides in calculating dose commitments from fallout. This procedure was described by the Committee [U2] and consists of weighting the integrated deposit of a radionuclide in a latitude band by the percentage of the world population in that latitude band. The population distribution is given in Table 9 and is used in Annex E (Exposures resulting from nuclear explosions). The resultant has been referred to as the population-weighted deposition of the radionuclide.

112. For calculations of local and regional doses, particularly if they are to yield the numbers of people receiving doses within given ranges as well as the collective dose, the population distributions may need to be fairly detailed as are those taken in Annex F (Exposures resulting from nuclear power production) around some model sites. Two examples are shown in Table 10 for the distribution around a model reactor site and a model uranium mining and milling site. The total population out to 2000 km is in each case about $2.5\ 10^{8}$ but the average population density up to 100 km is only 3 km^{-2} for the mining site compared with 300 km^{-2} for the reactor site. The average population density out to 2000 km is 20 km^{-2} for both sites. Another example of this type of data generation is the placing of the population distribution of the countries of the European Community into a computer programme on an approximate 10 km square grid, using census data [N1].

113. To calculate collective dose commitments it is necessary to specify the population distribution and magnitude as a function of time. In most cases it is implicitly assumed that the distribution and magnitude at the start of the exposure continues indefinitely. In Annex E (Exposures resulting from nuclear explosions) and Annex F (Exposures resulting from nuclear power production) that assumption is used for relatively short-lived radionuclides such as ^{3}H and ^{137}Cs. For current inputs of activity a world population of $4\ 10^{9}$ is taken, but for inputs in the 1960s the value at that time of $3.2\ 10^{9}$ was taken. For long-lived radionuclides such as ^{14}C and ^{129}I it is assumed that the world population increases to a value of 10^{10} and then remains constant.

V. TERRESTRIAL MODELS

114. The simplest methods for calculation of collective doses from deposited material are based directly on empirical relationships between measurements of activity concentrations in human organs or tissues and in environmental materials such as soil or foodstuffs. These have been discussed in chapter III and will be covered in more detail in section V.B. They are appropriate either for individual doses where specific data are available or for collective doses when broad average values are required and there is an adequate coverage of measurements. This procedure is used in Annex B (Exposures to natural radiation sources) for doses from naturally-occurring radionuclides. In many cases, however, the development of models based on the measurements can give more confidence to extrapolations to other situations and to predictions. In cases where direct measurements are not available then models may be the only means of assessing the doses to people.

115. As described in chapter III, the Committee developed models for the transfer of material through food chains in order to assess the doses resulting from radioactive fallout from nuclear explosions after deposition. The formalism developed by the Committee relates the infinite time integrals of appropriate quantities in successive compartments of the environment; this differs from that used in other models although the concepts are similar. Models of this type have been developed to assess doses from direct consumption of vegetables and intake via animals and animal products and are used in Annex E (Exposures resulting from nuclear explosions). Terrestrial transfer models are of two general types, time-independent models applicable to chronic conditions of radioactive release and dynamic models applicable to time-varying behaviour after accidents or isolated releases. This distinction is the same as that made by ICRP between the concentration factor and systems analysis models [I7]. Often, dynamic models can be extended to long times when they should approximate to time-independent models.

116. The most widespread contamination of the surface of the ground arises as a result of deposition of airborne radionuclides. The models required are similar whether the source is fallout from nuclear explosions or discharge from nuclear installations. There are many pathways by which deposited radionuclides can cause irradiation of man but not all of them are of importance for all radionuclides. The simplest mechanism is direct irradiation from the deposits on the ground but even this will be affected by the movement of deposited activity down from the surface soil into deeper layers. Radionuclides can also enter food chains by contamination of the surfaces of human food crops, through root uptake or indirectly through contamination of animal food crops. All these routes must be considered.

117. If the rates of movement of radionuclides and the integration periods over which results are required are such that the situation can be regarded for practical purposes as in quasi-equilibrium, i.e., such that the time variations can be ignored without introducing significant errors, then the models for assessing the concentrations of radionuclides in each compartment can be time-independent. Most models of this type use empirically derived transfer coefficients to calculate the radionuclide concentrations in selected compartments along each pathway. Several of these models in use for transfers of radionuclides through the environment [S5] are developed from the initial models incorporated in the computer programme HERMES [F2], but in general they are simple models incorporating only a few compartments and in some cases only a few pathways. For example, the programme FOOD [B3], which was developed for irrigation and its extension to include direct deposition which is the basis of the model for calculating nuclide concentrations in vegetation in the United States Nuclear Regulatory Commission Guide [U4] takes account only of direct foliar retention and root uptake.

118. The result given by each of these models is the equilibrium concentration of radionuclides per unit mass or volume in an end compartment, for example vegetation, for a continuous rate of deposition of activity onto the ground surface. The results may therefore be expressed as the ratio between the concentrations of activity in one compartment of the environment and the next compartment when these have reached equilibrium. This procedure is therefore formally identical to the use of transfer coefficients by the Committee in the context of fallout, where the ratio is that of the time integrals of activity.

119. Dynamic models also present the transfer pathways as a series of interconnected compartments, but the activity in each compartment is allowed to be a function of time and the transfers between compartments are represented as rates. A typical example of such a model is the programme TERMOD [B4] which is shown in diagrammatic form in Figure III. Models of

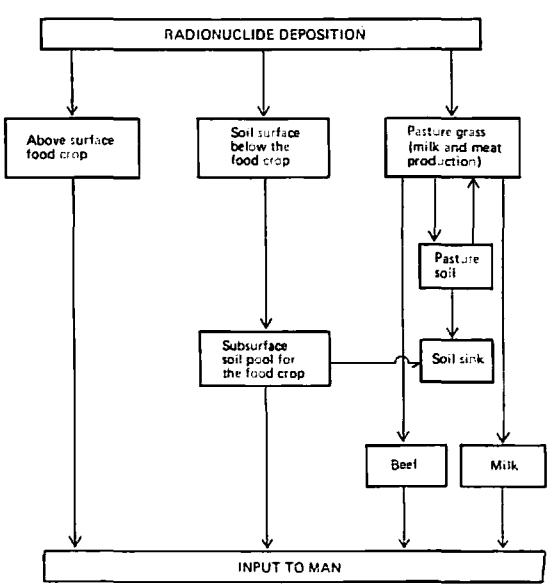

Figure III. Compartments in the TERMOD computer programme [B4]

this type can deal with pathways in parallel as well as in series, can allow for interconnections between different pathways and can take account of feedback routes such as the movement of activity from surfaces of pasture grass into the soil and back into the grass via root uptake. Although models of this type have many advantages and provide a more accurate qualitative description of the real situation, being particularly useful in assessing the consequences of accidental releases of activity, they require a very large amount of data as input values without giving necessarily more reliable answers than simpler techniques. They have however been used in Annex F (Exposures resulting from nuclear power production) for the assessment of doses from releases of activity to the environment.

A. EXTERNAL IRRADIATION FROM DEPOSITED RADIONUCLIDES

120. The most direct method for ascertaining the absorbed dose rate in air above a surface incorporating radionuclides, or on which radionuclides have been deposited, is by measurement. This is the normal method when estimating exposures to naturally-occurring radionuclides and has been the technique used for fallout radionuclides. Local and countrywide surveys for this purpose are described in Annex B (Exposures to natural radiation sources) and Annex E (Exposures resulting from nuclear explosions). However, in many situations direct measurements of dose rates from deposited radionuclides cannot be made because of the relatively much higher dose rate from natural radionuclides; absorbed dose rates must then be calculated from a knowledge of the activity and distribution of the radionuclide in and on the ground.

121. The simplest way to calculate the dose rate in air above a contaminated surface is to assume that this is an infinite plane source with the activity uniformly distributed on the surface. This method is appropriate for deposits with a short effective half-life on the soil surface, which includes most fallout radionuclides, and was used in Annex C (Radioactive contamination due to nuclear explosions) of the previous report of the Committee for all such nuclides except ^{137}Cs [U1]. Standard formulae are available for such calculations. In the case of ^{137}Cs from fallout the distribution with depth in the soil was assumed to be exponential with a mean depth of 3 cm. The same methods are used in Annex E (Exposures resulting from nuclear explosions).

122. When considering the naturally-occurring primordial radionuclides, the distribution in the soil may be taken to be uniform with depth. This distribution is also appropriate for ploughed land since in this calculation it makes little difference how deep the contamination is, provided it is assumed to be uniform to at least 30 cm [B5]. Standard methods are again available [N1] and are used where appropriate in Annex F (Exposures resulting from nuclear power production).

123. Intermediate between these extremes is the situation where the radionuclide has penetrated the ground but not to such an extent that it can be considered uniformly distributed. In this situation models are required to predict the concentration profile which may vary with time and to calculate the resultant dose rate. A simple model of this type which does not include variation with time is the assumption of an exponential distribution with depth of ^{137}Cs from fallout. A more complex time-varying model [N1] is used in Annex F (Exposures resulting from nuclear power production) in which the soil is divided into compartments, with depths of 0–1 cm, 1–5 cm, 5–15 cm, and 15–30 cm. Each compartment is well mixed, deposition is assumed to be into the top compartment and activity is lost from the system out of the bottom compartment. Transfers downwards are by simple transfer coefficients and do not vary with time but may be different for different chemical elements.

124. The absorbed dose rates in the human organs or tissues of interest can be assessed from the absorbed dose rates in air, taking into account the mass energy absorption in the body tissues, the depth transmission, the backscatter and the degree of isotropy (see the discussion in paragraphs 23 to 27). In Annex A (Concepts and quantities in the assessment of human exposures) of the 1977 report [U1], the Committee adopted a value of 0.82, which includes all the factors mentioned, for the ratio between the absorbed dose rate in the body and the absorbed dose rate in air outdoors, based on the work of Bennett [B1] and a value of 0.69 indoors based on Spiers and Overton [S1]. It now appears (paragraph 27) that the most appropriate average value of the quotient of effective dose equivalent rate to absorbed dose rate in air for males and females for use in this report is 0.7 Sv Gy^{-1} for environmental exposures (outdoors and indoors) for gamma rays of moderate energy. For medical exposures specific conversion factors are discussed in Annex G (Medical exposures).

125. Most studies of the shielding afforded by buildings were carried out in the context of determining the likely effects of nuclear explosions or reactor accidents. The transmission factor for an external source of radiation is defined as the ratio of the photon absorbed dose rate in air inside the building to the photon absorbed dose rate in air outside. The most extensive recent survey is that provided by Burson and Profio [B6] which is summarized in Table 11 together with some additional data on brick houses in the United Kingdom [S6]. The absorbed dose rate indoors may be increased by 10–20% if the roof and walls are contaminated with deposited activity but deposition which has penetrated inside the house is unlikely to add more than an extra 5% [M1].

126. The data given in Table 11 show that the transmission factors for buildings vary considerably. The highest transmission factor is 0.3 for a brick house relative to deposited activity (although wooden houses would be expected to have even higher values), whereas office and multi-storey buildings give considerably more shielding with transmission factors below 0.01. In trying to estimate a world-wide average the Committee assumes that about 80% of all buildings are masonry with the rest wooden; and that most time is spent in homes rather than in office buildings. If transmission factors for office buildings, masonry homes and wooden homes are taken as 0.05, 0.2 and 0.4, respectively, then assuming half the population to be workers in offices and that 25% of their time is spent at work, the average transmission factor is 0.22. Changing the percentage of time spent at work to 10% or 50% changes this average factor to 0.23 or 0.19, respectively. It therefore seems reasonable to retain the previous average value of 0.2 for the transmission factor of buildings with respect to activities of deposited radioactive materials.

127. A further important consideration is the amount of time spent outdoors compared with that within buildings. This will obviously vary greatly for different areas of the world, being as low as 10% in the United Kingdom and the United States [S7, R1] but probably much greater in warmer or less urbanized countries. The Committee has previously taken, as a world-wide average, that 20% of time is spent outdoors and there seems no reliable data on which to base any change to this estimate. Combining the transmission and occupancy factors, the overall conversion factor to apply to the calculated or measured absorbed dose rates in air from deposited radioactivity would now be strictly 0.25. This factor includes allowance for conversion to absorbed dose in tissue as discussed in section II.A.1 (paragraph 27), and for the proportion of time spent outdoors or indoors in various buildings. Changing the percentage of time spent outdoors to 10% or 30% changes this overall conversion factor to 0.20 or 0.31, respectively; for consistency, the Committee has decided to continue to use the overall factor of 0.3 adopted in Annex A (Concepts and quantities in the assessment of human exposures) of the 1977 report [U1].

128. In Annex C (Technologically modified exposures to natural radiation) account is also taken of the contribution to the dose rate indoors from natural radionuclides in the building materials themselves. A very simple model is used assuming the indoor space is a cavity in an infinite mass of the building material, so that the dose rate is proportional to the gamma-ray emission constants of the radionuclides of interest. The value obtained is only an index allowing comparison between building materials and not an estimate of the doses that would be received in houses constructed with those building materials. In many cases, adequate indoor measurements are available for assessment of actual doses.

B. DIETARY TRANSFER MODELS AND DOSE CALCULATIONS

129. Probably the simplest model is that which has become known as the specific activity model. This does not attempt to describe the environmental transfer behaviour of the radionuclide under study. It is based on the assumption that activity is dispersed so as to result in a uniform concentration in a defined receptor medium. In this situation the radionuclide will be present in the environment at a particular specific activity with respect to some stable analogue. The concentration of the radionuclide in body tissues is then assumed to bear the same relationship to the concentration of the stable analogue in the body. Given the knowledge of the mass of the stable analogue, then the activity of the radionuclide in the body can be found. This method is used for example in Annex B (Exposures to natural radiation sources) and in Annex E (Exposures resulting from nuclear explosions) to assess doses from tritium and carbon-14.

130. As described in the introduction to chapter V, models of several types can be used to describe the transfer of deposited radionuclides through vegetable and animal food chains to man. For the situation in which the integration periods over which results are required are relatively long, as when dealing with the long-term contamination from nuclear explosions, models have been developed by the Committee and used in Annex C (Radioactive contamination due to nuclear explosions) of the 1977 report [U1] and in earlier reports [U2, U3]. The same models are used in Annex E (Exposures resulting from nuclear explosions). As described in the introduction to chapter III, the results of transfer models are expressed as the relationships between appropriate time-integrated quantities in two compartments of the environment.

131. This formulation is used in Annex E (Exposures resulting from nuclear explosions) with regard to the most important radionuclides in fallout which enter dietary food chains. The transfer coefficients of concern for this aspect of the modelling are from deposition to human diet and from human diet to tissue, denoted as P_{23} and P_{34}, respectively. The transfer coefficient from deposition to diet is given by

$$P_{23} = \frac{\int_0^\infty C(t)\,dt}{\int_0^\infty \dot{U}(t)\,dt} \qquad (17)$$

where C(t) is the activity concentration of the considered radionuclide in the diet at time t and $\dot{U}(t)$ is the deposition density rate. For values of C(t) and $\dot{U}(t)$ assessed on a yearly basis, the integrations can be replaced by summation

$$P_{23} = \frac{\sum_{i=1}^{\infty} C(i)}{\sum_{i=1}^{\infty} \dot{U}(i)} . \qquad (18)$$

In the case of ^{90}Sr and ^{137}Cs, the following model is used to relate the activity concentrations in food groups or in the total diet to the annual deposition densities:

$$C(i) = b_1 \dot{U}(i) + b_2 \dot{U}(i-1) + b_3 \sum_{m=1}^{\infty} e^{-\mu m} \dot{U}(i-m) \qquad (19)$$

There are contributions to activity concentrations in diet from the annual deposition density in the year considered $\dot{U}(i)$, in the previous year $\dot{U}(i-1)$ and for all preceding years, expressed by the summation, with an exponential term describing the combined physical decay of the radionuclide considered and any decrease in availability to plants in soil. The values of b_1, b_2, b_3, and λ_s can be derived from measured data by regression analysis. The combination of equations (18) and (19) leads to

$$P_{23} = b_1 + b_2 + b_3 \frac{e^{-\lambda_s n}}{1 - e^{-\lambda_s n}} \qquad (20)$$

where n = 1 year, a constant in this case. A similar treatment is applied in calculating the transfer from diet to tissue (coefficient P_{34}) for ^{90}Sr. In some cases, a combined transfer coefficient P_{24} is used to directly relate the time-integrated concentration in human tissue to the integrated deposition density; this is the procedure used for deposited ^{137}Cs.

132. In the previous reports of the Committee the results have been expressed in terms of the quotient of the activity of ^{90}Sr per unit mass of calcium in diet or in bone. This treatment is retained in Annex E (Exposures resulting from nuclear explosions) but data are also given on the concentrations of calcium per unit mass in relevant materials where available. Standard values of the concentrations of calcium per unit mass are used with measurements of the activity concentration of ^{90}Sr in foodstuffs of various kinds and standard values of the intakes of these foodstuffs to calculate the intake of ^{90}Sr.

133. The most useful time-dependent models have compartments to represent the various environmental materials, vegetables, animals and animal products. The transfer between compartments is assumed to obey first order kinetics, so that the system forms a set of coupled first order differential equations as described in the introduction to chapter III and in more detail by ICRP [I7]. The compartment models used in Annex F (Exposures resulting from nuclear power production) are of this general form. The models are however composed of alternative subsets of compartments of varying degrees of complexity, depending on the radionuclide under consideration and to some extent on the availability of data. The general layout of the compartments is shown in Figure IV, which includes

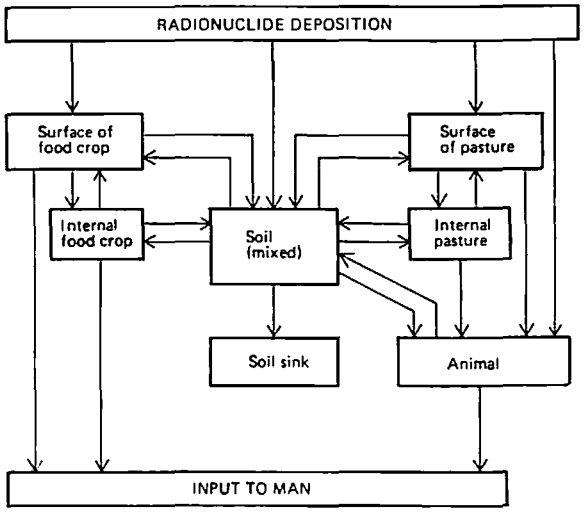

Figure IV. The major compartments in the terrestrial food chain models used in Annex F (Exposures resulting from nuclear power production)

more processes than Figure III, and more feedback loops. In further refinements, even these compartments can be divided into sub-compartments, if desired. For example, the single soil (mixed) compartment in Figure IV can be replaced by a four-layer compartment such as that described in [N1] and the "Animal" compartment can be replaced by either of the two alternative subsets shown in Figure V. The various adaptations of the general model used for specific transfer routes are considered in the following paragraphs. More details may be found in [N1].

134. Two models are used for the migration of radionuclides through soil. For soil which has been well mixed by ploughing or cultivation, a model consisting of a single compartment extending to a defined depth is used; loss, including radioactive decay, is represented by a single transfer coefficient out of the compartment.

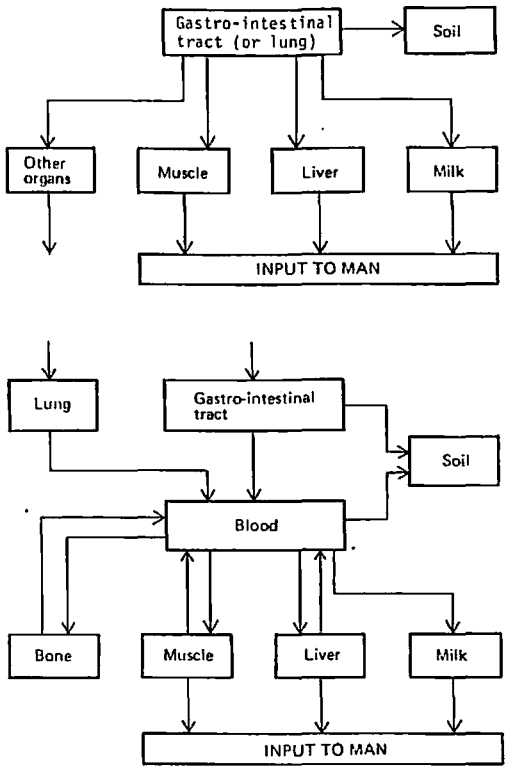

Figure V. Alternative sub-sets of compartments for the "Animal" compartment shown in Figure IV

The depth is taken as 30 cm in Annex C (Technologically modified exposures to natural radiation) and in Annex F (Exposures resulting from nuclear power production). For undisturbed land such as permanent pasture the model used in Annex F uses a set of four compartments representing soil depths of 0–1 cm, 1–5 cm, 5–15 cm and 15–30 cm. Transfers from the first to second and second to third compartments is one way downwards, transfers between the third and fourth compartments are in both directions and loss is represented by transfer out of the fourth compartment.

135. Transfer of radionuclides to food plant crops is modelled in Annex F (Exposures resulting from nuclear power production) by part of the general system illustrated in Figure IV; the portion of interest for this pathway is shown in Figure VI. The initial input of

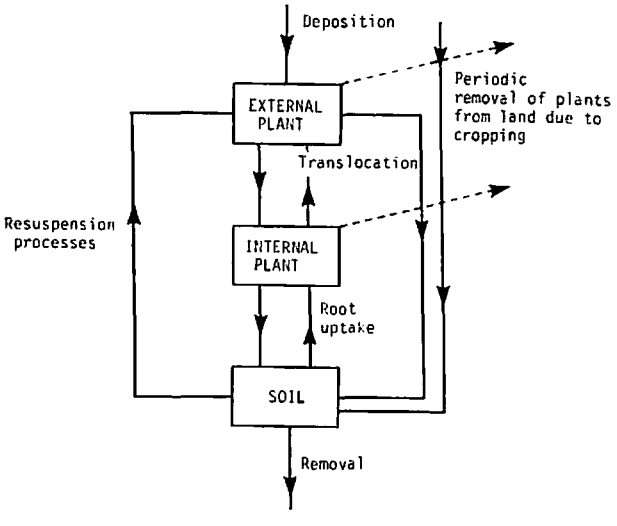

Figure VI. Schematic representation of the model for transfer of radionuclides to plants [N1]

radionuclides into the system is by deposition into the compartments representing surface soil and the external surfaces of the plant. Subsequent interactions within the system represent translocations between the external and internal parts of the plant and between the internal parts of the plant and the soil. Allowance is also made for direct transfers between the external plant surfaces and the soil, although it is assumed that when plants are harvested some form of washing or outer husk shedding removes 90% of the remaining surface contamination. This model is used for green vegetables, grain and root crops with the appropriate sets of transfer coefficients, some of which depend on the element being considered.

136. The intake of radionuclides by grazing animals is modelled in Annex F (Exposures resulting from nuclear power production) in a similar fashion to that shown in Figure VI for soil but incorporates the more complex soil model and several routes of transfer to the animal. The model is shown in Figure VII. Provision is made

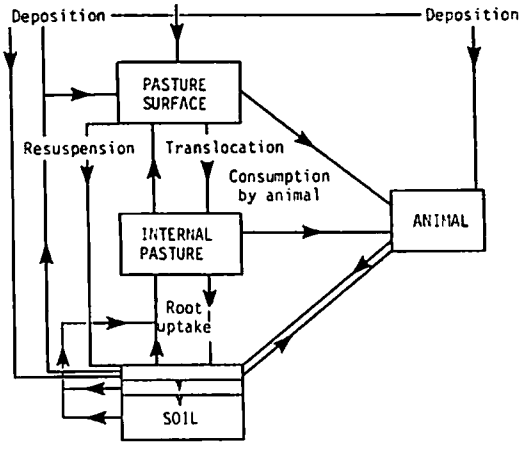

Figure VII. Schematic representation of the principal mechanisms for the transfer of radionuclides to grazing animals [N1]

not only for consumption by the animal of plants but also for some direct uptake of soil from the upper compartment, either by eating it or by inhaling resuspended soil particles. For all radionuclides other than the transuranium elements the simpler representation of the "Animal" compartment shown in Figure V is used; for transuranium elements the more complex representation is used. These models are used to represent cows and sheep with the appropriate sets of transfer coefficients [N1], some of which are element-dependent. The models are used to derive matrices of results for contamination by particular radionuclides. The results are expressed as the time integrals of the activity in unit mass of the foodstuff over different periods of time following deposition of the radionuclide on land at unit activity per unit area; these results are used in Annex F (Exposures resulting from nuclear power production).

137. The doses to particular individuals from ingestion of contaminated foodstuffs cannot generally be correlated with the local level of environmental contamination because most foodstuffs are transported some distance between harvesting and consumption. The local contamination will only predominate for rare individuals who subsist almost entirely on local products. In the more general case and in order to assess collective doses it is sufficient to know the quantity of food of each type derived from an area of known contamination, the fraction of the food ingested by the population and the delay between harvesting (or animal slaughter) and consumption. The time integral of the collective dose rate in tissue is obtained as the product of the collective intake of activity of the radionuclide and of the committed dose per unit intake of activity.

C. MODELS FOR TRANSPORT UNDER THE GROUND SURFACE

138. All the models so far reviewed in this chapter are confined to describing the behaviour of activity on the surface of the ground or in the layer of soil down to a depth of a few tens of centimetres. There is, however, a branch of modelling which is becoming of more interest with the various propositions to dispose of large quantities of radioactive wastes by burial in the ground [S8]. This branch is the modelling of radionuclide transport from the buried waste repository back to the surface or to portions of the terrestrial environment directly available to man, e.g., potable water supplies. The main transport route considered in studies of this type is transport in association with a flow of ground water [B7, H7, K2]. The major processes taking place when nuclides are transported in this way are advection, dispersion, sorption and radioactive decay; it appears from studies that axial convection and dispersion in the direction of flow predominate and therefore unidirectional paths have so far been generally assumed through the soil or rock column between the repository and the output point. Equations describing these processes can be solved analytically or numerically and a number of solutions have been derived for various boundary conditions [B7, H7, L3]. The output of the transport calculation is used as input for terrestrial or aquatic models of varying degrees of complexity in order to calculate doses to man. The Committee has decided for the present report not to assess this aspect in detail, but to rely for the time being on other reviews such as that carried out as part of the International Fuel Cycle Evaluation [I12].

VI. AQUATIC MODELS

139. The primary hydrodynamic mechanisms of radionuclide transport in aquatic systems are advection and diffusion/dispersion. Interactions with suspended matter and sediments are important physico-chemical processes and under some circumstances interaction with biota may provide a transport mechanism. There are perhaps more models of more different types available for modelling hydrologic transport than for any other sector of the environment. For example, in the report by Hoffman et al. [H2] which contained a review of hydrologic models, 24 models were identified of which 11 included provision for calculating radionuclide concentration. The majority of these models have been developed for some specific place such as a particular river system or estuary. In the following sections the calculations of activity concentration for each sector of the aquatic environment will be considered together with the pathways by which man utilizes this water. The sectors of the aquatic environment are linked together so that radionuclides which enter a lake or river may eventually reach the seas and oceans.

A. ISOLATED WATER BODIES

140. The simplest type of aquatic model considers the receiving water body as a single volume and assumes that the radionuclides are uniformly diluted in this volume. Allowance is normally made for some renewal of water in the receiving body and for removal processes such as sorption onto sediments and radioactive decay. The model previously used by the Committee in Annex D (Radioactive contamination due to nuclear power production) of the 1977 report [U1] is of this type. The change in activity concentration with time in such a water body is given by

$$\frac{d\chi_w}{dt} = \frac{\dot{A}_o}{V} - (\lambda_r + \lambda_s + \lambda)\,\chi_w \qquad (21)$$

where χ_w is the activity concentration per unit volume in the water body at time, t; $\dot{A}_o$ is the rate of input of activity; V is the volume of water; λ_r is the fractional rate of renewal of water; λ_s is the fractional rate of removal of activity by sorption onto sediments; λ is the physical decay constant.

141. Removal of activity onto sediments is assessed in Annex F (Exposures resulting from nuclear power production) with a particle scavenging model [N1]. This uses the equilibrium distribution coefficient between suspended sediment and water to calculate the activity concentration in the suspended sediment; the removal is then determined by the rate of settling of particulate material onto the bottom. The fractional rate of loss of activity by sorption onto sediments is therefore given by

$$\lambda_s = \frac{K_d\,\dot{m}_S}{z\,(1 + K_d\,\rho_{sed})} \qquad (22)$$

where K_d is the sediment to water distribution coefficient, defined as the quotient of the radionuclide concentration per unit mass in sediments to the radionuclide concentration per unit volume in the water; z is the average water depth in the water body; $\dot{m}_S$ is the rate of sedimentation expressed as mass per unit area and time; ρ_{sed} is the concentration of suspended sediment load in mass per unit volume of the water body. This type of model is appropriate for isolated water bodies such as lakes but can also be used as a reasonable approximation for relatively isolated and internally well mixed portions of larger water bodies [N1]. It is used in Annex F (Exposures resulting from nuclear power production) to describe the local behaviour of activity discharged to coastal waters.

B. RIVERS

142. Models of river systems either are extensions of the single compartment model described in the previous section or attempt to represent the physical mixing processes. Many examples of the latter type are based on solutions of diffusion/advection equations which include velocity and diffusion in the downstream direction, together with the rates of input of activity at the discharge point, and of loss of activity by radioactive decay and processes such as sorption on the bottom sediments. Most practically developed models do not incorporate all these processes, although they may treat one or more in a thorough fashion. For example, in the United States Nuclear Regulatory Commission treatment of non-tidal rivers [U6], which is of this general form, the diffusion has been considered in two dimensions to give horizontal and downstream concentrations (assuming vertical mixing) after Yotsukura [Y1, Y2] for meandering irregularly shaped river cross sections, but there is no treatment of sediment interactions.

143. The other major class of models divides the river into a system of interconnected compartments linked by transfer coefficients. Two of the most thorough models of complete river systems are of this type: the study of the Mississippi basin by Martin et al. [M2] and the study by Bayer of the Rhine-Meuse system [B9]. The model used by Bayer is a set of compartments, each corresponding to the single compartment represented by equation (21), and leads once again to the solution of a set of first order differential equations similar to those described in chapter III. Bayer chose to consider only equilibrium conditions and to ignore bulk transport of bed sediment by comparison with transport via suspended matter; under these conditions the solution is readily obtained analytically for single radionuclides. In the computer programme RVRDOS used by Martin et al. [M2], however, the emphasis is on the provision for daughter products and specific arrangements are made for impoundments (e.g., dams) at various positions downstream. Diffusion is not considered, nor is sedimentation. In effect, the only changes in concentration are due to additional inputs of activity, dilution from additional tributary water inputs and the effects of radioactive decay, including build-up of daughters. Impoundments are treated as uniformly mixed volumes at the end of each stretch of water.

144. A model which includes treatment of sediment interactions, not merely as a method for removal of activity, but with provision for transport of contaminated sediment downstream, has been developed by the National Radiological Protection Board jointly with the Commissariat à l'Energie Atomique [N1], based on the work of Schaeffer [S11]. This model assumes a rectangular river cross-section, ignores the effect of diffusion and thus simplifies the calculation to a system of linked first order differential equations. Solutions of these for an equilibrium situation show an exponentially declining activity concentration in the water downstream of the input point, but predict peaks in the activity concentrations in the bed sediments at positions downstream which are dependent on the bed sediment and suspended sediment velocities. This model has been used where appropriate in Annex F (Exposures resulting from nuclear power production). The model is based on the observation [S11] that the long-term average activity concentration in a transversely well-mixed river decreases exponentially with distance from the discharge point. The activity concentration χ_w in the water (including suspended sediments) at a distance, x, is therefore given by

$$\chi_w(x) = \frac{\dot{A}_o}{\dot{V}} \exp(-k\,x) \qquad (23)$$

where $\dot{V}$ is the volume flow rate of the river; and k is a coefficient dependent on the river and the radionuclide. For a given nuclide the value of k depends on the half-

life, the river velocity and the rate of sorption onto sediments and is given by

$$k = \frac{\lambda + \lambda_s}{v} \qquad (24)$$

where v is the river velocity; λ is the physical decay constant; λ_s is the fractional rate of removal of activity onto sediments. The measured values of the sediment to water distribution coefficient, K_d, defined in section VI.A. are taken to be indicative of the fractional rate of removal. Elements with K_d values greater than 10 m^3 kg^{-1} are taken to have strong interaction and λ_s is assigned the value 2 10^{-5} s^{-1}; elements with K_d values between 1 and 10 m^3 kg^{-1} are medium with a λ_s value of 4 10^{-6} s^{-1}; elements with lower K_d values are assigned a zero value of λ_s. All these values apply for a river velocity of 2 m s^{-1}.

145. Models of this type are designed to apply only to long-term conditions averaged over at least a year; no attempt is made to model seasonal changes such as spring floods or droughts. The outputs from the model are the concentrations of activity in the water and in the suspended sediments as a function of distance from the activity discharge point, together with the amount of activity on the river bed sediments as a function of distance and time. The routes of exposure of man are reviewed in section VI.E.

C. SEAS AND OCEANS

146. In some situations where the activity concentration of a radionuclide has been measured, as for some naturally-occurring radionuclides, there is no requirement for a model of the processes leading to the distribution. In other cases, especially when dealing with radionuclides introduced at a defined location rather than as a widely distributed source, the activity concentration may vary so much with space and time that complex models are required to assess either individual or collective doses.

147. Although the basic mixing processes in the seas and oceans are still advection and diffusion, a major difference in modelling activity distribution is introduced by the scale of the water bodies [N3]. The physical mixing processes in the seas have been the subject of extensive study for many years and the emphasis among most oceanographers has been on producing models to describe dispersion and dilution processes. Many of these are of a diffusion type although some include an advective term and may even allow for shear effects introduced by the change in wind-driven mean velocities with depth. In many situations, the seas tend to be vertically stratified and in coastal seas the depth is small in comparison to the horizontal extent, so these can often be assumed to be well-mixed vertically; in these cases one- or two-dimensional treatments of dispersion are usually sufficient. The starting point for many of these calculations is the solution of the radially symmetrical horizontal diffusion equation for a substance introduced instantaneously at a point in an infinite sea. Solutions to this radial diffusion equation [N3] may then be combined with advective terms obtained by empirical observations of current flows or theoretical treatments such as those of Gifford [G3]. In practice, it may be reasonable for mathematical convenience to ignore diffusion in the direction of mean flow. The result of calculations of this type is that the activity concentration at the centre of a plume of radionuclides in the direction of the current decreases approximately inversely in proportion with the distance from a point source.

148. Despite the existence of these rather well developed models many practical calculations of dispersion in coastal seas or in oceans use very simple models, although these may be based on more complex background calculations. For instance, in an example of a plume calculation used by the IAEA [I8] for deriving the definition and recommendations concerning high-level radioactive wastes unsuitable for dumping at sea, it is assumed that the width of the plume is about one-tenth of its length and that the activity concentration from a continuous release is inversely proportional to the current; this is in agreement with the results of the more rigorous treatment referred to above.

149. The simple single compartment model described in section VI.A is also applicable to relatively isolated and well mixed seas or ocean basins, especially if only integrated activity concentrations are required. This model is used in Annex F (Exposures resulting from nuclear power production) for some preliminary estimates of activity concentrations from coastal discharges into appropriate receiving bodies such as bays or local sea regions.

150. The same treatment can be extended to deal with more complex situations by adding compartments to represent adjacent water bodies. This leads once again to a system of differential equations of the form given in chapter III. An example of such a set of interlinked compartments is that developed to model the coastal seas around North-Western Europe [N1]. The geographical components are illustrated in Figure VIII while the volumes of the water bodies and volumetric exchange rates are presented in Figure IX. Removal to

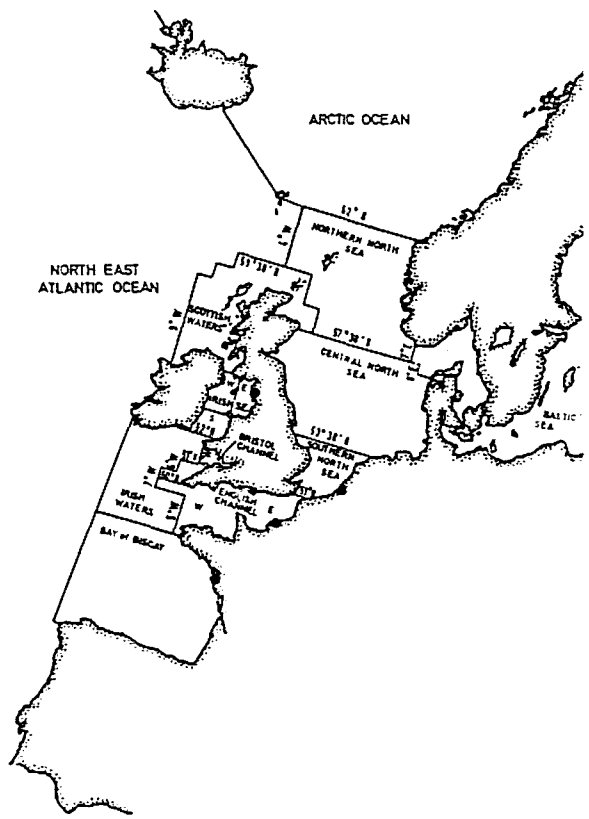

Figure VIII. Compartments into which North-Western European waters can be divided [N1]

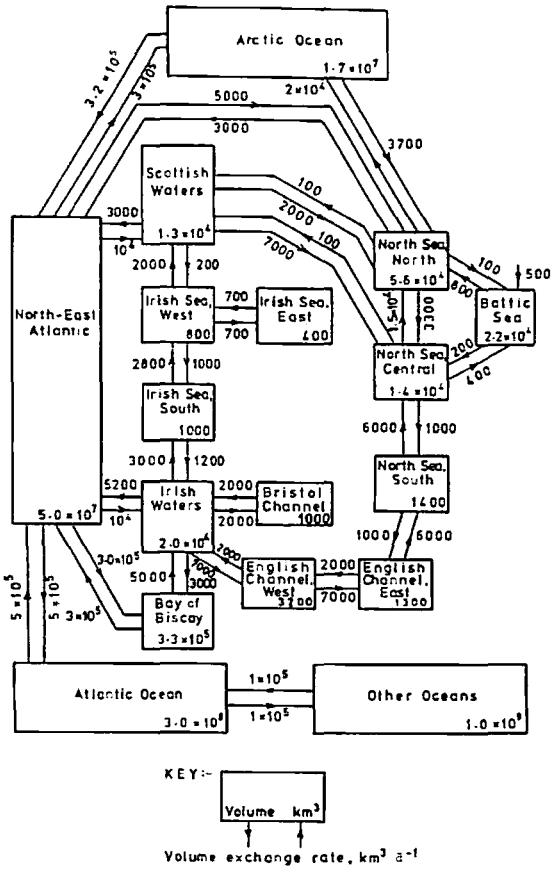

Figure IX. Compartments and their volumes and the exchange rates between compartments of the North-Western European regional model [N1]

sediments requires the specification of z, $\dot{m}_S$ and ρ_{sed} (see section VI.B.) for each water body. This model is used in Annex F (Exposures resulting from nuclear power production), where the values are given.

D. GLOBAL MODELS

151. For certain long-lived radionuclides other than noble gases and some naturally-occurring radionuclides the majority of the activity associated with the radioactive material discharged eventually resides in the aquatic compartments of the environment, irrespective of whether the radioactive material is discharged to atmosphere or to a water body. The normal treatment of these radionuclides is either by direct measurement of activity concentrations or by compartment models of an appropriate degree of complexity.

152. For radionuclides which are produced naturally such as ^{3}H and ^{14}C, it is possible to derive an empirical relationship between measurements of activity concentrations and estimates of production rates. The activity concentration per unit mass of hydrogen in human tissues from natural tritium has been estimated by assuming it is the same as that in continental surface waters before nuclear explosions began. This is then used to relate the annual average absorbed dose in the body to the annual production rate of natural tritium. In the case of ^{14}C the activity concentration of natural origin is taken to be that measured in biological samples such as wood from the time before nuclear explosions began. Using the concentration of carbon in the body given by ICRP [I6], the annual average absorbed dose in the body is related to the natural production rate, deduced from an estimate of the natural inventory. These procedures are used in Annex B (Exposures to natural radiation sources) to assess absorbed doses from natural production. In Annex E (Exposures resulting from nuclear explosions) the dose commitments resulting from the production of ^{3}H and ^{14}C in atmospheric nuclear explosions are based on the above relationships and on the quotients of the activity inputs from nuclear explosions to the annual rates of input from natural production. These procedures are compared in Annex F (Exposures resulting from nuclear power production) with the slightly more refined models described in the following paragraphs.

153. A compartment model can be used to assess the activity concentration of tritium, which is rapidly taken up in the circulating waters. The model is shown in Figure X and is made up of four compartments representing the circulating and deep waters of the northern and the southern hemispheres, respectively.

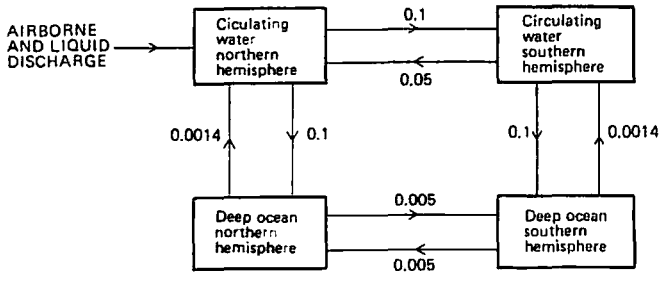

Figure X. The model used for global circulation of tritium. (Fractional exchange rates are given in units of a^{-1}) [N1]

154. A similar but rather more detailed model can be used for carbon-14, based on the extensive work on the carbon cycle. It is shown in Figure XI and is used in Annex F (Exposures resulting from nuclear power

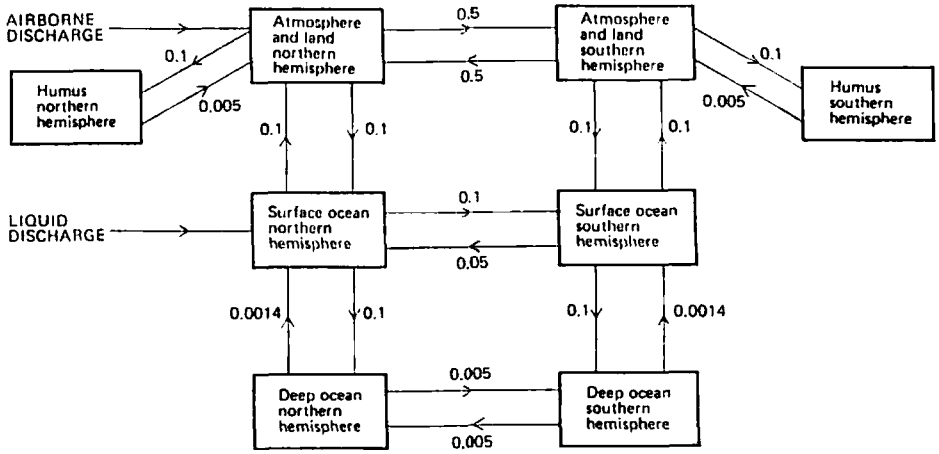

Figure XI. The model used for global circulation of carbon-14. (Fractional exchange rates are given in units of a^{-1}) [N1]

production) although this model does not incorporate uptake into deep ocean sediments. A model of this type was used in earlier reports of the Committee.

155. For nuclides as long-lived as ^{129}I, although, in principle, a model similar to that used for tritium may be applied, the activity concentrations in all compartments become equal over a time scale so short in comparison with the half-life that it is sufficient to assume uniform dispersion in all circulating waters after any local behaviour has been allowed for.

E. DOSE CALCULATION

156. The output from all of the models used is the activity concentration in the water and if appropriate in the suspended and bed sediments. There are a very large number of pathways by which man can be exposed, many of which are common to fresh and sea water, although a few such as irrigation and direct use as drinking water are only appropriate for fresh water. These pathways may need to be studied separately in detail to obtain individual doses, especially for a mixture of radionuclides. If only collective doses are required then it may suffice to know the quantity of activity transferred via a particular pathway and the fraction taken in by man, or even the total quantity of activity transferred to man via all pathways.

157. For some radionuclides such as tritium and ^{14}C, for which a relationship has been established by measurement between the natural activity concentrations in surface waters and the activity concentrations in the organs or tissues of the body then the dose estimates can be derived from these relationships.

1. Direct consumption of water

158. The simplest pathway to man for fresh water is direct ingestion. It is necessary in principle to allow for any decontamination by water treatment processes before supply although for freshwater the effect is small and no decontamination is included in Annex F (Exposures resulting from nuclear power production). The dose calculation then merely requires an assumption of the volume consumed together with the dose per unit activity intake via ingestion for the radionuclide concerned. In some circumstances where desalinated sea water may be used as drinking water, the calculation is the same although the effective decontamination by the desalination process may be much greater than that produced by freshwater treatment. This is rarely a major pathway compared with ingestion of marine foodstuffs.

2. Consumption of fish and other aquatic flora and fauna

159. The activity concentrations in fish and other aquatic fauna and flora are frequently derived on the assumption that they are in equilibrium with the water. The ratio of the activity concentration per unit mass in fish and other organisms to the corresponding activity concentration in water is, under this assumption, a constant. The edible fractions vary for the different fresh water and marine flora and fauna. The individual or collective dose calculation then requires only knowledge of the mass consumed by the individual or by the population and the dose per unit activity intake via ingestion for the radionuclide concerned.

3. Consumption of agricultural products

160. The most important route by which activity can reach man from irrigation is by spray irrigation of cultivated crops. The form of model used to assess this is the same as that used for any other deposition process and has been described in chapter V. The only difference is that the fraction deposited on the external surface of vegetation is taken as 0.05 rather than 0.2 for deposition from the atmosphere [D1, D2].

4. Other pathways

161. Most other pathways are relatively unimportant in terms of collective doses, although they may be important for individuals. An example is direct external irradiation from contaminated sediments along the shoreline in which a knowledge of occupancy times is crucial together with an assessment of the dose rate. A related pathway is inhalation of airborne activity either from contaminated sediment particles which have been resuspended from coastal sediments or those which have been directly transferred to the atmosphere from

the sea surface [P5]. Direct exposure to activity in water from swimming, boating, etc., can in principle be estimated in the same way.

VII. CONCLUSIONS

162. The main purposes of the Committee are to assess and compare natural and man-made sources of radiation by estimating the resulting individual and collective doses. Some of these sources are globally dispersed, as are most naturally-occurring radionuclides. Others are initially highly localized, such as discharges from nuclear installations. Some sources such as x-ray machines give only external radiation and lead to no contamination of the environment, others lead to widespread distribution of radionuclides in any or all sectors of the environment, air, ground and water. Exposure may be to external radiation, incorporated radionuclides or a combination of both.

163. Dosimetric quantities used to describe exposure of individuals or populations to radiation were reviewed. The most basic quantity is the absorbed dose in any organ or tissue. As the evaluations of risk made by the Committee are based on the assumption of proportionality between the absorbed dose and the probability of induction of stochastic health effects, results are where possible first reported in terms of absorbed dose. The dose equivalent is needed to combine the consequences of different radiation types and the effective dose equivalent to take account of the different relative stochastic risks of irradiation of different body organs or tissues. These quantities are appropriate to describe the irradiation of individuals and for any individual the effective dose equivalent can be used to estimate the probability of induction of a stochastic health effect, defined as cancers which prove fatal and serious hereditary effects in the first two generations.

164. When dealing with populations analogous collective quantities are generally defined as related to the sources of exposure, but some additional quantities are also needed for particular reasons. Although for individuals it may be appropriate to produce an overall probability of a health effect, for populations it may be appropriate to separate hereditary effects from somatic effects and for some organs or tissues the cancers which do not prove fatal may also be identified separately. The Committee has therefore retained the genetically significant dose equivalent and discussed the possible use of another similar quantity, the somatically significant dose equivalent, for the purpose of broad intercomparisons.

165. The dosimetric models needed to assess doses in organs or tissues from measurements of absorbed dose rates in air are described, as are those needed to assess doses in organs or tissues from intakes of activity or from activity concentrations in the same or other organs or tissues. These are based on measurements of the movement of radionuclides in the body, the rate of elimination from particular organs or tissues and from the body, the characteristics of the organ or tissue and of the radiations emitted by each radionuclide.

166. In assessing doses from any source, the first recourse is to direct measurements. These may be either of the external dose rate, as in most estimates of occupational exposures, external doses from fallout or doses from medical x rays; or of the activity concentrations in human organs or tissues, as for many exposures to naturally produced incorporated radionuclides.

167. Slightly less direct estimates can be made from measurements of activity concentrations of radionuclides in air or in foodstuffs which are consumed by people. In this case some additional information is required on the intake rates of the radionuclides from air or from the foodstuff concerned before using the appropriate dosimetric models. These less direct methods are used for many environmentally dispersed radionuclides, particularly to assess exposures to individuals irradiated as a result of discharges from nuclear installations and to assess doses from some radionuclides resulting from nuclear explosions.

168. When direct measurements are not possible or practicable, either because of technical difficulties in measuring the activity concentration of the radionuclide concerned in an appropriate medium, because the number of radionuclides or media are too large or because predictions or extrapolations are required, then some form of model has to be used to describe the environmental transfer processes.

169. In general the simplest type of model should be used which will produce the required answer and is appropriate to the radionuclide concerned, its mode of introduction and its environmental behaviour. For natural radionuclides in equilibrium in the environment, simple empirical relationships between measured activity concentrations are adequate. This treatment, or slight elaborations of it, may also be used for the same or analogous radionuclides widely dispersed in the environment and which may be taken for practical purposes to be in equilibrium; these include some fallout radionuclides and globally dispersed radionuclide releases from nuclear installations. For other individual radionuclides such as ^{90}Sr produced in fallout it may be necessary to model their transfer through the environment in a time-varying fashion often using simple compartment models.

170. For mixtures of artificial radionuclides released to atmosphere and water from nuclear installations at rates which vary considerably over time and for which both individual and collective dose estimates are required, then quite complex models may be needed. These should be capable of accepting time-varying inputs and of giving maximum individual doses, dose distributions as a function of space and time, and collective doses. Models of this type are described which are used mainly for assessing the consequences of releases from the nuclear power industry.

171. When models are used to describe a given situation, it is important to carry out comparisons between calculated and observed results where possible and to refine the models on the basis of such comparisons. This has in general been done for the models used by the Committee. In some circumstances predictive models cannot be directly verified by that method. For such models, techniques such as sensitivity analysis are being developed to assess the variability of predictions and their dependence on the model form and available data. The Committee wishes to encourage wider comparisons of different forms of models for the same sectors of the environment as well as analyses of the effects of uncertainties in the data bases. These comparisons will improve confidence in the general results from such models. Similar analyses could also be more widely applied to dosimetry models. Models which have been developed to describe the movement of radionuclides through the environment can also be used in an appropriate fashion for stable elements.

Table 1

Units of the SI system and other basic, derived and experimental units used in this report

Quantity	Symbol	Unit name	Unit symbol
Length	l	metre	m
Mass	m	kilogram	kg
		tonne	t
Time	t	second	s
		minute	min
		hour	h
		day	d
		year	a
Electric current	I	ampere	A
Electric charge	Q	coulomb	C
Thermodynamic temperature		kelvin	K
Energy	E	joule	J
		electron volt a/	eV
Power	P	watt	W
Volume	V	cubic metre	m^3
		litre	l
Amount of substance	n	mole	mol

a/ 1 eV = 1.60219 10^{-19} J (approximately).

Table 2

Quantities, units and symbols

Quantity	Symbol	Unit	SI restricted unit	
			Name	Symbol a/
Activity	A	s^{-1}	becquerel	Bq
Anterior	A			
Administered activity	A_0	s^{-1}	becquerel	Bq
Activity Median Aerodynamic Diameter	AMAD	µm		
Breathing rate	B	$m^3\ s^{-1}$		
Energy absorption build-up factor at a distance, x, for a radiation of energy, E, having an attenuation coefficient, µ, in the material of interest	$B_{en}(E,\mu x)$			
Bone lining cells designator	BLC			
Activity concentration per unit mass	C	$s^{-1}\ kg^{-1}$		Bq kg^{-1}
Potential α-energy concentration	C_{pot}	$J\ m^{-3}$ b/		
Potential α-energy exposure	$\tilde{C}_{pot}$	$J\ s\ m^{-3}$		
Cortical bone designator	CB			
Count Median Aerodynamic Diameter	CMAD	µm		
Absorbed dose	D	$J\ kg^{-1}$	gray	Gy
Class of inhaled substance	D			
Per caput (arithmetic mean) absorbed dose	$\bar{D}$	$J\ kg^{-1}$	gray	Gy
Absorbed dose index	D_I	$J\ kg^{-1}$	gray	Gy
Mean absorbed dose in tissue, T	D_T	$J\ kg^{-1}$	gray	Gy
Absorbed dose commitment	D^c	$J\ kg^{-1}$	gray	Gy
Absorbed dose commitment from a source, k	D_k^c	$J\ kg^{-1}$	gray	Gy
Mean energy of particles of type i per nuclear transformation of the parent nuclide	$\bar{E}_i$	J		
Potential α-energy	E_{pot}	J		
Equilibrium factor (radon or thoron)	F			
Fraction of photons of initial energy, E, emitted per disintegration	F_E			
Fraction of air admitted	$F_{a,in}$			
Fraction of foodstuff, g, consumed	F_g			

Table 2 (continued)

Quantity	Symbol	Unit	SI restricted unit	
			Name	Symbol a/
Equilibrium factor of nth daughter	F_n			
Fraction of free daughters compared with all such daughters	F_{fd}			
Fraction of free daughters compared with all such daughters as if they were in equilibrium with radon or thoron	F'_{fd}			
Emanating power	F_r			
Genetically significant dose equivalent	GSD	$J\ kg^{-1}$	sievert	Sv
Dose equivalent	H	$J\ kg^{-1}$	sievert	Sv
Per caput (arithmetic mean) dose equivalent	$\bar{H}$	$J\ kg^{-1}$	sievert	Sv
Committed dose equivalent	H_{50}	$J\ kg^{-1}$	sievert	Sv
Effective dose equivalent	H_{eff}	$J\ kg^{-1}$	sievert	Sv
Dose equivalent index	H_I	$J\ kg^{-1}$	sievert	Sv
Dose equivalent in tissue, T	H_T	$J\ kg^{-1}$	sievert	Sv
Uniform whole-body dose equivalent	H_{wb}	$J\ kg^{-1}$	sievert	Sv
Dose equivalent commitment	H^c	$J\ kg^{-1}$	sievert	Sv
Effective dose equivalent commitment	H^c_{eff}	$J\ kg^{-1}$	sievert	Sv
Dose equivalent commitment from a source, k	H^c_k	$J\ kg^{-1}$	sievert	Sv
Intake of radionuclide	I	s^{-1}	becquerel	Bq
Intake of radionuclide by ingestion	I_{ig}	s^{-1}	becquerel	Bq
Intake of radionuclide by inhalation	I_{ih}	s^{-1}	becquerel	Bq
Kerma	K	$J\ kg^{-1}$	gray	Gy
Sediment/water distribution coefficient	K_d			
Sorption equilibrium constant	K_s			
Linear energy transfer	L	$J\ m^{-1}$		$keV\ \mu m^{-1}$
Collision stopping power	L_∞	$J\ m^{-1}$		$keV\ \mu m^{-1}$
Lateral	LAT			
Collective absorbed dose	M	$J\ kg^{-1}$	man gray c/	man Gy
Incomplete collective absorbed dose commitment to time τ, from a source, k	M^τ_k	$J\ kg^{-1}$	man gray	man Gy
Collective absorbed dose from absorbed doses in the range 0 to D	M_D	$J\ kg^{-1}$	man gray	man Gy
Collective absorbed dose ratio	MR			
Modifying factor (in definition of dose equivalent)	N			
Integral number (population, windrose sectors, etc.)	N			
Posterior	P			
Atmospheric stability category designator	P			
Transfer coefficient from compartment m to compartment n	P_{mn}			
Probability of a value, x	P(x)			
Quality factor (in definition of dose equivalent)	Q			
Exhalation rate	R	$m^{-2}\ s^{-2}$		$Bq\ m^{-2}\ s^{-1}$
Exhalation coefficient	R_v	$m^{-3}\ s^{-2}$		$Bq\ m^{-3}\ s^{-1}$
Relative biological effectiveness	RBE			
Red bone marrow designator	RM			
Collective dose equivalent	S	$J\ kg^{-1}$	man sievert	man Sv
Surface area	S	m^2		

Table 2 (continued)

Quantity	Symbol	Unit	SI restricted unit	
			Name	Symbol a/
Collective effective dose equivalent	S_{eff}	$J\ kg^{-1}$	man sievert	man Sv
Beam area	S_{beam}	m^2		
Filter area	S_{filter}	m^2		
Collective dose equivalent commitment from a source, k	S^c_k	$J\ kg^{-1}$	man sievert	man Sv
Collective effective dose equivalent commitment from a source, k	$S^c_{eff,k}$	$J\ kg^{-1}$	man sievert	man Sv
Incomplete collective dose equivalent commitment to time, τ, from a source, k	S^τ_k	$J\ kg^{-1}$	man sievert	man Sv
Somatically significant dose equivalent	SSD	$J\ kg^{-1}$	sievert	Sv
Tissue or organ designator	T			
Half-life (physical)	$T_{1/2}$	s		
Half-life (effective)	T_{eff}	s		
Trabecular bone designator	TB			
Activity surface density	U	$s^{-1}\ m^{-2}$		$Bq\ m^{-2}$
Class of inhaled substance	W			
Exposure	X	$C\ kg^{-1}$ d/		
Number per unit volume	X	m^{-3}		
Number of condensation nuclei per unit volume in air	$X_{a,cn}$	m^{-3}		
Number of radon atoms per unit volume in air	$X_{a,Rn}$	m^{-3}		
Class of inhaled substance	Y			
Atomic number	Z			
Air designator	a			
Particle diameter	d	µm		
Foodstuff designator	g			
Height	h	m		
Particle type designator	i			
Radionuclide designator	j			
Source designator	k			
Compartment designator	m			
Mass per unit area	m_s	$kg\ m^{-2}$		
Compartment designator	n			
Integer	n			
Mean number of particles of type i per nuclear transformation of the parent nuclide	n_i			
Target designator	q			
Radial distance	r	m		
Range of a particle of energy, E	r(E)	m		
Age/sex class designator	s			
Surface density	s	$kg\ m^{-2}$		
Child expectancy weighting factor	v			
Velocity	v	$m\ s^{-1}$		
Deposition velocity	v_d	$m\ s^{-1}$		
Water designator	w			
Weighting factor for organ or tissue, T (in definition of effective dose equivalent)	w_T			
Horizontal axis	x			
Horizontal axis	y			
Vertical axis	z			
Depth	z	m		
Air kerma-rate constant	Γ_δ	$m^2\ J\ kg^{-1}$		$m^2\ Gy\ Bq^{-1}\ s^{-1}$

Table 2 (continued)

Quantity	Symbol	Unit	SI restricted unit	
			Name	Symbol a/
Dispersion coefficient	Δ_σ	$s\ m^{-3}$		
Turbulent diffusion coefficient	Δ_T	$cm^2\ s^{-1}$		
Washout coefficient (including rainout)	Λ	s^{-1}		
Product	Π			
Sum	Σ			
Particle fluence	Φ	m^{-2}		
Specific absorbed fraction	Φ	kg^{-1}		
Energy fluence	Ψ	$J\ m^{-2}$		
Radiation type	α			
Radiation type	β			
Radiation type	γ			
Life span of red cells	γ	s		
Energy imparted	ε	J		
Angular direction	ϑ			
Resuspension factor	$\varkappa$	m^{-1}		
Physical decay constant	λ	s^{-1}		
Attachment rate (of free radon daughter atoms to aerosol particles)	λ_a	s^{-1}		
Biological elimination rate constant	λ_b	s^{-1}		
Deposition rate of radon daughter atoms on indoor surfaces	λ_d	s^{-1}		
Physical decay constant of radionuclide, j	λ_j	s^{-1}		
Effective elimination rate constant out of compartment, m	λ_m	s^{-1}		
Ventilation rate (fractional change in volume per unit time)	λ_v	s^{-1}		
Linear attenuation coefficient	μ	m^{-1}		
Mean, median or mode of a log normal distribution	μ			
Energy absorption coefficient	μ_{en}	m^{-1}		
Air flow rate	ν	$m^3\ s^{-1}$		
Density	ρ	$kg\ m^{-3}$		
Population density	ρ_N	m^{-2}		
Density of rock	ρ_{rock}	$kg\ m^{-3}$		
Standard deviation	σ			
Geometric standard deviation	σ_g			
Standard deviation with respect to parameter, x	σ_x			
Time of duration (of a practice)	τ	a		
Mean residence time	τ	s		
Mean lifetime	τ	s		
Particle fluence rate	φ	$m^{-2}\ s^{-1}$		
Activity concentration per unit volume	χ	$s^{-1}\ m^{-3}$		$Bq\ m^{-3}$
Time integrated activity concentration per unit volume	$\tilde{\chi}$	m^{-3}		$Bq\ s\ m^{-3}$
Energy fluence rate	ψ	$W\ m^{-2}$		

a/ Symbol for the special name of the SI unit restricted to specified quantities.
b/ Some of the referenced data are given in terms of working levels. The working level (WL) is a potential α-energy concentration of $1.3\ 10^5$ MeV per litre of air.
c/ The term "man" is not a physical unit but is retained to reinforce understanding of the collective quantities.
d/ Some of the referenced data are given in terms of röntgen (R). The required conversion factor is: $1\ R = 2.58\ 10^{-4}\ C\ kg^{-1}$.

Table 3

Weighting factors recommended by the ICRP for calculation of effective dose equivalent and the reference risk coefficients on which they are based [12]

Tissue	Reference risk coefficient a/ 10^{-2} Sv^{-1}	Weighting factor w_T
Gonads	0.40	0.25
Breast	0.25	0.15
Red bone marrow	0.20	0.12
Lungs	0.20	0.12
Thyroid	0.05	0.03
Bone surfaces	0.05	0.03
Remainder b/	0.50	0.30

a/ The average probability per unit dose equivalent over both sexes and all ages of induction of a fatal tumour or a hereditary effect in the first two generations.

b/ A weighting factor, w_T, of 0.06 applies to each of the five remaining organs or tissues receiving the highest dose equivalents; exposure of all other organs or tissues can be neglected. (When the gastro-intestinal tract is irradiated, the stomach, small intestine, upper large intestine and lower large intestine are treated as four separate organs).

Table 4

Comparison of the source regions included by UNSCEAR and ICRP in the calculation of dose equivalent in bone-lining cells or red bone marrow from α emitters in bone

Target volume	Type of radionuclide distribution	Source region a/ b/		
		UNSCEAR (1977 report)	ICRP	UNSCEAR (this report)
Bone lining cells	Surface	TB(E)+RM	TB+CB	TB(E)+RM+CB
	Volume	TB(E)+RM	TB+CB	TM(E)+RM+CB
Red bone marrow	Surface	TB+RM	TB	TB+RM
	Volume	TB(E)+RM	TB	TB(E)+RM

a/ The notation (E) indicates that the coefficient in the equation relating dose equivalent rate to activity concentration and energy is itself a function of energy.

b/ TB - Trabecular bone; RM - Red bone marrow; CB - Cortical bone.

Table 5

The Pasquill stability categories [P2, P3]

Surface wind speed ($m\ s^{-1}$)	Insolation			Night b/	
	Strong	Moderate	Slight	≥ 1/2 cloud	≤ 3/8 cloud
< 2	A a/	A - B	B	-	G
2 - 3	A - B	B	C	E	F
3 - 5	B	B - C	C	D	E
5 - 6	C	C - D	D	D	D
> 6	C	D	D	D	D

a/ Weather categories are arranged in order of increasing atmospheric stability, A being the most unstable and G the most stable condition; category D is used for any sky conditions during the hour preceding or following night as well as for overcast conditions, day or night, regardless of windspeed.

b/ Night is from 1 h before sunset to 1 h after dawn.

Table 6

Comparison of the time integrated activity concentrations in air predicted by dispersion models with those predicted by a simple global model

Model	Distance (km)	Time integral of activity concentration per unit release ($Bq\ s\ m^{-3}/Bq$)
Dispersion model [C2]	10	$3\ 10^{-9}$ to $3\ 10^{-8}$
	100	$2\ 10^{-10}$ to $2\ 10^{-9}$
	1000	$1\ 10^{-11}$ to $1\ 10^{-10}$
Approximate dispersion model with $f = 3\ 10^{-7}\ s\ m^{-3}$, $x_1 = 10^3 m$, and $p = 1.5$	10	$1\ 10^{-8}$
	100	$3\ 10^{-10}$
Uniform global dispersion model for krypton-85		$1\ 10^{-10}$

Table 7

Conversion coefficients from absorbed dose in air to dose equivalent in tissue as a function of the initial photon energy [P1, N1]

Photon energy (MeV)	Absorbed dose in air per unit photon fluence (10^{-16} Gy m^2)	Quotient of effective dose equivalent or dose equivalent in the specified organ or tissue to absorbed dose in air ($Sv\ Gy^{-1}$)			
		Effective	Gonads	Thyroid	Skin
$1.0\ 10^{-2}$	7.5	0.002	0.004	0.0004	0.19
$1.5\ 10^{-2}$	3.1	0.014	0.014	0.0002	0.35
$2.0\ 10^{-2}$	1.7	0.054	0.07	0.033	0.44
$3.0\ 10^{-2}$	0.7	0.23	0.22	0.27	0.58
$5.0\ 10^{-2}$	0.3	0.57	0.43	0.60	0.76
$6.5\ 10^{-2}$ a/	0.3	0.63	0.46	0.71	0.80
$1.0\ 10^{-1}$	0.4	0.77	0.53	0.97	0.90
$2.0\ 10^{-1}$	0.9	0.80	0.73	0.76	0.95
$5.0\ 10^{-1}$	2.3	0.72	0.57	0.63	0.91
1.0	4.6	0.71	0.57	0.55	0.98
1.5	6.2	0.80	0.70	0.84	0.91
2.0	7.5	0.78	0.65	0.76	1.0
4.0	12	0.97	0.71	1.6	0.95
10.0 a/	23	0.97	0.71	1.6	0.95

a/ These energies were not considered by Poston and Snyder [P1] but are included to facilitate interpolation.

Table 8

Conversion coefficients from activity concentration in air of particular radionuclides to absorbed dose rate in air and to absorbed dose rate in skin from the beta radiation emitted [N1]

Nuclide	Absorbed dose rate[a] per unit activity concentration [10^{-7} Gy a^{-1} (Bq m^{-3})]	
	In air	In skin
^{3}H	0.25	0
^{14}C	2.1	0.22
^{41}Ar	16	7.6
^{51}Cr	0.002	0.001
^{54}Mn	0.008	0.004
^{59}Fe	5.0	1.8
^{58}Co	0.01	0.005
^{60}Co	4.3	1.4
^{83m}Kr	1.0	0
^{85m}Kr	9.7	4.4
^{85}Kr	8.9	3.9
^{87}Kr	43	21
^{88}Kr	13	5.8
^{89}Kr	39	19
^{86}Rb	22	11
^{88}Rb	62	31
^{89}Rb	30	14
^{89}Sr	19	9.3
^{90}Sr	7.3	3.0
^{90}Y	30	15
^{91}Y	21	9.8
^{95}Zr	5.2	1.9
^{95}Nb	2.2	0.26
^{99}Mo	14	6.7
^{99}Tc	3.9	1.1
^{99m}Tc	0.61	0.18
^{103}Ru	3.1	0.72
^{106}Ru [c]	45	22
^{103m}Rh	1.4	0
^{124}Sb	14	6.5
^{125}Sb	5.1	1.5
^{125m}Te	3.9	1.0
^{127m}Te	3.1	0.6
^{127}Te	9.2	4.0
^{129m}Te	9.6	4.1
^{129}Te	19	9.0
^{131m}Te	6.0	2.5
^{132}Te	4.3	0.87
^{129}O	2.8	0.19
^{131}I	8.2	3.4
^{132}I	18	8.8
^{133}I	15	7.2
^{134}I	22	10
^{135}I	15	6.9
^{131m}Xe	5.4	2.0
^{133m}Xe	7.4	3.2
^{133}Xe	5.9	1.6
^{135m}Xe	3.7	1.8
^{135}Xe	13	6.0
^{137}Xe	56	28
^{138}Xe	23	11
^{134}Cs	6.9	2.9
^{135}Cs	2.8	0.54
^{136}Cs	5.3	1.8
^{137}Cs [c]	9.6	4.2
^{138}Cs	39	19
^{140}Ba	12	5.0
^{140}La	19	9.3
^{141}Ce	7.3	2.8
^{144}Ce	4.2	1.2
^{144}Pr	40	19
^{147}Pm	3.0	0.63
^{154}Eu	9.9	4.3
^{155}Eu	2.6	0.26
^{239}Np	11	3.9
^{238}Pu	0.27	0.001
^{239}Pu	0.28	0.09
^{240}Pu	0.25	0.001
^{241}Pu	0.28	0.000004
^{242}Pu	0.06	0.008
^{241}Am	0.89	0.003
^{242}Cm	0.24	0.0000001
^{244}Cm	0.20	0

a/ Multiply by an 1.0 to convert to dose equivalent rate in skin.
b/ Assuming an inert layer thickness of 70 μm.
c/ Including the short-lived decay products.

Table 9

Distribution of the world population by latitude band in each hemisphere

Latitude band (degrees)	Population distribution (per cent)	
	Northern hemisphere	Southern hemisphere
0-10	6.3	54.0
10-20	11.0	16.7
20-30	32.7	14.9
30-40	20.4	13.0
40-50	15.5	0.9
50-60	13.7	0.5
60-70	0.4	0
70-80	0	0
80-90	0	0

Table 10

Population distribution around model release locations

Distance (km)	Population distribution around model release locations	
	Model reactor site	Model uranium mining and milling site
0-1	$1.3\ 10^3$	
1-2	$3.0\ 10^4$	
2-5	$2.6\ 10^4$	
5-10	$9.0\ 10^4$	
10-20	$4.3\ 10^5$	
20-50	$2.8\ 10^6$	
50-100	$6.1\ 10^6$	
0-100	$(9.5\ 10^6)$	$9.4\ 10^4$
100-200	$2.0\ 10^7$	
200-500	$7.0\ 10^7$	
500-1000	$1.4\ 10^8$	
1000-2000	$1.7\ 10^7$	
100-2000	$(2.5\ 10^8)$	$2.5\ 10^8$

Table 11

Effects of shielding by buildings on the ratio of indoor and outdoor photon absorbed dose rates in air under equilibrium conditions [B6, S6]

Structure or location	Transmission factor for immersion in a uniform cloud a/	Transmission factor for deposited activity b/
Brick house	0.6	0.05 - 0.3
Small multi-storey building c/		
Basement		0.01
Ground floor or first floor		0.05
Large multi-storey building c/		
Basement		0.005
Upper floors		0.01

a/ The ratio of the photon absorbed dose rate inside the building to the photon absorbed dose rate in an infinite uniform cloud of activity.

b/ The ratio of the photon absorbed dose rate inside the building to the photon absorbed dose rate 1 m above an infinite smooth plane with activity uniformly distributed on the surface.

c/ Away from doors and windows.

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ANNEX B

Exposures to natural radiation sources

CONTENTS

Introduction

1. The assessment of the radiation doses from natural sources in humans is of particular importance because natural radiation is the largest contributor to the collective dose of the world population. The natural radiation sources are classified into:

(a) External sources of extraterrestrial origin (cosmic rays) and of terrestrial origin, i.e., the radioactive nuclides present in the crust of the earth, in building materials and in the air;

(b) Internal sources, comprising the naturally-occurring radionuclides which are taken into the human body.

This Annex is to a large extent a summary of Annex B of the 1977 report of the Committee [U1]. Modifications have been made only for those components of the natural radiation environment for which knowledge has substantially improved since 1977. The doses due to the radon isotopes and to their short-lived decay products are briefly reviewed; a detailed treatment of the sources of exposure to those radionuclides and of the corresponding doses is provided in Annex D.

I. EXTERNAL IRRADIATION

A. COSMIC RAYS

2. The high-energy radiation that enters the earth's atmosphere from outer space is known as primary cosmic rays. When these interact with atomic nuclei in the atmosphere, secondary particles and electromagnetic radiation are produced which are called secondary cosmic rays.

1. Primary cosmic rays

3. Most of the primary cosmic rays originate outside of the solar system. In addition, there are also solar cosmic rays related to solar flares.

(a) Primary galactic cosmic rays

4. Primary galactic cosmic rays consist largely of high-energy protons which enter the solar system from

interstellar space, together with ^{4}He ions in the proportion of about 10% and much smaller proportions of heavier particles, and of electrons, photons and neutrinos. The primary flux density is affected by the earth's magnetic field, which deflects low-energy charged particles back into space. This effect is dependent on the geomagnetic latitude, so that the flux density of low-energy protons at the top of the atmosphere is greater at the poles than in equatorial regions. Thus, as shown in Figure I, the ion density production rate at a given altitude in the atmosphere (which is a function of the "atmospheric depth" i.e., of the mass of air above a unit of area at that altitude) is latitude dependent.

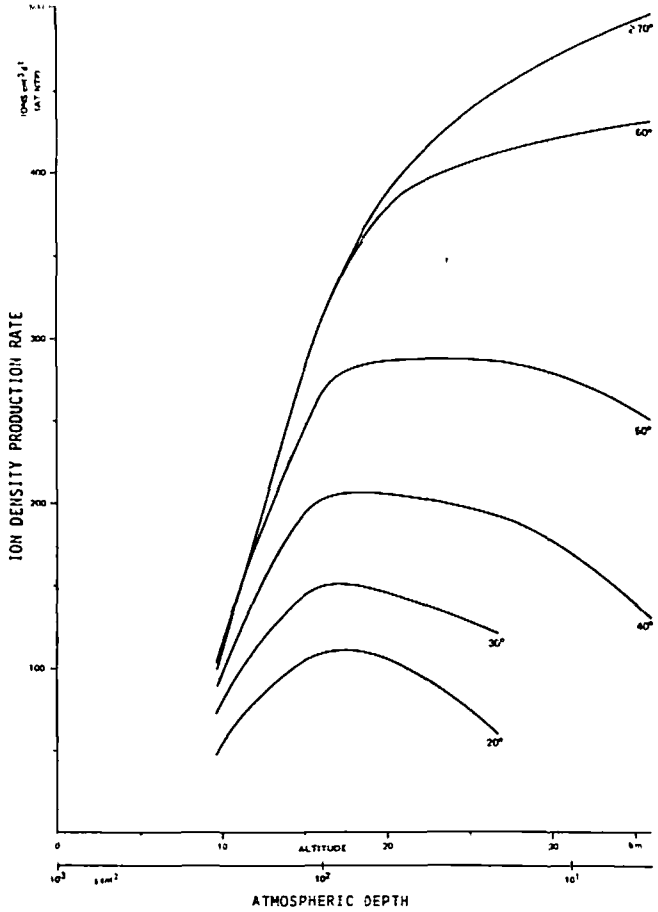

Figure I. Variation of ion density production rate with altitude and atmospheric depth at different geomagnetic latitudes. Based upon the results of Neher [N1]

5. The fluence rate of the galactic low-energy protons in the upper atmosphere varies with time according to the 11-year solar cycle. This is known as modulation. The fluence rate is at a minimum during times of maximum solar activity and passes through a maximum during the period of low solar activity.

(b) Primary solar cosmic rays

6. During the solar flares, large numbers of charged particles, mainly protons and alpha particles, are released. However, these particles have relatively low energies and do not usually cause significant increases in radiation doses at the earth's surface.

2. Secondary cosmic rays

7. When primary cosmic-ray particles enter the atmosphere, those with higher energy undergo nuclear reactions (spallation reactions) with nuclei of atoms present in the air, producing neutrons, protons, pions, and kaons, and quite a variety of reaction products (cosmogenic nuclides) such as ^{3}H, ^{7}Be, ^{10}Be, ^{22}Na, and ^{24}Na. The high-energy protons, neutrons and pions thus formed react further with nuclei in the air to form more secondary particles [G1, P1]. Such a process is called a cascade. The pions decay into muons or photons, initiating other cascades.

8. The protons and neutrons contribute significantly to the absorbed dose index rate[1] in the upper atmosphere. The neutrons lose energy by elastic collisions, and when thermalized they are captured by ^{14}N to form ^{14}C. Because nucleons rapidly lose energy by ionization and nuclear collisions, the nucleonic fluence rate is considerably attenuated in the lower part of the atmosphere and accounts for only a few per cent of the absorbed dose index rate from cosmic rays at sea level. The major contribution here is provided by the muons produced by the decay of charged pions at higher altitude and by the electrons that result from ionization, from muon decay and from cascade processes.

[1] The absorbed dose index rate is the maximum absorbed dose rate that would occur in a 30-cm diameter tissue equivalent sphere located with its centre at the point of interest.

3. Absorbed dose indexes from cosmic rays

9. The doses from directly ionizing components of cosmic rays and from neutrons will be examined separately.

(a) Ionizing component

10. The ion production rate per unit volume in free air is a measure of the fluence rate of the total charged-particle component of the cosmic-ray field and is usually expressed as the number of ions formed per second in each cubic centimetre of air at normal temperature and pressure (STP). The values of the cosmic ray ion density production rate at sea level reported after 1960 show a relatively good agreement, with a cluster of values around 2.1 cm^{-3} s^{-1} and extremes at 1.9 and 2.6 cm^{-3} s^{-1} [G2, G3, H1, K1, L1, O1, O2, S1, Y1]. Here, as in Annex B of the 1977 report [U1], a value of 2.1 cm^{-3} s^{-1} will be used for the purposes of computing the absorbed dose index rate. Assuming each ion pair in moist air requires 33.7 eV to be produced, the absorbed dose rate in air is 3.2 10^{-8} Gy h^{-1}. This value is taken to be numerically equal to the absorbed dose index rate. About 75% of the dose is from muon collision electrons, 15% from muon decay electrons, and 10% from other processes [N2]. If the shielding effect by building structures is not taken into account, the annual absorbed dose index is found to be 2.8 10^{-4} Gy at ground level. Using reported values of ion density production rate in the upper atmosphere, absorbed dose index rates have been computed there in a similar manner and are shown in Figure II [U1].

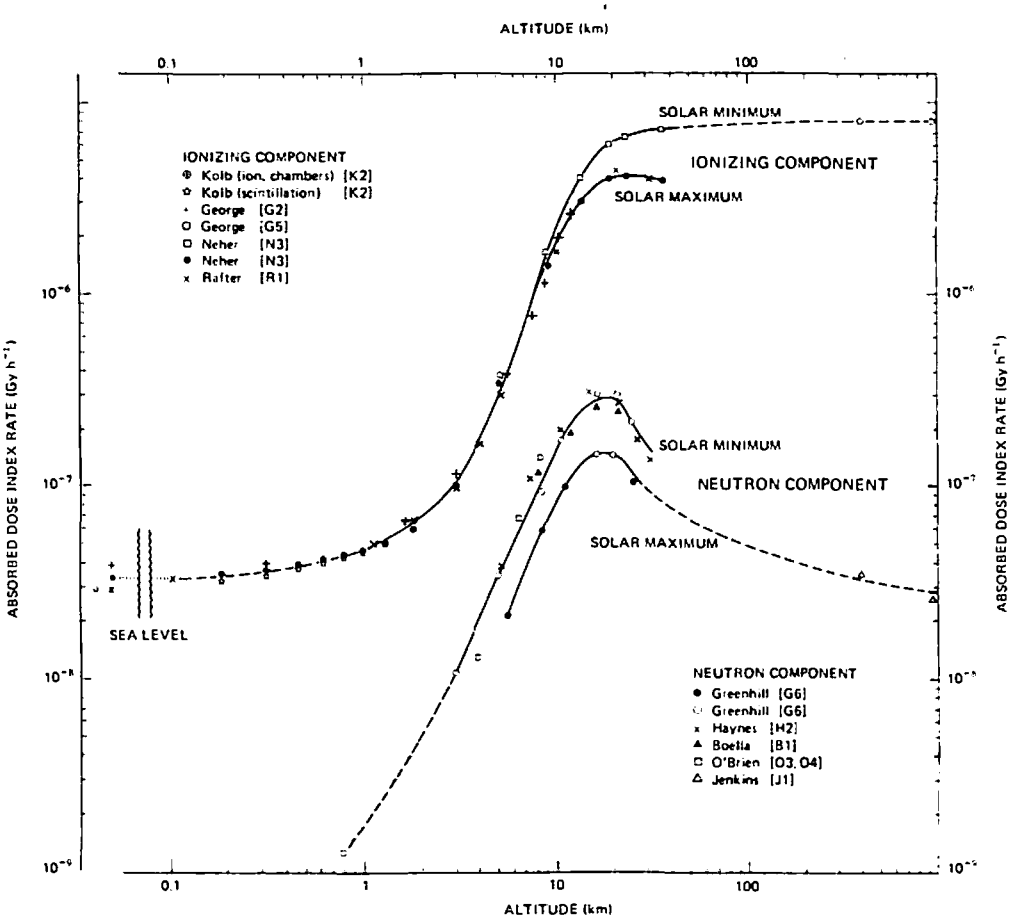

Figure II. Absorbed dose index rates at high geomagnetic latitudes (50°) from the ionizing and neutron components of cosmic rays at different altitudes for 1969 (solar maximum) and 1965 (solar minimum). The ionizing component of the absorbed dose index rate at 0.1 km is inferred from that at ground level

(b) Neutron component

11. As in Annex B of the 1977 report of UNSCEAR, a neutron fluence rate of 8 10^{-3} cm^{-2} s^{-1} at sea level is adopted for the purpose of estimating doses at high latitudes. Using a conversion factor from neutron fluence rate to absorbed dose index rate of 5 10^{-8} Gy h^{-1} cm^2 s [H3], the absorbed dose index rate would be 4 10^{-10} Gy h^{-1}, yielding an annual absorbed dose index of 3.5 10^{-6} Gy at ground level. The neutron absorbed dose index rate increases rapidly with altitude, reaching a maximum at altitudes between 10 and 20 km (Figure II).

4. Annual effective dose equivalents from cosmic rays

12. For both the ionizing and the neutron component, the absorbed dose index is assumed to represent sufficiently well the absorbed dose in all organs and tissues of the body. Using a value of one for the quality factor of the ionizing radiation, the annual effective dose equivalent is thus found to be 280 μSv at ground level.

13. For the neutron component a quality factor of 6 is adopted, as in Annex B of the 1977 report of the Committee [U1], on the basis of computations of the dose equivalent and of the absorbed dose by Hajnal et

al. [H3] for isotropic bilateral incidence on a slab averaged to a depth of 15 cm. The annual effective dose equivalent for the neutron component is thus estimated to be 21 μSv at ground level.

B. EXTERNAL RADIATION FROM NATURALLY-OCCURRING RADIONUCLIDES (TERRESTRIAL RADIATION)

1. Source radionuclides

14. The natural radionuclides in the environment are of two general classes, the cosmogenic and the primordial. The cosmogenic radionuclides (^{3}H, ^{7}Be, ^{14}C, ^{22}Na, ^{24}Na, etc.), which are mainly produced through interaction of the cosmic rays with target atoms in the atmosphere, do not contribute significantly to the external gamma radiation doses at ground level.

15. The main primordial radionuclides are ^{40}K, ^{87}Rb, and the elements of the two radioactive series headed by ^{238}U and ^{232}Th, which are presented in Figures III and IV and have existed in the earth's crust throughout its history. Other radionuclides, such as those present in the ^{235}U decay series, have been neglected as they contribute very little to the total dose from natural background.

16. It should be mentioned that ^{238}U is not only the head of a radioactive decay series but also gives rise to many radioactive nuclides by spontaneous fission. The inventory of the long-lived fission products in the earth's crust is rather large, but the average activity concentrations in soil are extremely small and the resulting doses trivial. Taking ^{90}Sr as an example, the inventory in the earth's crust is estimated to be $5\ 10^{16}$ Bq [S2]; its activity concentration in soil would be $2\ 10^{-6}$ Bq kg^{-1}, yielding an annual dose in red bone marrow of the order of 10^{-11} Gy.

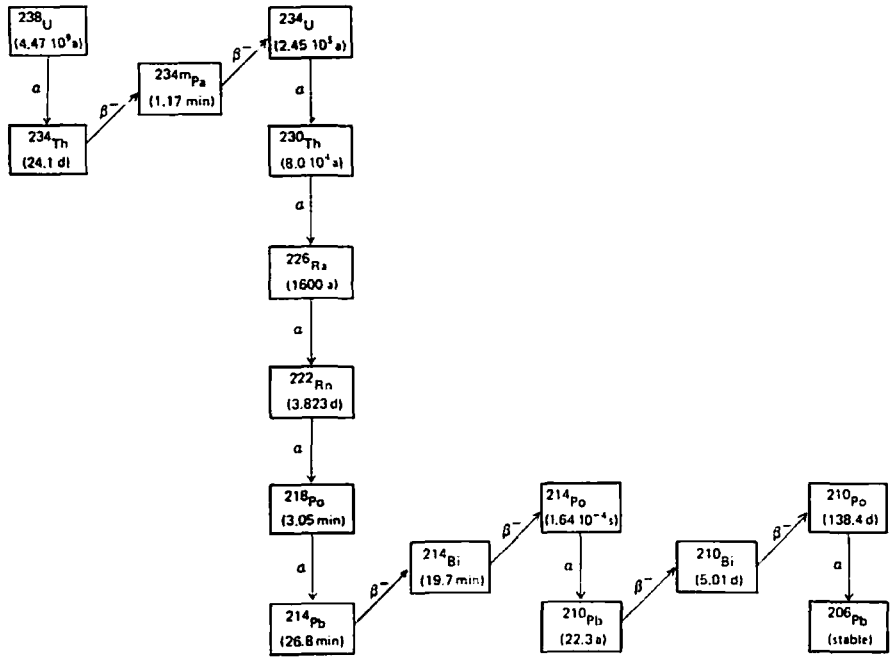

Figure III. Uranium-238 decay series. Radionuclides produced in less than one per cent of the transformations of the parent nuclide are not shown [L8]

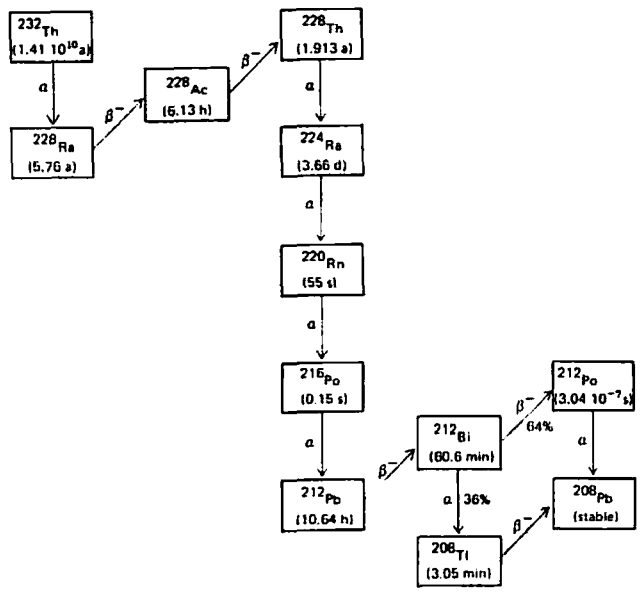

Figure IV. Thorium-232 decay series [L8]

2. Exposure outdoors

17. The concentration of radionuclides in soil, which is directly relevant to the outdoor exposure, is largely determined by the activity concentration in the source rock. Igneous rocks generally exhibit higher activity concentrations than sedimentary rocks, while metamorphic rocks have concentrations typical of the rocks from which they were derived. However, certain sedimentary rocks, notably some shales and phosphate rocks, are highly active [N2]. The average activity concentrations of ^{40}K, ^{238}U and ^{232}Th in soil and the corresponding absorbed dose rates in air 1 m above the ground surface, calculated on the assumption that all decay products of ^{238}U and ^{232}Th are in radioactive equilibrium with their precursors, are given in Table 1. The average outdoor terrestrial absorbed dose rate in air from gamma radiation would be 4.4 10^{-8} Gy h^{-1}, and the relative contributions of ^{40}K, ^{238}U and ^{232}Th about 35%, 25% and 40%, respectively.

18. Several surveys have been performed over whole countries and areas for the purpose of estimating the exposure of the relevant populations to outdoor external gamma radiation. Since the publication of the 1977 report of the Committee [U1], results have been reported from Denmark, France, Ireland, Japan, Norway, Poland and Romania: they are summarized in Table 2.

19. Intercomparisons between the above surveys are difficult as they were conducted using different methods and types of instrumentation. The results are also not altogether coherent as regards the quantity measured. Often in the same survey significant differences were shown when several types of instrumentation were used [N6]. Despite these difficulties, country-averaged absorbed dose rates in air fall within the relatively narrow range of 3.7 to 9.4 10^{-8} Gy h^{-1}, with a population-weighted average of 4.9 10^{-8} Gy h^{-1}. The population involved represents about 30% of that of the world, while the corresponding area covered is about 10% of the total land surface. The population-weighted value of 4.9 10^{-8} Gy h^{-1} is in relatively good agreement with the estimate of 4.5 10^{-8} Gy h^{-1} derived by the Committee in Annex B of the 1977 report [U1] for the global average of the absorbed dose rate in air, 1 m above ground, from gamma terrestrial radiation. A rounded value of 5 10^{-8} Gy h^{-1} will be adopted in this Annex.

20. The variability of the exposure around the mean values can be roughly assessed from the detailed results relative to the administrative subdivisions of France, the Federal Republic of Germany, Italy, Japan and the United States. Figure V presents the population-weighted frequency distribution of the outdoor absorbed dose rate in air from terrestrial radiation obtained from the combined data of the five countries.

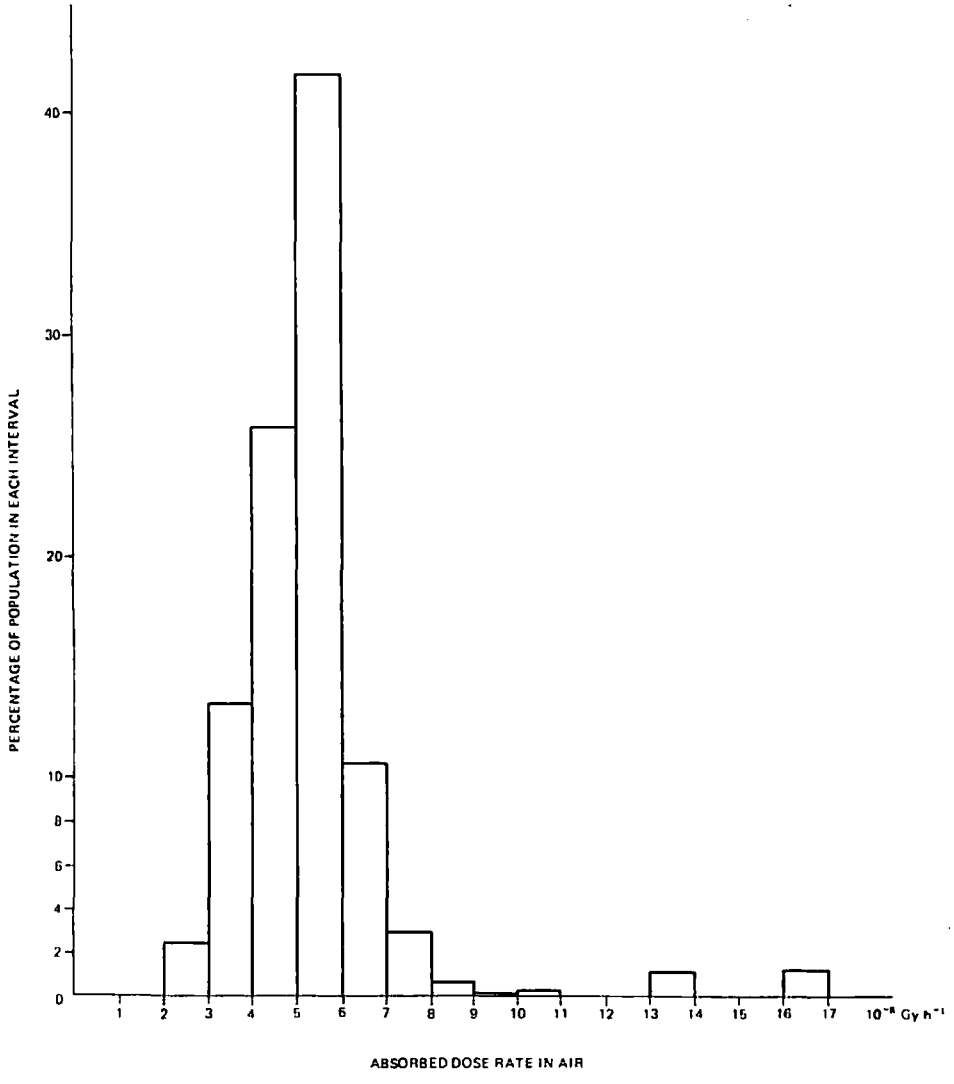

Figure V. Frequency distribution of outdoor absorbed dose rate in air from terrestrial radiation. Combined data from France [M8], the Federal Republic of Germany [C8], Italy [C2], Japan [A3] and the United States [O7]

From Figure V, it is seen that a large fraction of the population lives in areas where the population-weighted distribution of the outdoor absorbed dose rate in air is normally distributed, while another fraction, much smaller, lives in areas outside of the normal distribution. The average absorbed dose rate in air in the "normal" areas of the five countries is 5.2 10^{-8} Gy h^{-1}, with a standard deviation of approximately 1 10^{-8} Gy h^{-1}. Assuming that the distribution holds on a global basis, 95% of the world population residing in areas of "normal" natural radiation would live where the outdoor absorbed dose rate in air from the primordial radionuclides falls between about 3 and 7 10^{-8} Gy h^{-1}. However, it should be borne in mind that these values are themselves averages, corresponding to population groups of at least 10^5 people.

21. As shown in Figure V, there are regions in the world where the outdoor terrestrial radiation substantially exceeds the normal range of variation. In addition to the Italian provinces of Lazio and Campania, such regions are known to exist in Brazil, France, India, Iran, Madagascar and Nigeria [B3]. The best known from a dosimetric point of view are those located in Brazil and India.

22. Deposits of radioactive minerals rich in monazite occur in littoral formations along the coastal regions of India. Of particular interest is a stretch about 250 km long and about 0.5 km wide on the south-west coast in the states of Kerala and Tamil Nadu. The most concentrated deposits along the Kerala coast are located on a 55 km strip populated by about 70 000 persons, where the thorium concentration in the monazite ranges from 8.0 to 10.5% by weight, being the highest known in the world [G7]. Gopal-Ayengar et al. [G7, G8] carried out a dosimetric survey using thermo-luminescent dosimeters distributed to 8513 individuals of the population of that 55 km strip. Assuming an homogeneous whole-body irradiation, the average absorbed dose rate for the 70 000 people residing in the region can be estimated at 4.3 10^{-7} Gy h^{-1}; about 24% of the people would experience average absorbed dose rates in excess of 5.7 10^{-7} Gy h^{-1}, about 6% would exceed 10^{-6} Gy h^{-1} and about 0.7% would exceed 2.3 10^{-6} Gy h^{-1}. As the thermoluminescent dosimeters were worn on a 24-hour basis, these results represent an average (outdoors plus indoors) absorbed dose rate from terrestrial radiation.

23. Two types of high-background regions have been found in Brazil: the monazite sand region along the Atlantic coast of the states of Espirito Santo and Rio de Janeiro and the volcanic intrusive anomalies along a geological fracture that extends from the coast through the inland state of Minas Gerais [P2].

24. Along the Atlantic coast, the radiation levels in three towns (Guarapari, Meaipe and Cumuruxatiba) built over monazite sands were surveyed in detail by Roser and Cullen [R3]. Guarapari is a community of 12 000 people which receives an influx of about 30 000 vacationers every summer. In that town, the absorbed dose rates in air were found to range from 10^{-6} to 2 10^{-6} Gy h^{-1} in the streets and up to 2 10^{-5} Gy h^{-1} over selected spots on the beach [P3, R3]. Cullen [C1] by means of thermoluminescent dosimeters distributed to 317 inhabitants of Guarapari determined the average absorbed dose rate from external terrestrial irradiation (indoors plus outdoors) to be 6.3 10^{-7} Gy h^{-1}, with a range of 1 10^{-7} to 3.2 10^{-6} Gy h^{-1}.

25. Meaipe is a fishing village of about 3000 people, situated 50 km to the South of Guarapari, where the radiation environment is similar: the outdoor average absorbed dose rate in air is about 10^{-6} Gy h^{-1} with levels up to 10^{-5} Gy h^{-1} [P2]. In Cumuruxatiba, the average level is 5 10^{-7} Gy h^{-1} [R3].

26. In the state of Minas Gerais, two volcanic regions have been intensively studied, Poços de Caldas and Araxá-Tapira. There is a hill near the city of Poços de Caldas where absorbed dose rates in air of up to 2.8 10^{-5} Gy h^{-1} have been reported. However, this hill is small and uninhabited. In Araxá-Tapira, absorbed dose rates in air up to 4 10^{-6} Gy h^{-1} have been measured.

27. Quantitative information on the outdoor absorbed dose rates in air in other areas of high natural radiation levels is very limited. It is worth noting that in the city of Ramsar, Iran, absorbed dose rates in air ranging from 7 10^{-7} to 5 10^{-5} Gy h^{-1} have been measured within an area of a few square kilometres, characterized by the presence of ^{226}Ra-rich spring water [K3].

3. Exposure indoors

28. Knowledge of radiation levels in buildings is important in the assessment of population exposure, as most individuals spend a large portion of their time indoors. Table 3 summarizes the results obtained in the few large scale surveys of indoor exposure that have been reported. As the number of country-wide indoor surveys is relatively small compared to those conducted outdoors, the average absorbed dose rate in air indoors has been estimated from the outdoor value using an indoors to outdoors ratio.

29. The relationship between the indoor and the outdoor absorbed dose rates depends essentially on the type of building material used and on its origin. The building materials act as sources of radiation and also as attenuators of outdoor radiation. In wooden and prefabricated houses the source effect is negligible and the walls are an inefficient shield with respect to the outdoor sources of radiation, so that the absorbed dose rate is generally lower indoors than outdoors. The indoors to outdoors ratios presented in Table 3 range from 0.7 to 1.0 for wooden and prefabricated houses.

30. In massive houses made of bricks, concrete or stone, the gamma rays emitted outdoors are efficiently absorbed by the walls and the indoor absorbed dose rate depends mainly on the activity concentrations of natural radionuclides in the building materials. If they are of local origin, as is frequently the case, it may generally be assumed that the concentrations of natural radionuclides in the building materials are equal to those in the soil or the pavement surrounding the dwelling. Under these circumstances, it may be expected that the value of the indoors to outdoors ratio of the absorbed dose rates in air lies between 1 and 2, as the result of the change in source geometry and of the presence of doors and windows.

31. Calculations taking into account the thickness and the dimensions of the walls yielded ratios of 1.35 for typical brick dwellings and 1.48 for concrete buildings [K11], which are in good agreement with the results obtained in the extensive survey conducted in the Federal Republic of Germany [D2] and also with the large number of data from Norway [S6, S7] and Austria [T2]. In order to obtain a representative value of the indoor absorbed dose rate in air, the indoor to outdoor

ratios should be weighted according to the relative number of dwellings made of wood, brick or concrete. In Annex B of its 1977 report [U1], the Committee estimated the overall ratio to be about 1.2, which figure is also adopted in this Annex. This figure, combined with an average outdoor absorbed dose rate in air of $5\ 10^{-8}$ Gy h^{-1}, yields an indoor absorbed dose rate in air, averaged over the world, of $6\ 10^{-8}$ Gy h^{-1}. It is recognized that this figure is lower than the population-weighted average absorbed dose rates in air reported for a few countries (Table 3). It is felt however that these countries being all located in the northern part of Europe are not representative of the world-wide situation. More information would be required in order to provide a better estimate.

4. Annual effective dose equivalents from gamma terrestrial radiation

32. The most appropriate average value of the quotient of effective dose equivalent rate to absorbed dose rate in air appears now to be 0.7 for environmental exposures to gamma rays of moderate energy (see Annex A, paragraph 27). This value applies equally to males and females, and to the indoor and outdoor environments. Taking the outdoor occupancy factor to be 0.2, the annual effective dose equivalent from outdoor terrestrial gamma radiation is found to be

$$5\ 10^{-8}\,(\text{Gy h}^{-1}) \times 0.7\,(\text{Sv Gy}^{-1}) \times 8760\,(\text{h a}^{-1}) \times \times\ 0.2 = 6.1\ 10^{-5}\ \text{Sv}.$$

As to indoor exposure, using an occupancy factor of 0.8, the annual effective dose equivalent would be

$$6\ 10^{-8}\,(\text{Gy h}^{-1}) \times 0.7\,(\text{Sv Gy}^{-1}) \times 8760\,(\text{h a}^{-1}) \times \times\ 0.8 = 2.9\ 10^{-4}\ \text{Sv}.$$

33. The total (outdoors plus indoors) annual effective dose equivalent from terrestrial radiation, averaged over the world's population, would thus lie between $3\ 10^{-5}$ and $4\ 10^{-4}$ Sv. For the purpose of this report a representative value of $3.5\ 10^{-4}$ Sv has been adopted. From information contained in Annex B of the 1977 report of UNSCEAR [U1], 95% of the world population would thus receive annual effective dose equivalents in the range from about $2\ 10^{-4}$ to $5\ 10^{-4}$ Sv. In addition to the gamma radiation, the beta rays emitted by the naturally-occurring radionuclides contained in the soil and air contribute to a small extent to the effective dose equivalent from terrestrial radiation. According to O'Brien [O5], the annual effective dose equivalent resulting from beta radiation would be about $7\ 10^{-6}$ Sv. The radon and thoron decay products present in air contribute also to the total effective dose equivalent from external gamma radiation to a small extent [B2, O5].

II. INTERNAL IRRADIATION

34. Radioactive nuclides occurring in the biosphere enter the human body through ingestion and inhalation. The absorbed doses from internal exposure in lungs, gonads, red bone marrow, bone lining cells and other tissues will be estimated as well as the effective dose equivalent. For all radionuclides considered, ^{7}Be and ^{22}Na excepted, the absorbed doses are derived from measurements of the concentrations, in body organs or tissues, of the radionuclide concerned or of the most abundant stable isotope of the element. As discussed in Annex A, the conversion from the activity concentrations in tissues to the absorbed dose rates is based on ICRP models [I1].

A. COSMOGENIC RADIONUCLIDES

35. Very little of the dose from natural background is contributed by the cosmogenic radionuclides. Of the many nuclides produced by cosmic rays, only ^{3}H, ^{7}Be, ^{14}C and ^{22}Na contribute appreciably to the dose. The production and distribution of these nuclides in the environment is presented in Table 4, while Tables 5 and 6 show the resulting annual tissue doses in man.

1. Tritium

36. The major source of natural tritium is the atmosphere, where it is formed mainly from the interaction of cosmic-ray neutrons with nitrogen and oxygen. About 99% of the ^{3}H inventory, which is taken to be $1.3\ 10^{18}$ Bq is converted to tritiated water (HTO) and participates in the normal water cycle. Activity concentrations of surface waters, measured before nuclear explosions began, were found to be in the range 200–900 Bq m^{-3} for continental waters and about 100 Bq m^{-3} for ocean waters [K5]. In this report, the average activity concentration of natural tritium in continental surface waters is taken to be 400 Bq m^{-3}. Tritium enters food crops in the form of HTO and is partly incorporated into organic matter. Therefore, tritium in the diet can be in the form of HTO and of organic compounds. As the environment has been contaminated with artificial tritium since the early 1950s, there is no direct measurement of the natural tritium concentration in human tissues and the doses from natural tritium have to be estimated on the basis of indirect evidence.

37. In this Annex, as in Annex B of the 1977 report of UNSCEAR [U1], the absorbed dose rates due to natural tritium have been estimated by assuming that the specific activities of ^{3}H in body tissues are the same as those in the continental surface waters before nuclear explosions began; the annual absorbed doses obtained in that way are of the order of 10^{-8} Gy in all tissues (Table 5).

2. Beryllium-7

38. Environmental concentrations of ^{7}Be in the temperate zones are about 3000 μBq m^{-3} in surface air [K9] and 700 Bq m^{-3} in rainwater [A2]. The main pathway to man would be the ingestion of leafy vegetables, resulting in an annual intake of about 50 Bq [N4]. The tissue absorbed doses calculated using ICRP dosimetry [I1] are found to be 12 μGy in the walls of the lower large intestine and somewhat lower in the other tissues (Table 6). The annual effective dose equivalent would be about 3 μSv.

3. Carbon-14

39. Natural ^{14}C is produced in the upper atmosphere by the reaction ^{14}N(n,p)^{14}C induced by slow cosmic-ray neutrons. The specific activity in biological carbon, as measured in wood samples of trees grown in the nineteenth century, was 227 ± 1 Bq kg^{-1} of carbon [T1], corresponding to an atmospheric inventory of 140 PBq.

During the present century the specific activity of ^{14}C in air has decreased due to the diluting effect of releases into the atmosphere of carbon dioxide from the burning of fossil fuels; this is known as the Suess effect [S3].

40. In its 1977 report [U1], UNSCEAR estimated the world's inventory of natural ^{14}C to be about 60 times the amount found in the atmosphere, leading to a value of approximately 8500 PBq, corresponding to a production rate of 1 PBq a^{-1}.

41. Taking the natural specific activity of ^{14}C in the body to be 227 Bq kg^{-1} of carbon, and using the concentrations of carbon in body tissues indicated by ICRP for the Reference Man [I2], the annual absorbed doses in tissue are found to be in the range from 5 to 24 μGy (Table 5). The annual effective dose equivalent would be 12 μSv. This value is in agreement with the figure derived from ICRP [I1], assuming an annual intake of 93 kg of carbon [I2].

4. Sodium-22

42. The annual absorbed doses from ^{22}Na have been calculated on the basis of an annual intake by ingestion of 50 Bq [N4] and using ICRP dosimetry [I1]. The annual absorbed doses in tissues are in the range of 0.1 to 0.3 μGy (Table 6), corresponding to an annual effective dose equivalent of about 0.2 μSv. Even though the production rate and the atmospheric concentration of ^{22}Na are very small (Table 4), the estimated annual absorbed doses arising from the incorporation of that radionuclide (Table 6) are higher than those due to ^{3}H (Table 5) because of the metabolic behaviour of sodium and of the decay properties of ^{22}Na.

B. PRIMORDIAL RADIONUCLIDES

43. The primordial radionuclides include those belonging to the ^{235}U, ^{238}U and ^{232}Th series and some other nuclides, among which only ^{40}K and ^{87}Rb are significant sources of radiation.

1. Potassium-40

44. Potassium is an essential element, and is under close homeostatic control in the body. The average mass concentration for an adult male is about 2 g of potassium per kg of body weight [A1, K10]. The isotopic ratio of ^{40}K is 1.18 10^{-4} and the average activity concentration of ^{40}K in the body is about 60 Bq kg^{-1}. The distribution of potassium in various tissues and organs of the body [K10] and the corresponding absorbed dose rates are presented in Table 7. The highest annual absorbed dose (270 μGy) is received in the red bone marrow. The annual effective dose equivalent is estimated to be 180 μSv.

45. The variation of the mass of potassium in the total body with age and sex has been investigated by several groups. In the United States during the period 1956–1961, total body potassium was determined in about 3000 subjects who ranged from less than one year to 79 years of age [A4, I2]. The results of this study show that the concentrations of potassium in the total body increase from birth to about 10 years for girls and 18 years for boys, when they reach estimated average values of about 2.1 and 2.3 g kg^{-1}, respectively; the concentrations then decrease rather sharply until the age of 20 and more gradually later on [A4, I2]. Actually the variation with age and sex of the concentration of potassium in the total body reflects the amount of relatively potassium-free adipose tissue which is present with the "lean body mass" in the total body at different ages [I2]. Similar results were found by Oberhausen [O8] in the Federal Republic of Germany in a study involving 12 000 subjects. The relationship between the mass of potassium in the total body and the age was found to be linear for boys and girls under 12 [S10]. With respect to adults, Andrasi and Beleznay [A1], from measurements on about 600 subjects derived the following linear relationships between the quotient of the mass of potassium in the body C, in g kg^{-1}, for the whole body and the age A, in years:

$$C = 2.34 - 0.0110\ A \text{ for males and}$$

$$C = 1.99 - 0.0109\ A \text{ for females.}$$

2. Rubidium-87

46. Very little is known about the behaviour of rubidium in man's environment. From the mass concentrations of rubidium in the ICRP Reference Man [I2], the average activity concentration of ^{87}Rb in the body would be 8.5 Bq kg^{-1}. Table 7 presents the assumed distribution of rubidium in the body and the resulting absorbed dose rates from ^{87}Rb. Bone lining cells receive the highest annual dose (14 μGy). The annual effective dose equivalent is estimated to be about 6 μSv.

3. Uranium-238 series

47. Uranium-238 is the head of a series of 15 principal nuclides (Figure III). In its 1972 and 1977 reports [U1, U2], the Committee has classified the ^{238}U series in subseries in which the activity of the precursor controls to a large degree the activities of the decay products. The ^{238}U series has been divided into: (1) $^{238}U \rightarrow {}^{234}U$; (2) ^{230}Th; (3) ^{226}Ra; (4) $^{222}Rn \rightarrow {}^{214}Po$, which is discussed in detail in Annex D; (5) $^{210}Pb \rightarrow {}^{210}Po$. For each subseries, the intakes by inhalation and by ingestion as well as the concentrations in bone and in soft tissues will be estimated. The conversion from the activity concentrations in bone and in soft tissues to the absorbed doses is based on the models described in ICRP Publication 30 [I1].

(a) Uranium-238 subseries (^{238}U, ^{234}Th, ^{234m}Pa, ^{234}U)

48. In this Annex, uranium is assumed to consist of ^{238}U in radioactive equilibrium with ^{234}Th, ^{234}Pa and ^{234}U, so that 1 kg of uranium contains 12 MBq of each of the four radionuclides. The contribution of ^{235}U and its decay products to the total dose from natural background has been neglected.

49. In the atmosphere, the main natural source of uranium has been assumed to be the resuspension of dust particles from the earth. Assuming a dust loading of about 50 μg m^{-3} in surface air of populated areas, and taking an average ^{238}U activity concentration in soil of 25 Bq kg^{-1} (Table 1), the activity concentration in ground level air is estimated to be about 1.2 μBq m^{-3}. Measurements of the activity concentration in ground level air, as for example in Munich (Federal Republic of Germany) confirm the validity of the assumption

[J4]. The corresponding annual intake by adults through inhalation is approximately 0.01 Bq (Table 8).

50. The annual dietary intake of ^{238}U has been found to be about 5 Bq in areas of "normal" natural activity [U1] and the contribution of drinking water is generally negligible in comparison. However, it should be mentioned that very high concentrations of uranium in tap water have been reported. In France [R4, R5] and in the USSR [B6], activity concentrations as high as 1.0 and 2.6 kBq m^{-3}, respectively, have been observed. In Helsinki, Finland, activity concentrations of the order of 100 kBq m^{-3} have been measured in several wells, the highest concentration being about 200 kBq m^{-3} [K7]. According to the authors [K7], the very high concentrations of uranium in the water of those wells are probably caused by small, localized uranium-rich deposits.

51. Measured values of the activity concentrations of ^{238}U in bone of adults who have lived in areas with "normal" dietary levels are in the range of 100 to 200 mBq kg^{-1}, yielding an activity in bone of about 0.7 Bq [J4, U1]. In soft tissues, the activity concentrations of ^{238}U cover a much broader range. The measured values lie between 1 and 10 mBq kg^{-1} for most of the soft tissues and between 10 and 80 mBq kg^{-1} for kidneys [J4]. Assuming that the distribution of the activity in the body is 70% in bone and 30% in soft tissue [J4], and that the levels in kidney are 10 times higher than those in other soft tissues, the average activity concentrations are found to be about 150 mBq kg^{-1} in bone, 50 mBq kg^{-1} in kidneys and 5 mBq kg^{-1} in the other soft tissues. The resulting annual absorbed doses vary from $2\ 10^{-8}$ Gy in lung to $3\ 10^{-6}$ Gy in bone lining cells (Table 9).

(b) Thorium-230

52. The activity intake of ^{230}Th through inhalation, estimated in the same way as for ^{238}U, is about 0.01 Bq a^{-1}. There is no information on the dietary intake of ^{230}Th. However, the activity ingested is probably a negligible contribution to the body content of ^{230}Th because of the very low absorption of thorium through the gastro-intestinal tract.

53. Thorium is a bone seeker which has a long residence time in the skeleton and is assumed to remain on the bone surfaces [I1]. The distribution of ^{230}Th in human tissues has been investigated by Wrenn and his collaborators [S9, W1, W4]. In samples of two population groups living in Colorado and in Washington, D.C., the highest concentrations were in general measured in the lymph nodes, followed by bone, lung, kidneys, liver and spleen. The mass of bone being much greater than that of the lymph nodes, most of the thorium body content was found in the skeleton (about 70%). As thorium has a long residence time in the skeleton, the concentration of ^{230}Th in bone increases continuously with age for a constant rate of intake. On the basis of the available measurements [S9, W1, W4], it seems that a typical activity of ^{230}Th in bone is 140 mBq, resulting in activity concentrations of approximately 20 mBq kg^{-1} in cortical bone and 70 mBq kg^{-1} in trabecular bone. This is on the assumption that the deposit of thorium is proportional to the bone area. In soft tissues, representative values of the activity concentrations could be 300 mBq kg^{-1} in lymph nodes, 20 mBq kg^{-1} in lungs, 10 mBq kg^{-1} in kidneys, 7 mBq kg^{-1} in liver and 0.3 mBq kg^{-1} in the other soft tissues. The corresponding annual absorbed doses are presented in Table 10. The annual effective dose equivalent is estimated to be about 7μSv.

(c) Radium-226

54. For inhalation, as in the case of uranium and thorium, the main natural source of radium in the air at ground level is assumed to be the resuspension of soil particles; this corresponds to a calculated activity intake of about 0.01 Bq a^{-1}.

55. Food is a much more important source of radium for intake and blood uptake than is inhalation. The average annual dietary intake of ^{226}Ra in areas of normal radiation background is about 15 Bq (see Annex B in the UNSCEAR 1977 report [U1]). The contribution of drinking water is generally small when the drinking water supplies are drawn from surface waters. However, activity concentrations of 0.1 Bq l^{-1} are not exceptional in well and mineral waters [K12, K13, M7, P7, R4, R5]. In France, for example, an activity concentration of 2.7 Bq l^{-1} has been measured in a spring used as drinking water [R4, R5]. The population groups drinking exclusively those waters are expected to derive most of their ^{226}Ra intake from the water.

56. Two well-known populated areas with high concentrations of uranium in their soil are located along the coast of Kerala in India and in the Araxá-Tapira region in Brazil. The estimated average annual intake of ^{226}Ra of the Indian population along the Kerala coast is 40 Bq [C3, M1]. In Brazil, a survey in the Araxá-Tapira region showed that, out of a population of 1670 people living in and around the radioactive anomalies of Barreiro and Tapira, only 196 individuals ingested alpha emitters at a level 5 times or more than that of a similar group living in Rio de Janeiro. The annual ^{226}Ra intake of those individuals ranged from 140 to 540 Bq [P4].

57. When radium is taken into the body, its metabolic behaviour is similar to that of calcium, and an appreciable fraction is deposited in bone [E2]. About 70–90% of the radium in the body is contained in bone [I3], the remaining fraction being distributed approximately uniformly in soft tissues. Fisenne et al. [F1] have summarized the available data from 26 countries on measured activity concentrations of ^{226}Ra in human bone. The 26 countries sampled have $1.4\ 10^9$ persons and thus represent about 30% of the world population. The population-weighted distribution was found to have a median of 850 mBq per kg of calcium (corresponding to 170 mBq per kg of bone and to 850 mBq in the skeleton) and a geometric standard deviation of 1.6. If the fraction of ^{226}Ra distributed in the soft tissues is taken to be 17%, as given in ICRP publication 20 [I3], the average activity concentration in human soft tissues is found to be 2.7 mBq kg^{-1}.

58. The annual absorbed doses in tissues have been calculated using the same assumptions as in Annex B of the 1977 report, namely, that an average retention factor of 0.33 applies to ^{222}Rn in the skeleton and also, conservatively, in soft tissues; and that the concentration of radium and its decay products is uniform over the total mass of mineral bone. The results are presented in Table 11. The annual effective dose equivalent resulting from ^{226}Ra intake in "normal" areas is found to be about 7 μSv.

59. Data on the activity of radium in the skeleton of people living in the high radiation areas of Brazil and India are very scarce. In Brazil, the mean ^{226}Ra concentration in the teeth of the population living in the Araxá-Tapira region has been estimated as approximately 3 Bq kg^{-1} of ash, which corresponds to an activity in the skeleton of about 8 Bq, assuming that the concentration in teeth is the same as that in bone. In India, the analysis of a femur yielded a ^{226}Ra concentration per unit mass of ash of 5 Bq kg^{-1}, which corresponds to a skeletal activity of about 15 Bq [C3].

(d) Radon-222, and its short-lived decay products (^{218}Po, ^{214}Pb, ^{214}Bi, and ^{214}Po)

60. Man is exposed to ^{222}Rn (radon) and to its short-lived decay products mainly by inhalation. Mean annual values of radon concentration in outdoor air vary between 0.1 and 10 Bq m^{-3}. Over land, a reasonable estimate of the average concentration at ground level is 3 Bq m^{-3}; taking the equilibrium factor to be 0.6, the average equilibrium equivalent concentration of radon in outdoor air at ground level is estimated to be 1.8 Bq m^{-3}.

61. In temperate latitudes, the average equilibrium equivalent concentration of radon in air is several times higher indoors than outdoors. The mean values of the indoor equilibrium equivalent radon concentrations in different countries cover the range from 5 to 25 Bq m^{-3}, with the exception of Sweden, where the average value is 60 Bq m^{-3}. For the total population in the temperate regions of the world, 15 Bq m^{-3} seems to be an appropriate mean indoor equilibrium equivalent concentration.

62. Using the dose conversion coefficients derived in Annex D, the annual effective dose equivalents corresponding to the average equilibrium equivalent concentrations of radon outdoors and indoors in temperate latitudes are estimated to be 0.92 mSv from indoor exposure and about 0.06 mSv from outdoor exposure, giving a total of about 1 mSv for inhaled ^{222}Rn daughters.

63. For equatorial regions no measurements are available. Because of the different domestic conditions, the indoor level of radon daughters in this region might be considerably lower than in temperate regions. For large population groups this level will be comparable with the normal outdoor level, leading to an annual effective dose equivalent of about 0.2 mSv. Taking into account that about two thirds of the total world population is living in temperate regions, a global mean value of about 0.8 mSv per year—averaged over all age groups—from inhaled ^{222}Rn daughters should be expected.

64. Table 12 summarizes the estimated equilibrium equivalent concentrations of ^{222}Rn and the corresponding annual effective dose equivalents. A detailed treatment of the exposures to ^{222}Rn and its daughters is provided in Annex D.

(e) Long-lived decay products of ^{222}Rn (^{210}Pb, ^{210}Bi, and ^{210}Po)

65. For inhalation, the main source of ^{210}Pb and ^{210}Po in the atmosphere is ^{222}Rn emanation from the ground. In the mid-latitudes of the northern hemisphere, the average concentration of ^{210}Pb in surface air has been estimated to be 0.5 mBq m^{-3} [J2]. The $^{210}Po/^{210}Pb$ activity ratio in ground level air being about 0.2 [J3], the activity concentration of ^{210}Po is about 0.1 mBq m^{-3}. Assuming that the atmospheric concentrations are the same indoors and outdoors, the annual intakes of non-smokers would thus be 4 Bq of ^{210}Pb and 0.8 Bq of ^{210}Po. Cigarette smoking will lead to an increase in the intake of ^{210}Pb and ^{210}Po through inhalation [P5].

66. Consumption of food is usually the most important route by which ^{210}Pb and ^{210}Po enter the human organism. For the areas of normal intake, a value of 40 Bq was taken in Annex B of the 1977 report [U1] as representative of the annual intake of ^{210}Pb and ^{210}Po. Recent estimates for the populations of India and of Italy are in good agreement with that figure [C7, L7]. It should be noted however that lower values are consistently obtained for the populations of the United States [H9, H10]. High concentrations of ^{210}Po are observed in the edible portions of aquatic organisms, for which it is well established that the $^{210}Po/^{210}Pb$ activity concentration ratio is greater than 1 [C4]. The ^{210}Po concentrations in the muscles of fish and in molluscs are approximately 0.7 and 20 Bq kg^{-1}. The intakes of ^{210}Pb and ^{210}Po in populations consuming large proportions of seafood are therefore expected to be higher than those of populations with other types of diet.

67. A well-documented case of elevated intake is that of the tens of thousands of individuals living on reindeer or caribou meat in the arctic and sub-arctic regions of the northern hemisphere [H10, P8]. Their main food is the meat of these animals, which contains unusually high concentrations of ^{210}Po because in the winter they graze on lichens which accumulate ^{210}Pb and ^{210}Po. The annual intakes of ^{210}Pb and ^{210}Po by the populations living on reindeer or caribou meat are about 140 Bq for ^{210}Pb and about 1400 Bq for ^{210}Po. Another documented case of elevated intake relates to an uranium-rich area of Western Australia, where the annual intake of ^{210}Pb from the carcasses of local sheep and kangaroos is about 100 Bq and from the offal about 300 to 3000 Bq [W5].

68. In view of the short half-life of ^{210}Bi (5 d), the activity intakes of that radionuclide can be assumed to be the same as those of ^{210}Pb. Precise values are of no interest for the purpose of this Annex as ^{210}Bi can be assumed to be in radioactive equilibrium with ^{210}Pb in the body tissues so that the absorbed doses from ^{210}Bi mainly arise from the intake of ^{210}Pb and not from the intake of ^{210}Bi itself.

69. Concerning distribution in man, lead is a bone seeker which is found incorporated in bone mineral, from where it seems to be eliminated by long-term skeletal remodelling [H6, L6]. About 70% of the body content of ^{210}Pb is found in the skeleton [J2]. In continental areas of the northern latitudes, a typical activity concentration of ^{210}Pb in bone would be 3 Bq kg^{-1} [U1]. The skeletal activity would thus be 15 Bq and the activity in soft tissues would be 6.4 Bq distributed relatively uniformly throughout the body (Table 13).

70. Polonium, in contrast to all the other natural alpha emitters, is not a bone seeker but is rather distributed in soft tissues after intake. Therefore, the greatest part of the ^{210}Po bone activity arises from the decay of deposited ^{210}Pb [H7, W2]. Average measured ratios of ^{210}Po and ^{210}Pb activity concentrations in bone range

from 0.5 to 1.1 [B7, H4, K8, L5, M2]. A value of 0.8 is assumed to be representative for the purposes of this Annex. The ^{210}Po concentration in bone would thus be about 2.4 Bq kg^{-1} for the populations living in continental areas in temperate regions of the northern hemisphere.

71. In soft tissues, the activity of ^{210}Po is about the same as that of ^{210}Pb. Typical concentrations of ^{210}Pb and ^{210}Po in the gonads are about 0.2 Bq kg^{-1} [B7, L5, B8]. In lungs the concentrations in non-smokers are around 0.1 Bq kg^{-1} for ^{210}Po and 0.2 Bq kg^{-1} for ^{210}Pb [B7, H5]. In red bone marrow, Ladinskaya et al. [L5] measured a ^{210}Pb concentration of 0.14 Bq kg^{-1} and a ^{210}Po/^{210}Pb activity ratio of 0.8. Although in most of the soft tissues the ^{210}Po/^{210}Pb activity concentration ratio is about 1, it is clearly greater than 1 in a few organs such as the liver and kidney. The excess ^{210}Po is probably taken up directly from food and would be partly attributable to a higher rate of incorporation for ^{210}Po than for ^{210}Pb in those organs [J2]. The additional intake due to smoking leads to increased concentrations of ^{210}Pb and ^{210}Po in organs and tissues. As expected, it is in the lung that the increases are most clearly marked. The concentrations in that organ exceed on the average the levels found in non-smokers by factors of about 1.5 for ^{210}Pb and 3 for ^{210}Po [B7, H7, H10, P5, R2]. The figures given in Table 13 correspond to non-smokers.

72. With respect to the arctic and sub-arctic populations, measurements carried out on the blood, placenta and bone tissues of inhabitants of the northern regions who consume reindeer or caribou meat regularly show levels higher than those in the populations of the temperate latitudes. The increase is by a factor of 2 to 3 for ^{210}Pb in all tissues and for ^{210}Po in bone tissues and by a factor of about 10 for ^{210}Po in soft tissues [H10, K8, P8].

73. The absorbed doses from the ^{210}Pb subseries depend mainly on the highly energetic alpha particles of ^{210}Po, as the contribution from the beta emissions of ^{210}Pb and ^{210}Bi amounts to about 10% of the total. Table 13 presents the estimated annual absorbed doses from ^{210}Pb, ^{210}Bi and ^{210}Po for non-smokers in areas of normal dietary intake. The annual effective dose equivalent arising from the total intake of ^{210}Pb, ^{210}Bi and ^{210}Po would be about 130 μSv. The corresponding figure for the populations living on reindeer or caribou meat would be about 10 times higher.

4. Thorium-232 series

74. Thorium-232 is the head of a series of 12 nuclides (Figure IV). The ^{232}Th and the ^{238}U series present strong similarities: they include isotopes of the same elements (radium, radon, lead, bismuth, polonium) and contain a large proportion of α-emitters. The main difference between the two series is that ^{232}Th is the only very long-lived radionuclide in its chain.

75. The ^{232}Th series has been divided into three subseries: (a) ^{232}Th itself; (b) ^{228}Ra → ^{224}Ra; (c) ^{220}Rn → ^{208}Pb, which is discussed in detail in Annex D. The three subseries will be considered in turn.

(a) Thorium-232

76. The activity concentration of ^{232}Th in soil is estimated to be on average the same as that of ^{238}U and its decay product ^{230}Th (25 Bq kg^{-1}, see Table 1). Since the main natural source of ^{232}Th in air at ground level is assumed to be the resuspension of soil particles, the annual activity intake of ^{232}Th through inhalation, estimated in the same way as for ^{238}U and ^{230}Th, is also about 0.01 Bq. As in the case of ^{230}Th, the contribution of the ingestion pathway to the body content of ^{232}Th can be probably neglected because of the very low absorption of thorium through the gastro-intestinal tract.

77. The distribution of ^{232}Th in human tissues was mainly investigated by Wrenn and his collaborators [S9, W1, W4] in their studies on the comparison of uranium, thorium and plutonium in man. In comparison with ^{230}Th, the activity concentrations of ^{232}Th were found to be lower by a factor of about 10. On the basis of those measurements, the body content of ^{232}Th would be about 80 mBq, 60% of which is in the skeleton. The activity concentrations adopted in this Annex are presented in Table 14, along with the resulting annual absorbed doses. The annual effective dose equivalent is calculated to be about 3 μSv.

(b) Radium-228 subseries (^{228}Ra, ^{228}Ac, ^{228}Th, ^{224}Ra)

78. Radium is much more available to plants and to animals than ^{232}Th so that the activity concentrations of ^{228}Ra in man are mostly due to the dietary intake of ^{228}Ra itself and not to the decay of ^{232}Th in the body. Radium-228 can thus be considered to be the head of a subseries in which ^{228}Th (1.9 a) and ^{224}Ra (3.6 d), as alpha emitters, are the most important contributors to the dose.

79. The annual activity intake arising from inhalation of resuspended soil particles is estimated to be about 0.01 Bq, as for all precursors of radon isotopes (Table 8). However, food consumption is a much more important source of ^{228}Ra intake than inhalation. In areas of normal radiation background the annual intake is about 15 Bq (Table 8).

80. In the high-background area along the Kerala coast in India, the estimated average annual intake of ^{228}Ra is about 2000 Bq [M1] whereas a survey conducted in the Araxá-Tapira region of Brazil showed that about 200 individuals ingested ^{228}Ra at a rate of between 700 and 3000 Bq a^{-1} [U1].

81. Radium and thorium are bone seekers. In Annex B of its 1977 report [U1], the Committee estimated the average ^{228}Ra activity concentrations in bone and in soft tissues to be 90 mBq kg^{-1} and 4 mBq kg^{-1}, respectively, in areas of normal background radiation. With respect to ^{228}Th, Wrenn and Singh [S9, W4] showed that approximately 80% of the body content (about 300 mBq) is in bone. The values of the activity concentrations adopted in this Annex are shown in Table 15; they are mainly based on the measurements of Wrenn and Singh [S9, W4].

82. The annual absorbed doses in tissues have been calculated using the same assumptions as in Annex B of the 1977 report [U1], namely, that complete retention in the body of the ^{220}Rn activity arises from decay of ^{224}Ra; and that the concentrations of ^{228}Ra and its decay products over the total mass of bone is uniform. The results are presented in Table 15. The corre-

sponding annual effective dose equivalent for the subseries is found to be about 13 μSv.

(c) Radon-220 and its decay products (^{216}Po, ^{212}Pb, ^{212}Bi, ^{212}Po, ^{208}Tl)

83. As is the case with ^{222}Rn, inhalation is the major pathway through which man is exposed to ^{220}Rn (thoron) and to its short-lived decay products. A detailed treatment of the sources of exposure to ^{220}Rn is provided in Annex D. In outdoor air, the equilibrium equivalent concentration of ^{220}Rn is about 0.2 Bq m^{-3}. With respect to indoor air, very few measurements of ^{220}Rn daughters have been reported, if compared with the available information on ^{222}Rn daughters. However, the simultaneous measurements of ^{222}Rn and ^{220}Rn daughters in houses in the Federal Republic of Germany and in the United Kingdom indicate a ratio of about 20 between equilibrium equivalent ^{222}Rn concentration and the equilibrium equivalent ^{220}Rn concentration. Applying this factor it can be concluded that the mean value of the indoor equilibrium equivalent ^{220}Rn concentration in different countries should be in the range 0.2–1.2 Bq m^{-3}. For the total population in temperate regions of the world a mean value of about 0.7 Bq m^{-3} should be expected. Taking into account the dose conversion coefficients for ^{220}Rn daughters given in Annex D, the annual effective dose equivalents corresponding to the average equilibrium equivalent concentrations of radon indoors and outdoors in temperate latitudes are estimated to be 0.20 mSv from indoor exposure and about 0.02 mSv from outdoor exposure, giving a total of 0.22 mSv for inhaled ^{220}Rn daughters.

84. For equatorial regions no measurements are available. Because of the different domestic conditions, the indoor levels of ^{220}Rn daughters might be considerably lower than in temperate regions. For large population groups this level will be comparable with the normal outdoor equilibrium equivalent concentration, leading to an annual effective dose equivalent in equatorial regions of 0.08 mSv from inhalation of ^{220}Rn daughters. Taking into account that about two thirds of the total world population is living in temperate regions, a global mean value of the annual effective dose equivalent of about 0.17 mSv from inhalation of ^{220}Rn daughters should be expected. Table 16 summarizes the estimated average equilibrium equivalent concentrations of ^{220}Rn and the corresponding annual effective dose equivalents.

III. RECAPITULATION

85. Table 17 summarizes the contributions of natural sources to the radiation exposure of human populations living in areas of normal radiation background. The exposures refer to adult persons and are expressed in terms of effective dose equivalent in order to facilitate the comparison of the various sources of radiation. The effective dose equivalent from all internal sources is estimated to be about twice that from external irradiation. Among the various contributors to the internal irradiation, the short-lived decay products of ^{222}Rn are by far the most important as they are responsible for about 60% of the effective dose equivalent from internal emitters. Then follow, by decreasing order of importance, ^{40}K (13%), the short-lived decay products of ^{220}Rn (13%), and ^{210}Pb-^{210}Po (8%). With regard to external irradiation, the effective dose equivalent from cosmic rays is slightly lower than that from terrestrial radiation.

86. Significantly higher doses from external radiation are received by population groups living at high altitudes or in regions of high natural radioactivity. A number of population groups are exposed to elevated internal absorbed doses, such as the people living in houses with a low rate of ventilation or the caribou and reindeer eaters. The importance of the contribution of areas of high natural radiation to the global effective collective dose equivalent cannot yet be assessed. As a first approximation the global annual collective effective dose equivalent from natural radiation sources is estimated to be of the order of 10^7 man Sv.

87. From Table 17 a median annual effective dose equivalent of about 2 mSv from natural sources in areas of normal background results. This average value refers to the adult part of the population. For children the values of the annual effective dose equivalent, particularly for inhaled radon daughters, are higher than for adults. Estimates yield a mean annual effective dose equivalent from natural sources of about 3 mSv for children in the 0 to 10-year age group.

88. The available data, particularly on the relevant contributions from radon daughters and terrestrial gamma radiation, indicate that on a global scale the distribution function of the natural radiation exposure can be approximated in its central part by a normal or log-normal distribution. With this assumption a standard deviation of about 0.3 to 0.6 mSv can be estimated.

Table 1

Average activity concentration of potassium-40, uranium-238 and thorium-238 in soil and absorbed dose rate in air 1 m above the ground surface

Radionuclide or decay series	Dose rate per unit activity concentration in soil (10^{-10} Gy h^{-1} per Bq kg^{-1})	Average concentration in soil a/ (Bq kg^{-1})	Absorbed dose rate in air a/ (10^{-8} Gy h^{-1})
^{40}K	0.43	370 (100-700)	1.6 (0.4-3.0)
^{238}U	4.27	25 (10- 50)	1.1 (0.4-2.1)
^{232}Th	6.62	25 (7- 50)	1.7 (0.5-3.3)

a/ The typical range is given within brackets.

Table 2

Estimates of the average absorbed dose rate in air 1 m above ground level (based on country- and area-wide surveys)

Country or area	Average absorbed dose rate in air and range a/ (10^{-8} Gy h^{-1})	Number of measurements	Period of survey	Type of survey and instrumentation used	Ref.
Austria	4.3 (0.2-15)	> 1000	1970-1974	Ground survey in populated areas with a Geiger-Müller counter	[T2]
Denmark	3.8 (1.7-5.2)	14 sites	1978	Ground survey with an ionization chamber and a gamma spectrometer	[N5]
France	8.1 (0.9-29)	865	1978	Ground survey with thermolumi-nescent dosimeters (preliminary results)	[M3, M8]
German Dem.Rep.	9.4 (2.4-27)	1005	1965-1966	Ground survey with an ionization chamber	[O1]
Germany, Fed.Rep. of	5.3 (0.4-35)	24739	1973-1974	Ground survey with scintillation detectors	[C8, D2]
India	4.2 (normal areas)	35 sites	1965-1972	Analysis of soil samples by gamma spectrometry	[M4]
Ireland	4.2 (0-18)	264	1978	Ground survey with an ionization chamber	[M5]
Italy	5.7 (0.7-50)	1365	not indicated	Ground survey with an ionization chamber	[A3]
Japan	4.9 (0.5-10)	1127	1967-1977	Ground survey with an ionization chamber and scintillation detectors	[A3]
Norway	7.3 (2-110)	234	1976	Ground survey with an ionization chamber placed in a car	[S6]
Poland	3.7 (1.5-9)	352 sites	1975-1978	Ground survey with thermolumi-nescent dosimeters	[N6]
Romania	8.1 (3.2-21)	2372	not indicated	Analysis of soil samples by gamma spectrometry	[T3]
Switzerland	8.7	not indicated	1962	Ground survey with an ionization chamber	[H1]
United States	4.6 (1.3-10)	25 areas covered b/	1958-1963	Aerial survey with scintillation detectors	[O7]
Other Asia	6.9	26	1969	Analysis of soil samples by gamma spectrometry	[W3]

a/ The range is given within brackets.
b/ Inhabited by approximately 30 % of the country's population.

Table 3

Results of surveys of indoor absorbed dose rate in air due to gamma terrestrial radiation

Country	Period of survey	Number of dwellings	Type of building	Indoor average absorbed dose rate in air (10^{-8} Gy h^{-1})	Population-weighted average absorbed dose rate in air (10^{-8} Gy h^{-1})	Indoors to outdoors ratio	Population-weighted indoors to outdoors ratio	Ref.
Austria	1975-1978	1900	Brick	10.8	7.1		1.65	[T2]
			Concrete	8.1				
			Wood	7.5				
			Natural stone	10.9				
France (1)	1978	946	Various types	8.8		1.09		[M3]
(2)	1977-1979	1020	Various types	9.9		1.11		[B9]
German Dem.Rep.	1965-1966	667	Various types		7.4		0.78	[01]
Germany, Fed.Rep. of	1973-1974	29996	Solid	7.0	7.0	1.37	1.36	[D2]
			Frame	7.1		1.34		
			Prefabricated	4.0		0.94		
			Wood	4.5		1.02		
Norway	1963+1976	2026	Brick	11.9	9.5	1.60	1.12	[S6, S7]
			Concrete	10.5		1.42		
			Wood	7.1		0.95		
Poland	1978	49	Red Brick			1.2		[N6]
			Concrete			1.1		
			Building material containing blast furnace slag			1.8		
Sweden	1977	1189	Brick	9.2	9.6			[M6]
			Concrete	11.6				
			Aerated concrete	17.2				
			Wood	5.3				
United Kingdom	1959	501	Solid: sedimentary rock					[S8]
			- Dundee	7.6		1.07		
			- Edinburgh granite	6.8		1.24		
			- Aberdeen	9.7		0.82		
			- Aberdeenshire	9.4		1.17		
United States (1)	1971	110	Wood	3.9 a/		0.75		[L2]
(2)	1962	160	Wood			0.70		[L3]

a/ Median value.

Table 4

Data on naturally-occurring ^{3}H, ^{7}Be, ^{14}C, and ^{22}Na

Item	Radionuclide				Ref.
	^{3}H	^{7}Be	^{14}C	^{22}Na	
Half-life	12.3 a	53.6 d	5730 a	2.62 a	[L8]
Numbers of atoms produced per unit time and per unit area of the earth's surface ($m^{-2}s^{-1}$)					
Troposphere	840	270	11000	0.24	[L4]
Total atmosphere	2500	810	16000-25000	0.86	[L4,U1]
Global inventory (PBq)	1300	37	8500	0.4	[L4,U1]
Distribution as a percentage of inventory					
Stratosphere	6.8	60	0.3	25	[L4]
Troposphere	0.4	11	1.6	1.7	[L4]
Land surface and biosphere	27	8	4	21	[L4]
Mixed oceanic layers	35	20	2.2	44	[L4]
Deep ocean	30	0.2	92	8	[L4]
Oceanic sediments			0.4		[L4]
Activity concentration in surface air ($\mu Bq\ m^{-3}$)		3000		0.3	[K9]
Activity concentration in continental surface waters ($Bq\ m^{-3}$)	200-900				[B5,K5]
Specific activity in terrestrial biosphere ($Bq\ kg^{-1}$)			230		[S3]

Table 5

Estimated tissue concentrations and annual absorbed doses from ^{3}H and ^{14}C

Organ or tissue	Hydrogen			Carbon		
	Mass concentration of element ($g\ kg^{-1}$)	Activity concentration of ^{3}H ($Bq\ kg^{-1}$)	Annual absorbed dose (μGy) β	Mass concentration of element ($g\ kg^{-1}$)	Activity concentration of ^{14}C ($Bq\ kg^{-1}$)	Annual absorbed dose (μGy) β
Gonads	100	0.4	0.01	89	20	5.0
Lungs	99	0.4	0.01	100	23	5.7
Red bone marrow	100	0.4	0.01	410	93	24
Bone lining cells			0.01			22
Thyroid	100	0.4	0.01	105	24	5.9
Other tissues	105	0.4	0.01	230	52	13

Table 6

Absorbed doses in tissues from internal irradiation by ^{7}Be and ^{22}Na

Organ or tissue	Annual absorbed dose (μGy)	
	^{7}Be γ	^{22}Na β^{+},γ
Gonads	5.7	0.14
Breast		0.13
Lungs		0.12
Red bone marrow	1.2	0.22
Bone lining cells		0.27
Thyroid		0.12
Stomach wall		0.14
SI wall	5.4	0.15
ULI wall	7.3	
LLI wall	12	0.15
Remainder		0.10

Table 7

Average tissue concentrations in adult males and annual absorbed doses from ^{40}K and ^{87}Rb

Tissue or organ	Potassium			Rubidium		
	Mass concentration of element ($g\ kg^{-1}$)	Activity concentration of ^{40}K ($Bq\ kg^{-1}$)	Annual absorbed dose (μGy) β^{-},γ	Mass concentration of element ($mg\ kg^{-1}$)	Activity concentration of ^{87}Rb ($Bq\ kg^{-1}$)	Annual absorbed dose (μGy) β^{-}
Gonads (Testes)	2.1	64	180	20	18	10.0
Lungs	2.1	64	180	9.2	8.1	4.5
Red bone marrow	4.4	130	270	7.8	7.0	7.0
Bone lining cells			140			14.0
Thyroid	1.1	33	100	6.0	5.3	3.0
Other tissues	2.0	61	170	7.8	7.0	4.0

Table 8

Intakes in normal areas of ^{238}U, ^{232}Th and their decay products

Source	Annual intake (Bq)	
	Inhalation	Ingestion
^{238}U series		
^{238}U	0.01	5
^{234}Th	0.01	5
^{234}Pa	0.01	5
^{234}U	0.01	5
^{230}Th	0.01	-
^{226}Ra	0.01	15
^{210}Pb	4	40
^{210}Po	0.8	40
^{232}Th series		
^{232}Th	0.01	-
^{228}Ra	0.01	15
^{228}Ac	0.01	15
^{228}Th	0.01	15

Table 9

Average activity concentrations in tissues and annual absorbed doses resulting from internal irradiation by radionuclides from the uranium-238 subseries

Organ or tissue	Activity concentration of ^{238}U a/ (mBq kg^{-1})	Annual absorbed doses (10^{-7} Gy)			
		^{238}U α	^{234}Th β,γ	^{234m}Pa β,γ	^{234}U α
Gonads	5	1.1	0.02	0.2	1.2
Breast	5	1.1	0.02	0.2	1.2
Lungs	5	1.1	0.02	0.2	1.2
Cortical bone	150				
Trabecular bone	150				
Red bone marrow	5	2.1	0.11	1.4	2.4
Bone lining cells		17	0.34	4.3	20
Thyroid	5	1.1	0.02	0.2	1.2
Kidneys	50	11	0.15	2.1	12
Other tissues	5	1.1	0.02	0.2	1.2

a/ ^{238}Th, ^{234m}Pa, and ^{234}U are assumed to be in radioactive equilibrium with ^{238}U in all organs and tissues.

Table 10

Average activity concentrations in tissues and annual absorbed doses resulting from internal irradiation by thorium-230

Organ or tissue	Activity concentration (mBq kg^{-1})	Annual absorbed doses (10^{-7} Gy) α
Gonads	0.3	0.07
Breast	0.3	0.07
Lungs	20	4.7
Cortical bone	20	
Trabecular bone	70	
Red bone marrow	0.3	5.6
Bone lining cells		74
Thyroid	0.3	0.07
Kidneys	10	2.4
Other tissues	0.3	0.07

Table 11

Average activity concentrations in tissues and annual absorbed doses resulting from internal irradiation by radium-226 and its short-lived decay products [a/]

Organ or tissue	Activity concentration (mBq kg^{-1})		Annual absorbed doses (10^{-7} Gy)					
	^{226}Ra	^{222}Rn [b/]	^{226}Ra α	^{222}Rn α	^{218}Po α	^{214}Pb β,γ	^{214}Bi β,γ	^{214}Po α
Gonads	2.7	0.9	0.7	0.3	0.3	0.01	0.03	0.4
Breast	2.7	0.9	0.7	0.3	0.3	0.01	0.03	0.4
Lungs	2.7	0.9	0.7	0.3	0.3	0.01	0.03	0.4
Cortical bone	170	60						
Trabecular bone	170	60						
Red bone marrow	2.7	0.9	2.0	0.8	0.9	0.2	0.6	1.1
Bone lining cells			22	9.1	9.9	0.7	1.7	13
Thyroid	2.7	0.9	0.7	0.3	0.3	0.01	0.03	0.4
Other tissues	2.7	0.9	0.7	0.3	0.3	0.01	0.03	0.4

a/ Includes doses resulting from the formation of radon-222 and its short-lived decay products in the body by decay of radium-226 but does not take into account the doses arising from inhalation of radon-222 and its daughters.

b/ ^{218}Po, ^{214}Pb, ^{214}Bi, and ^{214}Po are assumed to be in radioactive equilibrium with radon-222 in all organs and tissues.

Table 12

Estimated equilibrium equivalent concentration of radon-222 and annual effective dose equivalents arising from inhalation

		Populations in temperate regions	Global population
OUTDOOR EXPOSURE			
Equilibrium equivalent concentration	(Bq m^{-3})	1.8	1.8
Range of mean annual values	(Bq m^{-3})	0.1-10	0.1-10
Average annual effective dose equivalent	(mSv)	0.06	0.06
Range of mean annual values	(mSv)	0.003-0.3	0.003-0.06
INDOOR EXPOSURE			
Equilibrium equivalent concentration	(Bq m^{-3})	15	
Range of mean values in various countries	(Bq m^{-3})	5-60	
Average annual effective dose equivalent	(mSv)	0.92	0.7
Range of mean values in various countries	(mSv)	0.3-3.7	
Total average annual effective dose equivalent	(mSv)	1.0	0.8

Table 13

Estimated average activity concentrations of ^{210}Pb, ^{210}Bi, and ^{210}Po in tissues of non-smokers in areas of normal dietary intake, and corresponding annual absorbed doses

Organ or tissue	Lead-210		Bismuth-210		Polonium-210	
	Activity concentration ($Bq\ kg^{-1}$)	Annual absorbed dose (μGy) β	Activity concentration ($Bq\ kg^{-1}$)	Annual absorbed dose (μGy) β	Activity concentration ($Bq\ kg^{-1}$)	Annual absorbed dose (μGy) α
Gonads	0.2	0.04	0.2	0.4	0.2	5.4
Breast	0.2	0.04	0.2	0.4	0.2	5.4
Lungs	0.2	0.04	0.2	0.4	0.1	2.7
Cortical bone	3		3		2.4	
Trabecular bone	3		3		2.4	
Red bone marrow	0.14	0.17	0.14	1.7	0.11	5.1
Bone lining cells		0.44		4.2		36
Thyroid	0.2	0.04	0.2	0.4	0.2	5.4
Other tissues	0.2	0.04	0.2	0.4	0.2	5.4
Annual effective dose equivalent (μSv)		0.07		0.7		130

Table 14

Average activity concentrations in tissues and annual absorbed doses resulting from internal irradiation by thorium-232

Organ or tissue	Activity concentration ($mBq\ kg^{-1}$)	Annual absorbed doses (10^{-7} Gy) α
Gonads	0.15	0.03
Breast	0.15	0.03
Lungs	20	4.0
Cortical bone	6	
Trabecular bone	24	
Red bone marrow	0.15	1.7
Bone lining cells		20
Thyroid	0.15	0.03
Kidneys	3	0.6
Liver	2	0.4
Other tissues	0.15	0.03

Table 15

Average activity concentrations in tissues and annual absorbed doses resulting from internal irradiation by radium-228 and its decay products [a/]

Organ or tissue	Activity concentration (mBq kg^{-1})		Annual absorbed doses (10^{-8} Gy)									
			^{228}Ra	^{228}Ac	^{228}Th	^{224}Ra	^{220}Rn	^{216}Po	^{212}Pb	^{212}Bi	^{212}Po	^{208}Tl
	^{228}Ra[b/]/^{228}Th[c/]		β	β,γ	α	α	α	α	β,γ	α,β,γ	α	β,γ
Gonads	4	0.5	0.03	1.1	1.4	1.4	1.6	1.7	0.05	0.5	1.4	0.07
Breast	4	0.5	0.03	1.1	1.4	1.4	1.6	1.7	0.05	0.5	1.4	0.07
Lungs	4	15	0.03	1.1	41	43	48	51	1.4	16	43	2.0
Cortical bone	50	50										
Trabecular bone	50	50										
Red bone marrow	4	0.5	0.14	4.1	5.9	6.2	6.9	7.4	1.1	2.3	6.2	1.6
Bone lining cells			0.30	10	74	78	87	93	3.4	29	77	5.5
Thyroid	4	0.5	0.03	1.1	1.4	1.4	1.6	1.7	0.05	0.5	1.4	0.07
Kidneys	4	10	0.03	1.1	27	29	32	34	0.9	11	28	1.3
Liver	4	5	0.03	1.1	14	14	16	17	0.5	5.4	14	0.7
Other tissue	4	0.5	0.03	1.1	1.4	1.4	1.6	1.7	0.05	0.5	1.4	0.07

a/ Includes doses resulting from the formation of radon-220 and its decay products in the body by decay of radium-224 but does not take into account the doses arising from inhalation of radon-220 and its daughters.

b/ Actinium-228 is assumed to be in radioactive equilibrium with radium-228.

c/ ^{224}Ra, ^{220}Rn, ^{216}Po, ^{212}Pb, and ^{212}Bi are assumed to be in radioactive equilibrium with thorium-228; owing to the decay characteristics of bismuth-212, the activity concentrations of polonium-212 and of thallium-208 are 64 % and 36 % of those of bismuth-212, respectively.

Table 16

Estimated equilibrium equivalent concentration of radon-220 and annual effective dose equivalents arising from inhalation

		Populations in temperate regions	Global population
OUTDOOR EXPOSURE			
Equilibrium equivalent concentration	(Bq m^{-3})	0.2	0.2
Annual effective dose equivalent	(mSv)	0.02	0.02
INDOOR EXPOSURE			
Equilibrium equivalent concentration	(Bq m^{-3})	0.7	
Annual effective dose equivalent	(mSv)	0.20	0.15
Total annual effective dose equivalent	(mSv)	0.22	0.17

Table 17

Estimated per caput annual effective dose equivalents from natural sources in areas of normal background

Source of irradiation	Annual effective dose equivalent (μSv)		
	External irradiation	Internal irradiation	Total
COSMIC RAYS			
- Ionizing component	280		280
- Neutron component	21		21
COSMOGENIC RADIONUCLIDES		15	15
PRIMORDIAL RADIONUCLIDES			
^{40}K	120	180	300
^{87}Rb		6	6
^{238}U series			
$^{238}U \rightarrow ^{234}U$		10	
^{230}Th		7	
^{226}Ra	90	7	1044
$^{222}Rn \rightarrow ^{214}Po$		800	
$^{210}Pb \rightarrow ^{210}Po$		130	
^{232}Th series			
^{232}Th		3	
$^{228}Ra \rightarrow ^{224}Ra$	140	13	326
$^{220}Rn \rightarrow ^{208}Tl$		170	
TOTAL (rounded)	650	1340	2000

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ANNEX C

Technologically modified exposures to natural radiation

CONTENTS

Introduction

1. There are circumstances where man finds himself in a natural radiation environment to which he would not be exposed if some kind of technology had not been developed. Examples are travelling by air, using natural gas for cooking or heating purposes, living in the neighbourhood of a coal-fired power plant. The resulting exposures have been labelled "technologically enhanced" natural radiation exposures by Gesell and Prichard [G1], who defined them as exposures to truly natural sources of radiation (that is, naturally-occurring radionuclides and cosmic radiation) which would not occur without (or which are increased by) some technological activity not expressly designed to produce radiation.

2. In some cases, technology helps to reduce the natural radiation exposure. For example, when drinking water supplies are drawn from surface waters, the use of water-purification processes brings about a decrease in the concentration of radium and other naturally-occurring radioactive elements. Another example is the burning of fossil fuel, which reduces the

specific activity of ^{14}C in the biosphere and therefore lowers the doses from that radionuclide. This Annex deals with "technologically modified" exposures to natural radiation and presents some assessments of the doses arising from such exposures.

3. The Committee recognizes that the definition given in paragraph 1 is not rigorous and that, in reality, radiation is either natural or artificial in origin. It also realizes, however, that there has been scientific interest in recent years in radiation exposure from the variety of sources which will be discussed in this Annex. The Committee believes that consideration of these sources in a separate Annex is justified at least for this report.

4. Although they do not properly fall within the above definition, there are a number of other sources of exposure to radiation which are a direct consequence of man's technological activities, and which are included for convenience within this Annex. Examples of these are consumer products incorporating radionuclides, and electronic and electrical devices. Other man-made sources of exposure such as the explosion of nuclear devices and the operation of nuclear power plants are discussed in Annexes E and F, respectively.

I. RADIATION EXPOSURES DUE TO COAL-FIRED POWER PLANTS

A. SOURCE TERMS

5. Coal, like most materials found in nature, contains trace quantities of the naturally-occurring primordial radionuclides. Therefore, the combustion of coal results in the release to the environment of some natural activity and in the re-distribution of that natural activity from deep in the earth to locations where it can modify ambient radiation fields and population radiation exposures.

6. The annual world production of coal (including brown coal and lignite) was about 3.7 10^{12} kg in 1979 [U5], the main producers being China, the Union of Soviet Socialist Republics, and the United States of America. Coal is used most commonly for industrial purposes, power generation, and space heating. In 1974, about 70% of the coal consumed in the United States was burnt in electric power stations, while only 2% was used for space heating in household and commercial markets [U3]. The situation may however be quite different in other countries. In Poland, for example, about 15% of the coal consumed in 1976 was burned as household fuel [G10].

7. In view of the importance of coal for generating electricity, this section will deal essentially with the radiation exposures arising from its use to produce electric power. Most documented exposures are those due to the atmospheric releases of gases and particulates from power stations. There is more particulate emission during combustion of coal than of any other fuel because of its high ash content; for example, the ash content of coal burned in the United States in power plants with a capacity of more than 25 MW(e) ranged from 4 to 25% in 1977 [W10]. The combustion of about 3 10^9 kg of coal is required to produce an electrical energy of 1 GW a [B1, E1, K1, K2].

8. The activities of natural radionuclides discharged in the atmosphere from a power plant per unit electrical energy produced depend on a number of factors such as the activity concentrations in coal, the ash content of the coal, the temperature of combustion, and the efficiency of the filtering system. Marked differences should therefore be expected between the measured activities discharged per unit energy produced from different power plants. The currently available information on the activity concentrations in coal and ash and on the atmospheric discharges will be briefly reviewed.

1. Activity concentrations in coal

9. Since the publication of the 1977 report of UNSCEAR [U2], a substantial number of publications have dealt with the measurement of activity concentrations of natural radionuclides in coal. Table 1 presents results of measurements of radionuclides in coal samples originating from mines or from power plants. The most significant study is that of Beck et al. [B2], who listed the concentrations measured in almost 1000 samples obtained directly from mines providing most of the coal presently used in the United States. These authors found that the activity concentrations measured in the coal samples varied over two orders of magnitude (0.7 to 70 Bq kg^{-1} for ^{40}K, less than 3 to 520 Bq kg^{-1} for ^{238}U, and 3 to 320 Bq kg^{-1} for ^{232}Th). Variations can be quite large even in the same area. Gluskoter et al. [G2] obtained concentrations ranging from 4 to 300 Bq kg^{-1} for ^{238}U, 0.4 to 10 Bq kg^{-1} for ^{232}Th and 3 to 100 Bq kg^{-1} for ^{40}K in five different seams of coal mined in Illinois. In general, the concentrations of natural radionuclides in coal are less than those in the earth's crust. Occasionally, however, usually as a result of leaching from abnormally radioactive overburdens of volcanic origin, very high concentrations of some radionuclides, in particular uranium, can be found in various coal deposits. Those uraniferous coals are the exception and occur almost invariably in low grade coal deposits [A1, D1, V1, V2]. It will be assumed in this Annex that the average activity concentrations in coal are 50 Bq kg^{-1} of ^{40}K and 20 Bq kg^{-1} each of ^{238}U and ^{232}Th and that all the decay products of ^{238}U and of ^{232}Th are in radioactive equilibrium with their precursors, although that might not be always the case for ^{210}Pb and ^{210}Po (see for example the results of Kaakinen et al. [K1] in Table 1). Enhanced activity concentrations of ^{210}Pb could conceivably occur if large quantities of ^{222}Rn diffuse from adjacent high activity rocks into a lower activity coal seam with subsequent trapping of the decay products in the coal [B2].

2. Activity concentrations in ash

10. In the production of electric power, coal is burned in furnaces operating at temperatures of up to 1700° C. Most of the mineral matter in the coal is fused into a vitrified ash. A portion of the heavier ash, along with incompletely burned organic matter, drops to the bottom of the furnace as bottom ash or slag. The fly-ash, however, is carried through the boiler along with the hot flue gases and any volatilized mineral compounds to the stack where, depending on the efficiency of emission control devices, some fraction is collected while the rest (escaping fly-ash) is released to the atmosphere [B2].

11. The radionuclides included in the non-combustible mineral matter are thus partitioned between the bottom ash and fly-ash, except for the gases and volati-

lized minerals which will be incorporated directly into the flue gases. Table 2 presents a list of reported activity concentrations of natural radionuclides in bottom ash, collected fly-ash and escaping fly-ash. Owing mainly to the elimination of the organic component of the coal, there is very approximately an order of magnitude enhancement of the activity concentrations from coal to ash. Consequently, the natural radionuclide concentrations in ashes and slags from coal-fired power stations are significantly higher than the corresponding concentrations in the earth's crust [L4]. The arithmetic averages of the concentrations in escaping fly-ash from Table 2 are, in Bq kg^{-1}, 265 for ^{40}K, 200 for ^{238}U, 240 for ^{226}Ra, 930 for ^{210}Pb, 1700 for ^{210}Po, 70 for ^{232}Th, 110 for ^{228}Th and 130 for ^{228}Ra.

12. In the United States, a number of recent studies have aimed at understanding the mechanisms of aerosol formation in the coal-fired power plants [C1, K1, K2, K3, L1, N2, O1, R1]. It has been observed that certain trace elements partition unequally between bottom ash and fly-ash. They become concentrated on the smaller fly-ash particles which have larger surface-to-volume ratios as the hot flue gases cool down on their way to the stack [K1, K2, L1, N2, R1]. This process results in the depletion of certain elements in bottom ash and their consequent enrichment in fly-ash, an effect which increases as the size of the fly-ash particles decreases [C1, L1, N2]. These smaller particles are less efficiently collected by emission control devices such as electrostatic precipitators and scrubbers, and thus preferentially escape from the plant.

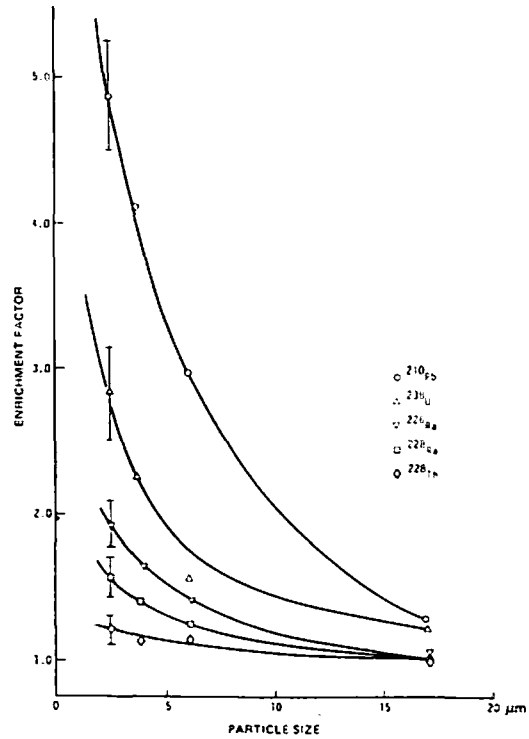

Figure I. Enrichment factors of ^{210}Pb, ^{238}U, ^{226}Ra, ^{228}Ra and ^{228}Th versus size (mass median diameter) in stack fly-ash collected downstream from an electrostatic precipitator [C1]

13. The apparent enrichment of some radionuclides in escaping fly-ash particles can be characterized by the enrichment factor EF, defined as the ratio of the concentrations of the radionuclide (X) and of ^{40}K in the sample divided by the corresponding ratio in coal:

$$EF = \frac{(X)\ \text{sample} / (^{40}K)\ \text{sample}}{(X)\ \text{coal} / (^{40}K)\ \text{coal}} \qquad (1)$$

Potassium-40 is used as a reference because its activity concentration remains more or less constant in all types of ash in a given plant and thus is assumed to be a tracer for the alumino-silicate dominated ash matrix [C1]. Figure I shows the variation of the enrichment factors of ^{238}U, ^{226}Ra, ^{228}Ra, ^{210}Pb and ^{228}Th as a function of the size of the escaping fly-ash [C1]. The enrichment factors given in that figure are derived from measurements of samples obtained at a power plant equipped with Venturi scrubbers and electrostatic precipitators [C1]. The escaping fly-ash was collected by a large cyclone separator; the four fractions obtained had measured mass median diameters of 18.5, 6.0, 3.7, and 2.4 µm and count median diameters of 2.7, 2.6, 1.1, and 0.9 µm, respectively [F6]. Among the radionuclides measured by Coles et al. [C1], the most enriched was ^{210}Pb, followed by ^{238}U, ^{226}Ra, ^{228}Ra and ^{228}Th. It is likely that a large fraction of ^{210}Pb and ^{210}Po volatilizes during the combustion, then condenses somewhere down the flue line on the finer fly-ash particles, whereas ^{40}K and isotopes of thorium melt with the alumino-silicate minerals and drop out as bottom ash or coalesce and are carried through the flue line as fly-ash particles. According to Coles et al. [C1], the uranium isotopes could behave in either way according to their mineralogical or chemical form in the coal; the uranium that is associated with the clays, or which is mineralized as coffinite, would remain with the bottom ash whereas the uranium that is dispersed in the coal as uraninite could become volatile as UO_3 and later condense on the fly-ash particles [C1]. As a decay product of ^{238}U, ^{226}Ra would behave in an analogous manner; on the other hand, ^{228}Ra, as a decay product of ^{232}Th, would tend to be associated with the matrix of the fly-ash particles.

14. The mechanisms described above are supported by evidence from studies of fly-ash particles which show that they consist of an insoluble matrix composed mainly of iron and aluminium silicates coated with a layer of soluble compounds [K3, L1, P3]. However, other physical-chemical processes such as segregation (diffusive transport to the surface of the particle) and gas-surface reactions may also contribute to the surface enrichment of the ash particles [S11]. Table 3 presents published enrichment factors, which may or may not use ^{40}K as a reference, while Figure II, extracted from a study made in the Federal Republic of Germany, illustrates the increase in specific activity as one proceeds from one stage of particle retention to the next [C5, J7]. As expected, the enrichment factors are higher for ^{210}Pb and ^{210}Po (range of 1 to 11) than for uranium, radium or thorium (range of 1 to 2). As a general rule, the values of the enrichment factors increase with the temperature of combustion and decrease with the particle size, at least for sizes above 1 µm.

15. Measurements of the size distribution of escaping fly-ash particles are very few. In the Federal Republic of Germany, a nearly log-normal size distribution has been found with an activity median aerodynamic diameter of 3–5 µm for uranium, thorium and radium, and of about 1 µm for ^{210}Pb and ^{210}Po [J7]. In the United States, the size distribution of particles collected in a plant down-stream from an electrostatic precipitator has been found to be bimodal, the two modes being at 0.06 and 0.5 µm [O1]. A similar size distribution, with two modes at 0.04 and 0.25 µm, has been observed in the plume of a coal-fired power plant [P3]. The mass activity concentration of enriched radionuc-

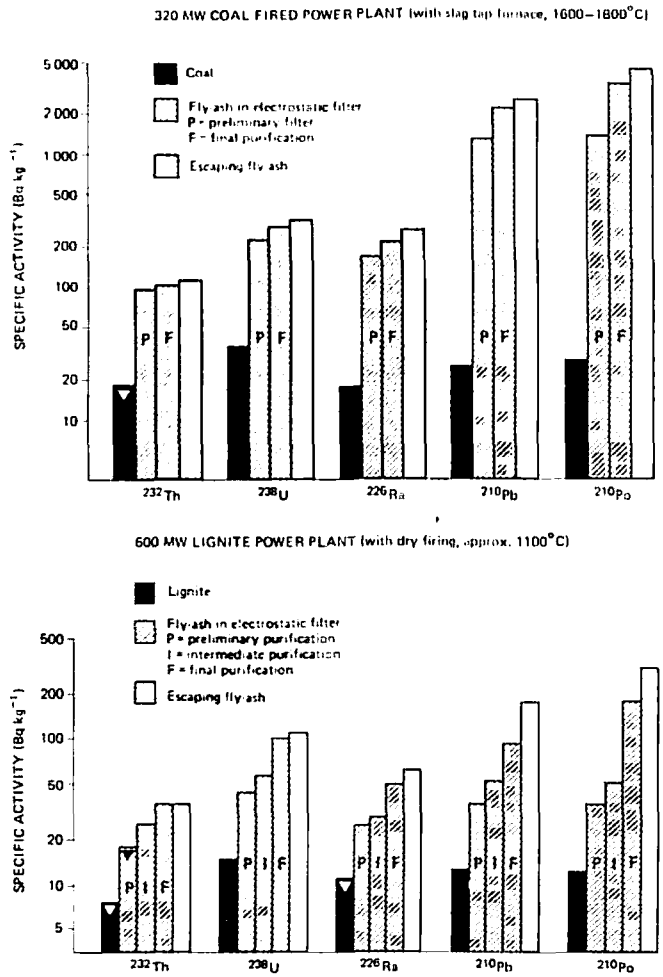

Figure II. Measured mean values of specific activity in the coal, in the fly-ash deposited in the electrostatic filter stages and in the escaping fly-ash [C5]

lides, such as ^{210}Pb and ^{210}Po, may be much higher in those small particles than suggested by the values given in Table 3 and Figure I [N2, O1]. However, an analysis of the submicron particles with respect to the concentrations of elements volatilized during combustion has shown these concentrations to be independent of particle size, in contrast to the larger particle sizes where an inverse relationship with particle size applies [S12]. These results would be consistent with a mechanism for formation of submicron particles involving "bursting" of larger particles due to gas release during rapid heating, followed by coagulation and condensation of volatilized elements to form particles in the 0.1–1.0 μm size range [S12].

3. Atmospheric discharges

16. The atmospheric discharges of natural radionuclides are obtained as the products of the mass of fly-ash released per unit of energy produced by the activity concentrations in escaping fly-ash. The mass of fly-ash released per unit of energy produced depends heavily on the efficiency of the particulate control. In the United States, the average atmospheric releases in 1972 from 696 major steam plants amounted to about 8% of the total ash in the coal burned [M3, F5]. However, all plants in the United States must eventually meet the clean air standards of the Environmental Protection Agency which are set at 1.4 10^6 kg of ash per GW a of electricity generated [M3], which corresponds to a release of about 1% of the total ash. The average releases in that country are thus likely to lie at present between those two values. In the Federal Republic of Germany, the emission of dust is limited by the legal authorities at 0.15 g per m^3 of flue gas, which corresponds to a release of about 1% of the total ash [S1]. In Italy, typical coal-fired power plants are equipped with electrostatic precipitators allowing an ash retention of 95%, and thus a release of 5% [M1]. In Poland, the fraction of ash released is estimated at 20% [J4], while in India it has been assumed to be 10% [M12]. With regard to the USSR, it has been reported that the modern coal-fired power stations are equipped with electrofilters allowing an ash retention of 98.5–99%. However, there are other power stations for which the efficiency of retention of the fly-ash particles is about 90%, corresponding to an atmospheric discharge of about 10% of the ash produced. So the power plants which have the same power as the Zaporozhje station (1.2 GW(e)) and an ash retention efficiency of 90%, burning 3.4 10^6 tonnes of coal with a high ash content (35–40%), discharge about 1.3 10^5 tonnes of ash to the atmosphere annually [K11, I1, I5].

17. It thus seems that by and large there are two types of coal-fired power plants throughout the world, namely those which release about 10% of the total ash produced and those, equipped with sophisticated retention devices, which release only about 1% of the ash. Although it would probably be more realistic to estimate the radiation impact resulting from the releases

of the two types of plants, it has been decided in this Annex to derive only one set of activities discharged per unit of energy produced.

18. Table 4 presents the estimates of atmospheric discharges adopted in Annex B of the 1977 report of UNSCEAR [U2] and other estimates which originate mainly from highly industrialized countries and were published after the preparation of the 1977 report. On this basis, "average" discharges have been estimated for the purpose of assessing the doses arising from coal combustion in power plants. Those "average" atmospheric discharges per unit energy generated are also presented in Table 4; in terms of MBq (GW a)$^{-1}$, they amount to 4000 for ^{40}K, 1500 for ^{238}U through ^{226}Ra, 5000 for ^{210}Pb and ^{210}Po, and 1500 for the radionuclides of the ^{232}Th decay series, from ^{232}Th to ^{224}Ra. These normalized discharges are taken to be representative of the current situation on the world-wide scale. For the purpose of comparison with the values given in the previous paragraphs, it can be calculated that they correspond, for example, to a plant burning coal with a 10% ash content and equipped with a filtering system allowing an ash retention of 97.5%, the enrichment factors would be 1 for ^{40}K, the isotopes of radium, uranium and thorium, and 3 for ^{210}Pb and ^{210}Po.

19. Releases of ^{222}Rn and of ^{220}Rn have to be estimated separately as radon is not collected by the particulate control devices. The activities of ^{222}Rn and ^{220}Rn released per GW a have been assessed at 60 GBq on the basis of the following assumptions: ^{222}Rn and ^{220}Rn are in radioactive equilibrium with ^{238}U and ^{232}Th, respectively, in coal and are discharged in their entirety when coal is burned; the average activity concentration of ^{238}U or ^{232}Th in coal is 20 Bq kg^{-1}; and the combustion of 3 10^9 kg of coal is required to produce 1 GW a of electrical energy.

B. ENVIRONMENTAL LEVELS AND DOSES

20. Measurements in surface air, carried out about ten years ago, had clearly shown the presence of enhanced concentrations of the natural radionuclides precursors of the radon isotopes. Bedrosian et al. [B3] measured downwind of a coal power plant in Alabama, concentrations of up to 50 μBq m^{-3} of ^{226}Ra, 10 μBq m^{-3} of ^{232}Th and 100 μBq m^{-3} of ^{238}U, compared with the "normal" concentrations of about 1 μBq m^{-3} for each of the three radionuclides. However, recent measurements [F2, S2, T3] have failed to reveal a significant increase in the surface air concentrations around the plant. This is probably due to the fact that the activities discharged are smaller now than what they used to be; another reason is the taller stacks which result in a much greater atmospheric dilution [B2].

21. Snow, which can be expected to have a low background concentration of the natural radionuclides considered, was sampled by Jaworowski et al. [J5] around coal-fired power plants. The measured ^{226}Ra concentrations ranged up to 60 mBq kg^{-1} and were related to the distance from the power plants. In addition, studies of a glacier 150 km away from a Polish industrial centre have revealed a 50-fold increase in ^{226}Ra concentration over the preceding 80 years [J5].

22. Since the concentrations in fly-ash are on average a few times higher than the corresponding concentrations in soil, and since the activity deposited remains for a relatively long period of time in a thin superficial layer of soil, measurements in soil have been conducted by several investigators. In Poland, the concentrations of uranium, thorium, and ^{226}Ra were found to be higher in the upper 5 cm layer than in the 5–10 cm layer of soils of industrial areas, while this effect was not observed in rural soils [J2]. In the United States, Beck et al. [B2] attempted to detect increases in natural radionuclide concentrations in surface layers of soil in the environs of three large coal-fired power plants, but only obtained positive results for the oldest and most poorly controlled of the three plants. Other recent studies [F2, S2] have also been unsuccessful. The annual enhancement in the concentrations of ^{238}Th, ^{226}Ra and ^{40}K in the upper 30 cm layer of soil within 20 km of coal-fired power stations has been theoretically estimated in a study of the USSR to represent, on average, only 0.08%, 0.12%, and 0.03% of the corresponding typical natural concentrations in soil [L4].

23. The main pathways through which the populations living around coal-fired power plants are exposed to enhanced levels of natural radionuclides are inhalation during the passage of the cloud, and external irradiation, inhalation and ingestion resulting from the activity deposited on the ground.

24. The collective dose commitments due to inhalation during the passage of the cloud have been roughly estimated as follows. Assuming that there is no decay during the atmospheric transport, all the activity released A_o (Bq) will eventually be deposited on a surface S (m^2). The average activity density is A_o/S (Bq m^{-2}) and corresponds to an integrated atmospheric concentration at ground level of $A_o/S\ v_d$ (Bq s m^{-3}), where v_d is the deposition velocity. The collective dose commitment M_q^c in organ or tissue q is given by:

$$M_q^c = \frac{A_o}{v_d S} S\delta_N\, B\, \frac{D_q}{I_{ih}} \qquad (2)$$

where $v_d = 10^{-2}$ m s^{-1}, value which takes into account both dry and wet deposition; $S\delta_N$ is the population affected, which is the product of the area of the deposition region S and of the population density δ_N, assumed to be uniform and equal to 10^{-4} m^{-2} around the plant. The areal dependence is removed by the product of the quantities A_o/v_dS and $S\delta_N$; B is the individual adult breathing rate, taken to be equal to 2.3 10^{-4} m^3 s^{-1}; D_q/I_{ih} is the committed absorbed dose in organ or tissue q per unit activity inhaled (Gy Bq^{-1}). In this assessment, the values adopted have been derived from those calculated by Jacobi [J7] using a quality factor of 20 for α particles (Table 5). These figures were estimated assuming that the radionuclide content of the particles was 80% insoluble and 20% soluble and using ICRP dosimetry [I6]. No account is taken of the possible reduction of the atmospheric concentration indoors.

25. This method was used to calculate the collective dose commitments during the passage of the cloud for most of the natural radionuclides, one notable exception being ^{222}Rn and its short-lived decay products. In that case, the activity A_o of radon distributed over a surface S of land was compared to the quotient of the atmospheric concentration and of the natural emanation rate for ^{222}Rn. One obtains

$$M_q^c = \frac{A_o}{S}\, \frac{1.8\ (\text{Bq m}^{-3})}{2\ 10^{-2}\ (\text{Bq m}^{-2}\ \text{s}^{-1})}\, S\delta_N\, B\, \frac{D_q}{I_{ih}} \qquad (3)$$

where A_o is the activity of ^{222}Rn daughters associated with the release of ^{222}Rn (the equilibrium factor

between ^{222}Rn and its daughters is taken to be 0.6); 1.8 Bq m^{-3} is the average outdoor equilibrium equivalent concentration of ^{222}Rn over land and 2 10^{-2} Bq m^2 s^{-1} is the average emanation rate of ^{222}Rn (see Annex D); as in the previous paragraph, the values of δ_N and B are taken to be equal to 10^{-4} m^{-2} and 2.3 10^{-4} m^3 s^{-1}, respectively; the values of D_q/I_{ih} are derived from Annex D and presented in Table 5.

26. The collective dose commitments due to inhalation during the passage of the cloud, as estimated by the methods described above, are presented in Table 6 for the most important radionuclides discharged into the atmosphere as a consequence of the production of 1 GW a of electrical energy by coal-fired power plants. The corresponding effective dose equivalent commitments are also included in Table 6. The doses due to inhalation of ^{220}Rn and its decay products, estimated in a similar way, are found to be about 1000 times smaller than those from ^{222}Rn and its decay products; they have been neglected here. Finally, the doses from ^{40}K were not calculated because of the homeostatic control by potassium in the body.

27. The collective dose commitments incurred after deposition can be very crudely evaluated by comparison with the natural soil activity concentrations and the corresponding annual absorbed doses in tissues given in Annex B. Assuming that the deposited activity becomes unavailable to the vegetation with a mean life of 100 years for all the natural long-lived radionuclides, and that only the upper 30 cm of soil are involved in the uptake of radionuclides by vegetation, the collective dose commitments per unit energy generated, M_q^ε, due to deposition can be assessed as

$$M_q^\varepsilon = \frac{A_o \dot{D}_q \delta_N \tau}{h C} \qquad (4)$$

where A_o is the activity associated with the release of a given radionuclide; $\dot{D}_q$ is the natural dose rate in organ or tissue q due to the radionuclide under consideration; δ_N is the population density; τ is the mean life of the long-lived natural radionuclides in soil taken to be 100 years; h is the thickness of soil involved, expressed as mass per unit area (assumed to be 500 kg m^{-2}); and C is the natural concentration of the nuclide in the soil. In the case of the short-lived radionuclides, especially the isotopes of radon and their daughters, the major contribution to the source term $A_o\tau$ arises from the decay of their long-lived precursors in soil.

28. The collective dose commitments per unit energy generated obtained in this way are presented in Table 7 for external and internal irradiation. It should be noted that the values chosen for $\dot{D}_q$ correspond to the assumption that the contaminated soils and rocks will not be used as components of the building materials. With respect to internal irradiation, the fly-ash particles have been assumed to behave physically and chemically in the same manner as the soil particles, even though the fly-ash particles, being in a vitrified form, are highly insoluble. On the other hand, the doses resulting from direct deposition on vegetation and foodcrops have not been taken into account. The collective effective dose equivalent commitments corresponding to the collective dose commitments presented in Table 7 have also been calculated; they are included in Table 7.

29. The conversion of the collective dose commitments into collective effective dose equivalent commitments allows a better evaluation of the impact of the various radionuclides and of the various pathways. Table 8 summarizes the collective effective dose equivalent commitments arising from the atmospheric discharges of coal-fired power plants. The production of one gigawatt year of electrical energy is estimated to lead to a total collective effective dose equivalent commitment of 2 man Sv. Inhalation during the cloud passage and internal irradiation due to the activity deposited are found to contribute significantly to the total collective effective dose equivalent commitment. The predominant radionuclides are the isotopes of thorium with regard to inhalation during the cloud passage and ^{210}Pb and the isotopes of radon with respect to internal irradiation due to the activity deposited. Assuming that 70% of the coal produced is used by the power utilities and that the combustion of 3 10^9 kg of coal is necessary to generate 1 GW a, the collective effective dose equivalent commitment resulting from the use of coal in 1979 is estimated to be about 2000 man Sv, on the basis of a world coal production of 3.7 10^{12} kg [U5].

30. The specific activity of ^{14}C in the atmosphere will decrease as a result of the airborne release from coal-fired power plants, thus leading to "negative" collective dose commitments. The Committee has not calculated a numerical value to this effect.

31. Annual individual effective dose equivalents resulting from inhalation during the cloud passage have been estimated. Assuming an effective stack height of 100 m and a uniform wind rose, the annual average of the ground level air concentration per unit release rate experiences a maximum of about 4 10^{-8} Bq m^{-3} per Bq s^{-1} at approximately 1 km from the stack [C6]. On the basis of the activity discharged per unit energy produced given in Table 4 and of the effective dose equivalents per unit activity inhaled presented in Table 5, the annual effective dose equivalent resulting from inhalation during the cloud passage would be about 5 μSv for an individual of the critical group living around a coal-fired power plant producing one GW of electrical power. The annual effective dose equivalents due to ingestion and external irradiation could be of about the same importance [J7].

C. OTHER SOURCES OF RADIATION EXPOSURE RESULTING FROM THE USE OF COAL

32. In the coal fuel cycle, radiation exposures above the natural background are expected to occur mainly when coal has been converted into ash. The production of ash was reported to be 10^7 tons in 1973 in at least four countries: German Democratic Republic, Federal Republic of Germany, Poland and the United States [G11]. Most fly-ash is pumped as a water slurry to settling ponds but some of it, amounting to more than 35% of the production in Belgium, Finland, France and the Federal Republic of Germany [G11], is used in a variety of applications, the largest of which is the manufacture of cement and concrete. Some concretes contain 80% of fly-ash [T2]. Other major uses are as road stabilizers, light-weight aggregates, road fill, and in asphalt mix [M6]. Fly-ash is also used to some extent in agriculture to improve soils [F7, J4]. All those utilizations of ash might lead to increased radiation exposures but very little has been published in this field.

33. Outside of the coal fuel cycle, the combustion of coal for various purposes results in airborne discharges

that have received very little attention. The use of coal for cooking and heating in private homes may lead to high collective dose commitments as the chimneys are low and not equipped with ash removal systems, and as the population densities around the sources of emission are high. Assuming that 5% of the coal produced and that 50% of the resulting ash escapes to the atmosphere means that domestic heating contributes about equally with power production, where 70% of the coal produced releases 2.5% of the ash. The further assumption that the population density around the houses is 10^4 km^{-2} leads to a collective effective dose equivalent commitment due to the world-wide use of coal in 1979 that is very roughly estimated to be of the order of 10^5 man Sv.

II. RADIATION EXPOSURES DUE TO GEOTHERMAL ENERGY PRODUCTION

34. Geothermal energy is produced in Iceland, Italy, Japan, New Zealand, the USSR and the United States. At the present time, it accounts for only 0.1% of the world's energy production [U5] but its relative importance may grow in the future as the potential resources of geothermal energy are believed to be very large. In geothermal energy extraction, use is made of hot steam or water derived from high-temperature rocks deep inside the earth. The geothermal fluids carry natural radionuclides and especially ^{222}Rn, which is discharged into the atmosphere. From measurements of ^{222}Rn activity concentrations in the hot stream used in three Italian power plants, the ^{222}Rn annual releases have been estimated to be 110 TBq from the 400 MW Larderello plant, 7.0 TBq from the 15 MW plant at Piancastagnaio, and 1.5 TBq from the 3 MW plant at Bagnore [M13]. These figures point to an average ^{222}Rn atmospheric discharge per unit energy generated of about 400 TBq per GW a. The corresponding collective effective dose equivalent commitment per unit energy generated is estimated to be about 6 man Sv per GW a if the assumptions used for the discharges from coal-fired power plants are applied. It is recalled that these assumptions are: equilibrium factor of 0.6 between ^{222}Rn and its short-lived decay products; population density of 100 km^{-2} around the plant; effective dose equivalent per unit activity inhaled of 1.3 10^{-8} Sv Bq^{-1}; indoor concentrations equal to the outdoor concentrations.

35. Annual individual effective dose equivalents resulting from inhalation of short-lived decay products of ^{222}Rn have also been estimated. Assuming, as in the case of discharges from coal-fired power plants, an effective stack height of 100 m and an annual average of the ground level air concentration per unit release rate of 4 10^{-8} Bq m^{-3} per Bq s^{-1} at 1 km from the stack, the annual effective dose equivalent resulting from atmospheric ^{222}Rn discharges would be about 3 10^{-5} Sv for an individual of the critical group living around a geothermal plant of 1 GW of electrical power. It is to be noted that the existing geothermal plants have a lower power, resulting in correspondingly lower estimates of annual effective dose equivalents.

III. RADIATION EXPOSURES DUE TO THE EXPLOITATION OF PHOSPHATE ROCK

36. Rock phosphate is used extensively, mainly as a source of phosphorus for fertilizers. The world production of phosphate rock was about 1.3 10^{11} kg in 1977, the main producers being Morocco, the Soviet Union and the United States [U1]. Table 9 presents average activity concentrations of natural radionuclides in phosphate rock from all major phosphate-producing areas of the world. Sedimentary phosphate ores, such as those found in Florida and Morocco, tend to have high concentrations of uranium, whereas magmatic ores, such as apatite from Kola, do not. Typical activity concentrations of ^{238}U are 1500 Bq kg^{-1} in sedimentary phosphate deposits and 70 Bq kg^{-1} in apatite. Uranium-238 is generally found in radioactive equilibrium with its decay products. The activity concentrations of ^{232}Th and of ^{40}K in sedimentary phosphate rock are much lower than those of ^{238}U, and comparable to those observed normally in soil.

37. Mining and processing phosphate ores redistribute ^{238}U and its decay products among the various products, by-products and wastes of the phosphate industry. Effluent discharges into the environment as well as the use of phosphate fertilizers in agriculture and of by-products in the building industry are possible sources of exposure to the public. This section deals mainly with the phosphates of sedimentary origin, as they are the most commonly found and the most likely to lead to enhanced radiation exposures.

A. DOSES ARISING FROM EFFLUENT DISCHARGES

38. Effluent discharges into the environment have been reported for a phosphate rock processing plant and two phosphoric acid production plants [P4], as well as for one uranium recovery plant [D2].

1. Effluents from phosphate rock processing operations

39. The preparation of phosphate rock generally involves strip mining to obtain ore, beneficiation to remove impurities, drying to remove moisture, and grinding to improve reactivity. The major airborne emissions occur in the form of fine rock dust from drying and grinding operations [P4]. The 1976 atmospheric discharges from an ore drying facility in Florida [P4] were about 250 MBq of ^{238}U, in radioactive equilibrium with its decay products down to ^{226}Ra (Table 10). Since that facility processed about 2.7 10^9 kg of wet phosphate rock in the same year, the atmospheric discharges of ^{238}U correspond to approximately 90 Bq per tonne of processed phosphate rock. The atmospheric releases of ^{222}Rn have not been reported; assuming a ^{226}Ra activity concentration in phosphate ore of 1500 Bq kg^{-1} and, conservatively, a 100% release of ^{222}Rn, they would amount to 1.5 10^6 Bq per tonne of processed phosphate rock.

40. During the beneficiation process, marketable rock is separated from sand tailings and clay slimes. These materials are produced in a 1:1:1 ratio. Clay slimes have about the same activity content as marketable rock whereas sand tailings are much less active. Mined-out areas are used in Florida for the disposal of sand tailings and slimes [M4]. Several Florida slime ponds have discharges to the environment. Although no chemical process is used to treat the discharges from the slime ponds, the measured activity concentrations of ^{226}Ra in liquid effluents were all found to be less than 100 Bq m^{-3}. The reduction of total ^{226}Ra from the raw slime to the effluent, primarily due to the removal of

suspended solids by settling, ranged from 92% to greater than 99.9% [M4]. Table 10 presents the ranges in ^{226}Ra activity concentration measured in the dissolved and in the undissolved fraction of the slime and of the effluent in seven mines and beneficiation plants in Florida [G4]. No information appears to be available to the Committee on the actual volume of liquid discharges from those plants.

2. Effluents from phosphoric acid plants

41. Phosphoric acid is produced by two principal methods, the wet process and the thermal process. In the wet process method, usually employed for the production of fertilizers, sulphuric acid is mixed with ground phosphate rock; the subsequent reaction results in the production of phosphoric acid and gypsum: $10\ H_2SO_4 + Ca_{10}F_2(PO_4)_6 + 20\ H_2O \rightarrow 10\ CaSO_4 . 2\ H_2O + 2\ HF + 6\ H_3PO_4$. In the reaction, radium is coprecipitated with the gypsum, while uranium and thorium follow the phosphorus into the acid, which is then used to manufacture various fertilizer products. Table 11 presents the estimated distribution of some natural radionuclides among various products of the phosphate industry, in the United States, along with the quantities involved [G5].

42. Apart from gaseous fluorides, which are not radioactive, the airborne effluents of wet phosphoric acid plants consist of dust resulting from the transferring of phosphate rock within the plant. Estimates of the airborne discharges from two wet process phosphoric acid plants located in Florida are given in Table 10 [P4]. The estimated releases, which are based on the measurement of the total particulate emissions and of the total activity concentrations of natural radionuclides in the raw products, are about 100 times higher in plant B than in plant A. However, a stack sampling survey, conducted by the United States Environmental Protection Agency to measure the actual emissions from selected stacks at each facility, showed that the releases from plant B were probably overestimated [P4]. On the basis of information contained in reference [P4] and on the chemical reaction given above, the throughput of marketable ore in plant A and in plant B has been assessed to be about $1.2\ 10^9$ kg. The atmospheric releases of ^{222}Rn have not been reported; assuming a ^{226}Ra activity concentration in phosphate ore of 1500 Bq kg^{-1} and, very conservatively, a 100% ^{222}Rn release, they would amount to $1.5\ 10^6$ Bq per tonne of phosphate ore.

43. Each wet process phosphoric acid plant in Florida incorporates a large cooling pond (about 2 km^2) of contaminated water for recycle in the facility. During periods of excess rainfall, it becomes necessary to discharge water from these ponds to nearby streams [M4]. Raw process water has a pH of 1.5–2.0 and contains 74 000 Bq m^{-3} of ^{238}U [G4, M4]. The United States Environmental Protection Agency permits for phosphoric acid plants usually stipulate an acceptable pH range of 6–9 for treated effluent. To accomplish this, slaked lime is normally added. This chemical treatment is highly effective in removing natural radionuclides from the raw process water, as shown in Table 10. No quantitative information on the actual discharges appears to be available to the Committee.

44. In the thermal process normally used for high-grade acid and phosphates, coke and silica are added to phosphate rock in an electric furnace. The chemical reaction at high temperature produces elemental phosphorus, which is relatively free of radioactivity, and several by-products among which calcium silicate slag, which carries the bulk of the activity initially contained in the phosphate rock, and ferrophosphorus are the most important [B4, G4, M14]. The smelting of the ore results in ^{210}Po and other volatile radioactive material releases [B4]. Actual airborne discharges are not available.

3. Effluents from uranium recovery operations

45. Various processes have been suggested for recovering uranium from phosphate rock [R2, R3]. The plants already existing or being designed for construction in central Florida employ solvent extraction of uranium from phosphoric acid produced at a new process phosphoric acid plant [D2].

46. Annual airborne discharges (Table 10) from a commercial uranium recovery plant in Florida have been estimated to be about 400 MBq of ^{238}U on the basis of limited measurements [D2]. The major contribution to atmospheric radioactive releases was found to occur in the drumming building; the material released was uranium with natural isotopic composition. The production rate of the plant was about 50 tonnes of uranium per year, corresponding to approximately $4\ 10^5$ tonnes of marketable phosphate rock.

4. Environmental concentrations and doses

47. As the heights of atmospheric releases are in general less than 50 m above ground level, surface air measurements in the vicinity of the plants usually show the presence of enhanced concentrations of natural radionuclides.

48. Air activity concentrations of ^{238}U, ^{226}Ra, and ^{230}Th were found to be about 200 μBq m^{-3} at approximately 400 m from the ore drying plant investigated [P4]. In comparison, the average background activity concentrations in the area are about 15 μBq m^{-3}.

49. Smaller increases were observed around the two wet process phosphoric acid plants. Average concentrations of about 30 μBq m^{-3} of ^{238}U, ^{226}Ra, and ^{230}Th were measured at approximately 1000 m from the plants [P4].

50. In Idaho, at about 800 m downwind from two adjacent phosphate plants, a wet process plant and a thermal process plant, the annual average gross alpha surface air activity concentration was about 700 μBq m^{-3} in 1974 [B4]. Most of this activity is attributed to ^{210}Po.

51. The main pathways through which the populations living around those plants are exposed to enhanced levels of natural radionuclides are inhalation during the passage of the cloud, and external irradiation, inhalation and ingestion resulting from the activity deposited on the ground. The collective dose commitments corresponding to those pathways have been roughly estimated using the methods already described in paragraphs 24–28 for airborne discharges from coal-fired power plants.

52. The collective dose commitments due to inhalation of all radionuclides except ^{222}Rn and its short-lived decay products are expressed in the form

$$M_q^c = \frac{A_o}{v_d} \delta_N B \frac{D_q}{I_{ih}} \quad (5)$$

where A_o is the annual release (Bq); B is the breathing rate, taken to be equal to 2.3 10^{-4} m^3 s^{-1} for an adult; $v_d = 10^{-2}$ m s^{-1}; δ_N, the human population density, is assumed to be uniform and equal to 100 km^{-2} around the plant; D_q/I_{ih} is the committed absorbed dose in organ or tissue q per unit intake (Gy Bq^{-1}). The values adopted for D_q/I_{ih} are those of Table 5, related to emissions from coal-fired power plants.

53. Regarding inhalation of ^{222}Rn and its short-lived decay products, the expression used is

$$M_q^c = \frac{1.8\ (Bq\ m^{-3})}{2\ 10^{-2}\ (Bq\ m^{-2}\ s^{-1})} A_o \delta_N B \frac{D_q}{I_{ih}} \quad (6)$$

where A_o is the activity of ^{222}Rn daughters associated with the release of ^{222}Rn (the equilibrium factor between ^{222}Rn and its daughters is taken to be 0.6).

54. The estimated collective dose commitments due to inhalation during the passage of the cloud are presented in Table 12 for some of the radionuclides discharged into the atmosphere as a consequence of processing one tonne of phosphate ore. The radionuclides considered are those for which discharge data have been measured or derived from measurements (see Table 10 and paragraphs 39, 42 and 46).

55. The collective dose commitments incurred after deposition (external irradiation and internal irradiation arising from inhalation of resuspended or emanated material and ingestion of contaminated foodstuffs) can be roughly evaluated by comparison with the natural soil activity concentrations and the corresponding dose rates. As in the case of the airborne discharges from coal-fired power plants (see paragraphs 26 and 27), the expression used is

$$M_q^c = \frac{A_o \dot{D}_q \delta_N \tau}{h C} \quad (7)$$

where A_o is the activity associated with the release of a given radionuclide; $\dot{D}_q$ is the natural dose rate in organ or tissue q due to the radionuclide under consideration; τ is the mean life of the long-lived natural radionuclides in soil, taken to be 100 years; h is the thickness of soil involved, expressed as mass per unit area (assumed to be 500 kg m^{-2}); and C is the natural concentration of the nuclide in the soil. The collective dose commitments per unit mass of marketable ore processed obtained in this way are presented in Table 13.

B. DOSES ARISING FROM THE USE OF PHOSPHATE FERTILIZERS

56. The world production of phosphate fertilizers was approximately 3 10^{10} kg of P_2O_5 in 1977 [U1]. Assuming that the activity distribution given in Table 11 holds on a global basis, the mass of marketable rock necessary to produce such an amount of phosphate fertilizers was about 10^{11} kg, which is approximately three-quarters of the world production of marketable ore in that year (1.3 10^{11} kg).

57. The application rate of fertilizers depends inter alia on the type of soil and on the type of crop. The average consumption of phosphate fertilizer per hectare of agricultural land varied in 1977 from 0.9 kg P_2O_5 for the African continent to 37.6 kg P_2O_5 for Europe, the world average being 6.3 kg P_2O_5 [F3]. The amounts of fertilizer applied annually by crop in the United States have been reported to range from about 30 kg P_2O_5 per hectare for barley, wheat and oats to about 150 kg P_2O_5 per hectare for potatoes and tobacco [N4].

58. Measured activity concentrations of naturally-occurring radionuclides in phosphate fertilizers from several countries are summarized in Table 14. With the exception of basic slag (a by-product of the manufacture of steel), all the fertilizers considered in Table 14 are derived from phosphate ore processing. For a given radionuclide and type of fertilizer, the concentrations vary markedly from one country to the other, depending on the origin of the components. Relatively high concentrations of ^{238}U are observed or should be expected when the phosphate ore is of sedimentary origin, while low concentrations are associated with ore of magmatic origin.

59. The degree of radioactive equilibrium between ^{238}U and its decay products depends on the type of manufacturing process used and more specifically on the relative contribution of phosphoric acid in the end-product, since phosphoric acid has usually a very low content of ^{226}Ra. The lack of equilibrium between ^{238}U and ^{226}Ra is particularly clear for triple superphosphates and ammonium phosphates. Other general features that can be observed in Table 14 are that the concentrations of ^{232}Th are always low; with the exception of the potassium fertilizers, the concentrations of potassium (and thus ^{40}K) are also generally low; that the concentrations of ^{226}Ra do not exceed 1000 Bq kg^{-1}; and that ^{210}Pb and ^{210}Po are generally close to radioactive equilibrium with ^{226}Ra.

60. Phosphate fertilizers contribute to the external radiation exposure of persons occupationally handling phosphates and of members of the public. Through the contamination of foodstuffs, they also contribute to internal irradiation of mankind.

61. Pfister and Pauly [P7] have estimated the external radiation exposure of members of the public and of the small group of persons working in production, transport, storage and application of rock phosphates and phosphate fertilizers in the Federal Republic of Germany. With regard to the dispersal of phosphate fertilizers in agricultural areas, they assessed the average addition to the soil activity in 1977–1978 at 17 Bq m^{-2} of ^{238}U, 11 Bq m^{-2} of ^{226}Ra, 7.4 Bq m^{-2} of ^{232}Th and 150 Bq m^{-2} of ^{40}K. Assuming an accumulation of ^{226}Ra in the soil during the last 80 years, a mean additional absorbed dose rate in air of about 8 10^{-4} μGy h^{-1} was calculated. Fertilizer application therefore results in a fairly small increase of the external radiation exposure over natural background which, on average, is 0.05 μGy h^{-1} (see Annex B). In contrast, the occupational radiation exposure of individuals can be much higher. Pfister and Pauly [P7] measured mean additional absorbed dose rates in air ranging from 0.02 to 0.23 μGy h^{-1} for various transport and loading operations and peak values of 0.8 μGy h^{-1}. In agricultural storehouses, they measured a mean additional absorbed dose rate in air of 0.09 μGy h^{-1}. It is possible, however, that inhalation of fertilizer dust might lead to higher doses.

62. A slight increase in the concentrations of natural radionuclides of the ^{238}U series is also expected to occur in food crops grown on soils supplied with high amounts of phosphate fertilizers. Kirchmann et al. [K5] measured the ^{226}Ra activity concentration in straw and grain of wheat harvested in plots fertilized for 11 years with controlled amounts of phosphate fertilizers. There was no significant difference in the ^{226}Ra concentrations of wheat harvested in the plots fertilized at high levels (1356 kg P_2O_5 per hectare) or at low levels (343 kg P_2O_5 per hectare). However, the ^{226}Ra soil contamination resulting from the application of phosphate fertilizers represented respectively only 1.08% and 0.25% of ^{226}Ra activity of natural origin observed in the upper layer of soil [K5]. The small relative contribution of the ^{226}Ra content in the fertilizer to the natural ^{226}Ra content in the soil, combined with the fact that the fertilizer was homogeneously mixed in the soil, is likely to have precluded experimental evidence of an increased ^{226}Ra concentration in wheat. Other tests with fertilizers labelled with ^{226}Ra have shown that the radionuclide uptake by plants is practically the same whether it is included in fertilizer or in soil structures [D5].

63. However, foodstuffs may be contaminated to a greater extent if, for example, fertilizers are applied in liquid form on the soil surface or if phosphate products are used to feed animals. Phosphate products are extensively used as a source of phosphorus in livestock feed supplements. Activity concentrations of ^{226}Ra in livestock feed supplements have been measured in the United States to range from 7 to 1600 Bq kg^{-1} [R5], which is consistent with the values presented in Table 14 for phosphate fertilizers. An assessment of the transfer to milk of ^{226}Ra ingested by dairy cows in their feed supplements showed that the maximum ^{226}Ra concentration in milk would be about 25 Bq m^{-3}, to be compared with "normal" concentrations of 3 to 10 Bq m^{-3} [R5].

64. The collective dose commitments arising from the decision to use one tonne of marketable ore to produce phosphate fertilizer can be crudely estimated with the method used in paragraph 55. According to the data presented in Table 11, one tonne of marketable rock produces 0.54 tonne of fertilizer. On the basis of the results presented in Table 14, the average activity concentrations of natural radionuclides in phosphate fertilizers are taken to be 600 Bq kg^{-1} for ^{238}U, ^{234}U and ^{230}Th, and 400 Bq kg^{-1} for ^{226}Ra and for each of its decay products. Therefore, one tonne of marketable ore is estimated to produce 0.54 tonne of phosphate fertilizers containing about $3\ 10^5$ Bq of ^{238}U and $2\ 10^5$ Bq of ^{226}Ra and of each of its decay products. The activity concentrations of ^{40}K and of the radionuclides of the ^{232}Th series are generally low and the corresponding doses have been neglected.

65. Assuming that the ploughed layer of soil is 30 cm deep; the availability to plants of natural radionuclides is the same whether in fertilizer or in the normal constituents of the soil; the deposited activity becomes unavailable to the vegetation with a mean life of 100 years for the long-lived natural radionuclides; and the fraction of time spent by the populations exposed on, or near, fertilized fields is 1%; then the collective dose commitments per unit mass of marketable rock arising from external irradiation and from internal irradiation (resuspension and emanation from soil and ingestion of contaminated foodstuffs) may be calculated as in Table 15.

C. DOSES ARISING FROM THE USE OF BY-PRODUCTS AND WASTES

66. The main by-products resulting from processing phosphate ore in phosphoric acid plants are gypsum (or phosphogypsum) in wet process plants and calcium silicate slag in the thermal process plants. Radiation exposure to members of the public can occur if those by-products are used in the building industry. Another source of exposure stems from the reclamation of land on which phosphate mining has been completed and houses have been allowed to be built.

67. Large quantities of phosphogypsum are produced in the wet process phosphoric acid plants. The annual world production of phosphogypsum was approximately 9 10^{10} kg in 1974, which is greater than the production of natural gypsum [F4]. As shown in Table 11, the mass of phosphogypsum produced is about the same as that of the phosphate ore processed and the bulk of the ^{226}Ra content of the phosphate ore is transferred to phosphogypsum. The average activity concentration of ^{226}Ra in phosphogypsum was taken to be about 900 Bq kg^{-1} in Annex B of the 1977 report [U2].

68. Phosphogypsum can replace natural gypsum in the building industry and thus be used to make blocks and plaster board, partition systems and also cement [N5, O2, O3]. The practice of using this waste product has been considered attractive, since overall building costs are reduced, natural resources are preserved, and environmental pollution is decreased. On the other hand, since phosphogypsum contains a much higher concentration of ^{226}Ra than its natural counterpart, its use increases the radiation doses to the public.

69. Japan was the first country to employ phosphogypsum for construction purposes in 1934 [S4]. In 1974, approximately $3\ 10^9$ kg of phosphogypsum was used in Japan in the construction industry, half of it as setting controller for cement. The use of phosphogypsum for plaster, plasterboard and building blocks has gained importance throughout the world [S4].

70. O'Riordan et al. [U2] estimated the additional doses that would be received by the occupants of a residential building in which 4.2 tonnes of by-product gypsum (considered to be a high, but realistic amount) would have replaced the established materials. Assuming the ^{226}Ra concentration of phosphogypsum to be 900 Bq kg^{-1}, they estimated the additional absorbed dose rate in air to be 0.07 μGy h^{-1}, and the additional radon concentration, using a ventilation rate of 1 h^{-1}, to be about 10 Bq m^{-3}.

71. If it is assumed that all the phosphogypsum produced by 1 tonne of marketable ore is used in the building industry, that on the average four persons live in the dwellings so constructed, and that the mean life of the dwelling is 50 a, the whole-body collective dose commitments due to external irradiation can be evaluated from the estimates provided by O'Riordan et al. [O2], to be about 0.02 man Gy t^{-1}. Assuming that the equilibrium factor between radon and its short-lived decay products is 0.6, the collective effective dose equivalent commitments arising from indoor inhalation would also be about 0.02 man Sv t^{-1}.

72. It should be indicated that phosphogypsum is also used in agriculture as an amendment to improve water movement in saline-alkaline soils and may also be substituted for limestone or lime to supply calcium to

alkaline soils [L3]. Owing to the low solubility of Ra SO_4 and to the effect of the presence of calcium, the ^{226}Ra soil-plant transfer coefficient for plants grown on phosphogypsum-treated soils should be smaller than under "normal" conditions [L3].

73. Calcium silicate slag is a by-product of phosphate ore processing by the thermal process. With the exception of ^{210}Po, which is driven off during smelting, the measured concentrations of the natural radionuclides of the ^{238}U series were found to be about the same in the phosphate ore and in the slag [B4, G4, P5].

74. In Idaho, about 2.4 10^9 kg of slag are produced each year [B4]. Measured activity concentrations in slag samples are 1300–1500 Bq kg^{-1} of ^{226}Ra, 740 Bq kg^{-1} of ^{230}Th and 1000 Bq kg^{-1} of ^{238}U. About one-tenth of this product is sold to slag crushing operations that market the material for railroad ballast, asphalt, concrete, and other uses. In that way, about 800 GBq of ^{226}Ra was distributed into the environment in the areas of Pocatello and Soda Springs in 1974. The number of structures and dwellings constructed with slag in concrete is estimated to be approximately 150. Gamma surveys were conducted in Soda Springs and Pocatello. Above asphalt containing slag, the average external gamma absorbed dose rate in air was found to be about 0.08 μGy h^{-1} above background, the maximum level being approximately 0.3 μGy h^{-1}. The preliminary results from the indoor survey indicate that the gamma absorbed dose rate in air can also be as high as 0.3 μGy h^{-1} above background in dwellings constructed with 43% by weight slags in concrete slabs [B4]. In comparison, the average gamma absorbed dose rate in air received indoors is estimated as 0.06 μGy h^{-1} in Annex B.

75. In Canada, about 21 000 tonnes of slag arising from a thermal process plant using Florida phosphate rock as input feed has been crushed and used in roadbeds, laneways, backfill around basements, and as a base for concrete floors in basements of dwellings [M14]. Measurements of slag samples indicated a ^{226}Ra activity concentration of 2150 Bq kg^{-1}. A gamma survey was conducted inside homes with slag and without slag. For 24 dwellings with slag, the average absorbed dose rate in air was 0.12 μGy h^{-1} with a standard deviation of 0.04 μGy h^{-1}. The range of values observed was 0.07 to 0.21 μGy h^{-1} (excluding two houses in which crushed slag had been spread over the basement excavation to form an unfinished floor, resulting in measured absorbed dose rates in air of 0.33 and 0.54 μGy h^{-1}, respectively). By comparison, the average absorbed dose rate in air for 54 homes without slag was 0.09 μGy h^{-1}, with a standard deviation of 0.02 μGy h^{-1} and a range of 0.05 to 1.5 μGy h^{-1}. Thus the use of slag has led to an apparent increase of 0.033 μGy h^{-1}. This difference is, however, not statistically significant because of the standard deviations given above [M14].

76. A similar situation has been discovered to occur in Florida [A2]. Approximately 250 000 tonnes of slag are used each year for paving roads, as ballast, as material for railroad beds, and for house roofing material. An investigation was conducted by the United States Environmental Protection Agency [A2].

77. Residents in structures built on "reclaimed" Florida phosphate land may also be exposed to enhanced radiation doses. About 600 km^2 of Florida land have been mined for phosphate rock in the last 80 years. Of that amount, about 200 km^2 have been reclaimed to various degrees. It is estimated that 4000 structures may be built on phosphate lands in central Florida [R6]. Absorbed dose rates in air were measured in and out of 672 structures built on reclaimed land. The average absorbed dose rate in air was found to be 0.092 μGy h^{-1} outdoors, the highest one 0.35 μGy h^{-1} [G7, G8]. By comparison, the natural background outside the phosphate area is approximately 0.05 μGy h^{-1}. The indoor levels reflected the degree of floor shielding present in the various structure categories. Absorbed dose rates in air in excess of 0.17 μGy h^{-1} were only observed in crawl space and trailer constructions, which have either wood or thin metal flooring [G7]. The equilibrium equivalent radon concentration in houses ranged from 4 to 500 Bq m^{-3} with a weighted average of about 40 Bq m^{-3} which is estimated to be 26 Bq m^{-3} above normal concentrations in houses of that area. This average additional concentration results in an annual effective dose equivalent of approximately 1.6 mSv.

D. RECAPITULATION

78. Table 16 summarizes the radiation exposures due to the exploitation of phosphate rock, expressed in terms of collective effective dose equivalent commitments resulting from the decision of using a unit mass of marketable ore to accomplish a defined purpose. The most important natural radionuclides have been taken into account.

79. The impact from one year of phosphate ore processing has been very crudely estimated on the basis of the following data and assumptions:

(a) The world production of marketable rock is 1.3 10^{11} kg in a typical year;
(b) All the marketable ore is processed in ore drying plants;
(c) Seventy per cent of the marketable ore production is used to prepare phosphate fertilizers;
(d) With regard to the wet process phosphoric acid plant, the results relative to plant A (see Tables 12 and 13, and paragraph 42) are adopted;
(e) Ten per cent of the by-product gypsum is used as building material in dwellings.

80. On the basis of these assumptions, the collective effective dose equivalent commitment resulting from the 1977 production of phosphate rock is estimated to be about 3 10^5 man Sv; by far, the most important contribution to the total dose is due to the use of by-product gypsum in dwellings. The total of the other contributions to the collective effective dose equivalent commitment is only about 6000 man Sv.

IV. ENHANCED INDOOR EXPOSURES

81. Indoor exposures result mainly from external irradiation and from inhalation of radon decay products. The general aspects of indoor exposures are discussed in Annexes B and D. This section deals essentially with elevated indoor exposures. High external irradiation rates usually arise from high concentrations of natural radionuclides (especially ^{226}Ra) in building materials and in soil. Elevated concentrations of radon decay products may be due to the same reasons or to high radon influx from the soil, or to high radon concentrations in water or natural gas used in homes.

82. *Building materials.* As exemplified in Table 17, the use of some building materials may lead to elevated indoor radiation levels. The building materials may be of natural origin, such as pumice stone (Federal Republic of Germany and the USSR), concrete containing alum shale (Sweden), lithoid tuff (Italy), and granite wherever it is used. They may also result from industrial processes. In the non-uranium industries, the use of phosphogypsum and of calcium silicate slag, two by-products of the phosphate industry have already been discussed. Other by-products that were shown to contain relatively high concentrations of naturally-occurring radionuclides were red mud, a waste product of aluminium mills, and blast furnace slag, a by-product of iron manufacture [K7].

83. In its basic radiation standards, the National Commission of Radiation Protection of the USSR [K8] used a dosimetric relationship. If the concentrations of ^{40}K, ^{226}Ra and ^{232}Th, expressed in Bq kg^{-1}, in materials made of industrial wastes satisfy the expression

$$\frac{C(^{40}K)}{4810} + \frac{C(^{226}Ra)}{370} + \frac{C(^{232}Th)}{259} \leq 1 \qquad (8)$$

it was estimated that the increase over background of the gonad absorbed dose indoors from external irradiation is less than 1.5 mGy in a year. In comparison, the average absorbed dose in all tissues received indoors from external irradiation of terrestrial origin is assessed as 0.3 mGy in a year in Annex B. The measurements of activity concentrations of naturally-occurring radionuclides in building materials in the Soviet Union [K8] showed that only a few materials would not satisfy the expression given above, while in the Federal Republic of Germany it was found that 12% of the analysed samples would exceed that limit [K7].

84. It should be pointed out that the average absorbed dose rates in air measured in buildings using these materials are much lower than what would be expected from the radioactive content of the materials considered, because materials usually less active are also used in the same buildings. For example, the average absorbed dose rate derived from measurements carried out in Swedish houses made of aerated concrete containing alum shale is about 0.17 μGy h^{-1} [M7], while the value given in Table 17, calculated from the activity concentration of radionuclides in that type of concrete, using very pessimistic assumptions, is 1.5 μGy h^{-1} [S6]. Measurements of radon daughters have been carried out in 32 single-family houses containing a large fraction of concrete based on alum shale in their building materials [S13]. The average equilibrium equivalent concentration of radon in those houses was found to be 260 Bq m^{-3}, corresponding to annual effective dose equivalents of 16 mSv.

85. Waste products of the uranium and radium industry have been used as building materials. In the United States, notably in Grand Junction, Colorado, tailings from uranium mills were used during the period 1952–1966 as fill material under houses and as building materials [U4]. Remedial action was deemed necessary by the national authorities more because of the elevated radon concentrations measured in houses than because of the external radiation doses. The average equilibrium equivalent concentration of radon measured in 47 houses was about 200 Bq m^{-3} [C7]. It is in many cases true that when building materials containing high concentrations of ^{226}Ra are used in dwellings, the occupants receive a higher effective dose equivalent rate from inhalation of ^{222}Rn and its short-lived decay products than from external irradiation.

86. In the town of Port Hope, Ontario, Canada, another type of problem arose from a plant which had recovered radium in the 1930s and the 1940s from pitchblend-radium-silver ores [S7]. In this particular case, the potential radon problem was not recognized and consequently much contaminated construction and fill material was used in and around the houses in the town. As in the case of Grand Junction, remedial action was deemed necessary by the national authorities.

87. *Radium in soil.* In Sweden, areas containing tailings from the alum shale industry have been built on. The radium concentration of the tailings is on average 2900 Bq kg^{-1} and the outdoor gamma radiation dose rate in air is of the order of 1 μGy h^{-1} [S14]. In houses, the equilibrium equivalent concentration of radon was found to be 500 Bq m^{-3} on average [S14], corresponding to annual effective dose equivalents of about 30 mSv. In March Township, Ontario, Canada, 343 houses were surveyed because of the discovery of nearby low-grade uranium deposits. The highest equilibrium equivalent concentration of radon was 700 Bq m^{-3} and the weighted arithmetic average 50 Bq m^{-3} [L5]. This weighted average is estimated to result in annual effective dose equivalents of 3 mSv received indoors.

88. *High radon influx from soil.* In the Chicago area, United States, high radon concentrations have been found in houses with unpaved crawl spaces while the radium concentration in soil was normal [R9]. In a total of 22 houses investigated, the radon concentration was more than 185 Bq m^{-3} in nine houses and more than 370 Bq m^{-3} in six of these. Most of the radon emanated from the unpaved crawl space under the house. In Sweden, it is estimated that about 75% of the total collective dose caused by inhalation of radon daughters arises from radon emanating from the ground. Houses have been found with more than 10 000 Bq m^{-3} of radon. An equilibrium equivalent concentration of radon of 10 000 Bq m^{-3} is estimated to yield an annual effective dose equivalent of about 600 mSv received indoors.

89. *Radon in water.* Radon in water may be a significant source of radon in the air in dwellings in many countries. In the region of Helsinki, Finland, very high concentrations of radon in water from deep wells, ranging up to 44 MBq m^{-3}, have been reported [C8]. From measurements of air concentration of radon in 20 houses [A5], it can be derived that the average equilibrium equivalent concentration of radon would be 360 Bq m^{-3} with a maximum value of 1200 Bq m^{-3}. In Canada, the area of Castlegar-Trail in British Columbia, was surveyed because of high radon concentrations in water. The weighted average equilibrium equivalent concentration of radon in indoor air was found to be about 70 Bq m^{-3} while the highest value was 2900 Bq m^{-3} [L5].

90. *Radon in gas.* Natural gas containing radon may also be a significant source of radon in indoor air if it is used in unvented appliances. Average radon concentration in natural gas in various distribution lines have been reported to be within the range of 40 to 2000 Bq m^{-3} [J9, W9]. Assuming that natural gas is used in unvented kitchen ranges, the resulting additional indoor air concentrations are estimated to be only about 0.01 to 0.3 Bq m^{-3}.

91. In conclusion, enhanced indoor exposures may be due to various reasons and may give rise to high individual doses. More detailed information on the elevated indoor concentrations of radon that have been measured in several countries is provided in Annex D. The collective doses have not been quantified owing to the lack of data on the number of houses involved. Further measurements are required in that field.

V. ENHANCED EXPOSURES TO COSMIC RAYS

A. PASSENGERS IN AIRCRAFT

92. The number of passenger kilometres flown throughout the world in scheduled commercial flights was $9.34\ 10^{11}$ in 1978 [12]. Taking the average speed to be 600 km h^{-1}, a total of about $1.6\ 10^{9}$ passenger hours was spent travelling in that year. The dose rates incurred during the flights vary according to the altitude and, to a smaller extent, to the latitude and to the solar activity. Table 18 shows the variation with altitude, from 4 to 20 km, of the dose rate and of the dose equivalent rate averaged over two geomagnetic latitudes and two periods of solar activity [O4]. The altitudes of subsonic flights depend on the type of aircraft used and on the distances covered in a given flight. They could be as low as 2–3 km for short flights and as high as 12 km for intercontinental flights, with intermediate values of 5–10 km for medium-range and continental flights [H2, W1, W2]. Table 18 shows that the dose rate and the dose equivalent rate vary by a factor of 20 between the altitudes of 4 and 12 km. Assuming that the average altitude of commercial flights is 8 km, the average dose rate would be 0.84 μGy h^{-1} and the average dose equivalent rate 1.35 μSv h^{-1}, yielding a collective effective dose equivalent to the world population of about 2000 man Sv from air transportation in 1978.

93. Supersonic aircraft (SST), which are used on a small scale, fly at altitudes ranging up to 20 km, compared with at most 12 km for standard jet aircraft. Assuming that SSTs fly at an average altitude of 16 km, the average absorbed dose rate would be about 6 μGy h^{-1} (Table 18). Actually, the absorbed dose rates measured on board the commercial SST flights of Air France, averaged over the years 1976–1980, amount to about 5 μGy h^{-1} [P8]. Taking from Table 18 the quotient of the dose equivalent to the absorbed dose to be 1.6 Sv Gy^{-1}, the corresponding dose equivalent rate is about 8 μSv h^{-1}.

94. Wallace [W2] calculated absorbed doses to passengers for a round trip, for both subsonic and supersonic transport between various city pairs. Some of these estimates are shown in Table 19. Doses for a round trip in supersonic aircraft are approximately 70% of those for subsonic speeds, because of the shorter flying time. However, the dose rates in supersonic aircraft are about twice as high as in subsonic aircraft. For a round trip across the Atlantic, the tissue absorbed doses in passengers may be estimated to be about $2\ 10^{-5}$ Gy for an SST and $3\ 10^{-5}$ Gy for a subsonic aircraft, under average solar conditions.

95. All the dose values given above refer to galactic cosmic rays. There is, in addition, a contribution due to the solar flares. From dose rate values given in the 1972 UNSCEAR report [U6], based on results obtained by an ICRP working group by averaging the effects of solar flares over the period 1952–1960 [I3], the average absorbed dose index rates from solar radiation can be estimated to be $4\ 10^{-8}$ Gy h^{-1} at 12 km and $9\ 10^{-7}$ Gy h^{-1} at 20 km. The average contribution from this source is thus small compared with that from galactic cosmic rays.

96. Although radiation of solar origin does not contribute significantly to the average absorbed dose index rate, during an occasional intense solar flare radiation levels at these altitudes may increase by several orders of magnitude. The giant solar flare events last only for about 10 h and occur a few times in each solar cycle, and therefore are not likely to add significantly to the collective dose of the world population. It is worth mentioning that SST aircraft carry radiation monitors, and the pilots will move the aircraft to lower altitudes when the dose rate reaches a prescribed level.

B. ASTRONAUTS

97. When travelling into space, astronauts are subjected to primary cosmic ray particles, the radiation from solar flares, and also the intense radiation present in the two radiation belts. Savun et al. [S8] have reported measurements in the radiation belts in 1971. Measurements inside a 0.7 g cm^{-2} shield indicate that the maximum absorbed dose rate crossing the inner belt was 0.22 Gy h^{-1} and crossing the outer belt 0.054 Gy h^{-1}.

98. Estimated absorbed doses received by astronauts on several Apollo missions (average for the three occupants) based upon measurements carried out with tissue-equivalent ionization chambers are shown in Table 20 [C3, E2, R7, G9]. A large part of this dose was received while the spacecraft was passing through the earth's radiation belts. For example, the higher dose received on the Apollo X mission was largely due to a different trajectory through the radiation belts. Analogous data in Table 20 from space flights of the USSR (Vostok, Voskhad and Soyuz series) indicate doses of comparable magnitude [G9]. Table 21 indicates the breakdown of the absorbed dose and of the dose equivalent on the first lunar landing mission, Apollo XI [E2].

99. In outer space, remote from the shielding influence of the earth's magnetic field, the absorbed dose index rate from solar protons emitted during solar flares can be very high. For example, it has been estimated that the absorbed dose indices in outer space from the solar proton event of 10 July 1959 were: from protons 3.6, 1.7, and 0.4 Gy behind shielding of 1, 2 and 5 g cm^{-2}, respectively, and from alpha particles the corresponding values were 1.5, 0.3 and 0.05 Gy, respectively [C3]. However, the Apollo missions did not experience any measurable solar particle events [E2].

VI. MISCELLANEOUS SOURCES OF RADIATION

100. In the present context the term miscellaneous sources indicates a variety of radiation sources which the general public is exposed to during the normal course of its activities, generally without being aware of them. Those sources of radiation result from man-made

activities. Most of them are consumer products containing radioactive substances that have been deliberately incorporated to satisfy a specific purpose.

A. CONSUMER PRODUCTS

101. The consumer products containing deliberately incorporated radionuclides can be broadly classified into five categories: radioluminous products; electronic and electrical devices; antistatic devices; smoke detectors; and ceramic, glassware, alloys, etc. containing uranium or thorium. Some of these products, such as the antistatic devices, are more widely disseminated in industry than among the general public.

102. Table 22 presents some information on the number of products and the activities involved in each category in the Federal Republic of Germany [W3]. Although the data shown are not contemporaneous as some correspond to the year 1973 and others to the year 1975, the table gives a good idea of the relative importance of each category in an industrialized country.

1. Radioluminous products

103. Radium-226, promethium-147, and tritium have been used extensively in the dial-painting industry for the illumination of timepieces, the radiation emitted by those radionuclides being converted into light by a scintillator, which is usually zinc sulphide containing small amounts of copper or silver. From the public health point of view, one of the major disadvantages of radium is its inherent emission of a great deal of penetrating radiation which is not useful for the production of light yet irradiates the whole body of the watch wearer. Radium tends to be replaced by ^{3}H and ^{147}Pm, which are soft beta emitters and thus cause much smaller external radiation doses to the watch users.

104. Table 23 presents estimates of the numbers of radioluminous watches and clocks in use in Switzerland, the United Kingdom and the United States. The values for the United States are based on production data assuming that the average useful life of a luminous timepiece is 3 years [M8]. The estimates from Switzerland are an extrapolation to the whole population of the country of the results of a survey involving 1032 consumers [K9]. The data for the United Kingdom are based on information from the watch trade [T1]. It is clear from the table that most of the radioluminous watches contain tritium; in clocks, ^{147}Pm and ^{226}Ra seem to be more used than ^{3}H.

105. The activities of ^{3}H and ^{147}Pm which produce the same brightness as 37 kBq of ^{226}Ra have been estimated to be about 200 TBq of ^{3}H and 6 TBq of ^{147}Pm for a newly manufactured timepiece [I4]. However, owing to radioactive decay, release of activity and deterioration of the phosphor, the brightness decreases continuously over the useful life of the timepiece at a rate that depends upon the radionuclide used. The activities of ^{3}H and ^{147}Pm required to produce the same average brightness as 37 kBq of ^{226}Ra over the useful life of the timepiece, taken to be three years, have been estimated to be about 300 TBq of ^{3}H and 10 TBq of ^{147}Pm [M9].

(a) Absorbed doses from ^{226}Ra-activated timepieces

106. The absorbed doses from ^{226}Ra-activated timepieces result mainly from external irradiation, the release of radon being usually insignificant. As indicated in Annex B of the 1977 report [U2], an annual gonad dose per unit activity of $1.6\ 10^{-8}$ Gy Bq^{-1} is estimated for wrist-watches worn continuously. According to the recommendations issued by a joint group of experts from OECD and IAEA [I4], the total activity of ^{226}Ra should be limited to 3.7 kBq. That limit corresponds to a gonad absorbed dose in a year of 40 μGy if the watch is worn on average 16 hours per day. However, as the production of ^{226}Ra-luminous watches has stopped in many countries, a significant fraction of the existing ^{226}Ra-painted watches is likely to have been manufactured in the 1950s or the early 1960s, and to contain greater activities than the limit.

107. The external radiation gonad dose per unit activity to the user of an alarm clock has been calculated for an exposure of 8 h per day at a distance of 2 m to be $1.6\ 10^{-10}$ Gy Bq^{-1} [M8]. Assuming that the ^{226}Ra activity contained in the alarm clock is 5.5 kBq, which is the limit recommended [I4], the annual gonad dose would be about 1 μGy; the annual effective dose equivalent would be about 1 μSv.

(b) Absorbed doses from ^{3}H-activated timepieces

108. As shown in Table 22, most of the radioluminous watches currently in use are luminized with tritium paint. The external dose from a tritium luminous watch is negligible because of the low energy of the β-particles and of the bremsstrahlung arising from the decay of ^{3}H. However, tritiated water or tritiated organic molecules evolve slowly from the tritium paints leading to internal absorbed doses to wearers from inhalation and skin absorption.

109. The relationship between the ^{3}H activity in watches and the resulting whole-body absorbed dose has been studied under controlled conditions by Moghissi and Carter [M9]. The average dose in a year per unit activity of tritium paint, from a watch worn continuously, was found to be $8\ 10^{-15}$ Gy Bq^{-1}, the range being $3\ 10^{-15}$ to $1.2\ 10^{-14}$ Gy Bq^{-1}.

110. There are as yet no published estimates of doses from ^{3}H-activated alarm clocks. The activity-to-dose relationship has been conservatively assumed to be the same as that adopted for watches. Taking into account the fact that the exposure occurs only 8 hours per day on average, the quotient of annual dose to activity would be about $3\ 10^{-15}$ Gy Bq^{-1} for alarm clocks.

111. The average content of tritium in luminous timepieces has been determined in Switzerland to be 37 MBq for wrist-watches and 60 MBq for clocks [K9]. In the United States, the records from the Nuclear Regulatory Commission suggest an average of 25 MBq for watches and 15 MBq for clocks [M8]. In this Annex, a single value of 40 MBq will be adopted for the purpose of dose calculations. It results in a whole-body dose of 0.3 μGy for the wearer of a tritium-painted watch, and of 0.1 μGy for the user of a tritium-painted clock. The corresponding annual effective dose equivalents would be 0.3 μSv and 0.1 μSv, respectively.

112. With the advent of liquid-crystal displays, the use of gaseous tritium light sources (GTLS) to illuminate

digital watches could become widespread in the near future. A GTLS consists of a hollow glass tube whose inside walls are coated with an inorganic phosphor. The tube is evacuated, back-filled with tritium gas, and laser sealed. For watch applications, the tritium content is much higher than in a painted watch; it was observed to range from 1.7 GBq to 7.4 GBq [W4]. A total of approximately 40 000 timepieces were distributed during 1976 in the United States [R8]. Preliminary tests indicate that the dose to the wearer will result from tritium permeating through the glass and being absorbed into the body [W4]. It appears at present that on average the dose to the wearer of a watch luminized with a GTLS containing 7.4 GBq of ^{3}H may be of the same order as that to the wearer of a typical watch luminized with ^{3}H paint [T1]. There will also be internal dose to a person breaking the source which is usually sealed in a metal or glass capsule with the liquid-crystal display and is not easily accessible to the wearer. Out of the 40 000 timepieces distributed in 1976 in the United States, two watches were returned for tritium tube breakage [R8]; thus only a small fraction of the tritium is returned to the environment.

(c) Absorbed doses from ^{147}Pm-activated timepieces

113. Since promethium is a solid, it does not evolve from a watch under normal conditions of usage, so that the risk of external radiation is the only one that has to be considered. Promethium-147 is a pure beta emitter. The maximum energy of its beta particles is 224 keV, corresponding to a range of 46 mg cm^{-2}. Since the standards set by the OECD and the IAEA recommend a minimum thickness of 50 mg cm^{-2} for the casing of timepieces, no exposure hazard from beta radiation should exist. However, a low external radiation dose from bremsstrahlung has to be expected. Moghissi and Carter [M9] have conservatively estimated the annual gonad dose per unit activity to be 1.4 10^{-12} Gy Bq^{-1}. The average ^{147}Pm content of timepieces is suggested to be 1.5 MBq on the basis of a search of the records of the United States Nuclear Regulatory Commission. The resulting gonad dose to the wearer of a ^{147}Pm-painted watch would be approximately 2 μGy and the annual effective dose equivalent would be about 2 μSv.

114. There are no published estimates of doses from ^{147}Pm-activated clocks. In the case of ^{226}Ra, the ratio of the gonad doses from a watch and from a clock is 100; the same ratio will be assumed for ^{147}Pm, although it is recognized that the energies of the electromagnetic radiation involved are much lower for ^{147}Pm than for ^{226}Ra. The gonad dose in a year to the user of a ^{147}Pm-painted alarm clock would therefore be approximately 0.02 μGy and the effective dose equivalent would be about 0.02 μSv.

(d) Collective doses from radioluminous timepieces

115. The annual collective effective dose equivalents arising from the use of radioluminous timepieces have been estimated, for the populations of Switzerland, the United Kingdom, and the United States, on the basis of the number of products presented in Table 23, of the activity contents per type of product and of the quotients of dose to activity given in previous paragraphs. It is assumed that the gonad dose and the effective dose equivalent have the same value. The annual collective effective dose equivalents obtained are 5, 33, and 17 man Sv for Switzerland, the United Kingdom, and the United States, respectively. Translated into per caput annual effective dose equivalent, they become 8 10^{-7}, 6 10^{-7}, and 8 10^{-8} Sv. The per caput annual effective dose equivalent for the United States population is underestimated because the ^{226}Ra-painted watches were assumed to be completely out of use. Taking an average value of 5 10^{-7} Sv to be representative of the per caput annual effective dose equivalent to the world population, the annual collective effective dose equivalent for the world population is found to be of the order of 2000 man Sv.

(e) Other radioluminous devices

116. It is known that radioluminous materials are being used in exit signs, compasses, gun sights, telephone dials, and many other devices, but there is not enough information available to make a reasonable estimate of the doses arising from their use. However, it is likely that the resulting collective dose is insignificant in comparison to that from radioluminous timepieces.

2. Electronic and electrical devices

117. Electronic and electrical equipment may give rise to radiation exposure if they contain radioactive substances or if they emit x-radiation owing to the deceleration of electrons. Television sets belong to the second category and will be discussed later.

118. Radioactive materials provide pre-ionization in gases for the purpose of passing an electric current, so that the equipment reads faster and more reliably, or displays more constant characteristics [D4]. Examples of application are starters for tubular fluorescent lamps, trigger tubes in electrical appliances and excess-voltage protection devices. The radionuclides mainly used are ^{85}Kr, ^{147}Pm and ^{232}Th. Although the number of articles produced is very large, and the activities involved significant (see Table 22), the doses resulting from the normal use of such equipment can be expected to be very small. It is only in the event of breakage through accident or disposal that the radiation exposure could be significant.

3. Antistatic devices

119. Static eliminators containing radioactive substances are widely used in industry to reduce the electrical charge build-up on certain materials. The radiation ionizes the air around a charged object and thereby allows the charge to be neutralized.

120. Static eliminators using alpha particles emitted from ^{210}Po are also manufactured and sold to the general public in the United States. These devices are used to remove dust from phonograph records, photographic negatives and slides, lenses, etc. Each static eliminator nominally contains about 20 MBq of ^{210}Po at the time of manufacture [N6].

121. During the fabrication, polonium is interspersed in microspheres of ceramic material, which are then fixed to an aluminium backing plate with epoxy adhesive [N6]. The physical size of the microsphere is large enough so that the inhalation of the material is unlikely in case of loose contamination. If ingested, the microspheres are claimed to be insoluble in body fluids. The only significant hazard to the user seems to result

from external irradiation due to the very small gamma component of the ^{210}Po decay scheme. The corresponding annual whole-body dose was estimated to be about 10^{-8} Gy [N3]; the annual effective dose equivalent would be about 10^{-8} Sv.

122. In the United Kingdom, ^{210}Po static eliminators were subjected by the National Radiological Protection Board to routine leakage tests and to special tests intended to simulate severe but credible abuse and accident with these devices [W5]. Under severe conditions (impact and fire), the containment integrity of ceramic microspheres was found unsatisfactory and it was considered possible that ICRP dose limits could be approached or even exceeded.

4. Smoke detectors

123. Ionization chamber smoke detectors (ICSDs) use alpha radiation to cause ionization in the air between two electrodes, thereby allowing an electric current to flow across the air gap under the influence of a small potential. Combustion products entering the air gap become attached to the moving ions comprising the electric current. Current flow is thereby reduced, and the potential between the electrodes rises. These changes trigger an electronic circuit, and an alarm is released [N3, J6]. ICSDs provide an early warning of a fire condition.

124. Although some of the ICSDs now on the market contain ^{226}Ra, ^{238}Pu, ^{85}Kr, and ^{63}Ni, the preferred radionuclide is ^{241}Am. The use of ICSDs is widespread in industrial, commercial and public buildings, and also, at least in Canada and in the United States, in private homes. During the normal use of ICSDs, the doses to members of the public are virtually limited to those resulting from external irradiation.

125. Since 1972–1973 the residential market for ^{241}Am ICSDs has increased rapidly in the United States. Fourteen million units containing 1.5 TBq of ^{241}Am were distributed in 1978 and 26 million units have been distributed since 1972 [B5]. Belanger et al. [B5] have analysed the radiation impact resulting from manufacture, distribution, normal use and disposal of those 1.4 10^7 ICSDs. Assuming that their useful life is 10 years and that disposal is by either sanitary landfill or incineration, they calculated the collective whole-body dose to be 11 man Gy, most of it resulting from external irradiation during the useful life of the ICSD. The corresponding effective dose equivalent would be about 10 man Sv.

5. Ceramic, glassware, alloys, etc., containing uranium or thorium

126. The main uses of uranium in consumer products are either as a pigment [S9] or in applications making use of its high density. Thorium is used in incandescent mantles and in certain optical lenses.

127. The principal hazard from the uses of uranium and thorium under normal conditions is the external irradiation from the beta-emitting decay products. In general, doses received will be small due to substantial attenuation over the distance between the device and the exposed person. In particular cases, this may not apply, however. Some optical lenses containing up to 30% by weight of uranium or thorium may deliver substantial doses to the lens of the eye [W7]. The air absorbed dose rate at the surface of a lens which contained 18% thorium by weight was measured by thermoluminescent dosimetry to be 10^{-5} Gy h^{-1} [M11].

128. High concentrations of uranium and thorium are occasionally found in ophthalmic glass as a natural consequence of the glass manufacturing process [G12]. In the United States, the Optical Manufacturers Association issued a voluntary performance standard [O7] to establish a uniform maximum limit for radioactive emissions for ophthalmic glass. The standard states that the concentrations of ^{228}Ac, ^{212}Pb and ^{214}Pb in manufactured ophthalmic glass should not exceed 30 dpm g^{-1} (0.5 Bq g^{-1}). This limit could produce a maximum annual dose equivalent of about 5 mSv to the corneal germinal layer [G12].

129. Another example which has attracted interest is the practice of incorporating uranium in the porcelains used in restorative and prosthetic dentistry. In the United Kingdom, it is estimated that about one in nine adults has artificial porcelain teeth [O6]; in the United States, that proportion is likely to be even higher [S10]. A combination of uranium and cerium compounds is incorporated in the majority of modern porcelains in order to simulate the fluorescence of natural teeth in day light and in artifical light. As all the isotopes of uranium are radioactive, the tissues of the mouth are exposed to ionizing radiation from fluorescent porcelains.

130. An analysis performed by O'Riordan and Hunt [O6] on 20 porcelain powders under five brand names showed that 17 of the powders contained uranium, on the average 0.041% by weight, with 2 having about 0.1%. It is estimated in that study that for people with fluorescent porcelain teeth, the absorbed dose from external irradiation in the basal layer of the oral epithelium would be the limiting factor. Assuming a mass concentration of depleted uranium in the porcelain of 0.1%, the absorbed dose in that basal layer, taken to be at a distance of 30 μm from the interface, was found to be of the order of 0.03 Gy in a year. As the ranges of the alpha particles emitted by the isotopes of uranium are less than 30 μm in soft tissues, most of the absorbed dose is due to beta radiation. On the basis of that estimate, the National Radiological Protection Board has recommended that the use of radioactive fluorescers in dental porcelain be discontinued in the United Kingdom [O6]. Following that decision, the false-teeth industry in the United States voluntarily agreed to standardize the uranium content of procelain at 0.025–0.03% by weight [W7].

131. In the Federal Republic of Germany and the United States, the two countries where most of the dental porcelain seems to be manufactured, the mass concentration of uranium is limited by law. The uranium content of porcelain powders and artificial teeth should not exceed 0.1% by weight in the Federal Republic of Germany and 0.05% in the United States. In the Federal Republic of Germany, an average concentration of uranium in porcelain of about 0.03% by weight was measured, none of the samples showing an uranium concentration in excess of 0.1% by weight [S15, S16]. In a recent survey conducted in Japan, the average uranium concentrations in four brands (one of which was from the United States) were found to be 0.0004%, 0.0009%, 0.002%, and 0.008%, the highest measured value being 0.02% [S17, S18].

B. OTHER MISCELLANEOUS SOURCES OF RADIATION

132. The general public may also be exposed to consumer products that do not contain radioactive materials but that emit x-radiation owing to the deceleration of electrons. The most familiar example of such consumer products is the television receiver. The exposures arising from the domestic use of television receivers, the inspection of hand luggage by x-ray equipment, and the use of x-ray tubes in secondary schools will be briefly discussed. Reference [N3] provides a more detailed treatment of the x-ray emitting consumer products.

133. As indicated in the 1972 UNSCEAR report [U6], several surveys conducted in the 1960s showed that a small proportion of the colour television sets emitted x-radiation in excess of the limit recommended by the ICRP, that is 0.5 mR h^{-1} (corresponding to 1.29 10^{-7} C kg^{-1} h^{-1}) at 5 cm from the surface of the television receiver. Modern television receivers have low x-ray emissions, as shown by several sets of data. This conclusion is supported by the results of measurements recently conducted in the Federal Republic of Germany [K10] and in Asia [W8]. In the first of these surveys, conducted in 1972, it was found that the average exposure rate 5 cm from the surface of the colour television receivers was about 3 10^{-8} C kg^{-1} h^{-1} and that the estimated annual gonad dose, under normal viewing conditions, was of the order of 10 μGy. Assuming that the effective dose equivalent (expressed in μSv) is approximately equal to the gonad dose (expressed in μGy), the corresponding annual effective dose equivalent would be about 10 μSv. In the second survey the exposure rate at the surface of 28 randomly chosen colour television receivers was found to vary from about 3 10^{-10} to 2 10^{-8} C kg^{-1} h^{-1} under normal working conditions.

134. X-ray fluoroscopic scanning systems are used at most airports to inspect hand-carried baggage. The traveller often walks alongside the cabinet-type x-ray equipment as his or her luggage is being examined. The average exposure to the traveller per air trip due to the inspection of hand luggage was estimated in 1973 to be less than 4 10^{-10} C kg^{-1} in the United States [N3]. The corresponding effective dose equivalent is about 7 nSv.

135. Surveys conducted in Canada and in the United States in the early 1970s revealed that significantly large numbers of demonstration devices capable of emitting x rays were being used in secondary schools of those countries [Z1]. In Canada, exposure rates of up to 9 10^{-3} C kg^{-1} h^{-1} were measured at a distance of 0.3 m from the surface of cold cathode x-ray tubes [Z1]. Assuming that the energy of the x rays involved is 50 keV, the corresponding effective dose equivalent rate would be about 0.1 Sv h^{-1}. Most of the school teachers demonstrating the x-ray tubes had little or no knowledge of radiation protection principles or practices.

VII. SUMMARY

136. This Annex deals with some examples of technologically modified exposures to natural radiation which have been brought to the attention of the Committee. It is very likely that those examples do not present the complete picture of technologically modified exposures to natural radiation; indeed, the lack of rigour in the definition of such exposures (see paragraph 3) makes a comprehensive picture impossible. From the assessments presented at the current level of industrial and nuclear and coal cycle wastes utilization, the exposures do not add significantly to the collective effective dose equivalent on the global scale but may give rise, in localized areas or for people exposed under extreme conditions, to appreciable increases in individual exposures from natural radiation. The present state of knowledge does not allow an accurate estimate of the collective effective dose equivalent from technologically modified exposures to natural radiation to be made, and further measurements are required in this field.

137. Some examples of miscellaneous sources of radiation exposure have also been considered in this Annex. Many millions of units of various types of consumer products containing deliberately incorporated radionuclides are in everyday use around the world. Estimates of doses in individuals resulting from the use of such products show that in all cases these doses are small. The highest calculated effective dose equivalents result from the wearing of radioluminous watches, which are the most widespread radioactive consumer product. The assessment of the global collective effective dose equivalent from these sources is hampered by wide gaps in the knowledge of important factors such as the activities involved, the number of products on the market, and the problems related to the disposal of those devices. Even for the most common product, watches, the data are not always available since watches are generally not subject to control. Nevertheless, owing to international recommendations, and national regulations in some countries, there is a gradual improvement of control. It is likely that the average annual effective dose equivalent due to the use of consumer products is less than 10 μSv, almost entirely due to radioluminous timepieces. However, in view of the growing number and diversity of consumer products, it is important to ensure that proper control is maintained over their use and disposal.

Table 1

Activity concentration of radionuclides in coal samples

($Bq\ kg^{-1}$)

Origin	^{40}K	^{238}U decay series				^{232}Th decay series		Ref.
		^{238}U	^{226}Ra	^{210}Pb	^{210}Po	^{232}Th	^{228}Ra	
Australia			30- 48					[B1]
Brazil	370		100			67		[S1]
Canada	440		30			26		[S1]
Czechoslovakia			4.1- 13					[J1]
China			7					[J1]
Germany, Fed. Rep. of								
Bituminous coal		< 40	20	25	30	< 20		[J8]
Brown coal		15	< 10	10	10	< 7		[J8]
Hungary			1.5					[J1]
India			25				35	[M12]
Italy								
Lignite from central Italy		15-25	4-15	25-50		70-110		[M1]
Lignite from Sardinia		250						[M1]
Poland								
Average	290	38				30		[T2]
Range	37-760	2-140				7-110		[T2]
South Africa	110		30			20		[S1]
USSR								
Average	120	28			22			[L4]
United Kingdom								
Average	120	17				17		[H3]
Range		11-29	7.4-94			2.4-19		[C4]
United States								
West	110	20	16	17		13	13	[C1]
Illinois and Kentucky	44	27				8.5		[K2]
Alabama, Tennessee, Kentucky	120		8.9			27		[B3]
Wyoming 1			0.52	10				[K1]
Wyoming 2		18		31	41			[S2]
Applachia, Illinois, Montana, Pennsylvania, and Wyoming	70	16	14			8.9		[B2]
Country average a/	52	18				21		[B2]
Venezuela	110		< 20			< 20		[S1]

a/ Arithmetic mean activity concentrations of 910 samples of coal originating from several United States mines. The results, given in reference [B2], are compiled from data contained in references [F2], [G2], and [S3].

Table 2

Activity concentrations of natural radionuclides in ash samples

($Bq\ kg^{-1}$)

Type of ash and origin	^{40}K	^{238}U decay series				^{232}Th decay series			Ref.
		^{238}U	^{226}Ra	^{210}Pb	^{210}Po	^{232}Th	^{228}Th	^{228}Ra	
BOTTOM ASH (slag)									
Australia			250						[B1]
Germany,									
Fed.Rep.of (1)			130				96		[J3]
(2)	520		170 a/				140		[S1]
Japan									
Central			4	740			560	44	[N1]
Southern			37	300			90	20	[N1]
Northern			20	3900			250	55	[N1]
Poland									
Average	500	48				44			[T2]
Range	280-1200	17-100				15-120			[T2]
USSR	370		78		7.4	70			[L4]
United States									
West	240	81	81	30		67		67	[C1]
Ill. and Kent.	480	180				59			[K2]
Pennsylvania	480	67	59			52			[B2]
Wyoming 1			20	37					[S2]
Wyoming 2		93		210	190				[S2]
FLY-ASH (collected)									
Germany, Fed.Rep.of									
Bituminous coal		300	200	2000	2000	100			[J7]
Brown coal		70	40	60	100	30			[J7]
India			100					130	[M12]
Italy									
Central		80-100	40-70	44-330		300			[M1]
Sardinia		1000							[M1]
Poland									
Average	730	97				74			[T2]
Range	180-1500	44-170				33-130			[T2]
United States									
Appalachia 1			140			96		89	[E1]
Appalachia 2	780		70			52			[B3]
Appalachia 3	410		100			44		44	[G3]
Appalachia 4	700	96	90			89			[B2]
Ill. and Kent.	590	130				81			[K2]
Pennsylvania	700	85	85			78			[B2]
Wyoming 1			30	370	480				[K1]
Wyoming 2		160		210	200				[S2]
West	260	110	100	78		81		81	[C1]
Appalachia, Midwest and West	480	89				170			[F1]
FLY-ASH (escaping)									
Australia			520						[B1]
Germany, Fed. Rep. of									
Bituminous coal		300	300	3000	5500	100			[J7]
Brown coal		100	70	200	300	40			[J7]
Hungary			20-560						[P2]
United States									
West b/	260-270			160-630			100-120	100-160	[C1]
Wyoming 1			15	630	700				[K1]
Wyoming 2 c/		200		410	250				[S2]

a/ Derived from the assumption that radium-228 is in radioactive equilibrium with thorium-228.

b/ Range of values obtained for four different size fractions (2.4 to 18.5 μm mass median diameter).

c/ Derived from the assumption that the enrichment between collected and escaping fly-ash is equal to 1.3 for uranium-238.

Table 3

Measured enrichment factors in escaping fly-ash [B2]

Enrichment factor in escaping fly-ash						Percentage of fly-ash released	Ref.
Uranium	^{226}Ra	^{210}Pb	^{210}Po	Thorium	^{228}Ra		
1.3	1-2	1-5	-	1.0-1.2	1.0-1.6	< 3	[C1] a/
-	1.7 b/	11 c/	-	1.4	1.7 b/	0.47	[K2]
-	-	1	-	-	-	3.5	[K2]
-	1	5	5	-	-	4.8	[K1]
-	2	-	-	-	-	7.5	[B1]
-	-	6-10 c/	-	-	-	-	[N2] d/

a/ Range for various size fractions; the variation with size is presented in Figure I.
b/ Estimate of Beck et al. [B2] from measurement of barium.
c/ Measurements for stable lead.
d/ Range of composite samples of different size fractions from 8 power plants; maximum enrichment for particles of 1-2 μm diameter.

Table 4

Estimates of average activity concentrations of natural radionuclides in escaping fly-ash and of annual atmospheric discharges per unit energy generated

Origin		^{40}K	^{238}U decay series				^{232}Th decay series			Ref.
			^{238}U	^{226}Ra	^{210}Pb	^{210}Po	^{232}Th	^{228}Ra	^{228}Th	
ACTIVITY CONCENTRATIONS IN ESCAPING ASH (Bq kg^{-1})										
UNSCEAR, 1977 report		600	200	40	400	400	40	40	40	[U2]
Averages of Table 2		265	200	240	930	1700	70	130	110	
Adopted values		500	200	200	600	600	200	200	200	
ESTIMATED ATMOSPHERIC DISCHARGES per unit energy generated (MBq per GW a)										
France	1981	3500	7000	7000			6000			[A4]
Germany, Fed.Rep., 1981										
Brown coal			100	70	200	400	40	40	40	[J7,S19]
Bituminous coal			500	500	4000	8000	200	200	200	[J7]
Bituminous dry ash removal			300	200	200	300	100	200	100	[H4]
Bituminous liquid ash removal			500	300	2000	6000	200	200	200	[H4]
India	1980			11000				15000		[M12]
Italy (1) a/	1979		4400	4400	15000		18000			[M1]
(2)			18000	18000	26000		26000			[M1]
USSR	1978	20000		2000	8100	7400	2000	1100		[I1]
United Kingdom	1980	1000	1000	1000	1000	1000	1000	1000	1000	[C4]
United States,	1964			640				400		[E1]
	1970		270	270			300	300		[M2]
	1977		300	300	300	300	200	200	200	[M3]
	1977		4900	5600			6300	6300	6300	[N3]
b/	1977	670-2000	150-410	140-410	670-2000	670-2000	110-370	110-370	110-370	[L2]
c/	1977	1100	1000	780	2600	2600	410	410	410	[B2]
d/	1977	10000	4700	4700	9300	9300	3800	3800	3800	[B2]
UNSCEAR, 1977 report		5500	1850	370	3700	3700	370	370	370	[U2]
This report		4000	1500	1500	5000	5000	1500	1500	1500	

a/ The two plants considered burn lignite of low heat content, high ash fractions, and high activity content, resulting in elevated discharges.
b/ Range of releases reported for plants burning different types of coal.
c/ Modern plant.
d/ 1972 reference plant.

Table 5

Committed doses per unit activity inhaled (μGy Bq^{-1}) of the most important natural radionuclides released from coal-fired power plants [J7]

Organ or tissue	Uranium decay series							Thorium decay series			
	^{238}U	^{234}U	^{230}Th	^{226}Ra	^{222}Rn a/ and daughters	^{210}Pb	^{210}Po	^{232}Th	^{228}Ra	^{228}Th	^{220}Rn and daughters
Lungs	5.5	6.6	6.0	0.4	0.0093 (T-B) 0.0012 (P)	0.2	0.5	26	0.2	15	0.011
Bone surfaces	0.06	0.07	46	0.17	-	0.8	0.01	240	0.15	20	0.013
Red bone marrow	0.004	0.004	3.6	0.015	-	0.085	0.01	20	0.015	1.7	0.001
Liver	0.0001	0.0001	0.075	0.002	-	0.35	0.01	0.065	0.004	0.15	0.002
Kidneys	0.025	0.029	0.01	0.002	-	0.17	0.25	0.007	0.004	0.02	0.008
Spleen	0.0001	0.0001	0.01	0.002	-	0.03	0.45	0.007	0.004	0.02	0.0003
G.I. tract	0.0007	0.0008	0.01	0.003	-	0.006	0.006	0.008	0.004	0.025	-
Other soft tissues	0.0001	0.0001	0.01	0.002	-	0.01	0.01	0.007	0.004	0.02	0.0001
Effective dose equivalent per unit activity inhaled (μSv Bq^{-1})	13	15	51	1.1	0.013	2.0	2.2	250	0.61	51	0.051

a/ The committed doses and effective dose equivalents per unit activity inhaled of the short-lived decay products of the radon isotopes are estimated from data in Annex D. For the radon-222 daughters the effective dose equivalent is obtained from the absorbed doses in the bronchial basal cell layer (T-B) and the pulmonary epithelium (P). Only the doses due to the α particles are taken into account.

Table 6

Estimates of collective dose commitments per unit energy generated resulting from atmospheric releases from coal-fired power plants

(10^{-3} man Gy per GW a)

Inhalation during the passage of the cloud.

Organ or tissue	Uranium decay series							Thorium decay series			Total (rounded)
	^{238}U	^{234}U	^{230}Th	^{226}Ra	^{222}Rn and daughters a/	^{210}Pb	^{210}Po	^{232}Th	^{228}Ra	^{228}Th	
Lungs	19	23	21	1.4	0.69 (T-B) 0.09 (P)	2.3	5.8	90	0.7	52	210
Bone surfaces	0.2	0.2	160	0.6	-	9.2	0.1	830	0.5	69	1070
Red bone marrow	0.01	0.01	12	0.05	-	0.1	0.1	69	0.05	5.9	89
Liver	0.0003	0.0003	0.3	0.007	-	4.0	0.1	0.2	0.01	0.5	5
Kidneys	0.09	0.1	0.03	0.007	-	2.0	2.9	0.02	0.01	0.07	5
Spleen	0.0003	0.0003	0.03	0.007	-	0.3	5.2	0.02	0.01	0.07	6
G.I. tract	0.002	0.003	0.03	0.01	-	0.07	0.07	0.03	0.01	0.09	0.3
Other soft tissues	0.0003	0.0003	0.03	0.007	-	0.1	0.1	0.02	0.01	0.07	0.4
Collective effective dose equivalent commitment per unit energy generated (10^{-2} man Sv (GW a)$^{-1}$)	4.5	5.2	18	0.4	0.1	2.3	2.5	86	0.2	18	140

a/ T-B and P stand for bronchial basal cell layer and pulmonary epithelium, respectively.

Table 7

Estimates of collective dose commitments per unit energy generated resulting from atmospheric releases from coal-fired power plants

(10^{-3} man Gy per GW a)

External and internal irradiation due to the activity deposited.

	Uranium decay series						Thorium decay series			
	^{238}U	^{234}U	^{230}Th	^{226}Ra	^{222}Rn and daughters a/	^{210}Pb and ^{210}Po	^{232}Th	^{228}Ra and daughters	^{220}Rn and daughters	Total (rounded) a/
Internal irradiation										
Lungs	0.2	0.1	0.6	0.2	140 (T-B) 19 (P)	5.2	0.5	3.0	20	170 (T-B) 49 (P)
Bone surfaces	2.6	2.4	8.9	6.8	-	69	2.4	5.5	24	120
Red bone marrow	0.4	0.3	0.7	0.7	-	12	0.2	0.5	1.9	17
Liver	0.2	0.1	0.008	0.2	-	9.7	0.5	1.0	3.6	15
Kidneys	1.6	1.4	0.3	0.2	-	9.7	0.7	1.9	14	30
Other soft tissues	0.2	0.1	0.008	0.2	-	9.7	0.004	0.1	0.2	11
Collective effective dose equivalent commitment per unit energy generated (10^{-2} man Sv/(GW a)$^{-1}$)	0.6	0.6	0.9	0.9	20	22	0.3	1.6	9.4	56
External irradiation										
All tissues (10^{-3} man Gy (GW a)$^{-1}$)			35					54		90

a/ T-B and P stand for bronchial basal cell layer and pulmonary epithelium, respectively.

Table 8

Estimates of collective effective dose equivalent commitments per unit energy generated resulting from atmospheric releases from coal-fired power plants

(10^{-2} man Sv per GW a)

Radio-nuclide	Inhalation during the cloud passage	Internal irradiation due to the activity deposited	External irradiation due to the activity deposited	Total
^{238}U	4	0.6		
^{234}U	5	0.6		
^{230}Th	18	0.9		
^{226}Ra	0.4	0.9	4	82
^{222}Rn+daughters	0.1	20		
^{210}Pb+^{210}Po	5	22		
^{232}Th	86	0.3		
^{228}Ra+daughters	18	2	5	120
^{220}Rn+daughters	-	9		
Total (rounded)	140	56	9	200

Table 9

Production of phosphate rock in 1977
and reported activity concentrations of natural radionuclides

	Production of marketable rock in 1977		Activity concentrations (Bq kg^{-1})				Ref.
	(10^9 kg)	Percentage of the world production	^{238}U	^{226}Ra	^{232}Th	^{40}K	
WORLD	125.7	100					
China a/	4.1	3.3	150	150	25		[M5]
Christmas Islands	1.3	1.0	330	300	7		[M5]
Israel	1.2	1.0	1500-1700				[D3]
Jordan	1.8	1.4	1300-1850				[D3]
Morocco (1)	17.6	14.0	1700	1700	30		[M5]
(2)			1500	1500	30	200	[C2]
(3)			1700	1570	20	10	[P6]
Nauru	1.1	0.9	810	850	7		[M5]
Senegal b/	1.8	1.4	1300	1400	67		[M5]
Togo	2.9	2.3	1300	1200	110	≤ 100	[C2]
Tunisia	3.6	2.9	590	520	92		[M5]
USSR	24.2	19.3					
Kola, apatite (1)			90	40	91	170	[C2]
(2)			70	70	92		[M5]
(3)			44	30	78	44	[P6]
Kola, phosphorite				390	25	230	[G6]
United States	47.3	37.6					
Central Florida (1)			1500	1600	16		[M4]
Central Florida (2) (pebble)			1700	2100			[R4]
North Florida, pebble			800	1000			[R4]
Florida, land pebble and soft phosphate			1900	2000	59		[M5]
Florida			1300	1270	30	48	[P6]
Arkansas			370	410	52		[M5]
Idaho			1850	1800	30		[M5]
Montana			1400	1500	25		[M5]
North Carolina			960	670	40		[M5]
Oklahoma			300	370	30		[M5]
South Carolina			4800	4800	78		[M5]
Tennessee, brown rock, blue rock, white rock, phosphatic limestone			150	150	20		[M5]
Utah			1600	1850	30		[M5]
Wyoming			2300	2300	10		[M5]
Viet Nam	1.5	1.2					[M5]

a/ Samples from China, India, and South-East Asia.
b/ Samples from Senegal and other African countries.

Table 10

Data on discharges from phosphate industry operations

Type of plant	Annual input of marketable ore (10^9 kg) a/	^{238}U	^{230}Th	^{226}Ra	^{232}Th	Ref.
		Airborne annual discharges (MBq)				
Ore drying plant	2.7	245	250	250		[P4]
Wet process phosphoric acid plant						
Plant A	1.2	9.2	8.7	6.8		[P4]
Plant B b/	1.2	1300	1200	540		[P4]
Uranium recovery plant	0.4	350	small	small	small	[D2]
		Activity concentrations in liquid discharges ($Bq\ m^{-3}$)				
Phosphate mine and beneficiation plant						
Heavy slime: undissolved				2500(400-80000)		[G4]
dissolved				65(20-80)		[G4]
Effluent: undissolved				20(5-40)		[G4]
dissolved				30 (1-80)		[G4]
Wet process phosphoric acid plant						
Plant 1: Field survey number 1						
Untreated process water		39000	2600	3000	170	[G4]
Outfall (after chemical treatment)		20	20	170	1.5	[G4]
Field survey number 2						
Untreated process water		15000	3700	2000	120	[G4]
Outfall (after chemical treatment)		620	30	70	4	[G4]
Plant 2:						
Untreated process water		68000	15000	3200	230	[G4]
Outfall (after chemical treatment)		12	5	17	ND	[G4]
Plant 3:						
Untreated process water		24000	320	2000	150	[G4]
Outfall (after chemical treatment)		10	ND	94	ND	[G4]

a/ Reported or estimated.
b/ The airborne discharges from plant B are very uncertain and likely to be overestimates.

Table 11

Estimated distribution of the activity (TBq) present in the phosphate fertilizers produced in the United States during 1974 [G4]

Material	Mass		Activity (TBq)			
	(10^9 kg)	(10^9 kg P_2O_5)	^{226}Ra	^{238}U	^{230}Th	^{232}Th
Marketable ore used for fertilizer production	25.6	8.0	40	39	40	0.4
Normal superphosphate	3.1	0.6	2.4	2.3	2.1	0.07
Concentrated superphosphate	3.4	1.6	2.6	7.0	5.9	0.04
Ammonium phosphates a/	5.3	2.4	1.1	13	13	0.07
Phosphoric acid	10.0	3.1	0.37	9.4	10	1.1
Other fertilizer production	2.0	0.3				
Gypsum	25.2		31	5.7	12	0.3

a/ Does not include phosphoric acid used to produce diammonium phosphates and concentrated superphosphates.

Table 12

Estimates of collective dose commitments per unit mass of phosphate ore due to atmospheric releases from phosphate industry plants: doses arising from inhalation during the cloud passage

Radio-nuclide	Airborne discharge (Bq t^{-1})	Collective dose commitments per unit mass of phosphate ore (10^{-9} man Gy t^{-1})							
		Lungs a/	Bone surfaces	Red bone marrow	Liver	Kidneys	Spleen	G.I. tract	Other soft tissues
					Ore drying plant				
^{238}U	90	1.1	0.01	0.0009	0.00002	0.005	0.00002	0.0001	0.00002
^{234}U	90	1.4	0.01	0.0009	0.00002	0.006	0.00002	0.0002	0.00002
^{230}Th	90	1.2	9.5	0.7	0.02	0.002	0.002	0.002	0.002
^{226}Ra	90	0.08	0.04	0.003	0.0004	0.0004	0.0004	0.0006	0.0004
^{222}Rn	$1.5\ 10^6$	[17 (T-B) 2.2 (P)	-	-	-	-	-	-	-
Total		[17 (T-B) 6.0 (P)	9.6	0.7	0.02	0.01	0.002	0.003	0.002
					Wet process phosphoric acid plant (Plant A)				
^{238}U	7	0.09	0.001	0.00006	0.000002	0.0004	0.000002	0.00001	0.000002
^{234}U	7	0.1	0.001	0.00006	0.000002	0.0005	0.000002	0.00001	0.000002
^{230}Th	7	0.1	0.7	0.06	0.001	0.0002	0.0002	0.0002	0.0002
^{226}Ra	6	0.006	0.002	0.0002	0.00003	0.00003	0.00003	0.00004	0.00003
^{222}Rn	$1.5\ 10^6$	[17 (T-B) 2.2 (P)	-	-	-	-	-	-	-
Total		[17 (T-B) 2.5 (P)	0.7	0.06	0.001	0.001	0.0002	0.0003	0.0002
					Wet process phosphoric acid plant (Plant B)				
^{238}U	1000	13	0.1	0.009	0.0002	0.06	0.0002	0.002	0.0002
^{234}U	1000	15	0.2	0.009	0.0002	0.07	0.0002	0.002	0.0002
^{230}Th	960	13	100	8.0	0.2	0.02	0.02	0.02	0.02
^{226}Ra	440	0.4	0.2	0.02	0.002	0.02	0.002	0.003	0.002
^{222}Rn	$1.5\ 10^6$	[17 (T-B) 2.2 (P)	-	-	-	-	-	-	-
Total		[17 (T-B) 44 (P)	100	8.0	0.2	0.2	0.02	0.03	0.02
					Uranium recovery plant				
^{238}U	850	11	0.1	0.008	0.0002	0.05	0.0002	0.001	0.0002
^{234}U	850	13	0.1	0.008	0.0002	0.06	0.0002	0.002	0.0002
Total		24	0.2	0.02	0.0004	0.1	0.0004	0.003	0.0004

a/ T-B and P stand for bronchial basal cell layer and pulmonary epithelium, respectively.

Table 13

Estimates of collective dose commitments per unit mass of phosphate ore due to atmospheric releases from phosphate industry plants: doses due to the activity deposited

Radio-nuclide	Airborne discharge ($Bq\ t^{-1}$)	Collective dose commitments per unit mass of phosphate ore (10^{-9} man Gy t^{-1})						
		External irradiation	Internal irradiation					
		All tissues	Lungs a/	Bone surfaces	Red bone marrow	Liver	Kidneys	Other soft tissues
			Ore drying plant					
^{238}U	90	2.1	0.009	0.2	0.03	0.009	0.09	0.009
^{234}U	90		0.009	0.1	0.02	0.009	0.09	0.009
^{230}Th	90		0.03	0.5	0.04	0.0005	0.02	0.0005
^{226}Ra	90		0.01	0.4	0.04	0.01	0.01	0.01
^{222}Rn			8.6 (T-B) 1.2 (P)	-	-	-	-	-
Total			8.6 (T-B) 1.3 (P)	1.2	0.1	0.03	0.2	0.03
			Wet process phosphoric acid plant (Plant A)					
^{238}U	7	0.1	0.0007	0.01	0.002	0.0007	0.008	0.0007
^{234}U	7		0.0007	0.01	0.001	0.0007	0.007	0.0007
^{230}Th	7		0.003	0.04	0.003	0.00004	0.001	0.00004
^{226}Ra	6		0.0008	0.03	0.003	0.0008	0.0009	0.0009
^{222}Rn			0.6 (T-B) 0.08 (P)	-	-	-	-	-
Total			0.6 (T-B) 0.09 (P)	0.09	0.009	0.002	0.02	0.002
			Wet process phosphoric acid plant (Plant B)					
^{238}U	1000	10	0.1	1.8	0.3	0.1	1.0	0.1
^{234}U	1000		0.1	1.6	0.2	0.1	1.0	0.1
^{230}Th	960		0.4	5.7	0.4	0.005	0.2	0.005
^{226}Ra	440		0.06	2.0	0.2	0.06	0.06	0.06
^{222}Rn			42 (T-B) 5.6 (P)	-	-	-	-	-
Total			42 (T-B) 6.3 (P)	11	1.1	0.3	2.3	0.3
			Uranium recovery plant					
^{238}U	850	-	0.09	1.5	0.2	0.09	0.9	0.09
^{234}U	850	-	0.08	1.4	0.2	0.08	0.8	0.08
Total			0.2	2.9	0.4	0.2	1.7	0.2

a/ T-B and P stand for bronchial basal cell layer and pulmonary epithelium, respectively.

Table 14

Activity concentrations of naturally occurring radionuclides in phosphate fertilizers

($Bq\ kg^{-1}$)

Type of fertilizer	Country	^{238}U	^{230}Th	^{226}Ra	^{210}Pb	^{210}Po	^{232}Th	^{40}K	Ref.
TREATED ROCK PHOSPHATES									
Apatite	USSR			30	25	30	60	100	[G6]
Phosphorite	USSR			390	380	480	25	230	[G6]
Concentrate obtained by flotation	USSR			420	390	290	20	73	[G6]
Calcined, ground soft, partly converted rock phosphate, etc. a/	FRG b/	670		480			25	110	[P6]
ONE-COMPONENT PHOSPHATE FERTILIZERS									
Superphosphate	FRG b/	529		520			15	140	[P6]
Superphosphate	USSR			110	300	150	44	120	[G6]
Superphosphate	USA c/	740	670	790			20		[M4]
Superphosphate	Belgium	1100		910			<25	<180	[C2]
Triple superphosphate	FRG b/	800		230			44	52	[P6]
Triple superphosphate	USA	2100	1800	780			48		[M4]
PK-FERTILIZERS d/	FRG b/	410		370			15	5900	[P6]
NP-FERTILIZERS									
NP-fertilizers a/	FRG b/	920		310			30	41	[P6]
Ammonium phosphate	USSR			100			48		[G6]
Nitrophosphate	USSR			850	870	920	10		[G6]
Nitroammonium phosphate	USSR				15	15	30		[G6]
Monoammonium phosphate	USA	2000	1800	20			63		[M4]
Diammonium phosphate	USA	2300	2400	210			15		[M4]
NPK-FERTILIZERS e/									
NPK	FRG b/	440		270			15	5200	[P6]
NPK	USSR			9	15	20	54	1200	[G6]
NPK	Belgium	470		210			<15	5900	[C2]
BASIC SLAG	Belgium	23		19					[K4]

a/ Assuming a P_2O_5-to-fertilizer mass concentration ratio of 0.28.

b/ Federal Republic of Germany.

c/ United States.

d/ Assuming a P_2O_5-to-fertilizer mass concentration ratio of 0.16.

e/ Assuming a P_2O_5-to-fertilizer mass concentration ratio of 0.13.

Table 15

Estimated collective dose commitment per unit mass of marketable rock arising from the use of phosphate fertilizers

(10^{-7} man Gy t^{-1})

	^{238}U	^{234}U	^{230}Th	^{226}Ra	^{222}Rn	^{210}Pb	Total
Internal irradiation							
Lungs	0.3	0.3	1.1	0.3	[190 (T-B) 26 (P)]	5.0	[190 (T-B) 33 (P)]
Bone surfaces	5.3	4.8	18	9.0		66	100
Red bone marrow	0.9	0.6	1.3	0.9		11	15
Liver	0.3	0.3	0.02	0.3		9.3	10
Kidneys	3.1	2.9	0.6	0.3		9.3	16
Other tissues	0.3	0.3	0.02	0.3		9.3	10
External irradiation							
All tissues				1.5			1.5

Table 16

Estimates of collective effective dose equivalent commitments per unit mass of marketable ore due to the exploitation of phosphate rock

(10^{-6} man Sv t^{-1})

Source of exposure	Cloud passage Inhalation	Activity deposited: Internal irradiation	Activity deposited: External irradiation	Total
Atmospheric discharges from an ore drying plant	0.04	0.01	0.002	0.05
Atmospheric discharges from wet process phosphoric acid plant A	0.03	0.0009	0.0001	0.03
Atmospheric discharges from wet process phosphoric acid plant B	0.2	0.06	0.01	0.3
Atmospheric discharges from an uranium recovery plant	0.05	0.007	-	0.06
Agricultural use of phosphate fertilizers	-	50	15	65

	Internal irradiation	External irradiation	Total
Use of by-product gypsum as building material in homes	17000	16000	33000

Table 17

Activity concentration of naturally occurring radionuclides in building materials expected to give rise to higher-than-average external absorbed doses

Type of building material	Country b/	No. of samples	Average activity concentration ($Bq\ kg^{-1}$) ^{40}K	^{226}Ra	^{232}Th	Absorbed dose rate in air a/ (10^{-8} Gy h^{-1})	Ref.
Natural origin							
Granite	FRG	34	1200	100	80	30	[S5]
Granite bricks	UK	7	1000	90	85	28	[H1]
Granite	USSR	2	1500	110	170	45	[K6]
Lithoid tuff	Italy	-	1500	130	120	40	[N5]
Pumice stone	FRG	20	1100	130	130	35	[S5]
Concrete containing alum shale	Sweden	83	850	1500	70	145	[S6]
Industrial origin							
Phosphogypsum from phosphorite	FRG	39	110	600	<5	54	[S5]
Phosphogypsum	UK	6	70	800	20	68	[H1]
Phosphogypsum	USA	-		1500	7	126	[G6]
Calcium silicate slag	Canada	-		2150		184	[P5]
Calcium silicate slag	USA	-		1300-1500		110-130	[B4]
Red-mud bricks	FRG	23	330	280	230	58	[S5]
Fly-ash	FRG	28	700	210	130	42	[S5]
Fly-ash type 1	UK	1	550	7	40	10	[H1]
type 2	UK	1	550	140	30	20	[H1]
type 3	UK	1	220	50	44	12	[H1]
Blast-furnace slag	USSR	29	240	70	20	11	[K6]
Slag aggregate c/	Finland	3	190	100	70	19	[N5]

a/ The absorbed dose rates in air have been calculated assuming a 4 π geometry and an infinite thickness of material. The values obtained are an index allowing the comparison between building materials and not an estimate of the doses that would be received in dwellings constructed with those building materials.

b/ Federal Republic of Germany = FRG; United Kingdom = UK; United States = USA.

c/ Mixture of coal clinker, ash, and cement.

Table 18

Variation of the galactic dose rate and dose equivalent rate with altitude a/
[O4]

Altitude (km)	Absorbed dose rate ($\mu Gy\ h^{-1}$)	Dose equivalent rate ($\mu Sv\ h^{-1}$)
4	0.14	0.20
6	0.33	0.51
8	0.84	1.35
10	1.75	2.88
12	3.01	4.93
14	4.62	7.56
16	5.92	9.70
18	7.09	11.64
20	7.72	12.75

a/ Values averaged over 2 geomagnetic latitudes (43^{o} and 55^{o}) and over two periods of solar activity (minimum and maximum).

Table 19

Comparison of calculated cosmic-ray doses to a person flying in subsonic and supersonic aircraft (average solar conditions)
[W2]

Route	Subsonic flight at 11 km		Supersonic flight at 19 km	
	Flight duration (h)	Dose per round trip (10^{-5} Gy)	Flight duration (h)	Dose per round trip (10^{-5} Gy)
Los Angeles - Paris	11.1	4.8	3.8	3.7
Chicago - Paris	8.3	3.6	2.8	2.6
New York - Paris	7.4	3.1	2.6	2.4
New York - London	7.0	2.9	2.4	2.2
Los Angeles - New York	5.2	1.9	1.9	1.3
Sydney - Acapulco	17.4	4.4	6.2	2.1

Table 20

Absorbed dose rates of astronauts on space missions
[C3, E2, R7, G9]

Mission or mission series	Launch date	Duration of mission (h)	Type of orbit	Dose (10^{-5} Gy)
Apollo VII	Aug. 1968	260	Earth orbital	120
Apollo VIII	Dec. 1968	147	Circumlunar	185
Apollo IX	Feb. 1969	241	Earth orbital	210
Apollo X	May 1969	192	Circumlunar	470
Apollo XI	July 1969	182	Lunar landing	200
Apollo XII	Nov. 1969	236	Lunar landing	~ 200
Apollo XIV	Jan. 1971	209	Lunar landing	~ 500
Apollo XV	July 1971	286	Lunar landing	~ 200
Vostok 1-6			Earth orbital	2-80
Voskhad 1, 2			Earth orbital	30,70
Soyuz 3-9			Earth orbital	62-234

Table 21

Breakdown of the absorbed dose and dose equivalent on spacecraft mission Apollo XI [E2]

Component	Absorbed dose (10^{-5} Gy)	Dose equivalent (10^{-5} Sv)
Protons	150	220
Stars	15	94
Fast neutrons	~ 1	~ 12
Heavy nuclei	5	46
Electrons and gamma rays	~ 30	~ 30
TOTAL (rounded)	200	400

Table 22

Consumer products in the Federal Republic of Germany [W3]

The data refer to the years 1973 or 1975, depending on the product.

Type of consumer product	Produced in the Fed. Rep. of Germany			Number of pieces imported into the Fed.Rep.of Germany
	Number of pieces or weight	Total activity and radionuclide used	Exported	
Radioluminous timepieces				
Devices containing scales or dials with luminous paint	$14\ 10^6$	40 TBq ^3H 10 TBq ^{147}Pm	50 %	$8\ 10^5$ (^3H) $1\ 10^5$ (^{147}Pm)
Electronic and electrical devices				
High-pressure mercury lamps	$7\ 10^6$	15 GBq ^{232}Th	20 %	
Ignition devices for fluorescent lamps	$26\ 10^6$	3 TBq ^{85}Kr	50 %	
Electronic components containing radioactive substances	$40\ 10^6$ $11\ 10^6$ $3\ 10^6$	200 TBq ^{85}Kr 10 TBq ^3H or ^{147}Pm 0.2 GBq ^{232}Th	40 %	$3\ 10^4$
Electronic tubes	$7\ 10^5$	^3H, ^{60}Co, ^{63}Ni ^{147}Pm, ^{226}Ra		
Antistatic devices	?	^{210}Po		
Smoke detectors	$1\ 10^5$	^{226}Ra, ^{241}Am		
Ceramic, glassware, alloys, etc. containing uranium or thorium				
Articles with uranium paints	$3\ 10^5$	0.6 GBq ^{238}U	50 %	$1\ 10^6$
Glassware containing uranium	$4\ 10^3$ kg	2 GBq ^{238}U	50 %	$3\ 10^5$
Glassware containing thorium	$16\ 10^3$ kg	7 GBq ^{232}Th	10 %	

Table 23

Estimated number of radioluminous timepieces in use in the various countries

Country	Year	Watches (10^6)			Clocks (10^6)			Ref.
		^3H	^{147}Pm	^{226}Ra	^3H	^{147}Pm	^{226}Ra	
Switzerland	1976	2.6	0.64	0.07	1.4	1.6	0.38	[K9]
United Kingdom	1978	5		0.8				[T1]
United States	1977	27	0.21	negli-gible	0.98	2.3	8.4	[M8]

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ANNEX D

Exposures to radon and thoron and their decay products

CONTENTS

Introduction

1. Radon and thoron are among the first of the natural radioactive nuclides which were discovered, identified and examined at the beginning of this century. They are noble gases and are produced in nature by the decay of the radium isotopes ^{226}Ra and ^{224}Ra, respectively. Radium and its progeny have been used for medical and technical purposes and for research for more than 70 years.

2. The interest of the Committee in radon and thoron lies in their detrimental effect on man. Since they occur in nature, man has always been exposed, mainly through inhalation of their decay products, to radon and thoron daughters. The detrimental effect has been

recognized since the sixteenth century, when miners in central Europe suffered from what was then called "Schneebergkrankheit". Later experience of mining of uranium in the middle of this century identified radon daughters to be a source of cancer.

3. Man is everywhere exposed to radon and thoron products. The major source of exposure consists of radon and its decay products, occurring in domestic housing. Radon emanates from building materials and from the ground below. In some countries the radiation dose to man caused by inhaled radon daughters constitutes more than 50% of the total radiation dose to man from other natural or artificial sources. Radon is also a major problem in the nuclear fuel cycle because it gives rise to an occupational exposure during uranium mining and is a source of exposure to the public during the storage of waste (tailings) from the milling of uranium ore. Other sources of radon include the burning of coal, emissions from geothermal plants, and radon dissolved in water.

4. There are no epidemiological data available about the effects of radon and thoron daughters on the public. However, the detrimental effect of radon and its decay products in indoor air can be estimated by extrapolation from information obtained from the exposure of uranium miners. Although the estimates of exposure in this case are far from perfect, they clearly demonstrate that high levels of radon and its daughters in air warrant close attention. The Committee wishes to draw particular attention to the fact that in a number of countries special efforts are now taken to conserve energy by insulation of houses and by decreasing the ventilation rate. It has been shown that such actions cause increased concentrations of radon and radon daughters in houses.

5. The purpose of this Annex is to provide information about the levels and doses of radon and thoron and their decay products and about physical parameters influencing and causing these levels and doses. The detrimental effects of radon and thoron daughters are not dealt with in this Annex.

I. GENERAL CONCEPTS AND PROPERTIES

A. PHYSICAL AND CHEMICAL PROPERTIES OF RADON AND THORON

6. Radon (^{222}Rn) and thoron (^{220}Rn) are naturally-occurring radioactive gases. Radon is produced by the decay of ^{226}Ra in the uranium series and decays by alpha particle emission to a polonium isotope (^{218}Po) which by further decay through isotopes of lead, bismuth, and polonium ends with a stable isotope of lead (^{206}Pb). The half-lives and radiation energies are shown in Table 1. Other physical data on radon are presented in Table 2. Thoron is produced by the decay of ^{224}Ra in the thorium series and decays by alpha particle emission to a polonium isotope (^{216}Po) which decays through isotopes of thallium, lead, bismuth and polonium to a stable isotope of lead (^{208}Pb), as shown in Table 1.

7. Radon and thoron are chemically inert, noble gases. They occur in almost all materials and for the most part (90% and more) are trapped in the solids carrying their precursors ^{226}Ra and ^{224}Ra. Accordingly, the measurement of the gamma radiation emitted from the materials provides an indication of its uranium and thorium content as most of the gamma radiation from the ^{238}U and ^{232}Th series arises from the radon and thoron progeny.

8. Some of the radon and thoron may diffuse into other media such as the surrounding water or air and frequently the concentration of radon and thoron in surrounding water and air is higher than the concentration of ^{226}Ra and ^{224}Ra. Occasionally there may be a deficiency of radon in water relative to ^{226}Ra if the water is in open contact with air so that the radon may diffuse into air.

9. Because of the short half-life of thoron its concentration in water is generally insignificant, unless the water has a high concentration of ^{224}Ra. Radon can be transported a long way from its precursor and often there is no simple correlation between the radon concentration in air and water and the concentration of ^{226}Ra in adjacent materials. However, radon concentrations in air in uranium mines and near mill tailings are usually well correlated to adjacent sources.

B. MEASUREMENT AND IDENTIFICATION OF RADON AND THORON AND THEIR DECAY PRODUCTS

10. Radon and thoron are identified by their radiation or their daughter products. In measurements of very low activity concentrations in air (less than a few Bq m^{-3}) radon and thoron can be concentrated or trapped, using activated charcoal filters at normal or low temperature. At higher concentrations they can be directly collected and measured by ionization or scintillation methods [I1]. They can also be measured continuously by passing air through the measuring equipment. In general the activity of radon and thoron in a sample is monitored by measuring the number of emitted alpha particles both from radon (thoron) and their progeny which build up in the collected sample. Radon in water is measured by gamma spectrometric methods directly on the sample (including liquid scintillation methods) or by measuring the radon released by bubbling a gas through the sample. The activity or potential alpha energy concentration (see paragraph 13) of daughters in air can be determined by drawing air through a filter and measuring the alpha particle activity with a ZnS or silicon surface barrier detector, thermoluminescent dosimetry or track etch detector. Because of the short half-lives of the radon daughters the measurement must be made simultaneously with the collection or shortly thereafter. Lead-212 and its decay products are measured some hours after collection following the decay of the short-lived radon daughters.

11. After decay of the short-lived radon daughters the long-lived isotopes of lead, bismuth and polonium complete the uranium series. The practical use of these isotopes as indicators of the current activity of radon and short-lived daughter products is limited. Even if the main part of ^{210}Pb in outdoor air comes from the decay of radon daughters in air, there is no simple correlation between ^{210}Pb and the local concentration of radon in air. Similarly, ^{210}Pb in water is not a reliable indicator of earlier radon levels in the water because of variable and unknown releases of radon from water to air during its passage from the radium source to the water outlet, of insufficient time to allow significant decay of radon in the water, of leaching of ^{210}Pb from the rock and finally because of depletion of the daughters by

adsorption on the rock surfaces. However, ^{210}Pb in the human body (in bone) has been used as an indicator for earlier inhalation of high concentrations of radon in mines [C8, H26].

C. SPECIAL QUANTITIES AND UNITS

12. The potential alpha energy $E_{pot,at}$ of an atom in the decay chain of radon or thoron is the total alpha energy emitted during the decay of this atom to ^{210}Pb or ^{208}Pb, respectively. The potential alpha energy per unit of activity (Bq) of a radionuclide j is $E_{pot,at}/\lambda_j$ where λ_j is the decay constant. Values of $E_{pot,at}$ and $E_{pot,at}/\lambda_j$ are listed in Table 3.

13. The potential alpha energy concentration of any mixture of (short-lived) radon or thoron daughters in air is the sum of the potential alpha energy of all daughter atoms present per unit volume of air. The usual unit for this quantity is MeV l^{-1}. This unit is related to the SI units J and m^3 according to 1 J m^{-3} = 6.24 10^9 MeV l^{-1}. A special unit for this quantity used for radiation protection purposes is the working level (WL). A WL is defined as a potential alpha energy concentration of 1.3 10^5 MeV l^{-1} of air. One WL corresponds approximately to the potential alpha energy concentration of short-lived radon daughters in air which are in radioactive equilibrium with a radon concentration of 3.7 kBq m^{-3}. For thoron daughters in radioactive equilibrium with thoron, one WL corresponds to a thoron concentration of 275 Bq m^{-3}. Quotients of potential alpha energy concentration (in WL) to activity concentration (in Bq m^{-3}) are listed in Table 3 for the individual isotopes. The conversions between the units used are as follows:

$$1\ J = 6.24\ 10^{12}\ MeV$$
$$1\ MeV = 1.6\ 10^{-13}\ J$$
$$1\ WL = 1.3\ 10^{8}\ MeV\ m^{-3} = 2.08\ 10^{-5}\ J\ m^{-3}.$$

14. The equilibrium equivalent concentration of radon or thoron, $\chi_{eq,Rn}$ and $\chi_{eq,Tn}$, respectively, corresponding to a non-equilibrium mixture of short-lived radon or thoron daughters in air, is that activity concentration of radon or thoron in radioactive equilibrium with its short-lived daughters which has the same potential alpha energy concentration C_{pot} as the actual non-equilibrium mixture. The potential alpha energy concentration of radon and thoron daughters in equilibrium with 1 Bq m^{-3} of radon and thoron is given in Table 3. Accordingly, if the potential alpha energy concentration is C_{pot}, the corresponding equilibrium equivalent concentration for radon and thoron is obtained as indicated in Table 4.

15. The equilibrium factor F is defined as the ratio of the total potential alpha energy for the actual daughter concentrations to the total potential alpha energy of the daughters which would be in equilibrium with the radon or thoron concentration. Accordingly, F is calculated from the ratio of equilibrium equivalent concentration of radon or thoron to the actual radon or thoron concentration in air

$$F = \frac{\chi_{eq,Rn}}{\chi_{a,Rn}} \text{ for radon} \qquad (1a)$$

and

$$F = \frac{\chi_{eq,Tn}}{\chi_{a,Tn}} \text{ for thoron} \qquad (1b)$$

Sometimes the equilibrium factor for radon is assumed to be known, and the value of $\chi_{eq,Rn}$ is calculated by multiplying the measured radon concentration $\chi_{a,Rn}$ by F.

16. The activity exposure of an individual to radon or thoron is the time integral of the activity concentration of radon or thoron, respectively, to which the individual is exposed over a given time. The unit used here is Bq h m^{-3}. The exposure to radon or thoron daughters is expressed as "potential alpha energy exposure" or "radon or thoron daughter exposure", and is the time integral of the concentration (C_{pot} or $\chi_{eq,Rn}$ or $\chi_{eq,Tn}$) of the daughter mixture to which the individual is exposed over a given time. Potential alpha energy exposure is expressed in the units:

$$1\ J\ h\ m^{-3} = 6.24\ 10^{12}\ MeV\ h\ m^{-3} = 4.8\ \ 10^{4}\ WL\ h$$
$$1\ WL\ h = 1.3\ \ 10^{8}\ MeV\ h\ m^{-3} = 2.08\ 10^{-5}\ J\ h\ m^{-3}$$

Radon or thoron daughter exposure using the quantity equilibrium equivalent concentration of radon or thoron, respectively, is expressed in unit Bq h m^{-3}. The potential alpha energy exposure of miners is often expressed in the unit Working Level Month (WLM). One WLM corresponds to an exposure to a concentration of 1 WL for the reference period of 170 hours.

$$1\ WLM = 170\ WL\ h = 2.2\ 10^{10}\ MeV\ h\ m^{-3} = 3.5\ 10^{-3}\ J\ h\ m^{-3}$$
$$1\ J\ h\ m^{-3} = 285\ WLM$$

One WL corresponds to an equilibrium equivalent concentration of radon ($\chi_{eq,Rn}$) of 3700 Bq m^{-3} and a potential alpha energy exposure of 1 WLM radon daughter corresponds to a radon daughter exposure of 6.3 10^5 Bq h m^{-3}. For thoron daughters 1 WL corresponds to a $\chi_{eq,Tn}$ value of 275 Bq m^{-3} and 1 WLM corresponds to 4.7 10^4 Bq h m^{-3}.

D. BUILD-UP AND EQUILIBRIUM RATIOS FOR RADON AND THORON DAUGHTERS

17. The build-up of radon or thoron activity is given by the expression

$$A(t) = F_r A_o (1 - e^{-\lambda t}) \qquad (2)$$

where A(t) is the activity of radon or thoron contained in a confined unventilated space at time t (at time t = 0 the activity is assumed to be zero), F_r is the emanating power which is the fraction of radon or thoron released into that space from the ^{226}Ra or ^{224}Ra source of activity A_o, and λ is the decay constant for radon or thoron. The activity concentration in a confined unventilated space increases according to the same formula divided by the volume V of the space. If the space is ventilated with ventilation rate λ_v the increase of radon or thoron concentration follows the expression

$$\chi_a(t) = \frac{F_r A_o}{V\left(1 + \frac{\lambda_v}{\lambda}\right)} (1 - e^{-(\lambda + \lambda_v)t}) \qquad (3)$$

where $\chi_a(t)$ is the activity concentration of radon or thoron in air, and λ_v is the ventilation rate defined as the number of air changes per unit time (h^{-1}), which is the quotient of the air flow rate ($m^3\ h^{-1}$) through the space and its volume (m^3). The build-up for radon is shown in Figure I for several values of λ_v. Because of the short half-life of thoron the equilibrium level of

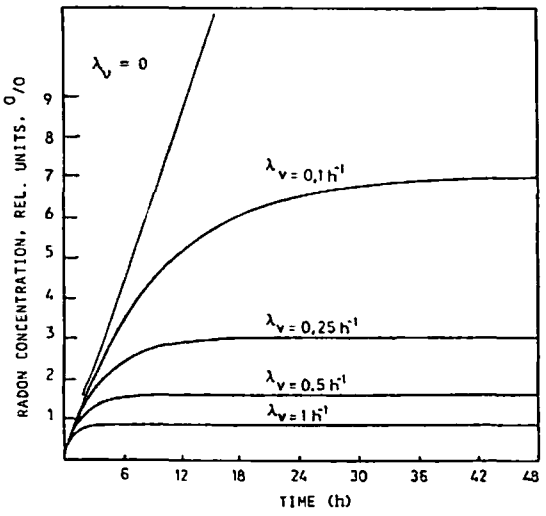

Figure I. The relative growth of radon concentration in a confined space as a percentage of the equilibrium value for no ventilation versus time for different ventilation rates λ_v (h^{-1}) [W14]

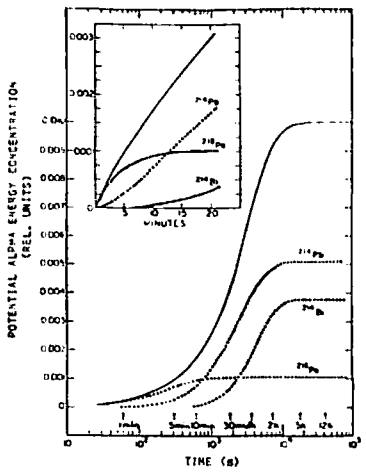

Figure II. Potential alpha energy concentration for an initially pure source of ^{222}Rn and the relative contributions to it from the progeny, as a function of time [C17]

thoron is reached within 5 minutes and in practice is independent of the ventilation rate (assuming $\lambda_v < 10$ h^{-1}).

18. Radon and thoron emanating into the air are practically free of decay products so that the daughter activity in air builds up with time. The build-up of daughter activity concentration in a volume of air containing a given radon or thoron activity concentration (the value of which is only affected by decay) is given by the following general expression

$$\chi_{a,j}(t) = \chi_a(0) \sum_{i=0}^{j} G_i e^{-\lambda_i t}$$

where

$$G_i = \frac{\prod_{k=1}^{j} \lambda_k}{\prod_{n=0}^{j} (\lambda_n - \lambda_i)} \quad (n \neq i) \qquad (4)$$

$\chi_a(0)$ is the radon or thoron activity concentration at time $t=0$, and λ represents a decay constant. Values of $j=1,2,3$, etc. stand for the first, second, third etc. radon or thoron daughter, while $i=0$ represents the parent radon or thoron. By multiplying the relative activity of the daughters by their potential alpha energy, the corresponding growth of the potential alpha energy of the radon daughters can be estimated. This is shown in Figure II for a constant radon concentration. The increase of the potential alpha energy concentration C_{pot} during the first 40 minutes is given approximately by [E6]

$$C_{pot}(t) = C_{pot}(t_1) \left(\frac{t}{t_1}\right)^{0.85} \qquad (5)$$

where t_1 is one minute.

19. It can be seen from equation (3) that the activity concentration of radon decreases as the ventilation rate increases, while the concentration of thoron is approximately independent of the ventilation rate (assuming $\lambda_v < 10\ h^{-1}$). The corresponding decrease of the activity concentration of the daughters can be estimated from the expression

$$\frac{\chi_{a,j}}{\chi_a} = \prod_{n=1}^{j} \frac{1}{1 + \frac{\lambda_v}{\lambda_n}} \qquad (6)$$

where $\chi_{a,j}$ is the activity concentration of daughter j in air and χ_a is the activity concentration of radon or thoron in air. It is assumed that factors influencing the concentration of radon or thoron daughters in air other than radioactive decay and ventilation rate can be disregarded and that there is a constant emission of radon or thoron into the ventilated space. The corresponding decrease of potential alpha energy concentration is estimated by multiplying the activity concentration of each daughter by the respective potential alpha energy as given in Table 3 and taking the sum of these products.

1. Attachment of radon and thoron daughters to aerosols

20. At the time of formation of the first daughter, ^{218}Po or ^{216}Po is an unattached, predominantly (more than 90% [D5]) positive small ion or neutral atom (size of the order of 10^{-3} μm). Some ions may be attached to molecules of water vapour and other gases. After a time of the order of 10–100 s the daughters will attach to an aerosol particle (normal size in the range 10^{-2}–1 μm). In the subsequent alpha decays the radioactive atom or ion may again become unattached because of the recoil energy when it decays. For example, the recoil energy in the decay of ^{218}Po (117 keV) is transferred to its daughter ^{214}Pb. Lead-214 will desorb, and appear as an unattached ion or neutral atom for a short time after its formation, but then becomes attached. This recoil effect has been found to apply to about 80% of the decays of ^{218}Po [M13]. The first decay product of thoron is ^{216}Po, which is very short-lived ($T_{1/2}$ = 0.15 s) and therefore unattached. The next decay product, ^{212}Pb, has a relatively long half-life ($T_{1/2}$ = 10.64 h) and therefore in room air it is predominantly attached.

21. Changes in the air concentration of the various radon and thoron daughters are governed by radon and thoron exhalation rate, radioactive decay, attachment and recombination, deposition and sedimentation, and transport by diffusion and air flow.

22. The attachment of radon or thoron daughters to aerosols depends on the diffusion coefficient of free ions and atoms and on the concentration and particle size distribution of the aerosol. The attachment to aerosols has been studied by several investigators [L6,

B2, B11, D8, K5, R2, W5]. The attachment rate can be expressed by

$$\lambda_a = \chi \int_0^\infty K(\Delta, r)\, n(r)\, dr \qquad (7)$$

where χ is the number of particles per unit volume of air; Δ is the diffusion coefficient of free atoms in air; n(r)dr is the relative number of particles in an increment (dr) of radius at the radius r; $K(\Delta, r) = 4\pi r^2 \Delta\, h(1+hr)$; $h = \bar{v}/4\Delta$; $\bar{v}$ is the mean gas kinetic velocity of free daughter atoms (= 1.7 10^4 cm s^{-1} at 20°C) [J1].

23. If one assumes that the aerosol distribution indoors and outdoors is log-normal with a Count Median Aerodynamic Diameter (CMAD) of 0.05 µm and a geometric standard deviation of 3, and if one adopts representative values of 10^4 cm^{-3} for particle density and 0.054 cm^2 s^{-1} for Δ, then the calculated attachment rate λ_a is about 10^{-2} s^{-1}, corresponding to a mean life of the unattached radioactive ion of about 100 s. For working rooms or rooms with smokers, the conditions will be different. In a mine, for example, with CMAD = 0.1 µm and $\chi = 10^5$ cm^{-3}, the attachment rate will be 0.28 s^{-1} and a corresponding mean life of only about 4 s. The mean lives of free ions and the correlation between the concentration of free ions and aerosols have been studied repeatedly [D8, K5, R3].

24. The deposition of attached daughters to surfaces is determined by the diffusion of their carrier aerosols and by the quotient of the surface area S to the volume V of the room containing the aerosols. The deposition rate λ_d is given by the expression

$$\lambda_d = v_d \frac{S}{V} \qquad (8)$$

where v_d is the deposition velocity (m s^{-1}). The value of v_d for the attached daughters depends on the size distribution of the carrier aerosols and normally lies within the range of 10^{-5} to 10^{-4} m s^{-1}. For unattached daughters the value of v_d lies in the range of 10^{-3} to 10^{-2} m s^{-1} [J1, A9]. For particles with normal Activity Median Aerodynamic Diameter (AMAD), i.e., 0.05–0.2 µm, a deposition velocity of 10^{-4} m s^{-1} and S/V quotient of about 2 m^{-1} (which is a "normal" value for rooms), the deposition rate is about 0.7 h^{-1} [J1] and the mean life is accordingly about 1.4 h. For unattached daughters the deposition rate is of the order of 1 min^{-1}.

25. The diffusion coefficient of the unattached decay products of radon and thoron in air is of the order of 0.05 cm^2 s^{-1}. Various values have been used within the range of 0.034–0.06 cm^2 s^{-1} [C5, D6, K11]. Decreasing diffusion coefficient with increasing humidity has been reported [R1] and may be due to clustering of the daughters or clustering of water molecules on daughter atoms [K11] in the air, which is not absolutely free of condensation nuclei (size in the range 0.01–0.1 µm). Theoretical studies on the mechanism of the interaction of radon daughters and water vapour are presented in [H23]. If the concentration of condensation nuclei is very low and constant but the relative humidity changes from 5 to 90%, the diffusion coefficient for unattached thoron daughters is found to remain fairly constant (0.05–0.06 cm^2 s^{-1}) [K10]. The diffusion coefficient is also independent of thoron concentration in the reported range of 70–4000 kBq m^{-3}. However, if the concentration of condensation nuclei increases several orders of magnitude (e.g., by decreasing the ventilation rate in a room) the diffusion coefficient decreases to about 0.007 cm^2 s^{-1} (at a concentration of 5 10^4 cm^{-3}). These experiments were made in an aerosol-free atmosphere. In other experiments [P10], the diffusion coefficient of positively charged decay products of thoron has been measured under very dry conditions (relative humidity 2%) to be 0.048 ± 0.003 cm^2 s^{-1} and with high relative humidity (30–90%) to be 0.068 ± 0.004 cm^2 s^{-1}. For neutral ^{212}Pb atoms the diffusion coefficient was 0.067 ± 0.004 cm^2 s^{-1}, irrespective of the humidity.

26. A study concerning the effects of charge, humidity and the number of condensation nuclei on radon daughter concentration in air has been made by Cooper et al. [C10]. The study laid particular emphasis upon uranium mines and showed great variations of the aerosol attachment and surface attachment (plateout) rates. The effect of humidity on the diffusion coefficient of radon daughters is dubious, although there seems to be agreement that the plateout effect strongly depends on the fraction of daughters which are not attached to particles [C9, M11]. The effect of turbulent air in mine environments has been found to lead to a reduction of the airborne radon daughters [W13, S9] owing to an increased plateout on the walls or plateout on the fan blades. The fraction of radon daughters which attaches to the blades of a fan that circulates the air is substantial if the relative humidity is low (5%) and negligible when the relative humidity is high (80%) [H14]. The effects under conditions of low humidity are illustrated in Figure III. Similar effects were also

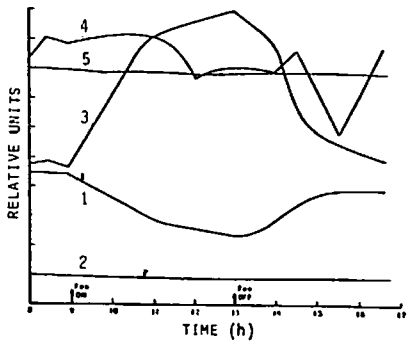

Figure III. Radon daughter concentration in the air (curve 1, full scale 10 WL), on the walls (curve 2, full scale 1000 counts/min), and on the fan (curve 3, full scale 3000 counts/30 min) in response to the switching on and off the fan. Curve 4 (full scale 10^5 cm^{-3}), the condensation nuclei concentration, and curve 5 (full scale 70 kBq m^{-3}), the radon concentration, are practically independent of the fan being on or off. Humidity was < 5% [H14]

studied in room air [J12] and from preliminary results it was concluded that the removal by a fan system mainly affected ^{218}Po. In experiments with monodisperse aerosols (diameters 2–10 µm) and radon and radon daughters the attachment rate of ^{218}Po was studied [H11]. It was concluded that the attachment rate was proportional to particle concentration and particle cross-section area, which implies that the attachment process of ^{218}Po to aerosols can be described by gas kinetic theory. The attachment rate was also found to be proportional to the radon or ^{218}Po concentration.

27. The equation governing the fraction of *unattached* radon or thoron daughters in a room involves terms for radioactive decay, attachment, deposition of aerosols and ventilation. Assuming that the outdoor concen-

tration can be neglected, the fraction of unattached ^{218}Po and ^{212}Pb atoms is given by

$$F_{fd} = \frac{1}{1 + \frac{\lambda_a}{\lambda_l + \lambda_v + \lambda_d}} \qquad (9)$$

where λ_a is the rate of attachment of free daughter atoms to aerosol particles; λ_l is the decay constant; λ_v is the ventilation rate; λ_d is the wall deposition rate for attached daughter atoms [J1]; and F_{fd} is the quotient of the number of unattached ^{218}Po or ^{212}Pb atoms to the total number of ^{218}Po or ^{212}Pb atoms, respectively. Sometimes a fraction F'_{fd} is given which is the ratio of the number of unattached ^{218}Po or ^{212}Pb atoms to the number of ^{218}Po or ^{212}Pb atoms assumed to be in equilibrium with radon or thoron, respectively. This fraction corresponds to F_{fd} F_l, where F_l is the activity equilibrium ratio of ^{218}Po or ^{212}Pb to radon or thoron, respectively; i.e., $F'_{fd} = F_{fd}$ F_l.

28. With the typical value of λ_d given above (paragraph 24), it is obvious that for daughters with a high decay constant like ^{218}Po, λ_l will be the most significant term in the above equation (9) for a given value of λ_a, while the ventilation rate λ_v within a normal range (0–1 h^{-1} in buildings) will be less significant. However, in mines with high ventilation rates the value of λ_v will significantly influence the value of F_{fd} for radon daughters. As increased ventilation may cause a decrease of the aerosol concentration, the value of λ_a will decrease, with an increase in the fraction of unattached radon daughters.

29. Measured values of F_{fd} and F_l in thorium plants [M16] are F_{fd} = (0.74 ± 0.02)% and F_l = (3.7 ± 2.5)% (= ^{212}Pb/Tn), giving F'_{fd} = 0.027 ± 0.021 [K11]. Several values of the fraction of unattached radon daughters have been reported. In Sutton, in the United Kingdom, F_{fd} for ^{218}Po varied between 0.07 and 0.40 (relative to ^{218}Po with no consistent difference indoors and outdoors [D7]). In New York City, F'_{fd} (unattached fraction relative to radon) varied in two series between 0.01 and 0.06 (average 0.04) and 0.05–0.12 (average 0.09) [F3]. In Sterling Forest, F_{fd} for ^{218}Po was measured to be 0.04–0.1 (average 0.08) [G4] with the lowest value occurring on a rainy day. F'_{fd} for ^{218}Po indoors in New York has been measured to be 0.04–0.07 [F3, G4].

30. The fraction F_{fd} of unattached ^{218}Po atoms has been measured [D8] in open air and in mines as a function of the concentration X_a of condensation nuclei in the air. The measured values were compared with the theoretical expression

$$F_{fd} = \frac{\lambda_l}{\lambda_l + k X_a} \qquad (10)$$

where λ_l is the decay constant for ^{218}Po and k X_a = λ_a. The values of k have been calculated by Jacobi and by Raabe to be 6 10^{-5} min^{-1} cm^3 and 4 10^{-5} min^{-1} cm^3, respectively [D8]. The comparison with experimental values is presented in Figure IV [D8].

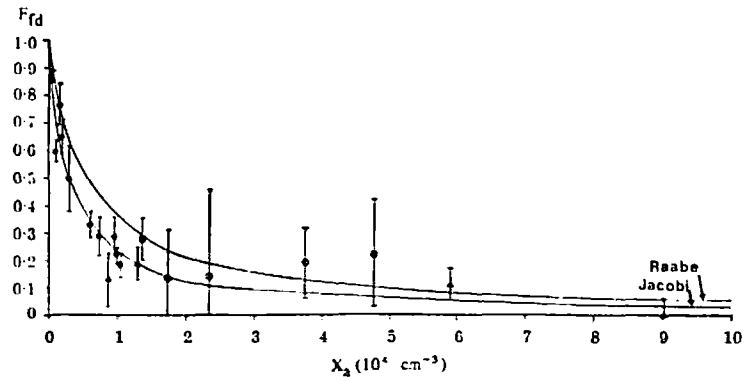

Figure IV. Variation of the fraction of unattached ^{218}Po as a function of the concentration of condensation nuclei. ▲ — Tin mine; ■ — Colley Hill (rural), ⊙ — Sutton (suburban); ● — artificial atmosphere [D8]

31. Activity concentrations of attached and unattached radon decay products in mines have been measured [R3] and the fraction F_{fd} (unattached activity/total activity of respective daughter) has been calculated for ^{218}Po, ^{214}Pb and ^{214}Bi [M12]. In 60 samples, mean and standard deviation for F_{fd} were obtained of (8 ± 10)% (range 0.3–55.4%) for ^{218}Po, (4.9 ± 6.8)% (range 0.06–31.4%) for ^{214}Pb and (2.7 ± 3.8)% (range 0.08–16.4%) for ^{214}Bi.

32. In summary, the rate of attachment of radon and thoron daughters to aerosols normally lies in the range 10^{-1}–10^{-2} s^{-1}, with higher values in dusty air. The rate of deposition (plateout) on indoor surfaces is about 1 h^{-1} for attached daughters, and 1 min^{-1} for unattached daughters. Low humidity and increased air turbulence increase the plateout. The unattached fraction of radon and thoron daughters is normally in the range 1–10%. The unattached fraction increases with decreasing aerosol concentration and with increasing ventilation rate.

2. Equilibrium factors for radon and thoron daughters in ventilated confined spaces

33. The daughter ratios given by equation (6) may be combined with the conversion coefficients of Table 3 to obtain the equilibrium factor F as a function of ventilation rate. These are presented in Table 5. Corresponding values for the potential alpha energy concentration of the daughters can be derived by multiplying F by the potential alpha energy concentration of the daughters if they were in equilibrium with the parent radon or thoron activity concentration χ_a. The potential alpha energy concentration for radon daughters calculated in this way is shown in Figure V as a function of ventilation rate [P12]. This calculation assumes no plateout, and negligible daughter concentration in the inlet air. For thoron daughters, the corresponding quantity simply follows the equilibrium factor F, as the thoron activity is fairly constant.

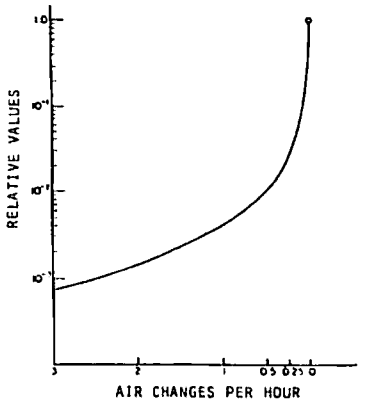

Figure V. Potential alpha energy concentration of radon daughters as a function of ventilation rate [P12]

34. When the effects of plateout and radon daughters in the inlet air are included, the simple description given above no longer applies. The degree of plateout to the walls is strongly influenced by the unattached fraction, which in turn affects the activity ratios and the equilibrium factor F. The equilibrium factor for radon daughters has been estimated from measurements made under varying aerosol conditions [W14] and the results are shown in Figure VI. It is apparent that average

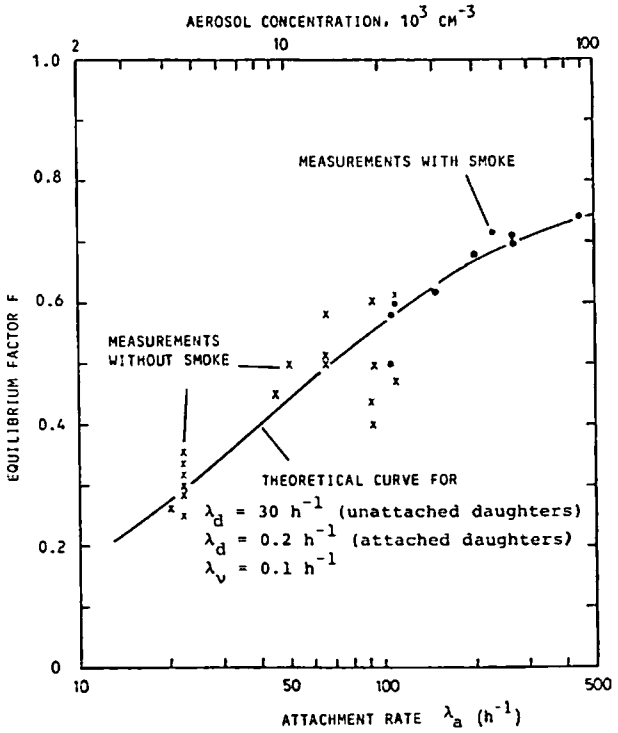

Figure VI. Equilibrium factor for radon daughters in a room as a function of the aerosol concentration and the attachment rate λ_a. The emanation rate into the room is 7.4 Bq m^{-3} h^{-1} [W14]

values of F corresponding to different values of the rate of attachment λ_a agree reasonably with the theoretical curve which includes the effect of plateout. Significant concentrations of radon daughters in the inlet air complicate the situation further. Figure VII illustrates the variation in the equilibrium factor F with ventilation rate for a number of exhalation coefficients R_v (Bq m^{-3} s^{-1}) defined as the exhalation rate R (Bq m^{-2} s^{-1}), multiplied by the quotient S/V (m^{-1}) of surface area to volume. For this calculation an equivalent equilibrium concentration of 2.6 Bq m^{-3} was assumed

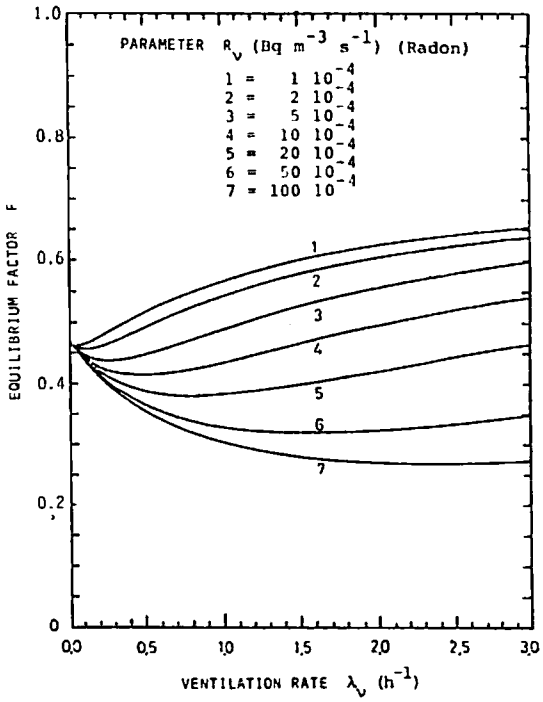

Figure VII. Equilibrium factor for radon daughters in a room as a function of ventilation rate λ_v with varying emanation rates into a room and the radon daughter concentration in outdoor air taken into account [W14]

for outdoor air, with an equilibrium factor of 0.75. In other theoretical calculations [J1] the equilibrium factor has been estimated to be as low as 0.2 for conditions of low aerosol concentration (λ_a = 100 h^{-1}) and a ventilation rate of λ_v = 1 h^{-1}. However, when allowance is made for the equilibrium factor for inlet air drawn from outdoors, the equilibrium factor increases to greater than 0.3 (calculated from [P9] for the reference house described in paragraph 105). For rooms with high aerosol concentrations (λ_a > 1000 h^{-1}) the equilibrium factor F will be larger (with λ_v = 1 h^{-1}, F = 0.35, according to [J1]). These results suggest that approximate estimates of F, which take plateout into account may be obtained by multiplying the values of F in Table 5 by 0.4 (λ_a = 100 h^{-1}) or 0.6 (λ_a = 1000 h^{-1}) for λ_v < 2 h^{-1} or by 0.5 if λ_a is unknown.

35. The effect of deposition on the walls (plateout) in radon daughter ratios in uranium mine atmospheres has recently been studied [H21]. It was concluded that selective plateout, particularly of ^{218}Po, is the main reason why it is impossible to find simple correlations between activity or potential energy concentrations and ventilation rate or age of the air.

36. Plateout also influences the factor F for thoron daughters. In rooms with low aerosol concentration and a ventilation rate of about 1 h^{-1}, F is about 0.009, instead of 0.058 as given in Table 5. In rooms with higher aerosol concentration F is about 0.013 [J1]. Other calculations show somewhat higher values [W14]. It seems appropriate therefore to assume that the equilibrium factor is generally less than half of the values given in Table 5.

37. If there is a ventilation system with recirculation of part of the air and also air filtration, there will be a decrease in the radon concentration proportional to the fraction of fresh air admitted (if the radon concentration in fresh air is neglected). However, if the air exchange rate, including recirculation, is unchanged,

the equilibrium factor F will not change, unless there is a decrease in the aerosol concentration because of recirculation.

II. RADON AND THORON IN OUTDOOR AIR AND IN WATER

38. The concentrations of radon and thoron and of their daughters vary substantially with time and space. In general, the activity levels in air make a much more significant contribution to radiation exposure than those in water. The levels of radon and thoron in air or water depend on four factors. These are the nature of the source, its emanating power, transport of radon and thoron from the source and their ultimate dispersal. These factors will be considered in this chapter.

A. SOURCES

39. Radium and thorium in soil are the main sources of radon and thoron in the global atmosphere. Both the radium and thorium concentrations usually lie in the range of 10–50 Bq kg^{-1} (Annex B). The average world-wide concentration of both elements in soil is assumed to be 25 Bq kg^{-1} (Annex B). In seawater the concentration of ^{226}Ra is 4 to 5 orders of magnitude lower [B25], and the concentration of ^{228}Th is 6 to 7 orders of magnitude lower [M27]. Nevertheless, for reasons which are discussed in paragraph 62, the exhalation rate from the oceans is only about 2 orders of magnitude lower than that for soil. Some published values of radon exhalation rates per unit area are listed in Table 6 [W15]. The estimated area-weighted average radon exhalation rate per unit area from soil, excluding Antarctica and the Greenland ice cap, is 16 mBq m^{-2} s^{-1} [W15] corresponding to a total exhalation rate of 1.9 10^{12} Bq s^{-1}. The values reported in Table 6 have a log-normal distribution with a geometric mean of about two-thirds of the arithmetic mean. In a study on the flow of ^{210}Pb into the global atmosphere good agreement has been achieved between calculations based on the geometric mean of the radon exhalation rates per unit area and those based on glacier ice concentrations of ^{210}Pb [J16]. Other estimates of world-wide average soil radon exhalation rates per unit area are 15 mBq m^{-2} s^{-1} [I7] and 19 mBq m^{-2} s^{-1} [B13]. Reported ranges are 0.2–70 mBq m^{-2} s^{-1} [W15, G17]. The total annual radon exhalation is then 5–10 10^{19} Bq, corresponding to a total equilibrium activity of the order of 10^{18} Bq. As may be seen in Table 23, the concentration of ^{222}Rn in ground level air varies widely with geographical location, and is up to two orders of magnitude higher over land masses than in maritime locations. Other sources of radon in air are plants and ground water ($< 10^{19}$ Bq a^{-1}), natural gas (about 10^{14} Bq a^{-1}) and the combustion of coal (about 10^{13} Bq a^{-1}) [H7]. Radon from houses may contribute about 10^{16} Bq a^{-1} (assuming 10^9 reference houses of the type presented in Table 13, the true value may be between 5 10^{15}–10^{17} Bq a^{-1}). The total annual radon release from uranium mines, mills and tailings is of the order of 10^{15} Bq (assuming 120 GW[e] installed nuclear capacity and a normalized radon release of 2 10^{13} Bq [GW(e) a]$^{-1}$) (see Table 2 of Annex F).

40. Geothermal power stations are a source of radon which is minor from a global perspective but may be of local significance. At present only a small part of the world energy requirement is produced from geothermal sources (0.1%) [U5] but increases in the future are possible. The production of hot steam in deep geological formations leads to releases of radon from water in the bed rock. Measurements performed in Italy [M4] indicate a radon release per unit energy generated of about 4 10^{14} Bq (GW a)$^{-1}$, which is three to four orders of magnitude higher than the normalized release from coal-fired plants. The radon concentration in geothermal steam at Wairakei and Broadland in New Zealand is 100–400 Bq kg^{-1} steam which results in an annual radon release of 10^{11} to 10^{12} Bq.

41. Another source of interest is phosphate mining. Rock phosphate is used mainly as a source of phosphorus for fertilizers. Morocco, the Soviet Union and the United States are the main producers. The United States produces 40% of the total world production of phosphate rock and more than 80% of the total United States production occurs in Central Florida. Sedimentary phosphate ores such as those in Morocco and Florida often have a higher concentration of uranium and its decay products than magmatic ores such as those from Kola. Most phosphate is mined in an open-pit or strip-mining process. In order to reach the phosphate rock, the overburden and a second layer called the leach zone have to be removed. The leach zone has generally a higher concentration of ^{226}Ra than the overburden and is afterwards frequently placed at or near the surface, resulting in increased ^{226}Ra concentrations [C17]. The subsequent radon exhalation rate from phosphate regions depends on land reclamation practices. A quantitative characterization is given in Figure VIII, which refers to phosphate regions in Florida [R8].

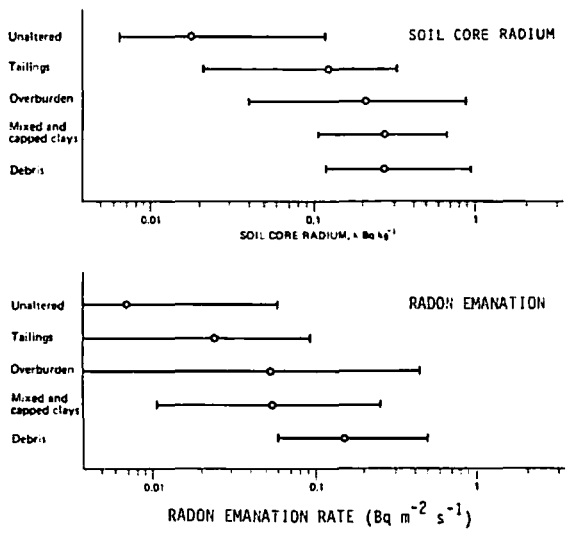

Figure VIII. Radiological characteristics of Polk County lands, Florida (geometric means and ranges by land type) [R8]

42. Volcanic activity as a source of radon in air has been investigated in Iceland, Japan and Hawaii [W16, B14, I8]. Radon concentrations in the volcanic plumes were observed to be above ambient air concentrations and in Hawaii concentrations of the order of 50 Bq m^{-3} were reported. The radon release rate was estimated to be of the order of 10 GBq h^{-1} which is negligible compared with the radon release rate from the island surface. The radon release from the eruption of Mount St. Helens in the United States on 19 May 1980 has been estimated to be about 10^{17} Bq of radon in the plume [F6], which corresponds to about 10% of the total atmospheric inventory. However, this estimate has not been confirmed by other observers.

43. Radium-224 in soil is the main source of outdoor thoron. However, because of the relatively short half-life of ^{224}Ra (3.7 d) it must be continuously supported by its precursors. Thus, in practice, ^{228}Th ($T_{1/2}$ 1.9 a) and ^{228}Ra ($T_{1/2}$ 5.8 a) control the thoron exhalation rate. Even though the activity exhalation rate for thoron is much higher (about 100 times) [B13, H7] than that for radon, the total global activity inventory in the atmosphere is much less (about 100 times less) than that for radon, primarily because of the shorter half-life of thoron.

B. MECHANISMS OF RADON AND THORON RELEASE

44. The physical process of the radon and thoron release from the structure of the rocks is not yet fully understood. Only a part of the radon and thoron atoms produced by decay in a particle is released to the sourrounding water or air. The fraction of the radon or thoron atoms formed in a solid which makes its way into the pores of the medium, and thereby becomes amenable to transport, is defined as the emanating power of the solid for radon or thoron. Some mechanisms describing the release of radon are reviewed in [A2, T6].

45. The transport and release of radon and thoron from a solid into air or water occurs through diffusion and flow of the air or water. High porosity increases the diffusion rate. In a very dry solid the release of radon or thoron is reduced by readsorption of radon and thoron atoms on surfaces in the pores and fractures in the solid. If the solid is slightly moist, the radon and thoron release is enhanced up to a certain moisture content, above which it decreases again because of the lower diffusion rate in water-filled pores [M10].

46. The exhalation of radon per unit area for large particles and pieces of uranium ore has been demonstrated to increase with the size of the particles [T4]. This effect may be due to the presence of microfracturing in the samples. Similarly, the exhalation of radon from ordinary rock samples may be less than the exhalation from rock walls in a mine, because of greater fracturing and the presence of cracks in the walls caused by blasting [L9, K7]. Table 7 shows the results of some measurements of radon exhalation from core material and a surface in a mine [L9].

C. MECHANISMS OF RADON AND THORON TRANSPORT IN THE GROUND

47. Once radon and thoron have entered the surrounding water or air phase, they are further transported by diffusion, mechanical and convective flow, and by percolation. The diffusion process can be expressed by the formula

$$\chi(x) = \chi(o) \exp\left(-x / \sqrt{\frac{\Delta_k}{\lambda}}\right) \qquad (11)$$

where $\chi(x)$ is the radon or thoron concentration at distance x in water or air from the surface; $\chi(o)$ is the radon or thoron concentration at the surface; Δ_k is the effective diffusion coefficient and λ is the decay constant [G8]. The diffusion coefficient Δ_k for radon is about 0.1 $cm^2\ s^{-1}$ in air and 10^{-5} $cm^2\ s^{-1}$ in surface water [T1]. In soil Δ_k is usually of the order of 10^{-2} $cm^2\ s^{-1}$ or less [T1]. This means that radon will have decayed to 10% of its original value after a diffusion through 5 m of air, 5 cm of water and about 2 m in soil. Migration of radon for much longer distances by diffusion is not important. Accordingly, the transport of radon over greater distances in water and air must occur through other mechanisms. The short half-life of thoron (55 s) limits its migration to less than one per cent of that of radon [J2]. Therefore, the remainder of this discussion relates mainly to radon.

48. Radon in rock or soil may also be transported by mechanical forces in the earth causing changes of pore space through compressive stresses. These may be caused by earth tides or by intermittent forces such as those of earthquakes. Such mechanisms may explain intermittent variations in radon exhalation from soil surfaces.

49. Another possible transport mechanism is thermally-induced fluid convection. Some data suggest that this process may be important, but further results are needed [M14].

50. In the main, however, the transport of radon though soil and bedrock by water probably depends on the percolation of water through the pores and along fracture planes of the bedrock. The radon concentration in water from a percolation zone $\chi_{w,Rn}$ is related to the radium concentration of the percolated rock $C_{rock,Ra}$, the rock density, ρ_{rock}, the emanating power, F_r, the fractional pore space of the rock (porosity), $F_{rock,ps}$, and the water velocity v, through the formula

$$\chi_{w,Rn}(x) = \frac{F_r\, \rho_{rock}\, C_{rock,Ra}}{F_{rock,ps}} (1 - e^{-\lambda x/v}) \qquad (12)$$

where λ is the decay constant and x is the distance which water travels through the rock [A2]. It follows from this formula that heavy rainfall causes a decrease in radon concentration as the velocity v increases. Thus, if the water in a well is supplied by water from a percolation zone of higher than normal radium content, the radon concentration in the well is likely to decrease after rainfall. However, if the percolation water is a minor source for the well, heavy rainfall might flush out radon-rich water from the percolation zone thereby causing an increase of radon concentration. Variations of radon concentration in well water are sometimes observed to be seasonal [A2, K8, S11].

51. The radon content in ground water and water in springs and wells is seen from equation (12) to depend on the radium concentration in the rock of the aquifer. Consequently, the highest radon concentrations are found in water in the vicinity of uranium ore bodies. High concentrations (> 400 kBq m^{-3}) are also found in wells bored in granite, pegmatite, syenite and porphyry. Low radon concentrations occur in ground water from basic rocks and sedimentary rocks, such as limestone and sandstone [K8].

52. In investigations of radon in ground water in six counties in Maine, United States, the highest concentrations were found in granites and adjacent sedimentary rocks which have experienced great metamorphic change. Low concentrations were found in ground water from non-granitic areas with little metamorphic change. The average radon concentration in ground water in granite zones was about 1 MBq m^{-3} and in chlorite zones 40 kBq m^{-3} [H10].

53. The radon concentration in water may vary with the depth of the wells if the size of the percolation zone depends on the well depth. This effect has been found to be significant for wells in granite up to depths of around 50 m, as can be seen in Figure IX. At depths

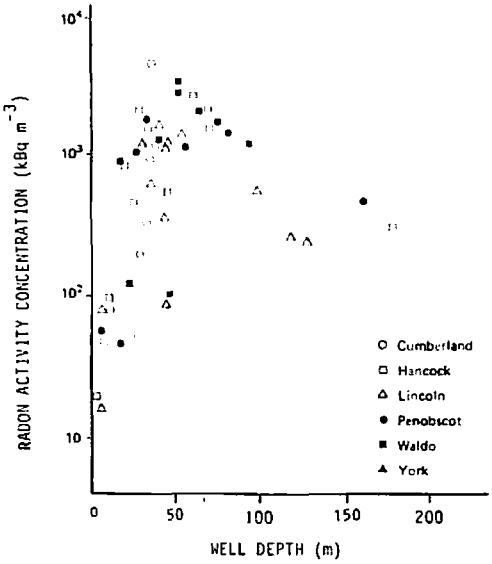

Figure IX. The variation of ^{222}Rn concentration as a function of water well depth in granites [H10]

beyond 100 m there was a tendency for radon concentrations to decrease [H10]. In other investigations no significant correlation of radon concentration with depth has been observed [S11].

54. Measurements of radon in soils can be used in uranium exploration, particularly when the uranium ore is covered by a thick layer of soil (more than about 0.5 m) [D9], although anomalies arising from selective radium or radon transport from the uranium ore may give rise to errors in interpretation. Meteorological factors, particularly those affecting the moisture content of the soil, can result in large variations in radon concentration in the soil [U6, C1].

55. Radon measurements in sub-surface waters and in dry boreholes have recently been used as an earthquake predictor [S10, S37, S38, K16, N1]. It is postulated that dilation of the rock caused by strain releases radon to the ground water and subsequently increases the radon content in well and spring waters in the vicinity. This method is however subject to many complicating factors and there is still considerable doubt about its practical applicability.

D. RADON AND THORON TRANSFER THROUGH SOIL AND EMANATION TO AIR

56. Radon and thoron enter the air contained in soil by diffusion from soil particles or sometimes from radon-rich ground water at greater depths. The concentration of radon and thoron in this air decreases with decreasing distance from the surface because the gases escape to the open air above the ground. As the exhalation increases, the gas concentration in soil air decreases, and vice-versa.

57. The diffusion mechanisms for radon and thoron are the same. For radon, the diffusion through soil to surface can be expressed by the diffusion equation [J2]

$$\frac{dX_{a,\,Rn}(z)}{dt} = \Delta_k \frac{d^2X_{a,\,Rn}(z)}{dz^2} + \frac{F_r \lambda_{Ra} X_{soil,\,Ra}}{F_{soil,\,ps}} - \lambda_{Rn} X_{a,\,Rn}(z) \qquad (13)$$

where $X_{a,Rn}(z)$ is the concentration (per unit volume of soil air) of radon atoms at depth z ($z=0$ at the ground surface); Δ_k is the effective diffusion coefficient ($cm^2\ s^{-1}$); F_r is the emanating power ($0 < F_r < 1$); λ_{Ra} and λ_{Rn} are the decay constants of radium and radon, respectively; $X_{soil,Ra}$ is the concentration (per unit volume of soil) of radium atoms; and $F_{soil,ps}$ is the porosity of the soil. Under steady state conditions $dX_{a,Rn}(z)/dt = 0$, and the concentration of radon activity at depth z is given by

$$[\chi_{a,\,Rn}(z)]_{soil} = \frac{F_r \chi_{soil,\,Ra}}{F_{soil,\,ps}} \left[1 - \exp\left(-z\sqrt{\frac{\lambda_{Rn}}{\Delta_k}}\right)\right] \qquad (14)$$

where $[\chi_{a,Rn}(z)]_{soil}$ is the radon activity concentration per unit volume of soil air at depth z; $\chi_{soil,Ra}$ is the radium activity concentration per unit volume of soil.

58. At great depths ($z \to \infty$) the equilibrium radon concentration in soil air is

$$\frac{F_r \chi_{soil,\,Ra}}{F_{soil,\,ps}}$$

For an infinitely thick soil, the exhalation rate is given by

$$R = \left(\Delta_{eff} \frac{d\,[\lambda_{a,\,Rn}(z)]_{soil}}{dz}\right)_{z=0} \qquad (15)$$

where $\Delta_{eff} (= F_{soil,ps}\ \Delta_k)$ is the effective bulk diffusion coefficient. The combination of equations (14) and (15) gives

$$R = \lambda_{Rn} F_r \chi_{soil,\,Ra} \sqrt{\Delta_k/\lambda_{Rn}} \qquad (16)$$

The rate of diffusion is highly dependent on the moisture content of the soil and the diffusion coefficient (Δ_{eff}) can vary by several orders of magnitude. A value of $5\ 10^{-2}\ cm^2\ s^{-1}$ for Δ_k has been suggested as typical for soil [S39]. Assuming that $F_r = 0.1$, $\chi_{soil,Ra} = 0.074\ Bq\ cm^{-3}$ and $\Delta_k = 0.05\ cm^2\ s^{-1}$,

$$R = 2.4\ 10^{-2}\ Bq\ m^{-2}\ s^{-1}$$

which compares reasonably with measured average values of $1.5–2.0\ 10^{-2}\ Bq\ m^{-2}\ s^{-1}$. The corresponding value for thoron is $1.9\ Bq\ m^{-2}\ s^{-1}$ if all constants except λ are the same. Several studies of thoron exhalation have been reported [D4; G16, M1, M10, S40] and the average observed value of the thoron exhalation rate from soil is around $1\ Bq\ m^{-2}\ s^{-1}$ [J2].

59. The concentration of radon and thoron in soil air is affected by meteorological factors each as barometric pressure, humidity, rainfall and temperature. Rising barometric pressure has been found to increase the radon concentration in soil air whereas falling pressure causes a decrease of the radon concentration [B15]. However, a tendency for decreasing concentration with increasing atmospheric pressure has also been observed for radon in soil air. This decrease is believed to be due

to a flow of air from outside into the soil surface layers forcing the soil gas initially in surface layer to greater depths. The results of some recent studies are shown in Tables 8 and 9 [I9], which show the influence of depth, barometric pressure and wind speed on the concentration of radon and thoron in soil air. The standard deviation of the observations are 50% for radon and 25% for thoron. The effect of wind speed is believed to be due to increased turbulence at the ground surface which causes a pumping effect on the soil gases.

60. Factors influencing the concentration in soil air also influence the exhalation rate, but in the opposite direction. Rain, snow, freezing and increased atmospheric pressure reduce the exhalation rate, while higher wind speeds and temperature increase it. Consequently, the radon concentration in soil has its maximum values in winter, when the ground is frozen, and in rainy periods, unless the rain flushes out the radon from the soil. Radon exhalation rates vary for different soils. In areas with a high radium burden, such as uranium mining areas, the exhalation rate is much higher than normal (more than two orders of magnitude greater for uncovered tailings) [U9]. Diurnal variations of exhalation rate have been reported for radon [M2], while others have found the exhalation rate to be relatively constant between day and night [W15, G11]. Studies of correlations between radon exhalation rate and temperature (at 1 m above ground) have given equivocal results.

61. The exhalation of thoron from soil is more dependent on soil conditions and meteorological factors than is the case for radon. Because of the short half-life of thoron, the effective exhalation depth is only a few centimetres and the thoron exhalation decreases rapidly when moisture content increases. Diurnal variations in thoron exhalation (± 30% of the mean) occur in dry summer days because of convection streams with maxima at sunset and at night and minima at sunrise and early in the day [D4, G16, M1, M10, S40].

62. Radon exhalation from sea water is about two orders of magnitude less than from soil. The radium concentration in sea water is about 1 Bq m^{-3} and varies with the depth, being higher (up to one order of magnitude) near the ocean floor than at the surface [S26]. The radon concentration, however, is not in equilibrium with radium in the sea water, but it is higher near the bottom owing to radon exhalation from the sea floor and to radium-enriched plankton in the water. This excess of radon decreases with increasing distance from the sea floor; in surface water there is actually a relative radon deficiency due to radon exhalation into the air. Measured values of radon concentration are about 1 Bq m^{-3} or less [H7, S26]. Using a diffusion coefficient of 10^{-5} cm^2 s^{-1} for radon in water leads to a predicted exhalation rate of about 10^{-9} Bq cm^{-2} s^{-1}. However, owing to water turbulence, the effective diffusion depth is much higher than that derived from molecular kinetic diffusion and the radon exhalation is at least an order of magnitude higher than the above value. This higher value is also in better agreement with the ratio between the radon concentration in air above oceans and land, which is around 10^{-2}.

E. DISPERSION OF RADON AND THORON IN AIR

63. The transport and dispersion of radon and thoron in air depend on the vertical temperature gradient, the direction and strength of the wind and on air turbulence. The radon and thoron daughters are also affected by precipitation. The temperature in the troposphere normally decreases with height up to about 11 km, above which the stratosphere begins. There the temperature is rather constant up to about 32 km, where it begins to rise again. Most of the air mass, water vapour and dust are found in the troposphere (75%), and for normal turbulence conditions most (> 99%) of the radon and its daughter products are found in the troposphere.

64. The vertical dispersion of radon and thoron takes place through turbulent diffusion and convection and is limited by the radioactive decay. The turbulent diffusion coefficient is much higher than the gas kinetic diffusion coefficient and increases with the height above ground. This increase with altitude is influenced by vertical variations in wind velocity and atmospheric stability in the upper part of the troposphere and in the lower part of the stratosphere, where the turbulent diffusion coefficient decreases again [J3]. Characteristic profiles of the turbulent diffusion coefficient corresponding to some typical conditions of turbulence are shown in Figure X (adapted from [J3]).

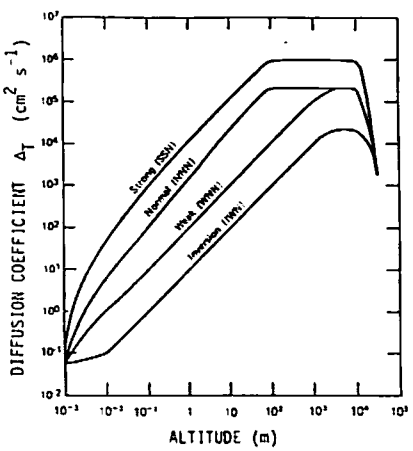

Figure X. Values of diffusion coefficient used in calculation of vertical concentration profiles of radon-222 and its daughters. NNN = normal turbulence conditions; WNN = weak turbulence conditions; SSN = strong turbulence [G19]

65. The vertical distribution of radon and thoron and their daughters in air can be calculated from the following system of differential equations

$$\frac{d}{dz}\left(\Delta_T(z)\frac{dX_{a,1}(z)}{dz}\right) - \lambda_1 X_{a,1}(z) = 0 \qquad (17)$$

$$\frac{d}{dz}\left(\Delta_T(z)\frac{dX_{a,j}(z)}{dz}\right) + \lambda_{j-1} X_{a,j-1}(z) - (\lambda_j + \Lambda) X_{a,j}(z) = 0 \qquad (j > 1) \qquad (18)$$

where $\Delta_T(z)$ is the turbulent diffusion coefficient at the height z; $X_{a,1}(z)$ is the concentration of radon or thoron atoms in air at the height z; $X_{a,j}(z)$ is the concentration of daughter j (j > 1) in air at the height z; λ_1 is the decay constant of radon or thoron; λ_j is the decay constant of radon or thoron daughter (j > 1); and Λ is the removal rate of daughters caused by washout and rainout and is assumed to be independent of altitude [J3]. Boundary conditions to equations (17) and (18) are $X_{a,j}(o) = 0$ for j > 1; and $X_{a,j}(\infty) = 0_{a,j}$ for j = 1, 2, 3 ...

66. By assuming a constant radon and thoron exhalation rate from an infinite plane (ground surface) which equals the radioactive decay of the total radon and thoron content in the atmosphere, it is possible to solve equations (17) and (18), which, in combination with different values of $\Delta\tau(z)$, give the vertical distribution of radon and thoron and their daughters for different atmospheric stabilities. The result of such calculations is shown in Figure XI. It is seen that the radon and

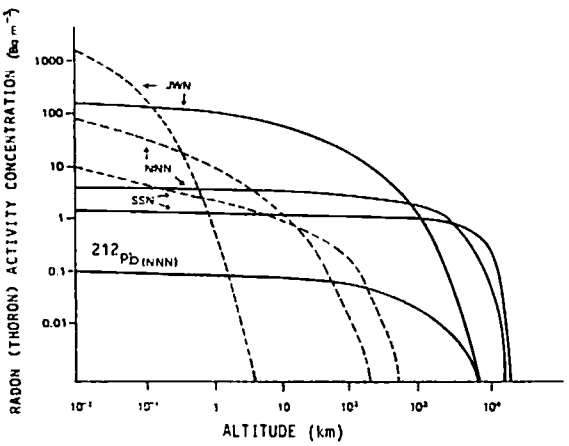

Figure XI. Vertical profiles of radon and thoron, assuming an emanation rate of 1 radon atom $cm^{-2} s^{-1}$ corresponding to about $2\,10^{-2}$ Bq $m^{-2} s^{-1}$ and 0.1 thoron atom $cm^{-2} s^{-1}$ corresponding to about 1 Bq $m^{-2} s^{-1}$. JWN = strong inversion; SSN = strong turbulence; NNN = normal turbulence. The full lines are for radon and the broken lines for thoron. The vertical profile of ^{212}Pb is also shown for normal turbulence conditions [J3]

thoron concentrations at ground level are expected to vary by a factor of 100 for the extreme conditions of atmospheric stability. Assuming a radon exhalation rate of 1 atom $cm^{-2} s^{-1}$ (corresponding to $2\,10^{-2}$ Bq $m^{-2} s^{-1}$), these variations of radon concentration lie between about 1 and 100 Bq m^{-3}. At higher altitudes these variations gradually reduce to become less than a factor of 5 at 1–2 km. Assuming a thoron exhalation rate of 0.01 atom $cm^{-2} s^{-1}$ (which is a fairly normal value) the thoron concentrations at ground level (0.01–1 m) are about the same or a little higher than those of radon. At 10–100 m height the thoron concentrations are insignificant.

67. Several measurements have generally confirmed the above theoretical model for the vertical distribution of radon. Radon concentrations at different altitudes over the Yukon Valley in Alaska were found to lie within the theoretical curves for the extremes of strong inversion and normal turbulence conditions, as shown in Figure XII. The radon concentration in air below 2 km corresponds to a radon exhalation rate of 0.33 atom $cm^{-2} s^{-1}$ (corresponding to $0.7\,10^{-2}$ Bq $m^{-2} s^{-1}$), which is remarkably high as the ground was frozen and had a thick snow cover. This may be explained either by a high radium content in the soil or by a high diffusion coefficient for radon from the snow cover [L3]. The radon may also have come from elsewhere. Radon concentrations at altitudes above 2 km probably depend on large-scale circulation of air and radon transport from very distant areas, which gives time for substantial decay.

68. In measurements made by Bradley and Pearson [B8] over Illinois, United States, from 150 m to 5 km above ground the radon concentration ranged from 2 to 10 Bq m^{-3} at 150 m and decreased approximately by

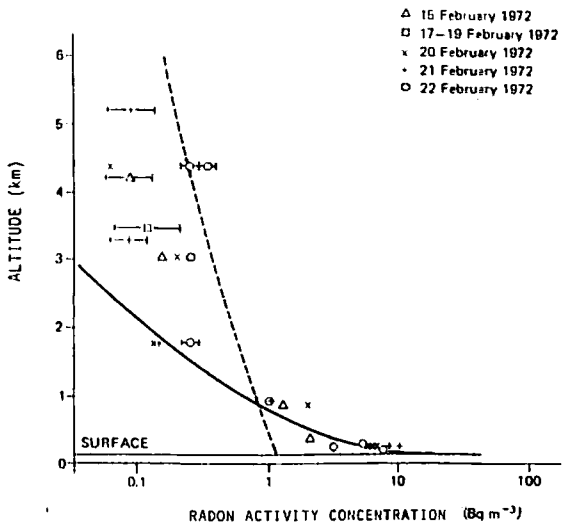

Figure XII. Radon concentration at different altitudes over the Yukon Valley in Alaska. The figure represents the average of 12 measurements over the Gulf and Alaska. The solid curve represents the theoretical profile of the exhalation rate of 0.33 atom $cm^{-2} s^{-1}$ and a strong inversion. The broken curve represents theoretical profiles with normal conditions of turbulence [L3]

one-half for every 700 m increase in altitude. This vertical decrease with height is greater than theoretically expected from the air mixing conditions.

69. Even if some measured radon levels do agree with the models described above, the models should only serve as a guide to the understanding of radon levels. They are not adequate to explain all the variations in radon levels with geographical place, altitude and meteorological conditions. In practice, the radon exhalation rate varies with geographical location and the land surface is not unlimited, as the theory assumes.

70. Studies of the correlation between radon concentrations in air and meteorological conditions in different environments in France have been reported [F8, F9, G20]. Measurements of radon concentration at ground level during several months in combination with acoustic sounding measurements give a reliable method for the monitoring of vertical stability above a site [G21]. Radon concentration has also been used as an atmospheric tracer to follow air mass movements in urban pollution studies [C19].

71. Because of the short half-life of thoron, there are substantial difficulties in measuring this gas in the presence of radon in air. Therefore, actual data on thoron distribution with height over a few hundred metres to compare with the models are not available. Measurements on ^{212}Pb in air are sometimes incorrectly reported as thoron concentrations. As shown in Figure XI, equilibrium does not occur at ground level under normal turbulence conditions (NNN). Only in case of strong inversions (not shown in the figure) does equilibrium occur at ground level (1 m above ground) [J3]. There are however some measurements [D4, I5] of thoron (Figures XIII, XIVa) showing the vertical profile up to a few metres. Figure XIVb shows the corresponding profile for radon. The lower values observed during the day are caused by greater turbulence in daytime than at night [J5]. The results illustrated in these figures may depend on local factors and in general are not applicable to all sites and under all conditions.

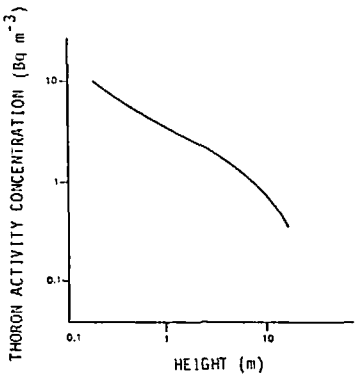

Figure XIII. Vertical profile of thoron in the atmosphere for wind speeds of 4 to 12 m s^{-1} [D4]

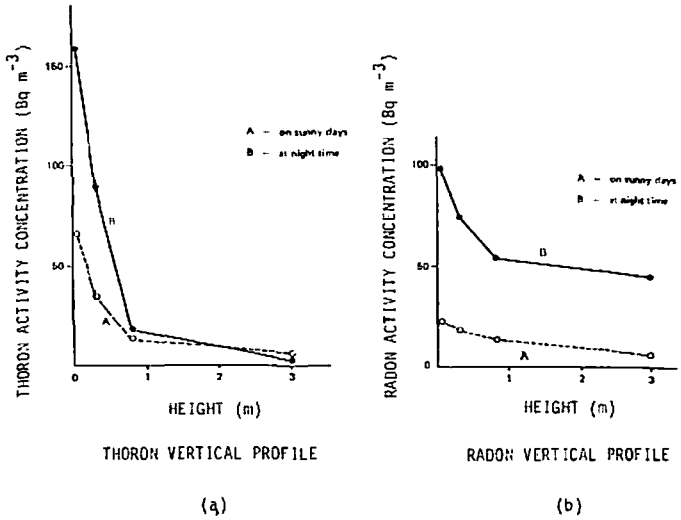

Figure XIV. Vertical profile of thoron (a) and radon (b) concentration near ground level [I5]

72. A great discontinuity in the transfer of radon to air occurs at the boundaries of large land surfaces, e.g., a continent. Owing to the small radon emanation from sea water it is to be expected that the radon concentration in surface air near the coast should be much smaller when the wind blows from the sea than when it blows from the land. This effect is evident during sea breeze conditions in the day time when low radon levels occur, while off-shore wind conditions during the night usually bring higher radon levels [M15, S12].

73. Under conditions of constant wind velocity from the sea the growth of radon concentration near ground level at increasing distances from the coast is determined by the exhalation rate, local turbulent mixing and the radioactive decay but in practice it cannot be predicted by current models. Even at distances of several kilometres from the coast variations caused by wind direction occur, indicating a degree of non-equilibrium in the growth of radon concentration [M15].

74. With constant offshore wind velocity the radon and thoron concentration in air above the sea still decreases at increasing distances from the coast. This decrease is mainly caused by radioactive decay. Because of its short half-life the concentration of thoron decreases rapidly to insignificant values over the sea. On the other hand, continental air can still be identified several thousands of kilometres from the coast by its radon content [P11].

75. The concentration of radon in air over the ocean at large distances from land depends on the direction of the prevailing wind. A low radon concentration in "marine" air (some tens of mBq m^{-3}), may rapidly increase by an order of magnitude or more in case of a change to "continental" air. Such "radonic storms" have been observed repeatedly [W8, L1]. Radon has therefore been used successfully as an indicator of the continental contribution to over-ocean air in studies on air pollution [L5, L4, W9, W10], and air transport mechanisms [W12].

76. Radon measurements during shipboard cruises show very low radon concentrations in maritime air (from less than a few mBq m^{-3} to about 0.1 Bq m^{-3}) far from land. In smaller seas like the Mediterranean the radon concentration in air may be of the order of 1 Bq m^{-3}, indicating that this air contains much more continental radon than that over the open oceans [L10]. Along the coasts of large continents at 10–100 km distance, the radon concentration may still be of the order of 1 Bq m^{-3}. The variations of the radon concentrations in air have also been demonstrated in the Arabian Sea and the Bay of Bengal [R10, E3]. The level of radon concentrations depended not only on the distance from land but also on changes in monsoon activity, causing varying degrees of interaction of continental and maritime air. Levels of ^{212}Pb are generally very low (less than 0.1 mBq m^{-3}) [R10].

77. The radon concentration over an island depends on the radon exhalation rate from the ground and on the meteorological conditions. With no wind the radon levels are caused only by radon exhalation from the island itself. In windy weather the radon levels may be increasing inland, in the wind direction, and partly consist of radon from the island itself and partly of radon from a distant continent. This has been observed in measurements on Hawaii, where about 25% of radon on the lower slopes of the island was attributable to distant continental sources [M15].

78. The time-variation of radon and thoron concentration in the surface layer of the atmosphere depends on the variation of the radon and thoron exhalation rates and the vertical and horizontal dispersal of radon and thoron. Maximum exhalation is usually observed during the summer and minimum in the winter. However, vertical turbulent mixing is also higher in spring and summer, resulting in a decrease of the radon and thoron concentration at the surface. In autumn and winter this vertical exchange is smaller and inversions are frequent. The effect of decreased mixing may greatly outweigh the decreased exhalation rate, resulting in increased radon and thoron concentrations in autumn and winter, and the overall effect may be a seasonal variation with a minimum radon and thoron concentration in the spring and summer and a maximum in the autumn and winter. This has been observed by several investigators [M1, B6, R4, M5]. However, recent studies performed at Chester, New Jersey, United States, of the variation of radon concentration in air show a seasonal maximum in summer and a minimum in winter. This seasonal variation has been consistent throughout three years. Since the variations

are out of phase with the normal pattern of the distribution of inversion strength and there is a poor correlation between the radon exhalation rate and radon concentration in air (at 1 m) no obvious explanation has yet been found for these seasonal variations [F5]. Figure XV shows the results, including studies on the

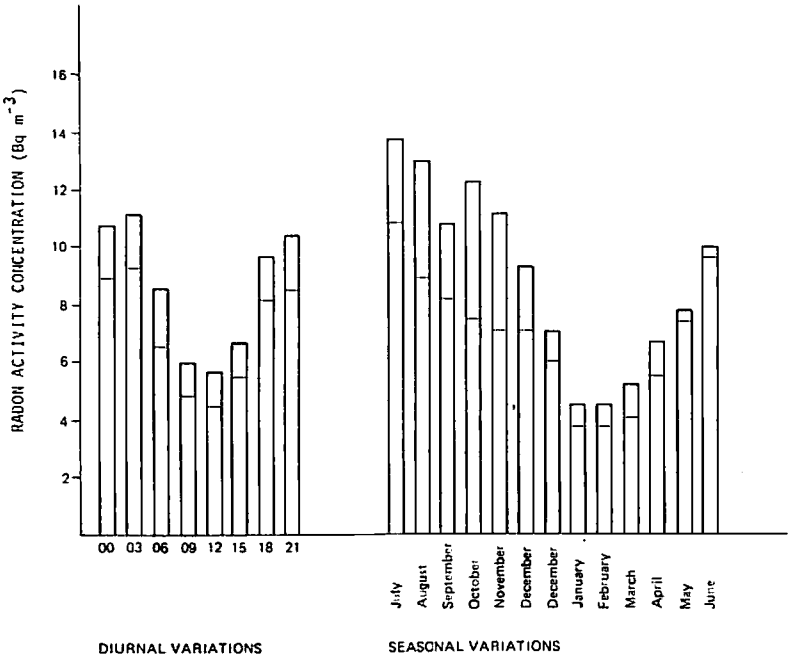

Figure XV. Variations in radon concentration. The diurnal variations show the annual means for the eight three-hour periods. The seasonal variations show the overall means for the thirteen four-week periods. The top lines in each column show the variations of the average for each observation period (1977/78, 1978/79, and 1979/80) [F5]

diurnal variations. The hourly data and three-hour averages were found to be log-normally distributed. The arithmetic mean and the median values (within parentheses) were 8.1 (6.3) Bq m^{-3} for 1977–1978, 8.5 (6.7) Bq m^{-3} for 1978–1979, and 7.0 (6.1) Bq m^{-3} for 1979–1980. Few thoron measurements exist to demonstrate its variations, but measurements of ^{212}Pb may indicate a similar behaviour by thoron. Examples of the variations of ^{212}Pb concentrations in air are presented in Figure XVI [B6].

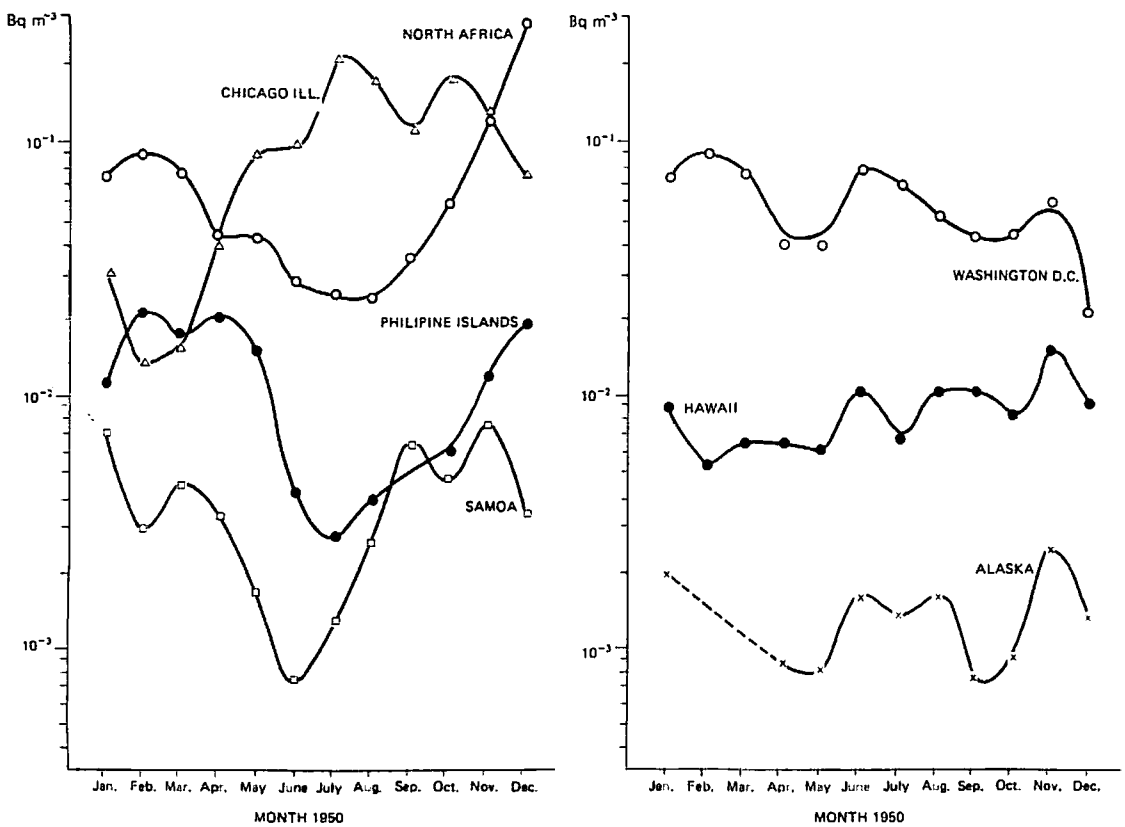

Figure XVI. Variations of the ^{212}Pb activity concentration in air, 1950 [B6]

79. Other extensive measurements in the United States of radon and thoron daughters were made over a period of 4 years in Cincinnati, Ohio in the early 1960s [G12]. Daily and seasonal variations were studied. Minimum radon daughter concentrations occurred in March and maximum values between August-October. The maximum levels were not so extended in time as they were at Chester, but the general shape is in fairly good agreement.

80. Several measurements of diurnal and seasonal variations of radon concentration in air in France have been reported [F20, D13]. The diurnal variations show a minimum at noon and a maximum at midnight and a decrease with increasing altitude (0–100 m) [D13]. Seasonal variations of thoron and thoron daughters at ground level have also been measured [F21] and show a maximum in March-April and a minimum in December-February. The variations were within a factor of ten and the concentrations of thoron lay in the range 2–20 Bq m^{-3} for thoron and 0.1–1 Bq m^{-3} for thoron daughters. Measurements of seasonal and diurnal variations of radon, radon daughters and ^{212}Pb have also been reported from Spain [G22, G23]. Maxima were observed in the winter and minima in the summer and the concentrations were 2–3 times lower in the afternoon than in the morning.

81. Another example of strong seasonal variations was found by Rangarajan et al. [R4]; it is illustrated in Figure XVII. Since these measurements were made on

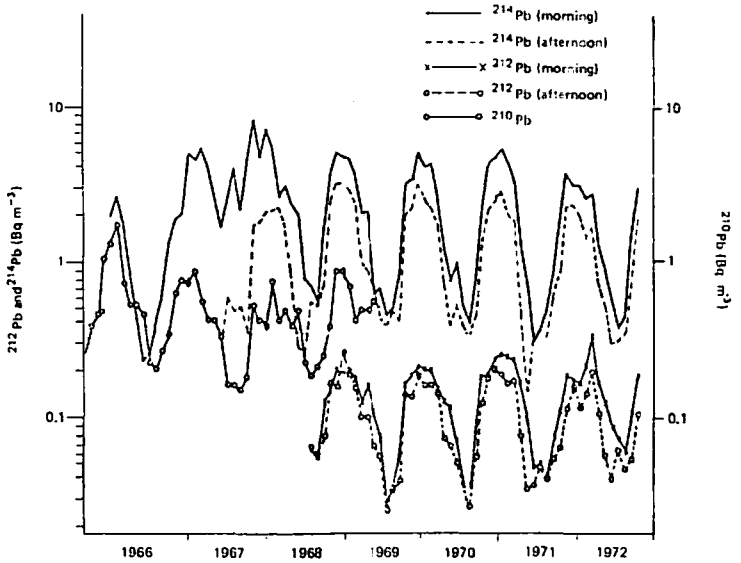

Figure XVII. ^{214}Pb, ^{212}Pb and ^{210}Pb activity concentrations in surface air in Bombay (monthly mean concentrations) [R4]

^{214}Pb and ^{212}Pb, the variations do not quite represent radon and thoron variations; nevertheless, they are of interest because they are a consequence of several contributing factors. The minimum in the spring and summer is caused by increased turbulent mixing, a predominant south-west wind over the Indian Ocean, higher mean wind speeds and intensive rainfall which affects both the ^{214}Pb concentration in air and the exhalation rates. Seasonal variations are less pronounced in areas with cold winters and an early snow cover, which greatly reduces the exhalation of the two gases. This has been demonstrated by the results of measurements made in Finland [M5] and at a high altitude station in India [R4]. Diurnal variations are mainly caused by variations in turbulent mixing.

82. Radon and thoron concentrations reach their maximum in the early morning and their minimum at noon or in the afternoon [R4, F5] and the variation is generally less than one order of magnitude. The results of repeated measurements are shown in Figure XV [F5]. Diurnal variations of radon concentration do not occur over the oceans [E3].

83. Dispersion of radon released from point sources such as geothermal power plants, mine ventilation outlets, etc., or from sources with a small area extension follows the normal dispersion kinetics of gases. If the source may be considered approximately as a point source, the concentration in the environment may be estimated by using the ordinary dispersion formula for atmospheric diffusion.

84. The average concentrations per unit release rate (also called "dispersion coefficients") at various distances from a "point" source have been calculated for normal conditions in the United Kingdom as mean concentrations weighted for the frequency of different meteorological conditions [B12, C20]. The results (based on [C20], fig. 36) are shown in Figure XVIII, curves 1a, 1b and 1c. The release point is assumed to be 0, 30 and 100 m, respectively, above ground and the deposition velocity to be zero. Radon releases from extended sources such as tailings can be considered as a number of small point sources distributed over the area of interest. The dispersion of radon from such sources has been calculated for two area sources, one 1 x 1 km^2 (10^6 m^2) and another 100 x 100 m^2 (10^4 m^2). The surface was divided into 250 and 100 equal elements, respectively, and the resultant dispersion coefficient at different distances from the outer frontier of the surfaces was calculated using curve 1a in Figure XVIII for each surface element. The values of the horizontal dispersion parameter σ_y have been calculated assuming a Pasquill D weather category and the formula $\sigma_y = 0.1471\ x^{0.9031}$, where x, in metres, is the distance from the source. The results are presented in Figure XVIII, curves 3 and 2, respectively.

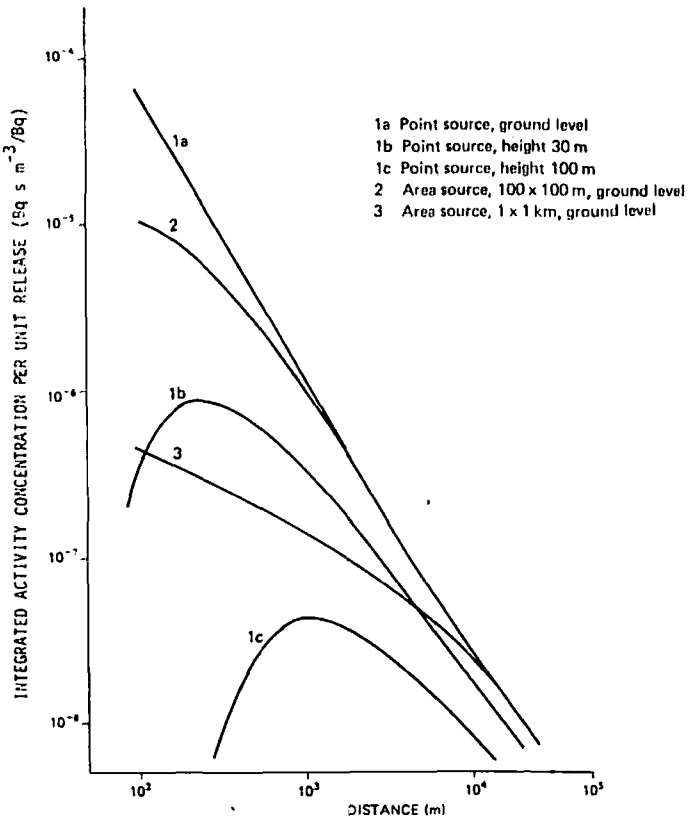

Figure XVIII. Integrated activity concentration of radon per unit release at various distances from point and area sources, calculated for normal conditions in the United Kingdom. The values are given as mean concentrations weighted for the frequency of different meteorological data as given in [C20]

85. The average concentrations per unit release rate taken from Figure XVIII curves 1a and 1b, for point sources are approximately inversely proportional to the distance x raised to the power p. If the activity concentration $\chi_a(x)$ at distance x is expressed relative to the concentration $\chi_a(x_o)$ at a reference distance x_o, $\chi_a(x)$ is given by

$$\chi_a(x) = \left(\frac{x}{x_o}\right)^{-p} \chi_a(x_o) \qquad (19)$$

With p = 1.5 the formula describes satisfactorily the dispersion and relative concentration at distances beyond 1 km from a point source (curve 1a, Figure XVIII) at ground level, with the reference distance x_o = 1 km. For releases from a height of 30 m or more a value of p = 1.2 approximates more closely the dispersion curves at distances beyond 1 km.

F. DISPERSION OF RADON AND THORON DAUGHTERS

86. The atmospheric diffusion model of Jacobi and André has also been applied to radon and thoron daughters [J3]. In the case of radon, the concentration at a given point and its vertical distribution are greatly dependent on the conditions of turbulence in the troposphere. At 1 m from the ground the relationship between the activity of radon daughters and radon depends on the turbulence but above 100 m the model predicts approximate radioactive equilibrium. This is also the case for ^{212}Bi relative to ^{212}Pb. Irrespective of turbulence conditions there is no general equilibrium between thoron and its daughters. Other similar models by Staley [S20] and Birot et al. [B5] include time variations for diffusion and dispersion by advection. Shapiro et al. have developed these models with some modifications of the boundary conditions [S7].

87. Measurements in the lower atmosphere indicate deviations from secular equilibrium for radon daughters. Shapiro et al. [S7] have measured the ^{214}Bi/^{214}Pb ratio at 20 m under various atmospheric conditions. They have found that afternoon samples taken for a period of several months had ^{214}Bi/^{214}Pb activity ratios from 0 to 2.2 with a mean value of 0.67 (morning samples had a mean value of 0.70). The predicted range of the ^{214}Bi/^{214}Pb activity ratios according to Jacobi and André [J3] is 0.68–0.98 at a height of 20 m. "Abnormal" ratios greater than 1, which were all associated with winds greater than 4 m s^{-1} are outside the framework of any simple theory since different mechanisms must be responsible for these abnormal conditions. Possible explanations could be selective removal of radon daughters (e.g., by washout) and different responses to advection owing to attachment to aerosols of different size ranges [S8]. Other measured values of the relative concentrations of radon daughters range from 0.8 to 1 for heights between 1 and 90 m (increasing with height) [H15, H16, G11].

88. Changes in the radon daughter concentration profiles may influence the natural gamma-ray background. Thus, after heavy rainfall there is a depletion of radon daughters in air and a consequent increase of radon daughters on the ground. The increase in external absorbed dose rate in air ranges from 0.5 10^{-2} to 4 10^{-2} μGy h^{-1} [B3, F2], to be compared with a "normal" background of 5 10^{-2} μGy h^{-1} (Annex B).

89. The occurrence and behaviour of the relatively short-lived radon daughters (^{218}Po, ^{214}Pb, ^{214}Bi and ^{214}Po) in the atmosphere are strongly dependent on the build-up from radon and by their short half-lives. Except for the circumstance of rainout, the radioactive decay time of these nuclides is short compared with any other removal mechanisms.

III. RADON AND THORON IN INDOOR SPACE

90. There is in principle no basic difference in the formal treatment of radon and thoron in a room or in the open air. However, there are other sources and factors which warrant separate discussion. The indoor space may be a house, apartment, mine, cave, tunnel or any other closed space, with or without ventilation. As for outdoor air, the levels of thoron and thoron daughters are low in comparison with those of radon and radon daughters. There are also very few data reported in the literature for thoron and its daughters and for this reason the emphasis of this chapter will be on radon and its daughters.

A. SOURCES

91. Radon and thoron in indoor space originate from emanation of the gases by the walls, floor and ceilings which are constructed of building material, rock or soil, by release from materials brought into the room, such as radon-rich water or gas and by radon or thoron in the inlet air, which may in turn have a normal concentration of the gases or an increased concentration derived from sources outside the room. The primary sources are in all cases ^{226}Ra or ^{224}Ra.

92. The radium and thorium concentration in building materials vary for different kinds of material, depending on their origin. Some published data are found in Table 10. More detailed information for building materials in Nordic countries is given in Table 11. The values in the tables are mean activity concentrations. Some materials such as phosphogypsum, aerated concrete with alum shale and uranium mine tailings, are known to be much more radioactive than others: some of them are used only in exceptional circumstances. Materials with low activity concentrations include wood and natural gypsum. The average values of radium and thorium concentrations in the above tables are of the order of 50 Bq kg^{-1}. In general the activity distribution of samples of individual building materials reflects the activity distribution of constituents of the building materials from different parts of a country. In an investigation of radium content of gravel in 23 of 24 provinces in Sweden, the standard deviation of all 146 samples was 30% and the range was within 0.5 and 2 times the average. The standard deviation for samples from each province was typically 20% [H1].

93. The highly radioactive materials are with few exceptions by-products from other processes. Phosphogypsum is produced in the manufacture of phosphoric acid from sedimentary phosphate ore; red mud bricks contain a waste product from the production of alumina from bauxite; blast-furnace slag is a by-product of iron production; fly-ash is a waste product from the combustion of coal; tailings are wastes from uranium mining and milling. In recent years there has been increasing interest in using waste products as substitutes for natural products in building materials. However, because of the relatively high radioactive contents their use is frequently subject to regulation [W20].

94. Alum shales in Sweden have been used for several decades in the manufacture of aerated concrete and for some years they provided about one-third of the market for building materials in Sweden. Production was stopped completely in 1979. The lower radium content in aerated concrete manufactured from alum shale between 1974 and 1979 results from a reduced content of alum shale.

95. The soil beneath a house can be a significant source of radon for individuals [O5]. This may be specially true if there are cracks in the base structure. The radium concentration in soil and rocks varies widely in different countries and in different regions of a country. Special areas having enhanced or naturally high radium concentration are some reclaimed lands in the United States following phosphate rock strip mining [U2], tailings from a radium factory in Australia [A8], uranium mine tailings in Colorado, United States [C16], and areas generally adjacent to uranium mining. The contribution from radium in the soil to the radon concentration in a house depends on the emanating power and the thickness and tightness of the base structure. In residential buildings in New Jersey and New York, United States, the radon exhalation rate per unit area from cellar floors has been determined. The average exhalation rate per unit of radium activity concentration (Bq m^{-2} s^{-1} per Bq Ra g^{-1} soil) for 16 houses was 0.07 ± 0.06 with a range of 0.007–0.21 [G1]. The thickness of the concrete floor required by local building codes is about 10 cm. The wide variations observed may have been due to differences in emanating power of the underlying soil. There may also have been a contribution from the concrete floor itself and from deeper layers of the soil. Bare soil in unpaved crawl spaces has been identified as a major radon source in some houses in the United States [R11]. In Sweden the soil under the house has recently been proved to be a more significant source of radon than building materials, both in cases of very high individual radon concentrations and for general radon exposure of the public [R15]. This is also confirmed by the general observation that the radon concentrations in high floors of multi-storey buildings tend to be lower than in ground floors.

96. Another source of indoor radon is radon-rich water. The release of radon from water to air depends on the circumstances in which it is used and the resulting radon concentration in air is determined by the ventilation rate. The radon release during typical household activities has been studied [P2] and for a house with volume 340 m^3 and ventilation rate of 1 h^{-1} the average air-to-water concentration ratio has been estimated to be 0.4 10^{-4}. The amount of water used each day was assumed to be about 500 l per person. The air-to-water concentration ratio in dwellings in Finland has been measured to be about 10^{-4} [C3]. In other studies the ratio has been calculated to be 1.5 10^{-4} if full desorption of radon in water is assumed [N2] and 10^{-4} by another research team [D14]. In Annex B of the UNSCEAR 1977 report [U6] the ratio was calculated to be 2 10^{-4}. The ratio has also been expressed as a formula [G5]

$$\frac{\chi_{a,Rn}}{\chi_{w,Rn}} = \frac{\sum_k F_{a,Rn,k} V_{w,k}}{24 \lambda_v V} \qquad (20)$$

where $\chi_{a,Rn}$ and $\chi_{w,Rn}$ are the radon concentrations in air and water, respectively; $V_{w,k}$ is the volume of water used daily for various applications k; $F_{a,Rn,k}$ is the fraction of radon released to air for each application k; λ_v is the ventilation rate of the dwelling h^{-1}; and V is the volume of the dwelling. If $\sum_k F_{a,Rn,k} V_{w,k} = 1$ m^3/d, $\lambda_v = 1$ h^{-1} and $V = 200$ m^3, the ratio is about $2\ 10^{-4}$. Using this ratio and taking typical values of the radon concentration in air (10–100 Bq m^{-3}), it is apparent that radon in water is a significant source for radon in houses only when the radon concentration in water is of the order of 10 kBq m^{-3} or more.

97. Natural gas containing radon may also be a source of significance. The industrial processing of raw natural gas involves the removal of impurities and separation of hydrocarbons. Some of these hydrocarbons (mainly propane) are bottled under pressure for sale as liquefied petroleum gas (LPG), while the others are used for fuel or as chemical feed stocks. When either gas is burned in houses, radon is released and enhances the radon level indoors [G6]. The contribution from this source depends on the amount of gas used, the original radon concentration and the elapsed time between production and consumption.

98. Radon enters the natural gas in the earth by diffusion from radium deposits. Uranium minerals are often associated with carbonaceous deposits and radon in natural gas is therefore not unexpected. Radon diffuses through the rock along with the natural gas to collection wells, from which the gas (and radon) is transported to the gas processing plant. The radon concentration in raw natural gas at production wells varies from undetectable values up to levels of the order of 50 kBq m^{-3} [U6, H8] (see Table 12).

99. The processing of raw natural gas results in the transfer of 30–75% of the radon from the natural gas into the LPG. The remaining radon may be further diluted if the gas becomes mixed in transit with gas from other wells with low radon concentration. During transport through long transmission lines and storage in reservoirs the radon concentration in natural gas in the distribution system is reported to lie within the range of about 0.04–2 kBq m^{-3} [W17, J8]. The average value for the United States is estimated to be 0.7 kBq m^{-3}, except for four States which have an average of about 2 kBq m^{-3} [B1].

100. The gas is used for kitchen appliances and domestic heating. Taking representative consumption levels of 0.8 m^3 d^{-1} and 2.8 m^3 d^{-1}, respectively, and a mean radon concentration of 0.7 kBq m^{-3}, the mean activity introduced in homes is 2500 Bq d^{-1} (with a range of 130–6500 Bq d^{-1} [J8]) if the appliances are unvented. If the combustion products are vented outside the house, this radon source is negligible.

101. The radon concentration in LPG depends on the radon concentration at the well, the transit time from the well to the processing plant, the composition of the inlet gas and the type of processing. The overall effect is an increase in the concentration of radon in the end product LPG and an enrichment factor of 10 ± 5 with respect to raw natural gas has been reported [G6].

102. However, the radon concentration in LPG delivered to the consumer depends, in addition, on the time delay in a complex network of supply, transit, storage and delivery facilities which vary in different countries and different parts of a country. Because of decay of radon the concentration may be lower in remote districts than in districts close to the processing areas. Seasonal variations may also occur owing to different storage times, with a minimum radon concentration in the winter when gas consumption is high. Seasonal variations in concentration of about a factor of 2 have been found [G6].

103. During storage of LPG in domestic tanks the radon concentration is further reduced by decay. With monthly deliveries the average concentration of radon at the point of gas consumption is about 20% of the concentration at delivery.

104. The magnitude of this radon source in homes is estimated by combining the radon concentration in LPG delivered to homes, the quantity of LPG used and the decay factor due to storage in domestic tanks. In one investigation in the United States the values of these quantities have been found to be the following [G6]: radon concentration = 0.4–5.6 kBq m^{-3}; quantity of LPG = 0.3 m^3 d^{-1} for cooking ranges and 1.1 m^3 d^{-1} for space heaters; decay factor = 0.18. For normal consumption of LPG, the range of radon activity introduced into homes is then approximately 100–1500 Bq d^{-1} with a customer-weighted average of about 200 Bq d^{-1}. The use of LPG is however small compared with natural gas and, on a national basis, natural gas is a 10–100 times greater radon source than LPG.

105. The relative significance of different radon sources for a reference house, defined as having a volume of 200 m^3 and an inner surface area of 350 m^2, are presented in Table 13 (the values refer to data in this report). For thoron and thoron daughters, the only significant sources are building materials and the outside air. The thoron exhalation from building materials may be up to two orders of magnitude higher than that of radon, but in practice wall paper and other sealants may reduce the thoron exhalation considerably.

106. In mines, tunnels, caves and other underground buildings the radon sources are rocks, soil and water. Faces of uranium ore in mines are apparently potential radon sources, although there are great variations in emanating power. Crushed rock in abandoned parts of a mine is also a significant radon source in non-uranium mines [S12]. Radon in water may often be a significant source. Drainage or use of large amounts of radon-rich ground water may cause radon release either locally or to the ventilation inlet air. This may be the case in mines, tunnels, caves, spas and underground hydroelectric power stations [S13]. With poor ventilation local radon and radon daughter concentration in air may become very high if the radon concentration in water is 0.1–1 MBq m^{-3} or more [S12].

B. RADON AND THORON DIFFUSION AND EXHALATION

107. The diffusion through and exhalation of radon and thoron from building materials, rock walls, etc., follow the principles described in paragraphs 56–62. The emanating power F_r varies for different materials. Normally the value of F_r varies between 1% and 10% although extreme values of 0.1% and 30% have been reported [P4, W4].

108. The diffusion coefficient in a concrete building material depends on the type of aggregates used in the

concrete, the water/cement ratio used in the mix and the curing conditions. The diffusion coefficient can be expressed as Δ_k or as $\Delta_{eff} = F_{build,ps} \cdot \Delta_k$, where $F_{build,ps}$ is the porosity. Δ_k is called the effective diffusion coefficient and Δ_{eff} the effective bulk diffusion coefficient. The presentation of diffusion coefficients in the literature is not always very clear on this point and misunderstandings arise easily. This problem is discussed by Culot et al. [C12]. Another name used in the literature for effective bulk diffusion coefficient is true diffusion coefficient.

109. Another source of error arises from the experimental conditions under which the diffusion coefficient is measured. By placing the material of interest in a closed vessel and measuring the equilibrium radon activity in the air, the estimated diffusion coefficient is lower than that corresponding to emanation into open air [J9]. This is due to the fact that the difference in partial pressure of radon in the pores of the material and in the air space of the vessel decreases with time and this influences the rate of diffusion.

110. The exhalation of radon and thoron from walls is dependent on the ^{226}Ra and ^{224}Ra concentration in the walls, the emanating power and the diffusion coefficient. The diffusion coefficient for building material varies by several orders of magnitude for different materials and values between 10^{-4} and 10^{-7} $cm^2\ s^{-1}$ have been reported [C12, J9, P8]. Changes of air pressure have been shown experimentally to influence the radon exhalation rate from concrete walls [M8]. On reducing the atmospheric pressure, the exhalation rate was found to increase linearly with the pressure drop, as seen in Figure XIX. This effect has also been found in uranium

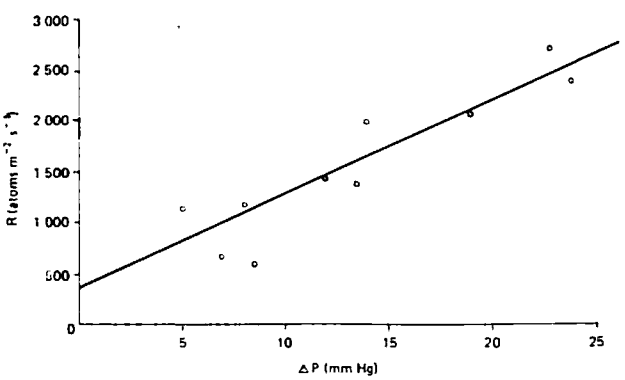

Figure XIX. Variation of the exhalation rate R as a function of the reduction of air pressure ΔP [M8]

mines and has been explained as the result of increased air flush through radon-rich cracks and fissures into the mine [P5, P6].

111. The exhalation rate of radon from building materials has been studied extensively. However, the values obtained are not always consistent and large variations are found for the same material and surface. There are obviously great experimental difficulties and factors influencing the measurement are not fully understood. Reported values of the radon exhalation rate per unit concentration of ^{226}Ra in building materials normally lie in the range of 10^{-6} to 10^{-4} Bq $m^{-2}\ s^{-1}$/(Bq kg^{-1}) with several values in the higher part of the range [G1, P8, J9, S25, M17, W4].

112. Radon emanation can be reduced by applying a sealant to the emanating surface. This is of particular interest for houses built on uranium tailings or other waste products. Although promising results have been achieved, there is not yet full acceptance of the methods proposed, partly for economic reasons and partly for uncertainties regarding the overall positive effect. A sealant may in itself cause harm by being toxic or electrostatic, etc. A possible negative effect is the increase in gamma radiation from the daughters trapped behind the sealant. This depends on the material and its thickness and may be as high as 10%. Data have been published on the qualities of some radon barriers [C14, H3] and on the experience gained in practical attempts to reduce radon and radon daughter concentrations indoors [C15]. By plastering the wall the radon exhalation may even increase if the radium concentration in the plaster is higher than that in the wall [W4]. By covering the walls with plastic materials such as polyamide, polyvinylchloride, polyethylene and epoxy paint (the thicknesses of which are of the order of 0.1 mm) or by painting three times with oil-based paints, the radon exhalation is reduced by one order of magnitude [E4, P13]. The effect of wall paper is always to decrease radon exhalation (e.g., 30% as given by [O3]), even if it is sometimes marginal. The reduction is probably higher for thoron, because of its short half-life.

113. The emanation of thoron from walls depends on ^{224}Ra concentration in the wall, the emanating power and the diffusion coefficients. Owing to the short half-life of thoron, the emanation may be considered as taking place only from the outer surface layers. There are very few measurements of the exhalation rate of thoron, because thoron daughters in houses are believed to be less important than radon daughters as a potential health hazard. There are also experimental difficulties in making such measurements. Experimental data have been reported [M9] on thoron exhalation rates from building materials, relative to exhalation rates of radon. Values of 0.1–0.4 $(\frac{\text{Bq of thoron}}{\text{Bq of radon}})$ were observed.

C. RADON AND THORON DISPERSION IN INDOOR SPACE

1. Indoor spaces other than tunnels

114. Assuming instantaneous mixing of radon or thoron in a room, there will be a homogeneous activity distribution and the concentration in a room can be found by solving the following equation

$$\frac{d\chi_a(t)}{dt} = R\frac{S}{V} + \frac{\dot{A}_k}{V} + \chi_{a,in}\lambda_v - \chi_a(t)(\lambda+\lambda_v) \quad (21)$$

where $\chi_a(t)$ is the radon or thoron activity concentration in the room at the time t; R is the radon or thoron activity exhalation rate per unit area; S is the emanating surface area; V is the volume of the room; $\dot{A}_k$ is the activity release rate of any other source in the room (water, gas); $\chi_{a,in}$ is the radon or thoron activity concentration in the inlet air; λ_v is the ventilation rate (h^{-1}); and λ is the decay constant of radon or thoron.

115. At equilibrium the concentration in the room is given by

$$\chi_a = \frac{R\frac{S}{V} + \frac{\dot{A}_k}{V} + \chi_{a,in}\lambda_v}{\lambda+\lambda_v} \quad (22)$$

In homes $0.1 < \lambda_v < 3\ h^{-1}$. Since for radon $\lambda = 7.6\ 10^{-3}\ h^{-1}$, $\lambda_v \gg \lambda$ and expression (22) takes the form

$$\chi_{a,Rn} = \frac{R\frac{S}{V} + \frac{A_k}{V}}{\lambda_v} + \chi_{a,Rn,in} \qquad (23)$$

As long as $\lambda_v \gg \lambda$ and $\chi_{a,Rn,in}$ is negligible, the radon concentration indoors is inversely proportional to the ventilation rate. As the ventilation rate increases from 0 to 0.1 and from 0.1 to 1 h^{-1}, the radon concentration decreases by a factor of 13 and 10, respectively. For thoron $\lambda = 45\ h^{-1}$ so that $\lambda \gg \lambda_v$ and expression (22) takes the form (A_k is assumed to be negligible)

$$\chi_{a,Tn} = \frac{R\frac{S}{V} + \chi_{a,Tn,in}\lambda_v}{\lambda} \qquad (24)$$

This means that the thoron concentration in room air is almost independent of the ventilation rate, as long as the contribution from outdoor air is small. The concentration of ^{212}Pb, on the contrary, is inversely proportional to the ventilation rate, down to about 0.5 h^{-1} and thereafter it approaches the activity concentration of thoron.

116. The numerical value of $\chi_{a,Rn}$ for radon in a reference house such as that described in paragraph 105 is

$$\chi_{a,Rn} = \left(2\ 10^{-3}\ Bq\ m^{-2}\ s^{-1}\ 3600\ s\ h^{-1}\ 1.75\ m^{-1} + \right.$$
$$\left. + \frac{4\ 10^3\ Bq\ d^{-1} + 3\ 10^3\ Bq\ d^{-1}}{24\ h\ d^{-1}\ 200\ m^3}\right)/0.5\ h^{-1} +$$
$$+ 4\ Bq\ m^{-3} = \frac{12.6 + 1.45}{0.5} + 4 = 32\ Bq\ m^{-3}$$

The relative importance of radon sources may be different in different parts of a house and in case of inhomogeneous mixing of air in the building the radon concentration will vary within the house. In the cellar the radon exhalation rate is often higher than in the upper floors. The ventilation rate is also often less and the radon concentration is therefore normally higher in the cellar than in the upper floors. Water as a radon source is of significance in the kitchen, bathroom and laundry. It contributes specifically to radon daughter exposure because it becomes available as a source when people are using it.

117. The variations of the radon concentration in a building are mainly dependent on the variations of the ventilation conditions and air exchange between rooms. These are caused by meteorological conditions (wind, barometric pressure, temperature) and by human activities such as opening windows and doors. Some of these effects are shown in Figures XX and XXI [S30]. There are also other variations caused by changes of the radon exhalation from surfaces. The variations can depend on pressure change (see paragraph 110) and a correlation between radon concentration in a room and barometric pressure has also been observed [J10].

118. Diurnal variations of the activity concentrations of radon, thoron and their decay products have also been measured [P14]. These variations follow the same pattern but the relative change is much smaller for thoron than for radon, as expected from equation (24) and as can be seen in Figure XXII. This figure also illustrates the effect of changes in ventilation conditions.

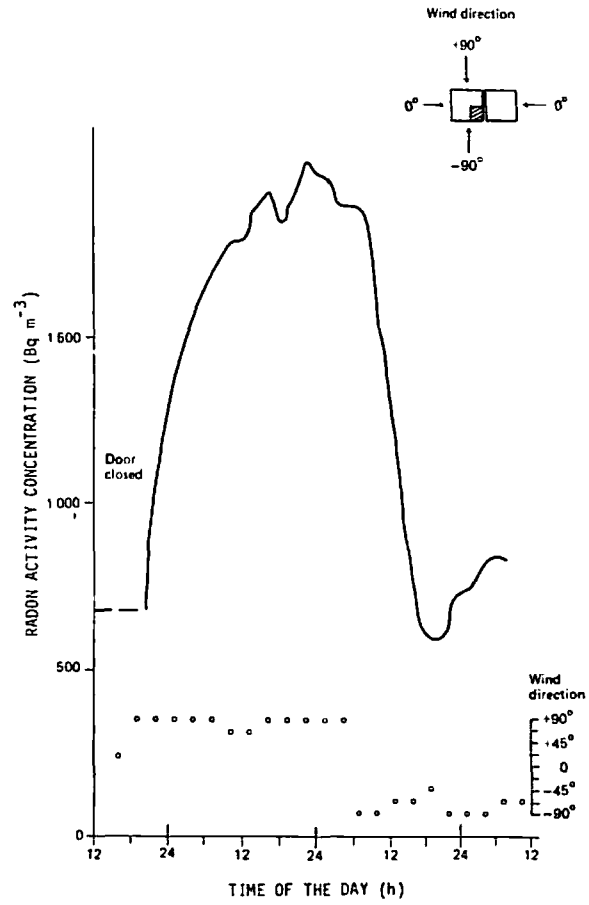

Figure XX. The dependence of the radon concentration in a detached house with a natural draught ventilation system on the wind direction. The door to the room was closed at the beginning of the measurement. (Measurements taken in winter) [S30]

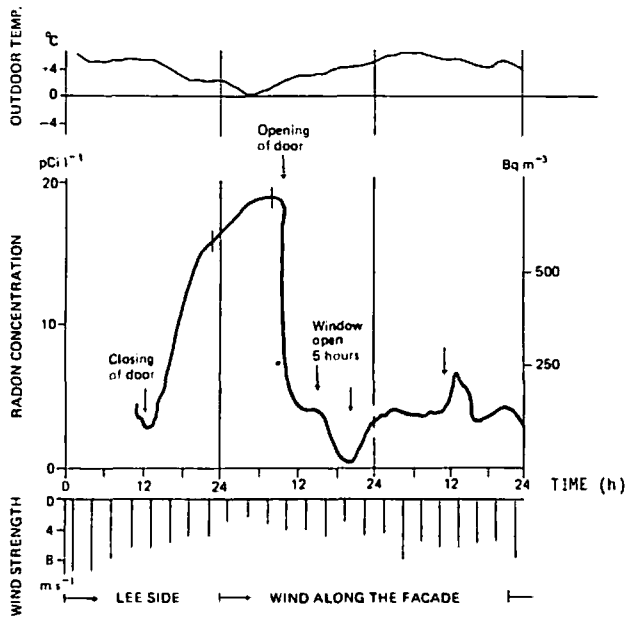

Figure XXI. Variation of the radon concentration in an apartment house built of elements of both ordinary concrete and aerated concrete based on alum shale and with forced ventilation system for the exhaust air. (Measurements taken in winter) [S30]

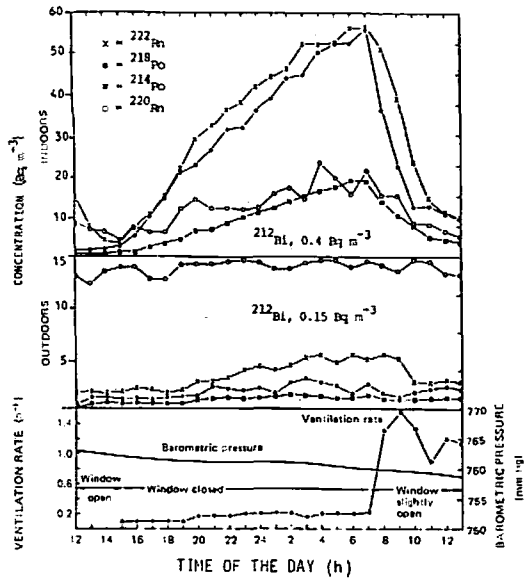

Figure XXII. Diurnal variation of concentration of radon, thoron, and their decay products indoors and outdoors of a typical dwelling [P14]

119. A study of the correlations between concentration of radon, radon daughters and thoron daughters and meteorological variables has been made in Innsbruck, Austria [S21]. About 750 measurements were made in 12 rooms and the concentration data together with 24 meteorological variables were used for regression analysis.

120. Tables 14 and 15 show the results of activity measurements in the houses, taken from this study [S21]. $\Delta\chi$ is the largest observed increase of the activity concentration within 24 hours. The mean radon concentration in the open air of Innsbruck was 13.3 Bq m^{-3} with a maximum of 96 Bq m^{-3}. The mean radon activity concentration in living and working rooms ranged from 28 Bq m^{-3} to 115 Bq m^{-3} with a maximum value of 276 Bq m^{-3}. The mean thoron activity concentration in all rooms ranged from 3.7 Bq m^{-3} to 41 Bq m^{-3}. About the same range of thoron concentrations were found in the open air near ground level (1.5–1 m). The observed concentrations of ^{212}Pb were all considerably lower than those of thoron, with mean values between 0.3 Bq m^{-3} and 4.7 Bq m^{-3}. The mean activity concentration ratio $^{212}Pb/^{220}Rn$ was 0.019 (range 0.009–0.49). Table 16 summarizes the results of the regression analysis for radon and thoron with the statistically significant meteorological variables. Other variables, such as mean cloud cover, daily maximum wind speed, change of temperature gradient between morning and noon and noon to morning, and all other variables with time scales greater than 24 h were found not to be significant.

121. Measurements made in Norway [S24] (Figure XXIII) also show the variation of radon concentration

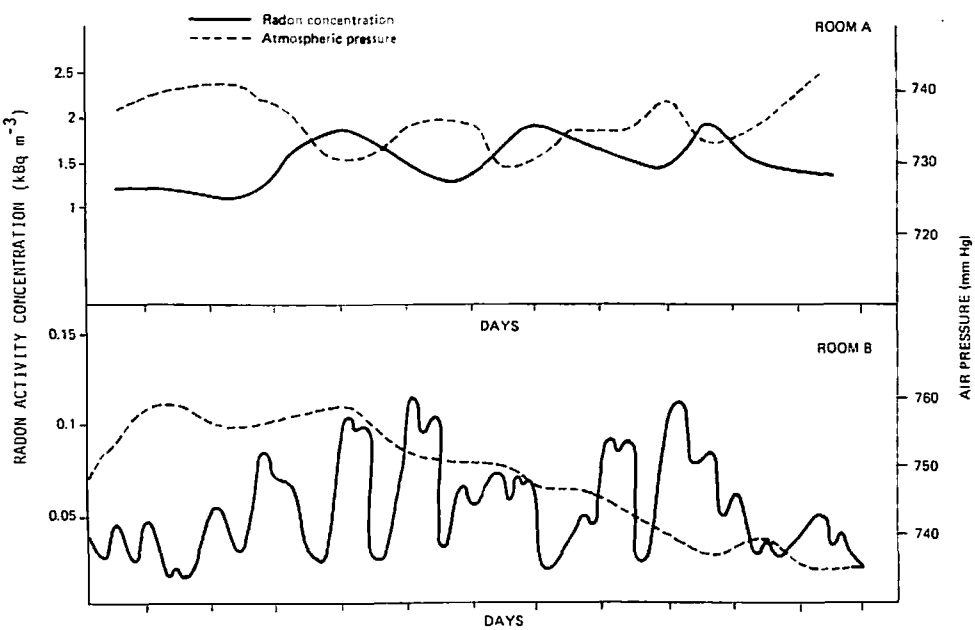

Figure XXIII. The variation of radon concentration in an unventilated room (A) and in an artificially ventilated room (B). Measurements taken in winter (A) and spring (B) [S24]

in rooms as a function of the atmospheric pressure changes. Room A had poor ventilation and room B had artificial ventilation which was different for day and night. This explains the great diurnal variations.

122. In houses built with a crawl space or with radium-rich waste products as filling material underneath the house, the radon concentration can change substantially with meteorological conditions [S31]. This is believed to depend on the variations in the pressure difference between the house and the crawl space and on the variation in the ventilation of the crawl space itself. In a special study of the influence of wind strength and direction [W2] it was found that in ordinary houses radon may decrease normally by a factor of 2–5 as the wind strength increases up to 10 m s^{-1}. This influence is particularly important when the wind flows along the facade of the room of interest. In houses built with a crawl space the radon decrease may be as much as a factor of 100.

123. Diurnal and seasonal variations in houses were studied over the long-term [S18, D1, S32, D2, H5, J11, M7, S44]. Diurnal variations depend on the climate, occupancy and kind of ventilation (natural or forced ventilation) all of which affect the air exchange rate. In measurements in the United Kingdom [D1] the radon concentrations showed maxima during the night. In Finland [M20] the average values of all measurements in 37 dwellings showed maxima in the early morning and minima at noon, as shown in Figure XXIV. In

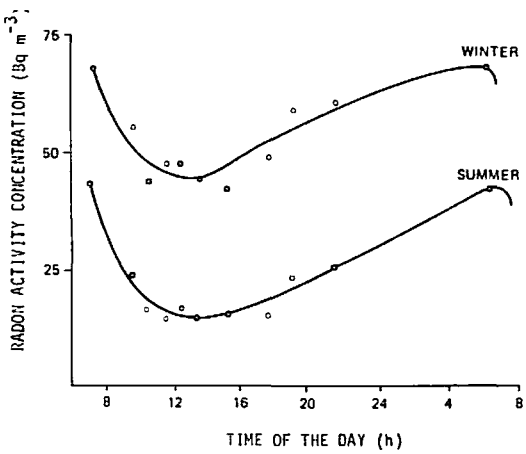

Figure XXIV. Diurnal variation of radon concentration in winter and summer [M20]

measurements made in the United States [S44] the maximum values were found in the morning and minimum at night. These diurnal variations occurred because of the use of cooling units during the nights [S44]. Variations by a factor of 10 or more between the minimum and maximum values were reported. However, the daily average values of the radon concentration during a week normally vary much less, within ± 50% of the weekly average. These observations emphasize the need of continuous measurements or of several samples over at least 24 hours in order to obtain a representative value of the mean radon concentration in a house. If the radon concentration indoors is of the same order of magnitude as that outdoors, the same diurnal variations occur indoors as outdoors [H5]. The variations found illustrate the difficulties in obtaining a representative value for radon and thoron daughter exposure. Some of the uncertainty derives from the fact that only the levels occurring when the house is occupied determine the exposure, while levels at other times are irrelevant. This is discussed in [S44].

124. There are very few measurements of the seasonal variation of radon concentration in houses. In New York City during a period of two years (1972–1973), the seasonal variation amounted to a factor of 3 between a maximum in summer and a minimum in winter, i.e., the variations were within ± 50% of the yearly average [F3]. A few measurements in New Jersey comparing the radon activity concentrations in the basement of a house in winter and summer indicate that 30% lower values occurred during the summer [S44]. In another study in Austria over six months, a minimum was obtained in May and a maximum in January. The variations of the monthly means were within ± 30% of the overall average. The maximum in winter depended on inversion outdoors [S21].

125. If all relevant factors were known quantitatively, it would be possible to determine the radon concentration indirectly by measuring the exhalation rate and the ventilation rate. However, the radon sources are not always easily identified and the ventilation rate may vary unpredictably due to human activities. Under controlled conditions it is possible to obtain good agreement between calculated and observed values [O6]. In 16 residential buildings in New Jersey and New York measurements were made, predominantly in cellars, of exhalation rate, ventilation rate and radon concentration [B10]. By taking the relevant factors into account, the correlation found between the calculated and measured radon concentrations was very good (correlation coefficient 0.94), as shown in Figure XXV [B10]. Figure XXVI shows the estimated variation of

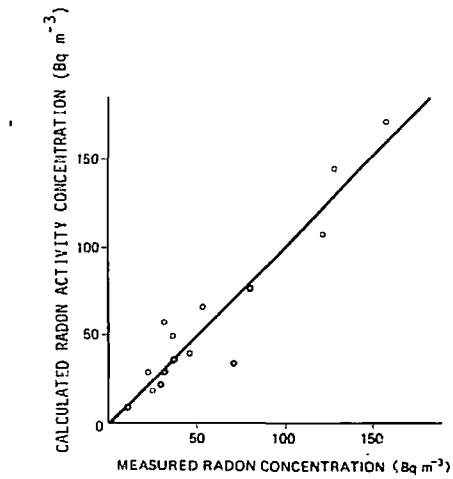

Figure XXV. Calculated radon activity concentration versus measured radon concentration in cellars [B10]

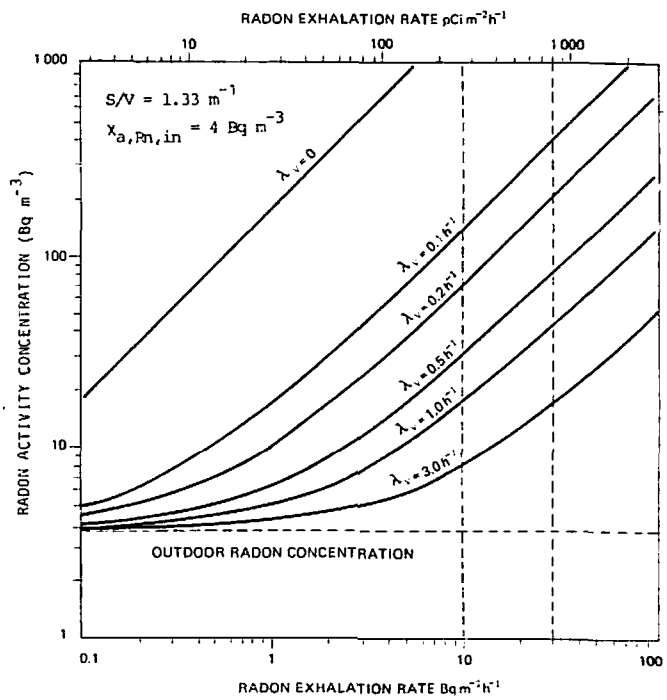

Figure XXVI. Radon activity concentration in room air as a function of the radon emanation rate for different values of the ventilation rate. The region marked with vertical broken lines corresponds to measured emanation rates from concrete [M17]

the radon activity concentration as a function of exhalation rate from building materials for various values of the ventilation rate [M17].

2. Tunnels

126. In principle, equation (23) for radon concentration in air is also applicable to mines and other underground spaces. However, owing to the great lengths of the tunnels in a mine, it is inappropriate to assume instantaneous mixing and homogeneous distribution of radon in the whole tunnel. Equation (23) may therefore be written in the form

$$\chi_{a,Rn}(x) = \frac{R\,p\,x + \dot{A}_k}{v} + \chi_{a,Rn,in} \qquad (25)$$

where R is the radon exhalation rate per unit area in the mine; p is the peripheral length of a section through a mine tunnel; x is the distance along the mine tunnel; $\dot{A}_k$ is the radon release rate for a source in the tunnel (e.g., radon-rich water); v is the volumetric air flow rate; and $\chi_{a,Rn,in}$ is the radon concentration in the inlet air (which may have passed other mine areas and which may have been contaminated with radon).

127. When $\dot{A}_k$ and $\chi_{a,Rn,in}$ are small, the radon concentration increases continuously along the tunnel. However, the kind of ventilation system and the nature of the radon sources will greatly influence the level and changes of level of radon in a mine. Large radon release rates $\dot{A}_k$ from uranium faces or radon-rich water will be rapidly diluted and transported along the tunnel or in ventilation tubes. Where radon-rich ventilation air $\chi_{a,Rn,in}$ from abandoned parts of a mine is allowed to enter active mining areas, it may give rise to an additional and rather constant radon concentration along the tunnels. The increase in potential alpha energy concentration of the radon daughters increases with the distance x along the tunnel from the ventilation point, and is proportional to $x^{1.85}$ [G24].

128. Diurnal and seasonal variations in radon concentration also occur in mines. The diurnal variation is especially pronounced at the time of the year when the temperature difference outdoors and in the mine changes sign over 24 hours. The resultant effect is a minimum during the night and a maximum during the day [S14]. The variation has been found to be ± 20% of the daily average. The seasonal variations may be greater, ± 50% of the yearly average or more, with a maximum during the summer and a minimum during the winter, as can be seen from Figure XXVII [S14].

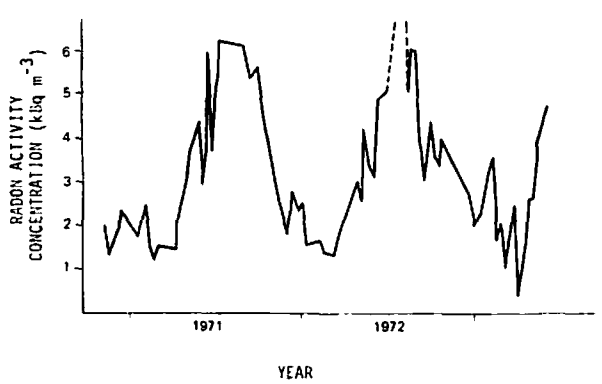

Figure XXVII. Radon activity concentration in the return air of Persberg Mine measured once a week [S14]

D. EQUILIBRIUM FACTOR F IN INDOOR AIR

129. A number of measured values of equilibrium factor F for radon daughters were given in Annex B of the 1977 report of UNSCEAR [U6]. No direct measurements on radon and radon daughters in houses with F values higher than 0.5 had been measured and the value chosen at that time was 0.5. Some new data have since been reported. In 21 New Jersey and New York residences the average fraction of unattached radon daughters was 0.07 and the F value for cellars was 0.52 ± 0.11, for first and second floors 0.63 ± 0.14, and for outdoor air 0.79 ±0.11 [G1]. The difference between F values for cellar and upper floors is not significant, but, if correct, could be explained by assuming that the cellar is the main radon source for the upper floors as well, and that the ventilation of the cellar is mainly determined by ventilation of these floors. The radon concentration in the cellar was on average 73 ± 44 Bq m^{-3} and on the upper floors 34 ± 26 Bq m^{-3}.

130. Measurements in apartments in the Federal Republic of Germany gave an average value of the equilibrium factor of 0.4 ± 0.1. The results were based on 38 measurements and Figure XXVIII shows the distribution of the results [W14].

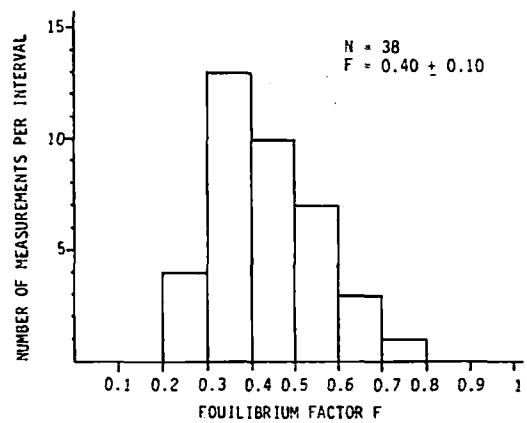

Figure XXVIII. Frequency distribution of equilibrium factor F for radon daughters in apartment rooms, based on 38 measurements [W14]

131. In an extensive investigation of the natural radiation in houses in Austria, radon and radon daughter activity concentrations were measured in 250 houses in Salzburg. The mean ratio $^{214}Pb/^{222}Rn$ was found to be 0.62 ± 0.08, corresponding to a value of F of slightly less than 0.62 [S22].

132. Measurements in single-family houses in Sweden [S33] have given an average value of F in 3 houses of 0.45 ± 0.11 (range 0.28–0.65 in different rooms) with a mean radon concentration of 470 Bq m^{-3}. The range of the distribution of F values in different rooms was narrower for each individual house than between houses and the standard deviation lay in the range 10–25%.

133. Another investigation concerned 12 single-family houses in Sweden [S34], 7 of which were built on waste piles from the milling of alum shale processing many years ago. With the exception of two houses, which were excluded because of extraordinary conditions, the average value of the equilibrium factor F was 0.60 ± 0.18 for the cellar and 0.60 ± 0.14 for the upper floor. In all houses the ventilation rate was measured by tracegas methods, and in Figure XXIX the values are

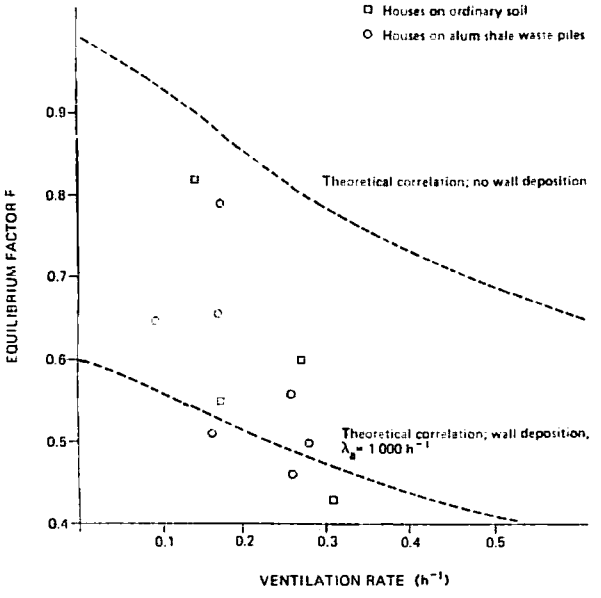

Figure XXIX. Equilibrium factor F in houses with different ventilation rates [S34]

plotted together with theoretical data taken from Table 5 and, also corrected for plateout, using a factor of 0.6 for λ_a = 1000 h^{-1} (see paragraph 34). There is no correlation between F and the ventilation rate in Figure XXIX and the F values are often higher than expected even for a rather dusty atmosphere. However, all values are less than predicted from Table 5, with no correction for wall deposition. Even if it is difficult to explain the high F values on a theoretical basis, there is experimental evidence that F values higher than those predicted do occur and are often higher than 0.5.

134. Other measurements, however, indicate lower values of F. In March Township, Ontario, Canada [L7] an average equilibrium factor of 0.38 was obtained. In measurements in 25 dwellings in Norway [S24] the mean value of F was 0.5 with a range of 0.3–0.8; in 35 dwellings in Finland [M20] the mean value of F was 0.47, with a range of 0.30–0.63 (Table 17), and in the United Kingdom a mean value of F = 0.5 ± 0.2 was observed from measurements in 200 houses [O7].

135. The equilibrium factor in mines is highly dependent on the ventilation rate and the distance from the radon source. It can be estimated from published data on radon and radon daughter concentrations. The results from 60 measurements in uranium mines in New Mexico and Colorado, United States [R3], corrected by Kotrappa and Mayya [K12], give an F value of 0.29 ± 0.16. Another compilation of several measurements in uranium mines in the United States gives an average value of F of 0.32 [H21] and in uranium mines in France an average value of F of 0.17 is used [P17]. In non-uranium mines average F values of 0.5–0.6 in Norway [M19, S54], 0.7 ± 0.1 in Sweden [S15], 0.7 in non-coal mines in the United Kingdom [S52] and 0.3 in Poland [D15] have been found.

136. In view of the variations in the F values found in the measurements there is no good reason to change the average value of 0.5 adopted in Annex B of the UNSCEAR 1977 report [U6] for houses, bearing in mind that this value may lead to an underestimate of the equilibrium equivalent concentration in poorly ventilated houses. For uranium mines an F value of 0.3 is probably applicable while for non-uranium mines an F value of 0.7 may be used. For many non-uranium mines the ventilation is good and F is lower than 0.7. In poorly ventilated mines however the value of F is likely to be higher than those given above.

IV. EXPOSURE-DOSE RELATIONSHIPS

A. INHALATION

137. The inhalation of ^{220}Rn—or ^{222}Rn—gas itself leads to a rather uniform distribution of these noble gases in the whole body. Due to the low solubility of these inert gases in body tissues the resulting effective dose equivalent from the inhalation of radon gas itself is normally small compared with the radiation dose from inhaled radon daughters; only in ore bodies with a very low equilibrium factor does the contribution from radon have to be taken into account. The following discussion is therefore concerned mainly with the estimation of the relationship between the exposure or potential α-energy intake of short-lived radon daughters by inhalation and the resulting dose in target tissues of the lung.

138. As mentioned in Annex B of the 1977 report [U6], in the special case of inhaled short-lived radon daughters the dose to the bronchial epithelium is considerably higher than the dose to the pulmonary tissue or the mean dose to the total lung. The cells at risk from the α radiation by radon daughters which are deposited on the surface of the bronchial airways and transported upwards in the bronchial tree by the mucociliary escalator are assumed to be located in the basal cell layer of the bronchial epithelium [I13]. Therefore the lung dosimetry for inhaled radon daughters has to consider two target tissues in the lung: the tracheobronchial basal cell layer (T-B) and the pulmonary epithelium (P), the latter including the alveolar region and the non-ciliated terminal bronchioles. In the cases of the longer-lived ^{222}Rn daughters ^{210}Pb and ^{210}Po, and of the ^{220}Rn daughter ^{212}Pb, a considerable fraction of the activity deposited in the respiratory tract is transferred to tissues other than the lung, particularly to bone and kidney. The dose to these other tissues can be evaluated by applying the dose assessment models for internal exposure described in Annex A.

139. The analysis of the dose distribution in the respiratory tract from inhaled radon daughters proceeds from the calculation of the equilibrium activity distribution, taking into account the deposition pattern, the mucociliary clearance in the bronchial tree, the possible uptake and retention in epithelial tissues and the transfer to blood. An important parameter for the evaluation of the dose to the bronchial basal cell layer is the depth distribution of this cell layer throughout the bronchial tree. The limited knowledge about this depth distribution has been one of the main sources of uncertainty in previous dosimetric models. Information now available, particularly the experimental data from Gastineau et al. [G25], offers the possibility of reducing this uncertainty. In addition, more realistic data about the fraction of unattached daughter atoms and about the activity median diameter (AMD) of the aerosol which carries the daughter atoms are now available, as outlined in the previous chapters. Together with improved models of the anatomical structure of the bronchial tree, this information allows a more realistic estimate of the exposure-dose relationships for the target tissues in the lung.

140. On the basis of this knowledge improved dosimetric models for the inhalation of short-lived radon daughters have been developed since the publication of the 1977 report [U6]. Of main importance are the studies of Harley et al. [H24], Hofmann et al. [H12], Jacobi et al. [J13, J18] and James et al. [J19]. The results of these studies have also been used by the ICRP for the assessment of occupational limits for the inhalation of ^{222}Rn, ^{220}Rn and their short-lived daughters on the basis of a dosimetric approach [I13]. A comprehensive summary and comparison of these dosimetric models and their results has been prepared by an expert group of the NEA/OECD (see [J19]). In this report a sensitivity analysis was also performed showing the influence of the various physical and biological parameters on the dose to the target tissues in the lung.

141. All of these new studies agree that under typical conditions in mines, as well as in houses, the dose distribution over the basal cell layer of the bronchial generations from inhaled radon daughters is not so inhomogeneous as was previously assumed but shows a rather broad maximum in the region from the lobar bronchi down to the upper bronchioles. This conclusion is strengthened by the fact that each study used different models for the anatomical lung structure, for the deposition and retention of radon daughters, and for the depth distribution of the basal cells. Only in the case of abnormally high values of the unattached fraction of the total potential alpha energy of the daughter mixture should a significant peak in the dose distribution be expected in the segmental bronchi, and this only if an increased deposition of unattached atoms due to turbulent air streaming in the upper bronchi is assumed. On the basis of these findings a mean dose to the bronchial basal cell layer can be derived, averaged over the above mentioned bronchial generations.

142. From the dosimetric models it follows that the conversion factors between the inhaled potential alpha-energy intake I_{pot} of the daughter mixture and the committed dose equivalent H to the bronchial basal cell layer and to the pulmonary epithelium shows a nearly linear relation with the unattached fraction f_P of the total potential alpha energy of the daughter mixture

$$H_{T-B}/I_{pot} = a_{T-B} + b_{T-B} f_P \qquad (26)$$

$$H_P/I_{pot} = a_P (1 - f_P) \qquad (27)$$

The first term a in these equations gives the conversion coefficient for the attached daughters, which depends on the activity median diameter (AMD) of the carrier aerosol. The influence of breathing rate on the quotient of the dose equivalent to the intake is relatively small. It is of great practical importance that these linear relationships are nearly independent of the equilibrium of the daughter nuclides ratios and therefore of the corresponding equilibrium factor F.

143. The available measurements in mine areas as well as in houses indicate that the unattached fraction f_P of the total potential α-energy of ^{222}Rn daughter mixtures is relatively small. Averaged over long periods of time f_P is equal to about 0.05 (see paragraph 20). Under these conditions with an AMD = 0.2 μm, the different dosimetric models give a mean dose equivalent to the bronchial basal cell layer per unit of inhaled potential alpha-energy intake of ^{222}Rn daughters of

$$(H_{T-B}/I_{pot})_{^{222}Rn\ daughters} = 15 - 40\ Sv\ J^{-1}$$

where a quality factor Q = 20 is applied for alpha radiation. For areas with relatively high dust concentration a value in the lower part of this range should be expected, whereas for highly-ventilated areas with low dust concentration a value in the upper half of this range might be more appropriate. For the pulmonary epithelium, the dose equivalent per unit potential alpha-energy intake is

$$(H_P/I_{pot})_{^{222}Rn\ daughters} = 2 - 5\ Sv\ J^{-1}$$

Thus, on average, the dose to the bronchial basal cell layer is about a factor of 5–8 higher than the dose to the pulmonary region. As mentioned earlier, the variation with breathing rate of these dose equivalents per unit intake is relatively small and falls within the quoted range. For an AMD of 0.1 μm, which might be typical for outdoor air, the dose equivalents per unit intake are about a factor of 1.5 higher than the values given above.

144. In the case of inhaled ^{222}Rn daughters the dose to tissues other than the lung is rather small and can be neglected in the evaluation of the effective dose equivalent. For the evaluation of the weighted lung dose equivalent a weighting factor w = 0.12 is usually applied to the mean lung dose equivalent, when the total lung is considered as target tissue (see Annex A). For the special case of inhaled radon daughters this "mean lung dose" concept might not be appropriate, because of the considerably higher dose to the bronchial epithelium. Following the recommendations of ICRP [I13], it might be reasonable to split the weighting factor for the total lung and to apply a weighting factor w = 0.06 to each of the two target tissues in the lung. From the values of the dose equivalents per unit intake given in paragraph 143, the following figures for the effective dose equivalent per unit inhaled potential alpha energy of ^{222}Rn daughters can be derived:

Mean lung dose concept ($w_{lung} = 0.12$) $H_{eff}/I_{pot} = 0.3 - 0.8\ Sv\ J^{-1}$

Regional lung dose concept ($w_{T-B} = w_P = 0.06$) $H_{eff}/I_{pot} = 1 - 3\ Sv\ J^{-1}$

These values refer to an AMD = 0.2 μm and can be applied for the occupational exposure in mines and for the indoor exposure in houses. In this report a reference value of $(H_{eff}/I_{pot})_{^{222}Rn\ daughters} = 2\ Sv\ J^{-1}$ is used, taking into account the high dose contribution to the bronchial basal cell layer. It should be noted that the ICRP recommends an effective dose equivalent per unit inhaled potential alpha-energy intake of ^{222}Rn daughters of 2.5 Sv J^{-1} for the radiation protection of workers in mines [I13]. This value was derived on the basis of a comparison of the dosimetric approach with the observed excess lung cancer risk of radon-exposed miners, particularly uranium miners. For the exposure in outdoor air a value of 3 Sv J^{-1} is used for ^{222}Rn daughters in this report.

145. Dose equivalents per unit intake of inhaled ^{220}Rn daughters can be derived in a similar way from the new

dosimetric models [J13, J19]. Table 18 shows the resulting dose equivalent in the target tissues of the lung and in other relevant tissues per unit of inhaled potential alpha energy, separately for ^{212}Pb and ^{212}Bi, which are the most important daughter nuclides of ^{220}Rn. The values refer to an AMD of 0.2–0.3 μm. The dose range given is based on a transfer half-life time from the lung to blood of 0.2–0.5 days, as it follows from human inhalation studies with ^{212}Pb [H18]. The dose equivalent per unit intake for tissues other than the lung were evaluated by applying the dosimetric models recommended by ICRP [I10] (see also Annex A). It follows from Table 18 that, in addition to the dose equivalent to the lung, the dose equivalents to bone surfaces, kidney and liver have to be taken into account. With respect to the effective dose equivalent the difference between the two weighting concepts for the lung is small. The potential alpha energy per unit activity inhaled is about 10 times higher for ^{212}Pb than for ^{212}Bi. This means that if a mixture of both radionuclides is inhaled the contribution to the dose equivalent from the inhaled ^{212}Pb is dominating. In this report a reference value

$$(H_{eff}/I_{pot})_{^{212}Pb+^{212}Bi} = 0.7 \text{ Sv J}^{-1}$$

is used for the evaluation of the effective dose equivalent per unit inhaled potential alpha energy of ^{220}Rn daughters. This value is applied to the occupational exposure in mines as well as to the natural exposure from these nuclides. The ICRP recommends an effective dose equivalent per unit inhaled potential alpha-energy intake of 0.8 Sv J^{-1} for occupational exposure to these nuclides [I13]. It should be noted that the effective dose equivalent per unit of inhaled potential alpha energy of these ^{220}Rn daughters is about one-third of the corresponding value for short-lived ^{222}Rn daughters. Compared with $^{212}Pb+^{212}Bi$ the contribution from inhaled ^{220}Rn to the effective dose equivalent is normally small. For the inhalation of $^{220}Rn+^{216}Po$ an effective dose equivalent per unit activity of inhaled ^{220}Rn of about 1 10^{-10} Sv Bq^{-1} has been estimated [J13], where the main contribution results from the alpha emission of these nuclides in the air volume of the lung.

146. The potential alpha-energy intake I_{pot} by inhalation during a time period T is given by the relationship

$$I_{pot}(T) = V(T)\, C_{pot} = \dot{I}_{ih}\, T\, C_{pot} = \dot{I}_{ih}\, \tilde{C}_{pot} \quad (28)$$

where C_{pot} is the mean potential alpha energy concentration in air and V the total breathing volume during the time period T. The inhaled air volume V is the product of T with the mean breathing rate $\dot{I}_{ih}$ during this period. The product $\tilde{C}_{pot} = C_{pot}\, T$ is called the potential alpha-energy exposure during the period T. On the basis of this relationship, conversion coefficients between alpha-energy exposure C_{pot} and dose equivalent can be derived from the given dose equivalents per unit intake. The SI unit for the potential alpha-energy exposure is J s m^{-3} or J h m^{-3}. Older units like WLM or WL h are defined in paragraphs 12 to 16, where the conversion coefficients between the potential alpha-energy concentration and the equivalent equilibrium concentration (EEC) of radon are also given.

147. For the occupational exposure of miners a mean breathing rate $\dot{I}_{ih}$ = 20 l min^{-1} = 1.2 m^3 h^{-1} is assumed [I13]. Taking into account a working period T = 2000 hours per year, this yields an inhaled air volume of V = 2400 m^3 during this period. In Table 19 the resulting conversion coefficients between potential alpha-energy intake $\dot{I}_{ih}$ or the radon daughter exposure $\tilde{C}_{pot}$, respectively, and the effective dose equivalent are summarized for occupational conditions in mines.

148. For the evaluation of the population exposure by inhalation of radon daughters in houses an average occupancy factor of 0.8 was assumed. This corresponds to an average residence time of

$$T_{in} = 19 \text{ h d}^{-1} = 6935 \text{ h a}^{-1}$$

indoors, and

$$T_{out} = 5 \text{ h d}^{-1} = 1825 \text{ h a}^{-1}$$

outdoors. In Table 20 the assumed breathing rates during the indoor and outdoor residence periods are given. The corresponding average breathing rates are as follows:

$$\dot{I}_{ih,\,in} = 0.8 \text{ m}^3 \text{ h}^{-1} = 15 \text{ m}^3 \text{ d}^{-1} = 5475 \text{ m}^3 \text{ a}^{-1}$$

during the indoor residence period, and

$$\dot{I}_{ih,\,out} = 1 \text{ m}^3 \text{ h}^{-1} = 5 \text{ m}^3 \text{ d}^{-1} = 1825 \text{ m}^3 \text{ a}^{-1}$$

during the outdoor residence period. The average volumes of air inhaled in a year are thus V_{in} = 5473 m^3 and V_{out} = 1825 m^3 during the indoor and outdoor residence periods, respectively.

149. The annual inhaled potential alpha-energy intake of radon daughers is

$$I_{pot,\,in} = (V\, C_{pot})_{in} = (\dot{I}_{ih}\, T\, C_{pot})_{in} = (\dot{I}_{ih}\, \tilde{C}_{pot})_{in} \quad (29)$$

for the indoor residence period, and

$$I_{pot,\,out} = (V\, C_{pot})_{out} = (\dot{I}_{ih}\, T\, C_{pot})_{out} = (\dot{I}_{ih}\, \tilde{C}_{pot})_{out} \quad (30)$$

for the outdoor residence period. $\tilde{C}_{pot}$ is the radon daughter exposure, which is the time integral of the radon daughter concentration during the time period considered. In Table 21 the reference values for the effective dose equivalent per unit of inhaled potential alpha energy and per unit of radon daughter exposure are summarized. These values are used in this report for the evaluation of the population dose from radon daughters indoors and outdoors.

150. For practical purposes it is reasonable to give direct conversion coefficients between the concentrations indoors and outdoors and the expected annual effective dose equivalent. The quotients of the annual effective dose equivalent to the potential alpha-energy concentrations are given by the relationships

$$\frac{H_{eff,\,in}}{C_{pot,\,in}} = (H_{eff}/I_{pot})_{in}\, V_{in} \qquad (31)$$

$$\frac{H_{eff,\,out}}{C_{pot,\,out}} = (H_{eff}/I_{pot})_{out}\, V_{out} \qquad (32)$$

where H_{eff}/I_{pot} are the effective dose equivalents per unit potential alpha-energy intake, given in Table 21; and V_{in} and V_{out} are the annual inhaled air volumes indoors and outdoors, as given in paragraph 148. The values of H_{eff}/C_{pot} are presented in Table 22. Taking into account the relative volumes of air breathed indoors and outdoors, the annual effective dose equivalent per unit inhaled activity of radon daughters is estimated to be 1.3 10^{-8} Sv Bq^{-1}.

151. The reference values for the dosimetric coefficients given in Tables 21 and 22 refer to adult members of the public. Correction factors should be applied for infants and children, taking into account the change of lung mass and breathing rate with age. An age-dependent lung model has been developed by Hofmann et al. [H12] and applied to the inhalation of radon daughters. This model indicates that for a given radon daughter concentration in air the effective dose equivalent probably reaches a maximum value at the age of about six years which is about 2.5 times higher than the effective dose equivalent at the age of 30 years. On the average, for the age group up to 10 years the effective dose equivalent might be about a factor 1.5–2 higher than for adults [J19]. This correction factor refers to the quotients of effective dose equivalent to exposure given in Table 21.

B. INGESTION

152. Ingestion of water containing dissolved radon results in a radiation dose to the body from the radon gas and the radon daughters in the water. The main part of the ingested radon is eliminated from the body very rapidly through the lungs. The resultant dose equivalent has been estimated by several investigators on the basis of experimental studies of exhaled radon following the ingestion of radon-rich water [A13, B23, B24, H25, K23, S17]. The stomach, whole body, liver, kidneys, fat and marrow have been considered as target organs. The largest dose is estimated to be received by the stomach.

153. For the stomach the absorbed dose per unit activity of ^{222}Rn ingested varies between about 50 and 200 nSv Bq^{-1}. Using a weighting factor of 0.06, the effective dose equivalent per unit activity of ^{222}Rn ingested is thus 3–12 nSv Bq^{-1}. In general, most of the daily intake of water is ingested in food and beverages such as tea and coffee, rather than by direct consumption. Much of the dissolved radon is released from water during cooking and boiling and the only significant radon intake comes therefore from the drinking of water itself. The amount of water consumed in this way varies between 0.3 and 1.2 l d^{-1} [S17]. Assuming a consumption of 0.5 l d^{-1}, and an effective dose equivalent per unit activity ingested of 3 nSv Bq^{-1}, a radon concentration of 1 kBq l^{-1} leads to an annual effective dose equivalent of 0.5 mSv (range 0.3–5 mSv).

V. LEVELS AND DOSES

A. RADON AND THORON IN OUTDOOR AIR

154. The concentrations of radon and thoron and their daughters in air vary with place, time, height above ground and meteorological conditions. Estimates of annual averages at different locations requires frequent sampling over the long term and such measurements are rare. Table 23 summarizes data for radon and ^{212}Pb concentrations at various geographic locations, as given in the references or calculated from published data. Some estimates of radon daughters assume radioactive equilibrium with radon, and this is seldom the case. The equilibrium factor F for radon daughters (as defined in paragraph 15) is assumed, as in Annex B of the 1977 report [U6], to be 0.6. The value of F in outdoor air depends on meteorological parameters and lower values of F (0.4–0.6) are not uncommon. The average value of the ratio of the thoron daughter ^{212}Pb to ^{222}Rn is observed to be 0.06 ± 0.04, and implies a thoron daughter activity concentration which is about a factor of 10 lower than for radon daughters.

155. Since the values in Table 23 are not necessarily representative of the locations concerned, they are not easily comparable. However, the average values for continental, island and ocean air probably are representative. These are 3 Bq m^{-3}, 0.1 Bq m^{-3} and 0.1 Bq m^{-3}, respectively. For the estimation of average dose equivalent, a radon concentration in air over land of 3 Bq m^{-3} might be used, corresponding to an equilibrium equivalent concentration of 1.8 Bq m^{-3}. Using the quotient of effective dose equivalent per unit equilibrium equivalent concentration given in Table 22, the corresponding average annual effective dose equivalent from radon daughters is 5.6 10^{-2} mSv, assuming that 5 hours are spent each day outdoors. Using a $^{212}Pb/^{222}Rn$ ratio of 0.06, the corresponding average annual effective dose equivalent from thoron daughters (assuming equilibrium between ^{212}Pb and ^{212}Bi) is 1.8 10^{-2} mSv.

156. Higher radon and radon daughter concentrations in outdoor air are likely in the vicinity of coal-fired and geothermal power stations and uranium tailings. Table 24 presents normalized annual effective dose equivalents from outdoor air for such sources, calculated from equations (19) and (20) using the dose conversion factors given in Table 22. An equilibrium factor of 0.6 and a value of 0.2 for the fraction of time spent outdoors were assumed. The radon dispersion coefficients used are illustrated in Figure XVIII. Normalized release rates of 60 GBq (GW a)$^{-1}$ and 370 TBq (GW a)$^{-1}$ were used for coal-fired and geothermal stations, respectively, and a stack height of 100 m was assumed. It is not easy to provide a clear-cut figure for the normalized release from tailings because it depends on their configuration and surface area. However, taking the figure of 10^9 Bq (MW a)$^{-1}$ (Annex F, Table 2) from an area of 0.6 hectare (or an exhalation rate of 5.3 Bq m^{-2} s^{-1}). Table 24 gives normalized annual effective dose equivalents for tailings areas of 10^4 and 10^6 m^2, respectively. To estimate the total radiological impact, the values in Table 24 should be increased by about a factor of 3 to include the effects of indoor exposure.

B. RADON IN WATER

157. Measurements of radon in water have mostly been associated with the study of correlations between uranium/radium concentration in rock and radon concentration in ground water. In general, they have

been undertaken only in uranium-bearing areas, or regions with a known high concentration of radon in the water. Measurements intended to estimate the weighted average radon concentration in water for a country or community are rare, because radon in water has not been considered to be a significant factor for human exposures, except in areas with very high radon levels. However, the recent interest in radon exposure in houses has indicated radon in water to be a potentially significant source in some cases. The results of some measurements of radon in water are shown in Table 25 and more extensive data may be expected in the future. It must be emphasized that surface water in many countries is the mean source of drinking water and this water is normally expected to have low radon concentration.

158. The data presented by Hess [H10] for the United States are probably not representative, and perhaps not even for the counties examined. Most of the wells were drilled artificially and selected with special emphasis on granite and pegmatite areas where high radon concentrations were expected. The measurements follow approximately a log-normal distribution. The results from North Carolina [S1] include only those water samples with statistically significant activity concentrations of radon (> 700 Bq m^{-3}), without mention of the number of values discarded. Other studies of radon concentrations in the United States have been reported for water samples from North Carolina [A1], Western United States [O1], Hot Springs, Arkansas [K15], Great Salt Lake, Utah [T2] and South Texas [G7]. The results were presented as examples of high values of radon in water supplies. Of these water sources 74% had a radon concentration of less than 74 kBq m^{-3} and 5% above 370 kBq m^{-3} [D14].

159. The results from Finland in Table 25 refer to 192 drilled wells. These include recent results together with other extensive measurements [A7, C4, A11, K18]. A summary of data is given in Table 26 and in Figure XXX. The results are found to follow a log-normal distribution. The population-weighted average is 56 kBq m^{-3}, which must be considered as a relatively high value.

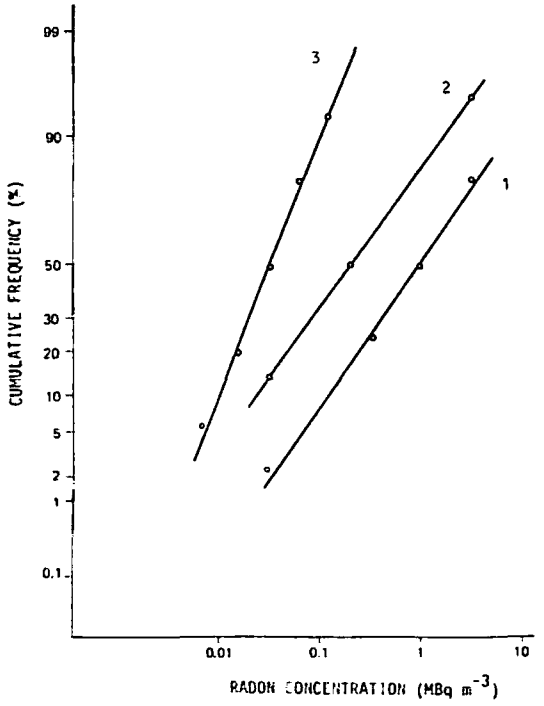

Figure XXX. The distribution of radon concentrations in (1) bored wells in the Helsinki area; (2) bored wells in Finland outside Helsinki; (3) other wells in Finland (excluding waterworks) [A7, C4]

160. The Swedish data represent water from almost all waterworks, delivering more than 10^5 m^3 of ground water per year to about 3 million people. In addition, 3.7 million people in Sweden use surface water from waterworks and the rest, about 1 million people, use private wells. If the weighted average of the radon concentration in private wells is assumed to be 10–100 kBq m^{-3} [S11], the weighted national average is 10–20 kBq m^{-3}.

161. In the United Kingdom natural radon levels in water supplies are lower than in many other countries [H9]. Two extensive surveys carried out in the early 1960s [T5, K6] found the highest radon concentration (26 kBq m^{-3}) in a reservoir on granite. However, in highly mineralized granite areas (Cornwall and Devon) the radon concentration in some water sources used for supply is about 700 kBq m^{-3}. Various spa waters have up to 70 kBq m^{-3}.

162. A report from the Federal Republic of Germany summarizes the concentrations of natural radionuclides in water, food and in man [M18]. For radon in drinking water the average values lie in the range of 0.4–4 kBq m^{-3}.

163. In conclusion, available measurements on radon in water cannot easily be used to estimate weighted mean values for a country as a whole. The measurements often refer to areas of special geological interest, because of their high content of uranium or radium or of special radiological interest because of their high radon levels. It seems likely that only a small proportion of the world's population, perhaps between 1% and 10%, consumes water containing concentrations of radon of the order of 100 kBq m^{-3} or higher, drawn from relatively deep wells. For the remainder who consume water from wells or surface sources, the weighted world average concentration from all sources is probably less than 1 kBq m^{-3}. A small proportion (< 1%) consumes water containing 1–10 MBq m^{-3} of radon, and there have been a few exceptional reports of concentrations in the range 10–100 MBq m^{-3}.

164. The radiation dose caused by radon in water is due partly to ingestion and partly to inhalation of the radon daughters produced by decay of the radon. The relevant annual effective dose equivalents from water containing 1 MBq m^{-3} of radon are 0.5 mSv (ingestion), and 6 mSv (inhalation of radon daughters). The latter value can be calculated from the relationships given in paragraphs 96 and 136 and in Table 22. If one assumes a value of 3 kBq m^{-3} for the average radon concentration in water, the corresponding annual effective dose equivalent is about 20 μSv.

C. RADON IN HOUSES

165. There is at present considerable interest in this area, particularly in the light of domestic energy conservation programmes. Radon concentrations in the domestic environment are also being affected by the use of land fill and of building materials which have radium concentrations significantly above normal. The following paragraphs summarize available data but it is expected that many new data will emerge in the literature from current studies.

(a) Austria

166. Extensive measurements of radon, thoron and their decay products have been made in Salzburg, Austria [S22]. To obtain representative values a number of test families and individuals were assessed (729 individuals in all). Special efforts were made to correct for time-variations in the activity concentrations. The values of radon concentrations were observed to be log-normally distributed. The mean concentrations were found to be 22 Bq m^{-3} for radon, 12 Bq m^{-3} for radon daughters (an equilibrium factor of 0.56 was used, based on reported mean radon/daughter ratios) and 1 Bq m^{-3} for ^{212}Pb. Maximum concentrations were more than a factor of 10 higher than the average. The reported radon daughter concentrations correspond to an annual effective dose equivalent of 0.7 mSv.

(b) Canada

167. An extensive survey was recently reported from Canada [M6, M26]. It concerned a total of 13 436 houses selected at random in 19 Canadian cities, and measured in 1977, 1978 and 1980. The sample corresponded to about 0.4% of the houses in the cities studied. Basements (or ground floors in houses with no basement) were the preferred sampling locations. The houses were regarded as typical for Canada, made with wood frames and little stone. Interior wall linings of painted natural gypsum were common and were found to be an insignificant source of radon. Results are summarized in Table 27. The average equilibrium equivalent concentration of radon is 17 Bq m^{-3}, corresponding to an annual effective dose equivalent of 1 mSv. Since the measurements were performed in summer periods, the annual average might in fact be higher. Radon appeared to originate from radium in nearby soil. Geographical differences were statistically significant. Variations within cities were however generally greater than variations between cities. The equilibrium factor calculated from the geometric means is on the average 0.52 ± 0.12. The results of all measurements show a log-normal distribution, which is illustrated in Figure XXXI.

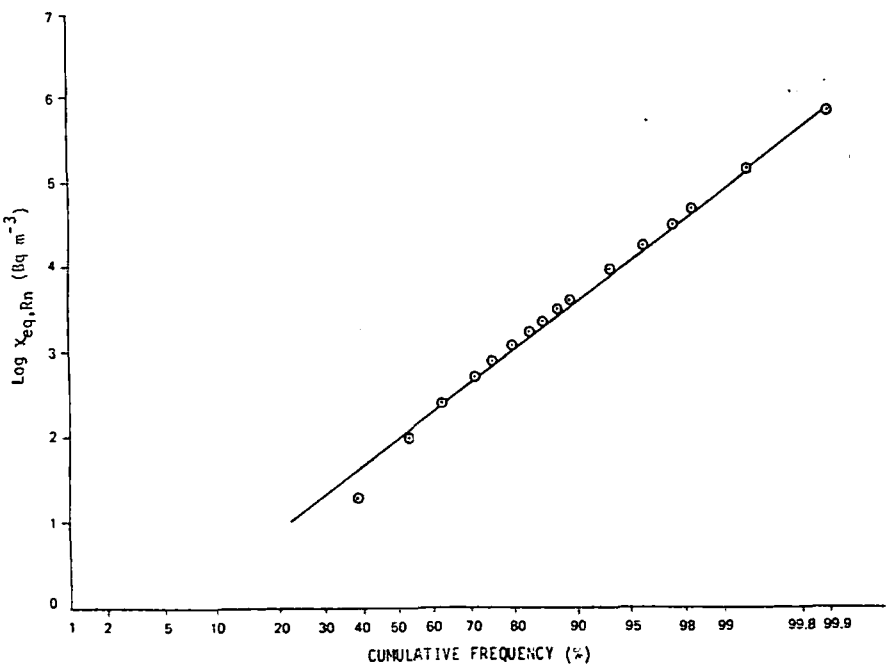

Figure XXXI. Log-normal cumulative frequency plot of radon daughter concentrations in Canadian homes (1977, 1978, 1980 surveys)

168. In March Township, Ontario, Canada, 343 houses were surveyed because of the discovery of nearby low-grade uranium deposits (5 ppm of uranium). Based on radon daughter measurements, 56.6% of the houses had equilibrium equivalent concentrations of radon lower than 19 Bq m^{-3}. The highest value was 700 Bq m^{-3} and the arithmetic average was 50 Bq m^{-3} [L7, T8].

169. The area of Castlegar-Trail in British Columbia, Canada, has been surveyed because of high radon concentrations in water. Based on radon daughter measurements, 46.2% of the homes had equilibrium equivalent concentrations lower than 19 Bq m^{-3}; the highest value observed was 2900 Bq m^{-3} and the average was 74 Bq m^{-3} [L7].

170. Other investigations have been made in Canada [K9] in areas where radioactive contamination was suspected for various reasons in radium-uranium refineries, metallurgical operations making use of refinery residues and uranium mining. One area was classified as a "normal" reference area. The results are shown in Table 28.

171. The influence of radon in water on the levels of radon and radon daughters in houses was studied in a survey in Canada including 6 houses, 5 trailer-homes and 2 schools. The water supplies originated from 15–62 m deep wells in granite. The results are seen in Table 29 [M7]. The air-to-water concentration ratio (see paragraph 96) is small (average $2\ 10^{-5}$), probably because of good ventilation. The low equilibrium factors F support such a conclusion. Table 30 shows the resulting increase of radon concentration in air due to a warm water shower with water containing 4.4 kBq m^{-3} radon [M7]. The decrease of the radon concentration after the shower corresponds to a ventilation rate of 1–3 h^{-1} and the radon daughter concentration increases only to about 10% of the equilibrium value. The air-to-water concentration ratio is (2–8) 10^{-4} in this case.

(c) Finland

172. Between 1977 and 1978 a preliminary survey on radon and radon daughter concentrations in 35 normal Finnish dwellings was carried out in the Helsinki area [M20]. Buildings of different ages, types and building materials were included. The radon concentration in tap water was below 100 kBq m^{-3} and therefore it was concluded that the main sources of radon were the building materials and the soil. The mean equilibrium equivalent concentration of radon during the day was 13 Bq m^{-3} and the radon concentration 27 Bq m^{-3}. The 24 h mean value of radon concentration was 44 Bq m^{-3} and the equilibrium equivalent concentration of radon 17 Bq m^{-3}, corresponding to an annual effective dose equivalent of 1 mSv. The survey included too many concrete houses and too few wooden ones for the mean to be regarded as representative of radon concentrations in Finnish dwellings. Later measurements in the same area with integrating-type instruments gave higher mean concentrations. This is believed to be due at least in part to higher concentrations during the night than those estimated in the first series of measurements. The highest concentrations (up to the level 10 000 Bq m^{-3}) were found in houses where the only contributor can be radon from the ground or bedrock.

173. Radon in water may be a significant source of radon to air in dwellings in many countries. In the region of Helsinki, Finland, very high radon concentrations in water have been reported [C3, K1, K2]. The highest concentration measured was 44 MBq m^{-3}. In a recent study, radon measurements in air were carried out in 20 houses with radon concentration in water between 150 kBq m^{-3} and 17 MBq m^{-3}. The rooms in a house were classified according to the use of water. The results are given in Table 31 [A3].

174. The table shows that the radon concentrations were sometimes remarkably high and, as expected, higher in rooms and situations where water was used (bathrooms, etc.). Under such conditions it is expected that the equilibrium factor F is smaller than average. The air-to-water concentration ratio was found to be the following in the three groups of rooms: $(21 \pm 9)\ 10^{-4}$ in wet rooms; $(6 \pm 3)\ 10^{-4}$ in ordinary rooms with water; $(0.6 \pm 0.3)\ 10^{-4}$ in living rooms, etc. (90% confidence level). A weighted average value would be $1.4\ 10^{-4}$, assuming 0.5 h spent in wet rooms, 2 h in ordinary rooms with water and 17 h in other rooms. Using an equilibrium factor F of 0.5 (which may be a slight over-estimate), and average values for the radon concentration in water and for the air-to-water concentration ratio, the weighted equilibrium equivalent radon concentration is 360 Bq m^{-3}. The maximum value would amount to 1200 Bq m^{-3}. The results of a follow-up study [A4] are within the range of the above-mentioned values. The air-to-water concentration ratios are higher and much more variable for wet rooms (10^{-4} to 10^{-2}) than for living rooms. Measurements of radon daughters by track-etch dosimeters carried by persons during three-day periods give a ratio of equilibrium equivalent radon concentration to radon concentration in water of $(0.4 \pm 0.3)\ 10^{-4}$.

(d) Germany, Federal Republic of

175. Measurements in the Federal Republic of Germany have recently been published [W14]. The study covers 32 houses, grouped according to their principal construction material; equilibrium equivalent radon and thoron concentrations, normalized to a ventilation rate of 0.5 h^{-1} are estimated from the measured exhalation rates. The results are summarized in Table 32. Mean values for radon and thoron are 8.1 Bq m^{-3} and 0.37 Bq m^{-3}, respectively, corresponding to annual effective dose equivalents of 0.5 mSv and 0.1 mSv. Other measurements [J15] on about 250 dwellings indicate a log-normal distribution with geometric means equilibrium equivalent concentrations of 7–18 Bq m^{-3} and 0.3–0.6 Bq m^{-3} for radon and thoron, respectively.

(e) Norway

176. A study has recently been made in Norway of the radon concentrations in 129 dwellings in the area around Oslo [S24] (see Table 33). Radon daughter measurements were made in 25 dwellings to estimate the average equilibrium factor F which was found to be 0.5. Extensive measurements were made to study the effects of ventilation and changes in barometric pressure and the emanating power of some building materials.

177. The measurements were carried out during the winter of 1977–1978. The radon concentrations were found to be dependent on radium concentration and porosity of the building material and on radon exhalation from the ground, but were even more dependent on the ventilation and the atmospheric pressure. It appeared of special interest to evaluate the influence of ventilation on radon concentration during the winter season, when the ventilation rate is relatively low because of energy conservation efforts. The distribution of people living in various types of houses was assumed to be 20% of the people in wooden buildings, 5% in brick buildings and 75% in concrete buildings in the Oslo region. Over the whole country the corresponding values are 75%, 3% and 22%.

178. The distribution of radon concentrations (see Table 33) was approximately log-normal. On average, wooden houses had higher radon concentrations than brick houses, an observation explained by the fact that wooden houses in Norway are mostly one- or two-storey buildings for which radon emanation from the ground can be expected to be of greater significance.

179. The data on the distribution of radon concentrations in houses in the Oslo region, combined with the data on the distribution of houses of different building materials in Norway, lead to an average radon concentration of 52 Bq m^{-3}. It it is assumed that the equilibrium factor is 0.5, the equilibrium equivalent concentration of radon would be 26 Bq m^{-3}, corresponding to an annual effective dose equivalent of 1.6 mSv. However, this may be too high an estimate for the whole country, as gamma-ray measurements in Norway indicate that the natural gamma-radiation background is relatively high in the Oslo region, compared with the mean value for Norway.

(f) Poland

180. Data on radon and radon daughters activity concentrations in flats in Poland have been reported [G13]. The results are summarized in Table 34. The radon values were given as maximum values and the significance of the weighted average as a representative value for the flats is therefore uncertain. Other data on measurements in dwellings indicate higher average values. From measurements in Puławy, Czestochowa

and Warzaw in the Ursynów district an average equilibrium equivalent concentration of radon is estimated to be 17 Bq m^{-3} (equilibrium factor = 0.5) [B16, B17], corresponding to an annual effective dose equivalent of 1 mSv.

(g) Sweden

181. A number of measurements have been carried out in Sweden [S35]. Following measurements made by Hultqvist in 1956 [H17] in about 300 dwellings built before 1946, radon in houses was not considered a matter of serious concern in Sweden until the last few years. The main reason for the recent change in attitude is the continuing tendency, in the development of building standards, to lower ventilation rates and to improve the airtightness in order to conserve energy. The ventilation rate in houses built during the years up to 1950 was 0.8 ± 0.5 h^{-1} in apartments and 0.9 ± 0.5 h^{-1} in detached houses. During the 1950s the ventilation rate in new dwellings was 0.6 ± 0.2 h^{-1} and 0.8 ± 0.2 h^{-1}; during the 1960s 0.5 ± 0.2 h^{-1} and 0.6 ± 0.2 h^{-1}; and during the 1970s 0.3 ± 0.15 h^{-1} and 0.45 ± 0.45 h^{-1}; in apartments and detached houses, respectively. This decrease in the ventilation rate causes an increased radon concentration in houses. Furthermore, more people live in apartment houses now than previously and modern detached houses contain more stone materials than older houses.

182. Up to 1975, a common building material was aerated concrete containing alum shale. This material contains more radium than other building materials and this has given rise to an increased exposure to gamma radiation and radon daughters. It is estimated that between 350 000 and 700 000 dwellings in Sweden contain aerated concrete based on alum shale. Of these, between 3000 and 20 000 are estimated to have radon daughter concentrations in indoor air requiring further investigation.

183. The radium concentration in this material varies as does the use of the material in the houses. From an investigation made in 1956 [H17] the average equilibrium equivalent radon concentration in these houses was estimated to be 58 Bq m^{-3}. The maximum value was about 5 times higher and the distribution of radon daughter concentrations was found to be more dependent on the ventilation than on the activity concentration in the building material.

184. However, some houses have been identified with an unusually large fraction of concrete based on alum shale in their building material. Measurements on radon and radon daughters have been made in 32 single-family houses where that is the case. The results are shown in Table 35 [S45]. The average of the radon daughter activity concentrations measured in all houses is 260 Bq m^{-3}, expressed as equilibrium equivalent concentration of radon. However, whether this average value is really representative of the true average is uncertain. There are reasons to believe that it may be an overestimate [S45].

185. In Sweden an unusual environmental situation has recently been described. Alum shale exists in many areas of central and southern Sweden and it has been used since the sixteenth century and up to the 1930s for the production of alum. It was also used for lime-burning. There are therefore many tailings piles from this production, the number and location of which are not yet known. Some of them have been used as housing areas. Measurements have been carried out in one such area, outdoors and in houses built on the tailings [S34]. It has been estimated that 200 to 2000 houses may have been built in such areas [S29].

186. The radium concentration of the tailings was on average 2900 Bq kg^{-1}. The gamma radiation dose rate in air above reclaimed areas was about 0.4 μGy h^{-1} and above unreclaimed areas about 1 μGy h^{-1}. In recreation areas the dose rates were 0.9–2.4 μGy h^{-1}. The radon concentration outdoors was 45–70 Bq m^{-3} at the time of measurement and the radon concentration in drinking water was about 10 kBq m^{-3}. Measurements were carried out in 7 single-family houses. The average radon concentration was 860 Bq m^{-3} (range 430–2100 Bq m^{-3}) and the equilibrium equivalent concentration of radon was 500 Bq m^{-3}. The ventilation rate was low (0.09–0.28 h^{-1}) and was in fact lower than the current Swedish standard (0.5 h^{-1}). If the ventilation rate were increased to 0.5 h^{-1}, the average radon concentration would be about 400 Bq m^{-3}, corresponding to an equilibrium equivalent concentration of radon of 200 Bq m^{-3} with an equilibrium factor of 0.5, provided that the increased ventilation rate does not cause a drop in pressure, which might effect the exhalation rate from the ground below.

187. In order to estimate the overall average radon daughter concentration in homes in Sweden, measurement of radon and radon daughters, gamma radiation, activity concentration in building material and of ventilation rates are being carried out in "typical" houses. The results are to be combined with other results on activity concentration in building materials, gamma radiation in houses, distribution of various ventilation systems and building materials, and variation of building practices with time. One part of the investigation includes 63 "typical" dwellings selected from seven types of houses built at the beginning of the 1970s in the town of Gävle in central Sweden. The results of the investigation are presented in Table 36 [E2].

188. The measurements on radon and radon daughters in houses in Sweden continue and new results indicate that the greatest problem is radon emanating from the ground. Houses have been found with more than 10 000 Bq m^{-3} of radon and it is estimated that about 75% of the total collective dose caused by inhalation of radon daughters depends on radon from the ground.

189. The estimated average radon concentrations for all homes in Sweden (dwellings existing in 1950, 1975 and estimates for 1985) are presented in Table 37 [S35]. Later recalculation has shown that the value for 1975 is probably underestimated by about 50% because of lower ventilation rates than assumed. Recent measurements in 600 houses representative for Sweden indicate an average value for radon daughters of 60 Bq m^{-3} in 1980. The national average of the equilibrium equivalent concentration is believed to lie within the extremes of 40 and 140 Bq m^{-3}. Therefore, the value for 1985 is probably also an underestimate. The values of the radon daughter concentrations are log-normally distributed. A concentration of 60 Bq m^{-3} corresponds to an annual effective dose equivalent of 3.7 mSv.

(h) United Kingdom

190. A wide-ranging survey in the United Kingdom has been reported [C6]. The measurements were carried out in 87 dwellings in England and Scotland varying in age from one to 300 years. They were in the main single-family houses made of clay brick, many with concrete floors at ground level. Measurements were made of the activity concentration of ^{218}Po and from these measurements, together with determination of ventilation rates, the radon exhalation coefficients (see paragraph 34) were calculated. Because the exhalation coefficient is practically independent of the ventilation rate within the range of variation occurring in houses, it was possible to calculate the radon daughter concentrations corresponding to an average ventilation rate in the houses, assumed to be 1 h^{-1}.

191. The median value for radon exhalation coefficient was found to be 11.8 Bq m^{-3} h^{-1} and the arithmetic mean was 22.2 Bq m^{-3} h^{-1}, with a range from 0.44 to 204 Bq m^{-3} h^{-1}. By excluding the extreme maximum value from a rather uncommon type of dwelling the arithmetic mean was reduced to 20 Bq m^{-3} h^{-1}. (The exhalation rate expressed in units of Bq m^{-2} h^{-1} can be arrived at by dividing by 2 m^{-1}, which is the appropriate value of the expression $\frac{S}{V}$, where S is the surface of walls, floors, etc., and V is the volume of rooms.)

192. Assuming an average ventilation rate of 1 h^{-1} and paying due consideration to the radon concentration in the outside air—assumed to be 3 Bq m^{-3}—the average equilibrium equivalent radon concentration in the houses was found to be 13 Bq m^{-3}. That corresponds to an annual effective dose equivalent rate of 0.8 mSv. The cumulative frequency distribution of dose from radon decay products is shown in Figure XXXII.

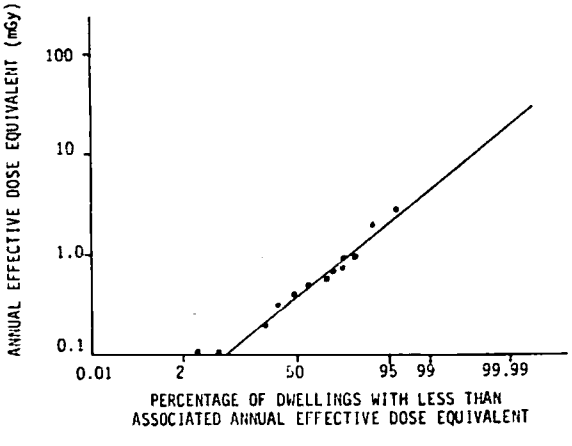

Figure XXXII. Cumulative frequency distribution of annual effective dose equivalent from radon decay products in some dwellings in the United Kingdom

193. Phosphogypsum can replace ordinary material in buildings. The radium concentration of phosphogypsum varies between 20–1500 Bq kg^{-1} (see Annex C). In a prospective study, the radon concentration in houses with phosphogypsum (radium concentration 900 Bq kg^{-1}) has been estimated to be about 7 Bq m^{-3} [O3, W20]. The ventilation rate was assumed to be 1 h^{-1}.

(i) United States

194. The distribution of radon and radon daughter activity concentrations has been investigated over a two-year period in 21 New Jersey and New York residences [G1]. Most of the buildings were single-family, of one or two stores, and of wood frame or brick construction. The geometric mean of the equilibrium equivalent radon concentration was 15.2 Bq m^{-3}, and the arithmetic mean 16.3 Bq m^{-3} (range 2.6 to 107 Bq m^{-3}) corresponding to an annual effective dose equivalent of 1 mSv.

195. Radon daughter concentrations in houses on phosphate-related land in Florida have been reported [U4, U8]. There are 1000–3000 houses built on phosphate lands and a classification of buildings and their equilibrium equivalent radon concentrations based on radon daughter measurements in Polk County are shown in Table 38 [U8]. In Colorado some waste products from the uranium industry have been used as filling material under a number of houses causing an enhanced radon concentration indoors. The radium concentration in this material was 4400 Bq kg^{-1} on average. Table 39 shows the distribution of equilibrium equivalent radon concentration in some of these houses [C11]. The average value estimated from the table is about 200 Bq m^{-3}; the weighted average for a population of 15 000 is about 37 Bq m^{-3}, corresponding to an annual effective dose equivalent of 2.3 mSv.

196. High radon concentrations have also been found in houses having unpaved crawl spaces. In a total of 22 houses investigated in the Chicago area, the radon concentration was more than 185 Bq m^{-3} in nine houses and six of these houses had more than 370 Bq m^{-3}. The highest values were about 1000 Bq m^{-3}. The radon emanated from the unpaved crawl space under the house and the exhalation rate was about 0.3 Bq m^{-2} s^{-1}. The radium concentration in the soil was normal (about 40 Bq kg^{-1}) [R12].

(j) Yugoslavia

197. In the neighbourhood of uranium ore deposits in Yugoslavia, radon concentrations have been measured in houses, some of which were built of stone from the uranium area [K20]. The concentrations were in the range of 30–100 Bq m^{-3}. All measurements were made in the daytime and because the radon concentrations were found to increase during the night the reported values underestimate the average by approximately a factor of 2. The radon concentration outdoors varied between 4 and 8 Bq m^{-3}.

(k) Other countries or areas

198. Other measurements were reported in Annex B of the 1977 report [U6]. There have also been estimates of the radon daughter exposures in houses, on the basis of the radium concentration in building materials [N2]. Using a model developed by Krisiuk et al. [K13] and applying "typical" values of radium concentration in building material (50 Bq kg^{-1}), an emanating power of 0.01–0.04, and a ventilation rate (1 h^{-1}), estimated typical values were obtained for the increases in exposure to radon daughters above outdoor levels. The results were given in WLM. These results are given in this Annex recalculated as average values of equilibrium equivalent concentration of radon. The equilibrium equivalent concentration for outdoor air is added, namely 1.8 Bq m^{-3}. These results, together with

those given in Annex B of the 1977 report [U6], are included in Table 40.

(l) *Summary*

199. The distribution of the radon daughter concentrations in houses is generally log-normal. With the exception of Sweden, 90% of buildings have concentrations less than about 50 Bq m^{-3}. A few per cent may have values greater than 100 Bq m^{-3}. Sweden seems to be exceptional with more than 30 % of buildings with indoor radon daughter concentrations above 100 Bq m^{-3}. The main source of radon is the soil and building materials (aerated concrete) containing alum shale. Another reason is the reduced ventilation rate in all houses over the last few years, as a result of energy conservation programmes.

200. Besides the general distribution of radon daughter concentration, there are in many countries exceptionally high levels because of high radium concentration in the ground or building materials, sometimes in combination with poor ventilation. Extreme values between 1000 and 10 000 Bq m^{-3} occur. The relative number of houses affected by extreme values (> 1000 Bq m^{-3}), such as some in Grand Junction and Florida in the United States, in Sweden and the United Kingdom, may be between 0.01 to 0.1%. The corresponding annual effective dose equivalent is 60 mSv or more.

201. However, the main contribution to the collective effective dose equivalent may not result from the small number of houses with elevated radon concentrations. If it is assumed that the radon daughter activity concentration is less than 50 Bq m^{-3} for 90% of the people, 50–100 Bq m^{-3} for 9%, 100–1000 Bq m^{-3} for 0.9% and 1000–10 000 Bq m^{-3} for 0.09% and the middle value in each range is used, the collective effective dose equivalent caused by exposure to radon daughter concentrations of less than 100 Bq m^{-3} correspond to about 75% of the total collective effective dose equivalent. For Sweden this estimate is not valid, as a larger fraction of the population is exposed to high radon daughter concentrations.

202. The average values of the equilibrium equivalent concentrations of radon in dwellings in different countries are summarized in Table 40, where the corresponding effective dose equivalents are calculated using the dosimetric coefficients given in Table 22. The values should be considered with some caution, as seasonal variations are, for instance, not taken into account.

203. It may be seen in Table 40 that with the exception of Sweden the mean values of the indoor equilibrium equivalent ^{222}Rn concentration in different countries cover the range from 5 to 25 Bq m^{-3}. Taking into account the dose conversion coefficients listed in Table 22, this corresponds to an annual effective dose equivalent ranging from 0.3 to 1.5 mSv. For the total population in the temperate regions of the world, 15 Bq m^{-3} seems to be an appropriate mean value for the indoor concentration, which is about 8 times higher than the mean activity concentration in outdoor air (1.8 Bq m^{-3}). This yields a mean annual effective dose equivalent of about 0.92 mSv from indoor exposure and of about 0.06 mSv from outdoor exposure, giving a total of about 1 mSv from inhaled ^{222}Rn daughters. This value refers to temperate regions of the world. For equatorial regions so far no measurements are available. Having regard to the different domestic conditions, the indoor concentrations of radon daughters in those regions might be considerably lower than in temperate regions. For large population groups this level will be comparable with the normal outdoor level, leading to an annual effective dose equivalent of about 0.2 mSv. Taking into account that about two-thirds of the total world population is living in temperate regions, a global mean annual effective dose equivalent of about 0.8 mSv—averaged over all age groups—from inhaled ^{222}Rn daughters would be expected (See Table 12 of Annex B).

204. By comparison with ^{222}Rn daughters, very few measurements of ^{220}Rn daughters have been reported [C6, S21, W14]. However, the simultaneous measurements of ^{222}Rn and ^{220}Rn daughters in houses in the Federal Republic of Germany (see Table 32) and in the United Kingdom (see Table 41) seem to indicate a ratio of about 20 between equilibrium equivalent ^{222}Rn concentration and equilibrium equivalent ^{220}Rn concentration. By applying this factor, it can be concluded that the mean value of the indoor equilibrium equivalent ^{220}Rn concentration in different countries should be in the range of 0.2–1.2 Bq m^{-3}. For the total population in temperate regions of the world a mean value of about 0.7 Bq m^{-3} could be expected. Taking into account the dosimetric coefficients for ^{220}Rn daughters given in Table 22, this corresponds to a mean annual effective dose equivalent of about 0.2 mSv from inhaled ^{220}Rn daughters. This means that the contribution from ^{220}Rn daughters to the effective dose equivalent is on the average about one-fifth of that from ^{222}Rn daughters. For reasons mentioned in paragraph 203, a global mean value of about 0.17 mSv per year from inhaled ^{220}Rn daughters should be expected (see Table 16 of Annex B).

D. OCCUPATIONAL EXPOSURES TO RADON AND THORON DAUGHTERS

1. Uranium mines

205. In Annex B of the 1977 report [U6], some data were reported about radon and radon daughter concentrations in uranium mines and it was noted that the improvement in working conditions noticed during the previous years was continuing. This is still the case, although the technical difficulties involved in making further improvements increase as the concentrations are decreased. Radon daughter concentrations and exposures in mines in some countries are shown in Table 42. The value for uranium mines in France in 1979 is calculated by using an equilibrium factor of 0.17. By using an effective dose equivalent per unit of potential alpha-energy exposure of 8.4 mSv WLM^{-1} (see Table 19), the annual effective dose equivalent for uranium miners is estimated to be 34 mSv in the United States in 1977, 12 mSv in France in 1979 and 6.2 mSv in Canada in 1979. The average annual effective dose equivalent, including the data from India given in paragraph 208, is 15 mSv.

206. The activity concentration of thoron daughters is not always insignificant. In measurements of radon daughters and other radiation variables in the presence of ^{220}Rn at Rio Algom mine, Canada, the representative average value for radon daughters was 0.084 WL and for thoron daughters 0.12 WL [B18]. Similar measurements have also been made in the Agnew Lake mine, Canada, and the corresponding values were 0.1 WL for

radon daughters and 0.09 WL for thoron daughters [B19]. Because the thoron daughter concentration is comparable to that of radon daughters, special consideration should also be given to the measuring technique [C18].

207. Radon daughter activity concentration in open-pit mines and its variation with meteorological variables have been studied at Nabarlek uranium mine, Australia [L13], which is a high grade (2%) uranium ore mine. The radon exhalation rate varied widely but the quotient of exhalation rate to ore grade was in general fairly stable, about 80 Bq m^{-2} s^{-1} per percentage of U_3O_8. The concentration of radon and radon daughters in air was strongly influenced by air movements and atmospheric stability and the variations could be up to an order of magnitude. Normally the radon concentrations were lower during daylight than during the night. However, during the hours just before dawn the air frequently becomes still and the radon and radon daughter concentrations rise to a maximum. The estimated radon daughter exposure during about half a year was 0.065 WLM, corresponding to an effective dose equivalent of 0.5 mSv.

208. Radon daughter measurements have been made in Jaduguda underground mines in India on a regular basis for many years. The radon daughter exposure has been estimated for different kinds of operations. The highest exposures occur most frequently during drilling. The results for India are presented in Table 43 [R13, K19, A12]. The average effective dose equivalents for the different categories of mine workers ranged from 14 to 22 mSv in 1979.

209. As a curiosity, the radon concentrations in the well-known old mines in Schneeberg and Jachymov may be mentioned. The measurements were performed at the beginning of this century and published in the 1920s [B21, L14]. The concentrations were given in "Mache" units, where 1 Mache = 13.3 Bq. The radon concentrations in various parts of Schneeberg mine ranged from 20 to 600 kBq m^{-3} and the average was about 100 kBq m^{-3}. In Jachymov mine the corresponding values were 10–300 kBq m^{-3} and 100 kBq m^{-3}. These average values correspond to about 30 WL.

2. Non-uranium mines

210. Since radon problems in many non-uranium mines were highlighted during the 1960s and the 1970s, the radon daughter concentration in these mines has decreased continuously, as can be seen in Table 44. The corresponding annual effective dose equivalents are for Finland (1977) 3.2 mSv, Norway (1980) 3.8 mSv, South Africa (1973) 14 mSv, Sweden (1980) 5.9 mSv, and for the United Kingdom (1981) about 1.0 mSv for most of the coal miners and 22 mSv for miners in other mines. In a research report on the health effects of radon exposure in non-uranium mines in Bavaria, Federal Republic of Germany, the radon concentrations in nine mines are reported [F7] for the years 1971–1973. The values reported correspond to potential alpha-energy exposures between 0.1 and 4 WLM, if an equilibrium factor of 0.7 is used.

211. Thoron daughter measurements have only been carried out in a few mines. In two non-uranium mines in Norway the average equilibrium equivalent concentrations of thoron were about 3 Bq m^{-3} and 20 Bq m^{-3} [B4]. In the United Kingdom the mean ^{212}Pb concentrations in seven metalliferous mines were 40, 20, 3, 1, 1, 1 and 0.4 Bq m^{-3} [D6]. Accordingly, the equilibrium equivalent concentration of thoron in mines seems to be in the range of about 4 to 40 Bq m^{-3}, corresponding to an annual effective dose equivalent of 0.5 to 5 mSv.

3. Other occupational exposures

212. Radon exhalation from ordinary rocks and soils and radon-rich water can cause high radon and radon daughter concentrations in underground spaces such as tunnels, hydroelectric power stations, caves, public baths and thermal spas. Often an occupational exposure occurs only for a fraction of the working time and this fraction is sometimes difficult to estimate. Table 45 shows concentrations of, and exposures to, radon daughters. In some cases the exposures are rough estimates made by assuming a 2000 h exposure per year; in other instances the real working time has been considered. The average annual exposures to radon daughters in spas have been studied over a period of between 15 and 32 years in the island of Ischia in Italy [B9]. The corresponding annual effective dose equivalents range from 1 to 120 mSv.

213. The levels and distribution of radon concentration have been measured in two calcite caves in Japan, Akiyoshi Cave and Kagekiyo Cave [M23]. The radon concentration increases by one order of magnitude between a point near the entrance and at points further away. The average value given in Table 45 (0.8 WL) refers to a point 400 m from the entrance. Great seasonal variations occur with substantial increases in the summer; a factor of 500 has been reported. The value in Table 45 refers to March 1978. The average radon exhalation rate was estimated to be about 7 10^{-3} Bq m^{-2} s^{-1} and the radium concentration in the cave wall was reported to be lower than that in the soil outside the cave.

214. In factories where work with thorium is carried out (thorium extraction from ore, manufacture of gas mantles, production of Mg/Th alloys) there is occupational exposure to thoron and thoron daughters. In some thorium factories in the United Kingdom, measurements were performed of thoron and thoron daughters [D6]. In one gas mantle factory extensive observations were made of the ^{220}Rn: ^{212}Pb:^{212}Bi ratios, absolute values and variations of the concentrations. Since such measurements are rare, they are shown fully in Table 46. The "inferred values" of thoron are those estimated on the basis of the ^{212}Pb and ^{212}Bi concentrations. There is little regularity in the activity concentration ratios, probably on account of sharp thoron gradients in the rooms. The thoron concentrations given in Table 46 are rather typical of some of the other factories examined. Most values are in the range of 1–10 kBq m^{-3}. Other factories had lower values, around 0.4–4 kBq m^{-3}. These values are rather similar to others reported (2–20 kBq m^{-3}) from two thorium plants in India [M16]. The average value of all ^{212}Pb measurements in the United Kingdom [D6] was 170 Bq m^{-3}, corresponding to an annual effective dose equivalent of about 20 mSv. Some typical variations of the potential alpha-energy concentration of thoron daughters in a thorium factory in India are shown in Table 47 [D10]. The average value is 0.15 WL and the corresponding exposure is less than 1.8 WLM, corresponding to an annual effective dose equivalent of about 5 mSv.

E. DELIBERATE EXPOSURES TO RADON

215. For several hundred years radon has been exploited in "balneology"—the use of spas or baths for the alleviation of illness. There are balneological facilities using radon in Badgastein, Austria, in Bulgaria, in Poland and in the USSR.

216. There is a large amount of information about the levels of radon in Badgastein, much of which has been summarized by Uzunov et al. [U10]; they have estimated the doses received by the general population of the town, by the employees of the spa and by the individuals deliberately exposed to the radon in the course of balneological procedures.

217. Thermal springs in the centre of the town supply radon-rich hot water at a concentration of about 10^6 Bq m^{-3}. Annually about 2 10^{12} Bq of radon diffuse from the water into the air, resulting in a mean indoor concentration of about 300 Bq m^{-3} in buildings situated in the central part of the town, and up to 10^5 Bq m^{-3} in the spa facilities [U10].

218. The annual exposures of employees of the spa, who inhale air with radon concentrations of up to 10^5 Bq m^{-3}, are estimated to be between 1 and 40 WLM [U10], corresponding to an effective dose equivalent of 8–300 mSv.

219. Individuals undergoing deliberate exposure include children recovering from poliomyelitis and other neurological diseases, who may spend up to several years in a special children's sanatorium. Their annual exposure is estimated to be about 0.7 WLM [U10] corresponding to an effective dose equivalent of about 4 mSv. Adults who breathe the radon-rich air in the inhalation facilities of the spa are estimated to receive 0.2 WLM from the standard two-week course, which involves a total exposure time of about four hours.

220. Uzunov et al. [U10] conclude their paper with the following statement: "The highly positive effects of balneological treatment for man as claimed by balneologists are not questioned by us. However, whether radon represents a necessary and justifiable component seems to be doubtful. Considering the world-wide attempts to reduce deliberate irradiation of man by ionizing radiation it seems an apparent anachronism to expose significant population groups, to a large extent, even uncontrolled, to one of the strongest known carcinogens, i.e. the atmospheric alpha emitting radon decay products."

VI. ENERGY CONSERVATION AND LEVELS OF RADON IN AIR

221. In recent years many countries have established significant programmes to conserve energy. This chapter will consider the consequences of energy conservation in terms of effective dose equivalents caused by inhalation of radon and radon daughters in the air.

222. Energy conservation in industry means a possible increase in the effectiveness of the use of machines and rooms and a decrease in energy consumption by maintenance and service systems. The ventilation system may be switched off or used at a reduced level, in compliance with regulations prescribed by the authorities. In general, a reduction of the ventilation rate increases the radon and radon daughter exposure, unless special countermeasures are taken. For example, reduced ventilation during nights and weekends requires consideration of the minimum time for ventilation before work starts. In mines particularly, the radon and radon daughter concentrations may increase by several orders of magnitude when ventilation is reduced and several hours of maximum ventilation may be necessary before work starts [S16]. It can be inferred from Table 19 that an increase of 1 Bq m^{-3} in the average equilibrium equivalent radon concentration in a mine leads to an increase in the annual effective dose equivalent of about 30 μSv.

223. In houses, energy conservation may involve reduction of ventilation by sealing of windows and doors or by reduction of exhaust ventilation. These measures enhance the radon concentrations approximately in inverse proportion to the ventilation rates (for ventilation rates $\lambda_v > 0.1$ h^{-1}). Other procedures which will influence the radon concentrations are recirculation of the air to reduce the effective ventilation, and the use of "heat-conserving beds", i.e., the circulation of air through pieces of rock under the house, which will enhance the radon concentration because of exhalation from the rock [N3, S47]. Similarly, a reduction in the admission of outside air by a cooling system in a house will reduce the ventilation rate.

224. The principal methods of calculating the increased radon and radon daughter concentrations as a result of decreased ventilation rates in an energy conservation programme will be given for houses. The radiological impact is expressed as the excess collective effective dose equivalent (man Sv). Decisions on energy conservation may relate to existing houses or new houses and practical energy conservation programmes may be different in these two cases. However, the methods of calculation of doses with and without a defined energy conservation programme are in principle the same in both cases.

225. To estimate the radiological impact, the difference has to be calculated between the collective doses before and after the programme has been realized. As the ventilation decreases from λ_{v1} to λ_{v2} (h^{-1}) the radon activity concentration increases from $\chi_{a,Rn,1}$ to $\chi_{a,Rn,2}$ (Bq m^{-3}) according to the formulae

$$\chi_{a,\,Rn,\,1} = \frac{\dot{A}/V}{\lambda_{v1}} \tag{33}$$

(the small correction required by a normal radon concentration outdoors has been neglected)

$$\chi_{a,\,Rn,\,2} = \frac{\dot{A}/V}{\lambda_{v2}} \tag{34}$$

$$\Delta\chi_{a,\,Rn} = \frac{\dot{A}}{V}\,\frac{\lambda_{v1} - \lambda_{v2}}{\lambda_{v1}\,\lambda_{v2}} \tag{35}$$

where $\dot{A}/V$ is the source term (Bq m^{-3} h^{-1}) including radon emanation (Bq h^{-1}) from building materials, the ground under the house, and releases from water and gas as seen in equation (21).

226. The number of people exposed are grouped according to the type of house (source terms and venti-

lation) and, after measurements or calculations of average radon and radon daughter concentration in these types of houses, the collective dose can be estimated. As can be seen from equation (35), as long as the source term remains constant and does not change as a consequence of an energy conservation programme, the change in radon concentration depends only on the ventilation rates. The radon daughter concentration (and hence the equilibrium factor F) will increase because of the decreased ventilation rate. Table 5 shows that the factor F will increase as λ_v decreases, if the deposition effect is not taken into account. An estimation which only takes into account the relative increase in the radon concentration will therefore underestimate the impact of reduced ventilation, as will be shown below.

227. The dose caused by inhalation of radon daughters in air with radon concentration $\chi_{a,Rn}$ is $J_c F \chi_{a,Rn}$ where J_c is the dose conversion coefficient and F the equilibrium factor. If the ventilation is changed from λ_{v1} to λ_{v2} the increase in the dose will be

$$(\Delta D)_1 = D_2 - D_1 = J_c \frac{A}{V} \left[\frac{F_2}{\lambda_{v2}} - \frac{F_1}{\lambda_{v1}} \right] =$$

$$= J_c \frac{A}{V} F_1 \frac{\frac{F_2}{F_1} \lambda_{v1} - \lambda_{v2}}{\lambda_{v1} \lambda_{v2}} \qquad (36)$$

If it is assumed that the equilibrium factor is unchanged and has the value F, the estimated increase in the dose will be

$$(\Delta D)_2 = D_2 - D_1 = J_c \frac{A}{V} F_3 \left[\frac{1}{\lambda_{v2}} - \frac{1}{\lambda_{v1}} \right] =$$

$$= J_c \frac{A}{V} F \frac{\lambda_{v1} - \lambda_{v2}}{\lambda_{v1} \lambda_{v2}} \qquad (37)$$

The ratio $(\Delta D)_1/(\Delta D)_2$ is a measure of the degree of underestimation. For values $0.5 < \lambda_v < 1$ h^{-1} and a value F = 0.5 (as recommended in this Annex, paragraph 136) the underestimation will be less than about a factor of 2.5. The formulae and conclusions above do not include houses with gas heating in which case, as mentioned earlier, the radon release rate will decrease because of the reduced consumption of gas. However, as can be seen in Table 13, the relative contribution of radon from gas may be of little significance.

228. As an example, the radiological consequences of a proposed energy conservation programme in Sweden is given [S36]. In Sweden the total electrical energy consumption (transformation and transfer losses excluded) was about 45 GW a in 1977. About 10 GW a was used in dwellings and of that about 7 GW a was used for heating. Of that, 25% was lost by ventilation. It has been postulated that significant amounts of energy could be conserved by reducing the ventilation and improving the ventilation systems. A decrease in the ventilation rate by 0.2–0.3 h^{-1} has been discussed.

229. By measuring ventilation and radon and radon daughters in different types of houses and building materials, it has been possible to estimate the average radon concentration and collective effective dose equivalents and their change with a change in the ventilation rate. The calculations have only included houses with natural draught ventilation systems and those with a ventilation rate greater than 0.5 h^{-1}. One alternative in the energy conservation programme was to reduce ventilation to a rate not lower than 0.5 h^{-1}. The results of comparing the amount of energy conserved and the resultant increase in the collective doses, are presented in Table 48 (after recalculation of the values in terms of effective dose equivalents and using the dosimetric coefficients given in Table 22). The equilibrium factor F is assumed to be 0.5 and unchanged. The values in Table 48 can be compared with the total annual collective effective dose equivalent from houses in 1975 of about 18 000 man Sv (8.2 10^6 persons multiplied by 2.2 mSv a^{-1}), assuming a radon daughter concentration of 36 Bq m^{-3} (see Table 37). Assuming that the weighted average figure of 5.6 man Sv (MW a)$^{-1}$ applies generally, the relative increase in individual annual effective dose equivalent per MW a of electrical energy saved is about 0.03%. The effects of the radon activity concentration in air in houses caused by an energy conservation programme is much dependent on local circumstances. The example given above from Sweden is relevant only for Swedish conditions because of existing high normal radon concentrations and low ventilation rates. However, energy conserved by decreasing the ventilation will always increase the radon and radon daughter concentration.

VII. SUMMARY

230. Radon and thoron are naturally-occurring radioactive gases, which are products of the uranium and thorium decay series, respectively. Uranium and thorium occur widely in the environment, in rock, soil, air, water, building materials, man, etc. Some of the radon and thoron diffuses from the material in which it is formed, is dispersed in ground water and in air. The total equilibrium amount of radon in air is of the order of 10^{18} Bq. The corresponding value of thoron is several orders of magnitude less. Of the total global inventory of radon, radium in soil contributes two orders of magnitude more than any other source.

231. The decay of radon and thoron and the subsequent decay of their daughters terminates with the formation of stable lead. The radon and thoron daughters occur in the same media as their precursors. It takes some time, of the order of one hour, for the daughter products to reach equilibrium. Because of this, and because of deposition on surfaces, there is often less than equilibrium amounts of the daughter products in air and water. The equilibrium factor is a measure of this deficit in air. Radon and thoron daughters in air are predominantly attached to aerosols. A minor part, normally less than 10%, occur as unattached atoms or ions. The relative distribution of attached and unattached daughters in air and the equilibrium factor depend on many variables, such as the decay constant, the concentration and size distribution of aerosols and the ventilation rates. Increased ventilation decreases the concentration of radon and thoron daughters in air.

232. The distribution of radon, thoron and their decay products in outdoor air depends on the vertical temperature gradient, the direction and strength of the wind and the air turbulence. Owing to its short half-life, thoron occurs only within a few tens of metres above ground, while radon occurs up to an altitude of several kilometres. The concentration at ground level depends on meteorological conditions and geographical location. Normally a minimum concentration occurs in the spring and summer and a maximum in the autumn

and early winter. Mean annual values of radon concentration in outdoor air vary between 0.1 and 10 Bq m^{-3}. The higher concentrations are found in air above continental areas and the lower concentrations in air over arctic areas and above the sea. An average value of 3 Bq m^{-3} over land and an equilibrium factor of 0.6 or less for radon daughters outdoors is probably a reasonable estimate. The concentration of ^{212}Pb is normally about one order of magnitude less than that of radon.

233. In closed spaces, e.g., a mine or a house, the concentrations in air of radon, thoron and their decay products are higher than outdoors. In houses the radon daughter levels may be enhanced by radon from radium-rich building materials, landfill, soil and bedrock under the house, radon-rich water and by poor ventilation. The radon activity concentration in water varies from practically zero to very high values of the order of 100 MBq m^{-3}. The radon levels indoors may be enhanced by any of these sources and reach values as high as 10 000 Bq m^{-3}. Normal values of radon daughter activity concentration indoors are of the order of 20 Bq m^{-3}. Annual occupational exposure to radon daughters in mines and other working places underground is generally less than 4 WLM corresponding to an equilibrium equivalent concentration of radon of about 1000 Bq m^{-3}. In well-ventilated mines the equilibrium factor is low (< 0.5). In unventilated parts of mines radon concentrations as high as 1 MBq m^{-3} or even more may occur.

234. Inhalation of radon and thoron daughters leads to deposition in the human respiratory tract and consequent irradiation. The deposition depends on various factors, such as the size distribution of the aerosols to which the daughter products of radon and thoron are attached, and the fraction of unattached daughters. On average, the dose to the bronchial basal cell layer in the lung is about 5 to 8 times higher than the dose to the pulmonary region. The effective dose equivalent for radon and thoron daughter exposures may be calculated using weighting factors for the regional distribution of lung dose and the mean lung dose. The Committee's present estimate of mean annual effective dose equivalent is 1 mSv and arises mostly from radon in houses. There is little experimental information to provide a good estimate of the annual effective dose equivalent from thoron daughters; a value of 0.2 mSv is tentatively proposed. The radon and thoron daughter concentrations in air, and resulting doses given in this Annex refer mainly to countries in temperate parts of the world. Taking into account that about two-thirds of the total world population is living in temperate regions, a global mean value of about 0.8 mSv per year—averaged over all age groups—from inhaled ^{222}Rn daughters and of about 0.17 mSv per year from inhaled ^{220}Rn daughters would be expected. Occupational exposure to radon daughters in uranium mines causes average annual effective dose equivalents of about 15 mSv, and similar exposures have been encountered in some non-uranium mines.

Table 1

Radioactive decay properties of ^{226}Ra and its daughters
[E5, L12]

Radionuclide	Historical name	Half-life	Major radiation energies and intensities					
			α		β		γ	
			MeV	%	MeV	%	MeV	%
$^{226}_{88}Ra$	Radium	$1.6\ 10^3$ a	4.60 4.78	6 94			0.186	3.3
↓								
$^{222}_{86}Rn$	Emanation Radon (Rn)	3.823 d	5.49	100				
↓								
$^{218}_{84}Po$	Radium A	3.05 min	6.00	~100				
↓								
99.98% 0.02%								
↓ |								
$^{214}_{82}Pb$ |	Radium B	26.8 min			0.67 0.73 1.02	48 42 6	0.295 0.352	19 37
| $^{218}_{85}At$	Astatine	~ 2 s	6.65 6.69 6.76	6 90 3.6	?	~ 0.1		
↓								
$^{214}_{83}Bi$	Radium C	19.7 min	5.45 5.51	0.012 0.008	1.0 1.51 3.26	23 40 19	0.609 1.12 1.764	46 15 16
99.98% | 0.02%								
↓ |								
$^{214}_{84}Po$ |	Radium C'	164 μs	7.69	100				
| $^{210}_{81}Tl$	Radium C"	1.3 min			1.3 1.9 2.3	25 56 19	0.296 0.795 1.31	80 100 21
↓								
$^{210}_{82}Pb$	Radium D	22.3 a			0.015 0.061	81 19	0.047	4
↓								
$^{210}_{83}Bi$	Radium E	5.01 d			1.161	~100		
↓								
~100% 0.0001%								
↓ ↓								
$^{210}_{84}Po$	Radium F	138.4 d	5.305	100				
$^{206}_{81}Tl$	Radium E"	4.2 min			1.53	100		
↓								
$^{206}_{82}Pb$	Radium G	Stable						

Radioactive decay properties of ^{228}Th and its daughters
[E5, L12]

Radionuclide	Historical name	Half-life	Major radiation energies and intensities					
			α		β		γ	
			MeV	%	MeV	%	MeV	%
$^{228}_{90}Th$	Radiothorium	1.913 a	5.34 5.43	27 73			0.084 0.216	1.2 0.3
↓								
$^{224}_{88}Ra$	Thorium X	3.66 d	5.45 5.68	6 94			0.241	3.9
↓								
$^{220}_{86}Rn$	Emanation Thoron (Tn)	55 s	6.29	100			0.55	0.1
↓								
$^{216}_{84}Po$	Thorium A	0.15 s	6.78	100				
↓								
$^{212}_{82}Pb$	Thorium B	10.64 h			0.331 0.569	83 12	0.239 0.300	43 3.2
↓								

Table 1, continued

Radionuclide	Historical name	Half-life	Major radiation energies and intensities					
			α		β		γ	
			MeV	%	MeV	%	MeV	%
$^{212}_{83}Bi$	Thorium C	60.6 min	6.05	25	1.55	5	0.040	1.1
			6.09	10	2.26	55	0.727	11.8
							1.620	2.8
64% 36%								
$^{212}_{84}Po$	Thorium C'	304 ns	8.78	100				
$^{208}_{81}Tl$	Thorium C"	3.05 min			1.28	23	0.511	23
					1.52	22	0.583	86
					1.80	51	0.860	12
							2.614	100
$^{208}_{82}Pb$	Thorium D	Stable						

Table 2

Properties of radon
[J7, H4, W3]

Property		Value	
Volume of 1 Bq of ^{222}Rn at NTP		$1.6\ 10^{-20}\ m^3$	
Boiling point		$-\ 61.8^{\circ}$ C	
Melting point		$-\ 71^{\circ}$ C	
Vapour pressure at	$-\ 144^{\circ}$ C	0.13 kPa	
	$-\ 126.3^{\circ}$ C	1.3 kPa	
	$-\ 111.3^{\circ}$ C	5.3 kPa	
	$-\ 99^{\circ}$ C	13 kPa	
	$-\ 71^{\circ}$ C	53 kPa	
	$-\ 61.8^{\circ}$ C	100 kPa	
Density at NTP		$9.96\ kg\ m^{-3}$	
Coefficients of solubility[a/] at atmospheric pressure			
in water	at 0° C	0.507	
	10° C	0.340	
	20° C	0.250	
	30° C	0.195	
	37° C	0.167	
	50° C	0.138	
	75° C	0.114	
	100° C	0.106	
		at 18° C	at 0° C
in glycerine		0.21	-
aniline		3.80	4.45
absolute alcohol		6.17	8.28
acetone		6.30	7.99
ethyl acetate		7.35	9.41
petroleum (liquid paraffin)		9.20	12.6
xylene		12.75	-
benzene		12.82	-
toluene		13.24	18.4
chloroform		15.08	20.5
ether		15.08	20.09
hexane		16.56	23.4
carbon bisulphide		23.14	33.4
olive oil		29.00	-

a/ The solubility coefficient or partition coefficient in water is defined as the ratio x_w/x_a, where x_w and x_a are the radon concentrations in water and air, respectively.

Table 3

Calculated potential alpha energy of radon and thoron and their short-lived decay products

Radio-nuclide	Potential alpha energy per atom $E_{pot,at}$		Potential alpha energy per unit of activity $E_{pot,at}/\lambda_j$		Potential alpha energy concentration (C_{pot}) per unit of activity concentration
	MeV	10^{-12} J	MeV Bq^{-1}	10^{-10} J Bq^{-1}	10^{-6} WL (Bq m^{-3})$^{-1}$
^{222}Rn	19.2	3.07	9150000	14700	
^{218}Po	13.7	2.19	3620	5.79	27.8
^{214}Pb	7.69	1.23	17800	28.6	137
^{214}Bi	7.69	1.23	13100	21.0	101
^{214}Po	7.69	1.23	0.002	0.000003	0.000016
Total (Rounded) a/			34500	55.4	266
^{220}Rn	20.9	3.34	1660	2.65	
^{216}Po	14.6	2.34	3.32	0.00532	0.0256
^{212}Pb	7.8	1.25	431000	691	3320
^{212}Bi	7.8	1.25	40900	65.6	315
^{212}Po	8.78	1.41	0.00000305	0.0000000062	0.00000003
Total (Rounded) a/			472000	757	3640

a/ The total is the sum of the potential alpha energies of the daughters only.

Table 4

Calculated equilibrium equivalent concentration of radon and thoron as a function of the potential alpha energy concentration C_{pot}

Radon $x_{eq,Rn}$ (Bq m^{-3})	Thoron $x_{eq,Tn}$ (Bq m^{-3})
2.90 10^{-5} (Bq MeV^{-1}) C_{pot} (MeV m^{-3})	2.12 10^{-6} (Bq MeV^{-1}) C_{pot} (MeV m^{-3})
1.81 10^{8} (Bq J^{-1}) C_{pot} (J m^{-3})	1.32 10^{7} (Bq J^{-1}) C_{pot} (J m^{-3})
3700 (Bq m^{-3} WL^{-1}) C_{pot} (WL)	275 (Bq m^{-3} WL^{-1}) C_{pot} (WL)

Table 5

Equilibrium ratios for radon daughters and equilibrium factor F for various ventilation rates

Ventilation rate λ_v (h^{-1})	Equilibrium ratio $x_{a,j}/x_{a,Rn}$			Equilibrium factor F
	^{218}Po	^{214}Pb	^{214}Bi	
0.0	1.0	1.0	1.0	1.0
0.1	0.993	0.956	0.913	0.928
0.3	0.978	0.820	0.718	0.784
0.5	0.965	0.729	0.590	0.689
0.7	0.951	0.655	0.530	0.628
1.0	0.932	0.566	0.384	0.526
1.5	0.900	0.473	0.277	0.436
2.0	0.872	0.381	0.195	0.356
3.0	0.820	0.279	0.115	0.269
5.0	0.732	0.173	0.051	0.182
10.0	0.577	0.077	0.013	0.103

Table 5, continued

Ventilation rate λ_v (h^{-1})	Equilibrium ratio $x_{a,j}/x_{a,Tn}$			Equilibrium factor F
	^{216}Po	^{212}Pb	^{212}Bi	
0.0	1	1	1	1
0.1	1	0.395	0.345	0.391
0.3	1	0.179	0.125	0.174
0.5	1	0.116	0.067	0.112
0.7	1	0.086	0.042	0.082
1.0	1	0.061	0.025	0.058
1.5	1	0.042	0.013	0.039
2.0	1	0.032	0.008	0.030
3.0	1	0.021	0.004	0.020
5.0	1	0.013	0.0016	0.012
10.0	1	0.006	0.0004	0.006

Table 6

Published values of radon exhalation rates per unit area [W15]

Location a/	Soil group	Radon exhalation rate per unit area (mBq m^{-2} s^{-1})	Original ref.
Austria			
Graz	Mountain	20, 9	[K21]
Innsbruck	Mountain	8.6	[Z1]
Innsbruck	Mountain	19	[Z2]
France			
Saclay (80)	Podsolic	15, 14	[S50]
Germany, Fed. Rep.			
Aachen	Podsolic	17	[I12]
Ireland			
Dublin	Podsolic	27	[S51]
Japan			
Osaka (4,4)	Latosolic	3.4, 8.8	[M24]
Philippines			
Manila	Latosolic	11	[W18]
United States			
Socorro, New Mexico (10)	Desertic	34 ± 3.4	[W19]
Socorro, New Mexico (6)	Desertic	38 ± 11	[P16]
Yucca Flat, Nevada	Desertic	18	[K17]
Lincoln, Massachusetts (10)	Podsolic	50	[K17]
Champaign County, Illinois (472)	Chernozemic	53	[P16]
Argonne, Illinois (8)	Chernozemic	21 ± 1.9	[P16]
USSR			
Kirov (36)	Podsolic	15	[M25]
Moscow (6)	Podsolic	3.8	[M25]
Central European Territory (40)	Podsolic	6.9	[S52]
Southwest Kazakhstan (5)	Desertic	5.0	[S52]
Sandy desert (Muyun Kum, Ashkhabad, Dzhusaly) (10,5)	Desertic	4.8, 13	[K22]
The North (Murmansk, Arkhangelsk)(6)	Podsolic	3.8	[K22]
Central European Territory (35) Leningrad, Moscow, Kaluga reg.	Podsolic Chernozemic	7.3	[K22]
The Caucasus (15) Grozny, Baku, Tbilisi, Adler	Mountain Chernozemic	11	[K22]
Middle Asia (10) Tashkent, Alma-Ata, Frunze	Mountain Desertic	19	[K22]
South Urals (5) Sverdlovsk	Mountain Podsolic	11	[K22]
Chelyabinsk	Mountain Podsolic	11	[K22]

Table 7

Radon exhalation from rock and uranium minerals
[19]

Type of rock	Radium activity concentration (Bq kg^{-1})	Radon exhalation rate for cores ($mBq\ m^{-2}\ s^{-1}$)	($\mu Bq\ m^{-2}\ s^{-1}$ / (Bq kg^{-1}))
Leptite a/	79	0.4	5.1
Aptite (1)	460	1.2	2.6
Aptite (2)	280	0.88	3.1
Pegmatite (1)	340	5.3	15.6
Pegmatite (2)	330	8.3	25.2
Uranium minerals			
Sample 1	110000	260	2.4
Sample 2	310000	780	2.5
Sample 3	81000	170	2.1
Sample 4	72000	63	0.9
Sample 5	4500000	190	0.04
Sample 6	240000	7.8	0.03
Sample 7	28000	10	0.36

a/ The radon exhalation rate from a gallery surface was 7.4 mBq $m^{-2}s^{-1}$.

Table 8

Activity concentrations (kBq m^{-3}) of ^{220}Rn and ^{222}Rn at different depths for different pressure conditions
[19]

Nuclide	Depth (m)	Barometric pressure (mb)			
		971	993	1007	1028
^{222}Rn	0.1	38	38	16	19
	0.4	47	51	22	24
	0.9	64	67	43	45
^{220}Rn	0.1	120	97	90	87
	0.4	130	120	120	140

Table 9

Concentrations (kBq m^{-3}) of ^{220}Rn and ^{222}Rn at different depths for different wind speeds
[19]

Nuclide	Depth (m)	Wind speed at a height of 10m ($m\ s^{-1}$)			
		1.5	3.3	5.7	7.9
^{222}Rn	0.1	36	26	20	23
	0.4	46	37	30	28
	0.9	75	58	44	44
^{220}Rn	0.1	100	99	74	91
	0.4	120	120	120	150

Table 10

Mean activity concentrations of some building materials

Country	Material	Number of samples	Mean activity concentration (Bq kg^{-1})		Ref.	Comments
			^{226}Ra	^{232}Th or ^{228}Th		
Germany, Federal Republic of	Building sand and gravel	50	< 15	< 19	[N2]	Many sources
	Granite	32	100	81	[N2]	Different types
	Bricks (traditional constituents)	109	59	67	[N2]	Different types
	Pumice-aggregate concrete blocks	31	74	81	[N2]	Adequate sampling
	Slag-aggregate concrete blocks	9	152	100	[N2]	Depends on feed materials
	Portland cement	14	< 26	< 19	[N2]	Several sources
	Natural gypsum	23	< 19	< 11	[N2]	Many sources
	Chemical gypsum (phosphogypsum)	33	555	< 19	[N2]	Depends on source of rock
	Red mud bricks	23	281	233	[N2]	Variable composition
	Fly ash	28	211	130	[N2]	Many sources
Hungary	Concrete	95	13	11	[T7]	Average weighted by the relative production
	Brick	176	56	48	[T7]	Average weighted by the relative production
Italy	Lithoid tuff (tufo litoide, Monte Cimino)	-	129	122	[N2]	Commonly used for house building
	Nenfro (a variety of tuff, Tuscania)	-	241	218	[N2]	Wall cladding material
Poland	Fly ash	106	63-610	33-320	[P4]	Typical building material used in Poland
	Slag	42	19-460	22-590	[P4]	
	By-product gypsum	4	26-740	11-44	[P4]	
	Red brick	3	19-22	22-44	[P4]	
	Silicon brick	3	7.4-15	<4-7.4	[P4]	
	Cement	4	7.4-26	11-67	[P4]	
	Soil	5	3.7-19	<4-15	[P4]	
United Kingdom	Granites	7	89	81	[H2]	Inadequate sampling
	Sand and gravel	10	4	7	[02]	Inadequate sampling
	Cement	6	22	18	[02]	Inadequate sampling
	Clay bricks	25	52	44	[H2]	Sampling probably inadequate
	White bricks (autoclaved flint and quicklime)	5	4	5	[H2]	Aggregate may vary
	Natural gypsum	73	22	7	[H2]	Adequate sampling
	Lightweight blocks various aggregates	10	59	26	[H2]	Inadequate sampling
	Phosphogypsum from sedimentary ores	60	629	18	[02]	Depends on ore source
United States (exceptional values)	Phosphate land fill, Florida	-	740	-	[U2]	Estimate depends on geological structure and reclamation procedure
	Gypsum from Florida phosphate rock	-	1221	10	[U3]	Samples from several processing facilities
	Uranium mine tailings	-	4625	-	[C11]	Personal assay of complex situation

Table 11

Mean activity concentrations of some building materials in Nordic countries

($Bq\ kg^{-1}$)

Building material	Country	No. of samples	^{226}Ra			^{232}Th			Comments	Ref.
			Min.	Aver.	Max.	Min.	Aver.	Max.		
Brick	Denmark	79	23	42	86	21	34	58	Adequate sampling	[U1]
	Finland	37	37	80	134	37	62	91	Adequate sampling	[M21]
	Norway	18		63			74			[S41]
	Sweden	12	41	96	152	100	127	178	Inadequate sampling	[S42]
Bricks of limestone	Denmark	5	6	8	11	4	7	11	Adequate sampling	[U1]
	Finland	3	20	22	25	18	23	29	Inadequate sampling	[M21]
	Sweden	3	7	10	15	4	8	10	Inadequate sampling	[S42]
Concrete	Denmark	6	13	16	24	9	13	17	Inadequate sampling	[U1]
	Finland	12	50	61	80	28	37	42		[M22]
	Norway	137	11	28	37	21	36	54	Standard deviation 38%	[S41]
	Sweden	14	32	47	58	56	80	105	Inadequate sampling	[H1]
Cement	Denmark	6	9	20	30	4	12	21	Adequate sampling	[U1]
	Finland	9	20	44	84	8.5	22	55	Inadequate sampling	[M21]
	Norway	4		30			19		Inadequate sampling	[S23]
	Sweden	16	20	41	168	24	40	81	Adequate sampling	[L11,S42]
Concrete ballast (gravel, shingle macadam)	Denmark	107	4	19	95	4	13	56	Adequate sampling	[U1]
	Finland	266	7	34	146	1.6	39	226	Adequate sampling	[M21]
	Sweden	306	7	48	167	3	72	463	Adequate sampling	[H1]
Aerated concrete based on sand	Denmark	2		18			10		Inadequate sampling	[U1]
	Finland	2	45	49	53	31	36	40	Inadequate sampling	[M21]
	Sweden	24	7	35	130	4	42	155	Adequate sampling	[S42]
Aerated concrete based on alum shale a/	Denmark	2		670			53		Swedish origin	[U1]
	Sweden	70	620	1300	2620	30	67	115	Adequate sampling	[S42]
Aerated concrete based on alum shale b/	Sweden	12	320	466	560	24	30	37	Adequate sampling	[S42]
Plasterboards										
Natural gypsum	Denmark	7	6	10	13	4	4	6	Adequate sampling	[U1]
	Sweden	8	1	4	9	1	1	12	Adequate sampling	[S42]
Phosphogypsum	Sweden	1		27		65			Inadequate sampling	[S42]
Gypsum										
Natural	Denmark	6	4	7	10	4	4	4	Adequate sampling	[U1]
	Finland	1		7		1.5			Inadequate sampling	[M21]
	Norway	2		11		3			Inadequate sampling	[S23]
Phosphogypsum	Finland	4	24	178	330	3.4	12	22	Inadequate sampling	[M22]
Light-weight aggregate	Denmark	3	36	40	43	37	45	51	Inadequate sampling	[U1]
	Norway	12		51			56		Inadequate sampling	[S42]
	Sweden	6	135	170	195	153	164	186	Inadequate sampling	[S42]
Slag aggregate	Finland	3	88	102	113	32	69	94	Inadequate sampling	[M21]
	Sweden	2	84	118	151	114	148	182	Inadequate sampling	[U1]
Insulation material wool of stone or glass	Denmark	5		40			40		Inadequate sampling	[U1]
	Finland	2	8.9	19	29	4.6	8.9	13	Inadequate sampling	[M21]
	Sweden	3	11	13	15	15	15	15	Inadequate sampling	[S42]
Tile	Finland	5	63	78	91	32	46	64	Inadequate sampling	[M21]
Fly ash	Denmark	10	110	150	210	74	90	160	Adequate sampling	[U1]
Wood	Finland	2	0.3	0.4	0.5	0.2	0.7	1.2	Inadequate sampling	[M21]
Clinker	Denmark	13	22	66	108	22	55	73	Inadequate sampling	[U1]

a/ In production 1929-1975.

b/ In production 1974-1979.

Table 12

Radon concentration in natural gas at the well
[H8, S43, J8, G18, W21]

Location of well	Radon concentration ($kBq\ m^{-3}$)	
	Average	Range
Canada		
Alberta	2	0.4-8
British Columbia	18	14 - 20
Ontario	6	0.15-30
Germany, Fed. Rep. of	-	0.04-0.4
Indonesia		
Borneo, Ampa field	-	0.06-0.12
Netherlands		
Slochteren	-	0.044-0.10
Other fields	-	0.14-2
Nigeria		
Niger delta	-	0.034-0.11
United States		
Colorado, New Mexico	0.9	-
Oklahoma, Kansas, Texas	4	0.2-54
Texas Panhandle	-	0.4-19
Colorado	0.9	0.4-2
Project Gasbuggy area	0.6	-
California	-	0.04-4
Kansas	4	-
Wyoming	0.4	-
Gulf Coast (Louisiana, Texas)	0.2	-
California, Louisiana, Oklahoma, Texas	-	0.04-4
North Sea		
Leman field	-	0.07-0.14
Indefatigable field	0.08	-
7 streams supplying United Kingdom	0.03	0.01-0.04

Table 13

The relative significance of different radon sources in a reference house

Source	Radon emission per unit time ($kBq\ d^{-1}$)	Comments
Building materials and soil under the building[a/]	60	Exhalation rate $2\ 10^{-3}$ Bq $m^{-2}s^{-1}$
Water	4	1 $m^3\ d^{-1}$ and 4 $kBq\ m^{-3}$, 100 % release
Outside air	10	Radon concentration outdoors 4 Bq m_1^{-3}, ventilation rate 0.5 h^{-1}
Natural gas	3	
LPG	0.2	

a/ In some houses the soil may be the dominating source.

Table 14

Description of the test sites in private and public buildings in Innsbruck, Austria [S21]

Test site No.	Purpose of the test site	Building material	Distance from the ground (m)	Time (d)
1	Control station: cellar	Brick	-1	84
2	Control station: living-room	Brick	4	234
3	Control station: office	Brick	15	58
4	Laboratory	Brick	20	22
5	School storage room	Brick	-1	21
6	School library	Brick	14	25
7	Storage room	Brick, concrete	-2	31
8	School library	Brick, stone	12	24
9	Storage room	Brick	1	25
10	School storage room	Brick	7	18
11	School classroom	Brick	5	18
12	Warehouse	Wood	0	17

Table 15

Activity concentrations in room air of private and public buildings in Innsbruck, Austria [S21]

Test site No.	^{222}Rn (Bq m^{-3})					^{214}Pb (Bq m^{-3})				
	Max.	Min.	Δ_x [a]	Median	Mean	Max.	Min.	Δ_x [a]	Median	Mean
1	276	26.3	81.4	108	115	184	26.3	71.4	98.1	103
2	174	<1.9	115	31.5	32.6	49.6	4.07	26.6	18.9	19.2
3	61.1	<1.9	37.4	29.6	30.7	52.2	8.88	30.0	24.8	25.5
4	34.0	<5.6	13.7	13.0	13.3	27.4	<1.9	17.8	8.88	10.7
5	82.9	22.9	21.8	45.1	46.3	73.3	21.5	25.5	38.9	40.0
6	74.0	15.2	24.8	42.6	43.3	57.0	9.25	21.1	29.2	30.0
7	124	<5.6	72.9	45.9	50.0	81.8	2.22	59.2	30.7	38.1
8	61.1	16.7	17.4	41.4	42.2	29.6	12.2	6.66	18.5	19.6
9	82.5	<5.6	53.3	35.5	37.0	46.6	2.22	25.2	20.0	20.7
10	80.7	42.9	20.4	57.4	58.1	71.4	28.1	30.0	45.5	46.3
11	45.9	6.29	36.3	27.0	27.8	45.1	5.55	34.0	24.4	25.9
12	58.8	11.5	24.8	32.6	33.7	54.0	2.96	30.0	21.1	22.9

Test site No.	^{220}Rn (Bq m^{-3})					^{212}Pb (mBq m^{-3})				
	Max.	Min.	Δ_x [a]	Median	Mean	Max.	Min.	Δ_x [a]	Median	Mean
1						5720	1500	1420	3350	3470
2						4110	755	2180	2000	2090
3						6560	2230	2340	4560	4700
4	28.1	<3.3	17.0	7.40	7.77	947	455	363	692	703
5	16.3	<3.3	11.1	8.51	8.51	4590	481	1910	2450	2850
6	10.0	5.55	52.2	37.0	40.7	3620	1340	555	1880	2180
7	35.9	<3.3	14.1	14.8	18.5	3300	747	1520	1860	1940
8	74.0	23.3	10.0	39.2	41.4	4920	2890	492	3570	3600
9	32.6	<3.3	17.8	10.4	11.1	2780	344	2080	1890	1900
10	35.5	11.8	16.7	19.2	20.7	3130	1580	718	2280	2320
11	8.88	<3.3	4.44	3.7	3.7	2600	710	881	1670	1750
12	33.7	7.77	13.0	19.2	20.7	507	59.2	259	285	329

[a] Δ_x is the largest observed increase of the activity concentration within 24 hours.

Table 16

Correlation between radon and thoron concentration in houses and meteorological variables
[S21]

Meteorological variable	Observation time of meteorological change	Sign of regression coefficient
Change of barometric pressure	24 h	-1
Change of barometric pressure	10 h	-1
Change of soil temperature at 50 cm depth	24 h	+1
Change of daily mean temperature in the open atmosphere	24 h	+1
Change of daily mean wind speed	24 h	-1
Temperature gradients between 574 and 918 m above sea level at 7 h		+1
Change of relative humidity in the open atmosphere	7 h	-1
Change of temperature in the open atmosphere	7 h	+1
Change of daily range of temperature in the open atmosphere	24 h	-1

Table 17

Equilibrium factors in dwellings in Finland 1977-1978
[M20]

Type and number of dwellings	Radon concentration ($Bq\ m^{-3}$) Max.	Mean	Min.	Equilibrium factor F
Block of flats, concrete (15)	140	48	7.4	0.45
Detached houses, concrete (2)	190	130	48	0.30
Block of flats, brick (7)	56	26	7.4	0.63
Detached houses, brick (5)	85	33	15	0.45
Detached houses, wood (6)	70	30	7.4	0.43

Table 18

Dose equivalents per unit inhaled potential alpha energy of ^{212}Pb and ^{212}Bi assuming an AMAD of 0.2-0.3 μm and a biological half-time of residence in lung for the transfer from lung to blood in the range of 0.2-0.5 day [J13]

Organ or tissue		Dose equivalent per unit inhaled potential α-energy (Sv J^{-1})	
		^{212}Pb	^{212}Bi
Lung	Bronchial basal cells (B)	3 - 5	9 - 10
	Pulmonary region (P)	1.2 - 2.5	4 - 5
	Total lung average (Lu)	1.5 - 3	5 - 5.5
Red bone marrow		0.25 - 0.15	0.01 - 0.005
Bone lining cells		3 - 2	-
Kidney		2 - 1.2	0.9 -0.4
Liver		0.4 - 0.25	0.02 - 0.01
Spleen		0.08 - 0.05	0.04 - 0.02
Other tissues		0.03 - 0.02	0.01 - 0.005
Effective dose equivalent per unit inhaled potential alpha energy	$w_B=w_P=0.06$	0.6 (0.54 - 0.63)	0.9 (0.84 - 0.93)
	w_{Lu} = 0.12	0.5 (0.47 - 0.54)	0.7 (0.66 - 0.70)
Recommended effective dose equivalent per unit inhaled potential alpha energy for mixtures of ^{212}Pb and ^{212}Bi		0.7	

Table 19

Dosimetric coefficients relative to inhalation of radon daughters by miners

Quantity	Unit	^{222}Rn daughters a/	^{220}Rn daughters b/
H_{eff}/I_{pot}	Sv/J	2	0.7
$H_{eff}/\bar{C}_{pot}$	Sv/(J h m^{-3})	2.4	0.84
	mSv/WLM	8.4	2.9
$H_{eff}/\bar{\chi}_{eq}$	nSv/(Bq h m^{-3})	14	64

a/ For inhalation of ^{222}Rn gas itself the effective dose equivalent per unit activity inhaled is about 1.5 10^{-10} Sv Bq^{-1}.

b/ The values refer to the inhalation of mixtures of ^{212}Pb+^{212}Bi. For inhalation of ^{220}Rn+^{216}Po the effective dose equivalent per unit inhalation intake is about 1 10^{-10} Sv Bq^{-1}.

Table 20

Breathing rates used for dose calculations
[12]

Location	Period	Breathing rate	Activity
Indoors (19 h)	5.5 h	20 l min^{-1}	light activity
	8 h	7.5 l min^{-1}	resting
	5.5 h	12.5 l min^{-1}	intermediate
Outdoors (5 h)	2 h	20 l min^{-1}	
	3 h	12.5 l min^{-1}	
	Indoor total	15 m^3 d^{-1}	
	Outdoor total	5 m^3 d^{-1}	
	Grand total	20 m^3 d^{-1}	

Table 21

Dosimetric coefficients relative to indoor and outdoor inhalation of radon daughters by members of the public[a/]

Quantity	Unit	^{222}Rn daughters		^{220}Rn daughters [b/]	
		Indoors	Outdoors	Indoors	Outdoors
H_{eff}/I_{pot}	Sv/J	2.0	3.0	0.7	0.7
$H_{eff}/\tilde{C}_{pot}$	Sv/J h m^{-3}	1.6	3.0	0.55	0.7
	mSv/WLM	5.5	11	1.9	2.5
$H_{eff}/\tilde{x}_{eq}$	µSv/Bq h m^{-3}	8.7 10^{-3}	17 10^{-3}	40 10^{-3}	53 10^{-3}

a/ See Table 19 for the values relative to inhalation of ^{222}Rn and $^{220}Rn+^{216}Po$.

b/ Inhalation of mixtures of $^{212}Pb+^{212}Bi$.

Table 22

Annual effective dose equivalents per unit of activity concentration, or of potential alpha energy concentration, for daughters of ^{227}Rn and of ^{220}Rn and for outdoor and indoor exposure

(Calculated with an annual breathing volume V_{in} = 5475 m^3 indoors and V_{out} = 1825 m^3 outdoors)

Inhaled	Contribution	H_{eff}/C_{pot} $\frac{Sv}{J\ m^{-3}}$	H_{eff}/x_{eq} $\frac{mSv}{Bq\ m^{-3}}$
^{222}Rn daughters	Indoors	1.1 10^4	0.061
	Outdoors	5.5 10^3	0.031
^{220}Rn daughters a/	Indoors	3.8 10^3	0.29
	Outdoors	1.3 10^3	0.10

a/ Inhaled mixtures of ^{212}Pb and ^{212}Bi.

Table 23

^{222}Rn and ^{212}Pb concentrations in outdoor air

Location	Mean value (Bq m^{-3})		Ref.
	^{222}Rn	^{212}Pb	
Austria	7.0		[S22]
Bolivia	1.5		[L8]
Finland	2.3		[M5]
	3.5		[M5]
	3.8		[M5]
	2.0		[M5]
	2.7		[M5]
	3.6		[M5]
France	9.3		[F4]
Germany, Fed.Rep. of	2.6		[I6]
India	3.7	0.11	[R4]
Japan	2.1		[L8]
Peru	1.5		[L8]
Philippines	0.3	0.01	[B6]
Poland	3.3		[P19]
Soviet Union	6.3		[M2]
	2.6	0.11	[M1]
	3.3	0.12	[M1]
	2.2	0.09	[M1]
United Kingdom	3.3		[H6]
United States (continental)			
Chicago	1.6	0.1	[B6]
	1.5	0.07	[B6]
Washington	2.9	0.07	[B6]
	4.4		[L8]
San Diego	0.1	0.007	[B6]
San Francisco	0.6	0.002	[B6]
Seattle	0.1	0.004	[B6]
Memphis	1.0	0.7	[B6]
New York City	4.8		[G10]
	3.7		[T3]
Chester, N.J.	7.9		[F5]
Cincinnati	9.6		[G12]
New Mexico	8.9		[W6]
Puerto Rico	0.005	0.001	[B6]
Alaska	0.2	0.001	[B6]
North Africa	0.5	0.008	[B6]
Norwegian Sea	0.2		[L5]
Pacific Islands			
Hawaii	0.2		[L3]
	0.05		[B6]
Marshall Islands	0.02		[B6]
Caroline Island	0.02		[B6]
Mariannas (Guam)	0.05		[B6]
Samoa	0.08	0.004	[B6]
Indian Ocean	0.07		[S6]
North Atlantic	0.2		[S6]
South Pacific	0.07		[S6]

Note: The values given in this table should not be considered to be mean values for the entire countries.

Table 24

Normalized annual effective dose equivalent from outdoor exposure (20 % of the total time) to radon daughters from radon released from coal and geothermal plants and from tailings

Distance (km)	Normalized annual effective dose equivalent					
	Coal power plant	Geothermal power plant	Tailings			
			Area = 10^4 m^2		Area = 10^6 m^2	
	nSv(GW(e) a)$^{-1}$	μSv(GW(e) a)$^{-1}$	μSv	μSv(GW(e) a)$^{-1}$	μSv	μSv(GW(e) a)$^{-1}$
0.5	0.88	5.5	2.7	11	21	0.9
1	1.5	9.4	1.1	4.3	14	0.6
2	1.3	7.9	0.3	0.08	8.8	0.4
5	0.57	3.4	0.08	0.3	4.6	0.2
10	0.31	1.8	0.03	0.1	2.4	0.09

Table 25

Radon concentration in water

Location	Number of wells with radon concentration in water				Radon concentration in water		Ref.
	< 37 kBq m^{-3}	37-370 kBq m^{-3}	0.37-3.7 MBq m^{-3}	3.7-37 MBq m^{-3}	Maximum kBq m^{-3}	Average kBq m^{-3}	
Austria							
Salzburg					7	1.5	[S22]
Finland							
Helsinki and Vantaa	4	12	65	29		1200	[C3]
Other areas	11	34	30	7	45000	280	[C3]
Italy	41	16	2	-		80	[M3]
Sweden	155	17	-	-	150	19	[K14]
United States							
Aroostock, Maine	13	19	-	-	200	48	[H10]
Cumberland, Maine	1	6	7	2	5800	1000	[H10]
Hancock, Maine	1	3	11	1	4600	1400	[H10]
Lincoln, Maine	3	6	10	1	1600	560	[H10]
Penobscut, Maine	-	10	6	-	2400	540	[H10]
Waldo, Maine	-	5	9	-	3100	1100	[H10]
York, Maine	-	6	9	-	2200	670	[H10]
All 7 counties	18	55	52	4	5800	660	[H10]
North Carolina	84	117	10	-	1700	100	[S1]

Table 26

Distribution of radon concentration in drinking water in Finland [A7, A11, C4, K18]

Water specification	Number of persons (million)	Radon concentration (kBq m^{-3})	
		Mean	Maximum
Waterworks	3.18	25	1600
Dug wells	1.39	59	1600
Drilled wells	0.15	630	44000
Drilled wells in Helsinki area	0.02	1200	
Weighted average		56	

Table 27

Radon and radon daughter concentrations in Canadian homes [M6]

Location	Radon concentration ($Bq\ m^{-3}$)		Equilibrium equivalent radon concentration ($Bq\ m^{-3}$)	
	Geometric mean	Geometric standard deviation	Geometric mean	Geometric standard deviation
Calgary, Alberta	11	3.6	7.0	2.3
Charlottetown, Prince Edward Island	15	5.3	6.7	2.6
Fredericton, New Brunswick	24	4.0	12	2.9
Halifax, New Brunswick	-	-	11	3.1
Montreal, Quebec	11	3.3	5.2	2.5
Quebec, Quebec	10	3.8	4.8	2.7
Saint John, New Brunswick	10	5.7	6.7	3.0
Sherbrooke, Quebec	13	5.4	8.5	3.3
St. John's, Newfoundland	11	4.4	5.6	2.7
St. Lawrence, Newfoundland	33	6.8	6.3	4.6
Sudbury, Ontario	21	4.0	13	3.0
Thunder Bay, Ontario	20	4.5	9.3	2.6
Toronto, Ontario	11	2.8	6.7	2.6
Vancouver, British Colombia	5.2	3.0	3.3	2.0
Winnipeg, Manitoba	51	4.1	26	3.4
Brandon, Manitoba	30	4.8	16	2.7
Regina, Saskatchewan	47	3.6	19	3.1
Saskatoon, Saskatchewan	16	4.3	16	3.3
Edmonton, Alberta	16	4.6	16	3.3

Table 28

Equilibrium equivalent radon concentration in houses in Canada suspected of having enhanced concentrations [K9]

Location	Number of houses	Average equilibrium equivalent radon concentration ($Bq\ m^{-3}$)
Port Hope (Radium/uranium refinery)	2961	11
Cobourg (reference area) (Spring)	106	5.2
(Autumn)	97	5.6
Uranium City (Uranium mining)	632	48
Elliot Lake (Uranium mining)	1921	30
Bancroft area (Uranium mining)	1162	26
Deloro (Metallurgical operations)	68	22

Table 29

Radon and radon daughter concentrations in indoor air and radon concentration in water supply in Canada
[M7]

Area	Location	Air: Radon ($Bq\ m^{-3}$)	Air: EEC a/ ($Bq\ m^{-3}$)	Air: F b/	Water ($MBq\ m^{-3}$)	Air-to-water concentration ratio (10^{-4})
Harriets-	Trailer	< 18.5	7.4	> 0.4	5.8	< 0.03
field	Trailer	118	37	0.3	6.1	0.2
	Trailer	< 22	7.4	> 0.3	5.6	< 0.04
	Trailer	< 74	26	> 0.3	5.8	< 0.1
	Trailer	152	30	0.2	6.2	0.2
School:	Washroom	93	11	0.1	5.5	0.2
	Library	< 18.5	11	> 0.6	5.5	< 0.03
Big Acres	Basement	< 18.5	7.4	> 0.4	5.5	< 0.03
Sheldrake	Basement	126	15	0.1	4.7	0.1
Hubley Lake	Basement	81	38	0.5	1.6	0.5
	Kitchen	26	15	> 0.6		< 0.2
Five Islands	Boiler room	< 44	3.7	> 0.1	3.6	< 0.1
Lake	Transformer	< 22	3.7	> 0.2		< 0.1
Woodland	Basement	707	93	0.1	14	0.5
	Kitchen	240	93	0.4		0.2
Highland Park	Basement	56	11	> 0.2	7	0.08
	Living room	110	7.4	0.1		0.2
West Timberlea	Laundry room	120	19	0.2	12	0.1

a/ Equilibrium equivalent concentration of radon.
b/ Equilibrium factor.

Table 30

Radon and radon daughter concentrations in indoor air due to warm water showers of 7 minutes

The radon concentration in water was 4.4 kBq m^{-3}.
[M7]

Bathroom	Time elapsed (min)	Concentration ($Bq\ m^{-3}$): Radon	Concentration ($Bq\ m^{-3}$): Radon daughters	Distribution ratio (10^{-4})
Before shower operation		19	7.4	< 0.04
During shower operation	0	148	-	0.3
	1	850	-	1.9
	2	1040	-	2.4
	3	1890	-	4.3
	4	2070	-	4.7
	5	2740	-	6.2
	8	3520	-	8.0
After shower operation	22	3100	2400	
	32	2660	110	
	99	148	26	

Table 31

Radon concentration in air in Finnish dwellings caused by radon in water
[A3]

House no.	Water	Radon concentration in air ($kBq\ m^{-3}$)									
		Rooms and situations where much water is used (showers)				Rooms and situations where little water is used (cooking)					Living rooms (no water)
	($MBq\ m^{-3}$)	Room or situation number 1	2	3	4	1	2	3	4	5	
1	5.2	4.2	4.0	1.2	1.5	0.81	1.2	5.8			0.34
2	7.4										0.53
3	5.8										0.093
4	3.7	2.1	22			0.93	0.59				0.23
5	5.3	3.9	2.1	13		1.6	4.6				0.30
6	3.0	15	9.2			6.7	0.67	0.85	9.3		0.23
7	4.2	2.6	2.5	2.4		0.19	0.41	0.41			0.13
8	17	39	29			5.9	27				0.36
9	7.6	6.0				0.81					0.31
10	5.0	23	10			4.7	3.4	1.4	6.0	3.0	0.31
11	8.0	11				6.8	0.3	1.0			0.20
12	9.2	10				0.74	1.8	0.26	0.30	2.9	0.13
13	13	19	22			8.7	13		4.2	3.3	0.77
14	0.48	0.22	2.7			0.89					0.019
15	1.5	3.2	1.8			0.037	0.037	0.11			0.059
16	1.0	3.8	2.1			0.15	0.56	2.6	0.78		0.041
17	0.15	0.85	0.67			0.074		0.037	0.074		0.037
18	2.5	3.6				0.56	0.44				0.11
19	1.9										0.056
20	0.52										0.078
Average	(5.1 ± 4.3)	8.5 ± 9.7				2.9 ± 4.7					0.22 ± 0.19

Table 32

Equilibrium equivalent concentration of radon and thoron in dwellings in the Federal Republic of Germany

Ranges are given between parentheses.
[W14]

Building material	Equilibrium equivalent concentration ($Bq\ m^{-3}$)	
	Radon	Thoron
Concrete based and mixed building material	10 (3.7-25)	0.44 (0.19-2.2)
Sandstone	5.6	0.30 (0.11-0.48)
Brick	4.8 (3.7-6.3)	0.70 (0.30-1.1)
Aerated concrete	3.3 (2.6-4.1)	0.11
Light-weight building material	3.7 (3.0-4.8)	0.19 (0.11-0.26)
Weighted average	8.1 (2.6-25)	0.37 (0.11-2.2)

Table 33

Radon concentration in dwellings in Norway 1977-1978
[S24]

Type of dwelling	Radon concentration ($Bq\ m^{-3}$)		
	Min.	Mean	Max.
Wood	7.4	48	140
Concrete	7.4	74	250
Brick	11	37	210

Table 34

Radon and radon daughter concentrations in flats in Poland [G13]

Location and building material	No. of flats	Maximum concentration of radon ($Bq\ m^{-3}$)	Equilibrium equivalent radon concentration ($Bq\ m^{-3}$)	
			Range	Weighted average
Warsaw				
Different types of concrete	11	2.2-28	1.1-14	7.0
Lublin				
Concrete and gypsum	39	15	0.4-7.8	2.0
Concrete, siporex and gypsum	32	23	0.4-13	3.7
Wood	9	2.1-9.4	1.0-4.8	2.9
Brick	29	1.2-33	0.63-17	8.9
Limestone	3	2.4-19	1.2-8.9	4.8
Clay	6	2.3-17	1.2-8.5	4.8
Clay and brick	4	1.6-17	0.81-8.5	4.8
Slag and cement	12	4.4-52	2.3-27	15
Clay, slag and cement	2	9.3-16	4.8-8.5	6.7
Brick and siporex	5	2.3-14	1.2-7.8	4.4
Concrete and siporex	7	1.5-7.4	0.78-4.1	2.4
Brick, slag and cement	10	2.9-28	1.3-14	7.8
Weighted average of all flats				5.6

Table 35

Average activity concentration of radon and radon daughters in air, absorbed dose rate in air from gamma radiation and air exchange rates in houses built of aerated concrete based on alum shale a/ [S45]

Date ready for moving in	Number of houses	Building material	Concentration		Air exchange rate (h^{-1})	Absorbed dose rate in air from gamma-radiation ($nGy\ h^{-1}$)
			Radon ($Bq\ m^{-3}$)	Radon daughters ($Bq\ m^{-3}$)		
1969	9	Entirely built of alum shale aerated concrete	780 (535-1160)	410 (190-770)	0.31 (0.21-0.43)	635 (580-690)
1962	7	All walls built of alum shale aerated concrete	490 (320-690)	185 (80-250)	0.41 (0.24-0.55)	380 (350-440)
1968	9	as above	370 (190-490)	170 (75-280)	0.49 (0.34-0.61)	425 (410-440)
1967	7	As above	590 (175-820)	245 (45-355)	0.27 (0.17-0.49)	540 (480-600)

a/ The lowest and highest values calculated as averages for a house are given in parentheses.

Table 36

The concentrations of radon and daughter products in 63 dwellings in a Swedish town [E2]

Building materials in the walls and ventilation system a/	Air exchange rate (h^{-1})		Radon ($Bq\ m^{-3}$) I	Radon ($Bq\ m^{-3}$) II	Equilibrium equivalent radon concentration ($Bq\ m^{-3}$) b/ I	Equilibrium equivalent radon concentration ($Bq\ m^{-3}$) b/ II c/
Multi-family houses						
Concrete, ME	0.3-0.6	low	59	48	22	11
		average	170	140	70	52
		high	590	780	260	310
Concrete and sandbased aerated concrete, ME	0.5-0.9	low	37	26	13	9
		average	89	85	31	23
		high	150	140	48	41
Concrete and sandbased and alum shale based aerated concrete, ME	0.4-0.8	low	74	93	22	11
		average	180	160	52	44
		high	440	410	150	140
Single-family houses						
Facade brick (sandstone), wood construction, ME	0.4-0.7	low	n d/		8	
		average	56		22	
		high	140		38	
Wood, cellar of alum shale based aerated concrete, ME	0.4-0.7	low	n d/		4	
		average	200		81	
		high	370		140	
Wood, no cellar, ME	0.8	low	100		33	
		average	100		37	
		high	100		41	
Alum shale based aerated concrete, DV	0.2-0.5	low	150		67	
		average	270		120	
		high	410		190	
Facade brick (clay), wood construction, DV	0.1-0.2	low	220		82	
		average	410		170	
		high	560		310	

a/ ME is a mechanical exhaust ventilation system, DV is a draught ventilation system in the houses studied with a fan over the cooker.
b/ The radon daughter concentrations were measured
c/ I and II mean the first and second phases between which the ventilation systems were adjusted
d/ n ≤ minimum detectable value, 26 $Bq\ m^{-3}$ for radon.

Table 37

Average radon concentrations in Swedish dwellings [S35]

Houses existing in	Radon concentration ($Bq\ m^{-3}$) Apartment houses	Detached houses	Average
1950	43	18	29
1975	89	48	71
1985 a/	88	51	73

a/ Predicted values.

Table 38

Equilibrium equivalent radon concentrations in houses built on phosphate land in the United States [U8]

Structure	Type of land	Equilibrium equivalent concentration[a] ($Bq\ m^{-3}$)	
		Geometric mean	Range
Slab-on-grade	Undisturbed	11	3.7-37
	Unmined, near-surface radioactive deposits and fill	70	11-170
	Tailings	30	7-140
	Lower activity overburden	30	15-67
	Higher activity overburden and debris	160	70-520
Crawl space and mobile homes	Undisturbed	11	3.7-37
	Reclaimed	22	3.7-52

a/ The weighted average was 37 $Bq\ m^{-3}$, which is estimated to be 26 $Bq\ m^{-3}$ above normal background.

Table 39

Equilibrium equivalent radon concentrations in houses in Colorado, United States [C11]

Number of houses	Equilibrium equivalent concentration ($Bq\ m^{-3}$)
15	> 196
26	52-196
5	19- 48
1	< 19

Table 40

Equilibrium equivalent concentrations of radon and annual effective dose equivalents for dwellings of different types in various countries

The equilibrium factor is assumed to be 0.5.

Country or area	Structure	Equilibrium equivalent concentration ($Bq\ m^{-3}$)	Annual effective dose equivalent (mSv)	Ref.
Austria	Average for Salzburg	12	0.7	[S22]
Canada	Typical Canadian homes	17	1.0	[M6]
Denmark	Basement room, thick structured elements	4.8	0.3	[N2]
Finland	Flats other than groundfloor	17	1.0	[N2]
Germany,Fed.Rep.	Average for 32 houses	8.1	0.5	[W14]
Hungary	Isolated rooms	20	1.2	[N2]
	As specified in Table 28, Annex B [U6]	120	7.3	[U6]
Norway	Flats other than groundfloor	11	0.7	[N2]
	Average value	26	1.6	[S24]
Poland	Average value	6-17	0.4-1.0	[G13,B16, B17, U6]
Sweden	Average value	60	3.7	[R15]
United Kingdom	Single-family houses	15	0.9	[N2]
	Average value	13	0.8	[C6]
United States	New Jersey and New York and as specified in Table 28, Annex B [U6]	15	0.9	[U6]
USSR	Flats other than groundfloor	4.8	0.3	[N2]
	Single-family houses and groundfloor flats	16	1.0	[N2]
Several countries	Mainly masonry houses and apartments	18	1.1	[U6]

Table 41

Radon and thoron daughter concentrations in different rooms in the United Kingdom [C6]

Equilibrium equivalent concentration ($Bq\ m^{-3}$)		Radon-to-thoron equilibrium equivalent concentration ratio
Radon	Thoron	
14	0.33	42
0.7	0.08	9
41	1.2	34
13	0.12	110
54	0.33	160
91	0.41	220
89	0.44	200
6.4	0.43	15

Table 42

Concentrations of, and exposure to, radon daughters in uranium mines

Country	Year	Average potential alpha energy concentration (WL)	Average annual potential alpha energy exposure (WLM)	No. of miners	No. of miners exceeding 4 WLM a/	Ref.
France	1971	0.18				[U6]
	1972	0.17				
	1973	0.18				
	1974	0.13				
	1975	0.11				
	1976					
	1977					
	1978		2.0	1284	~ 140	[B7]
	1979		1.4	1503	51	[B20]
United States	1975	0.71	5.68	~ 5000		[R6]
	1976	0.58	4.64	~ 5000		
	1977	0.51	4.08	~ 5000		
Italy	1975	< 1				[S4]
Canada	1978					[A6]
1 Leaching			0.38	630		
4 Underground			0.74	3690		
1 Open pit			0.41	276		
	1978		0.72	4535	9	b/
	1979		0.74	6883	1	
Argentina						
Underground	1977-79		2.4	286-379		[P18]
	1980		2.4	95	0	
Open pit	1980		0.12	285	0	

a/ The maximum permissible exposure in many countries.
b/ Data from the National Dose Registry in Canada.

Table 43

Estimated potential alpha energy exposure of different categories of mine workers in the Jaduguda underground mines, India [R13, K19, A12]

Year	Estimated potential alpha energy exposure (WLM)		
	Drilling crew	Mucking crew	Others
1965	4.9 ± 2.6	2.1 ± 1.0	1.7 ± 1.0
1966	2.3 ± 1.2	3.5 ± 1.8	1.2 ± 0.9
1967	2.0 ± 1.1	5.2 ± 2.7	1.6 ± 1.1
1968	3.8 ± 2.0	3.2 ± 1.6	2.3 ± 1.5
1969	4.1 ± 2.2	6.5 ± 3.4	2.4 ± 1.7
1970	2.1 ± 1.1	3.0 ± 1.4	0.7 ± 0.5
1971	1.7 ± 0.9	2.0 ± 1.1	1.1 ± 0.8
1972	0.7 ± 0.6	1.6 ± 1.4	1.4 ± 1.3
1973	0.6 ± 0.3	0.6 ± 0.3	0.7 ± 0.5
1974	1.6 ± 0.6	5.5 ± 5.0	2.0 ± 1.6
1975	2.2 ± 0.7	2.3 ± 1.9	3.5 ± 1.7
1976	5.5 ± 4.4	2.5 ± 1.1	0.7 ± 0.1
1977	1.6 ± 0.6	1.7 ± 0.7	1.4 ± 0.7
1978	0.8 ± 0.2	1.4 ± 0.7	
1979	2.6 ± 1.0	2.1 ± 0.6	1.7 ± 0.3

Table 44

Concentrations of, and exposure to, radon daughters in non-uranium mines[a/]

Country	Year	Average potential alpha energy concentration (WL)	Annual potential alpha energy exposure (WLM)	No. of miners /mines	No. of miners exceeding 4 WLM	Ref.
Finland	1972-1974	0.2-0.4		1300/23		[A5]
	1975-1977		0.38	1370/16	0	
Italy	1975	0.01-0.6		2500/16	~ 75	[S4]
Norway	1972	0.07	0.64	1870/33		[S54,S55]
	1980	0.05	0.45	1380/23		
Poland	1970					[D3]
Copper		1-2				
Iron		1				
Pyrite		4				
Phosphate		0.8				
Zinc and lead		0.9				
Baryte		0.2				
Coal		0.1				
South Africa	1973		1.7	320000		[U6]
Sweden	1970		4.8	4800/5	2000	[U6]
	1974		2.1	4600/50	360	[U6]
	1975		1.9	5300/45	270	[S13]
	1976		1.7	5300/46	225	[U6]
	1977		1.6	5200/45	475	[S13]
	1978		0.9	5300/47	270	[S13]
	1979		0.7	4400/35	0	[E1]
	1980		0.7	4400/35	0	[S56]
United Kingdom	1968	0.01 b/		220000/420		[04]
	1976		2-3 c/	2000/80	560	[04]
National coal	1981		0.12	185200		[08]
Private coal	1981		0.24	1500		[08]
Other than coal	1981		2.60	2346/108	94	[08]
United States	1975	0.31				[R6]
	1976	0.22				
	1977	0.12		/163		

a/ If not otherwise noted, the mines are iron, zinc, lead, copper or gold mines.
b/ In reference [04], this value is called "typical" for large nationalized coal mines.
c/ Based on measurements in about 80 % of all non-coal mines.

Table 45

Concentration of, and exposure to, radon daughters in working places other than mines

Country Kind of room or working place	Average potential alpha energy concentration (WL)	Annual potential alpha energy exposure (WLM)	Number of workers/ working places	Ref.
Austria				
Public baths (Badgastein)	0.5-0.9	6-11 b/	/>100	[P7]
Hungary				
3 caves	0.45 a/	5 b/	/3	[R9]
Italy				
20 spas	0.001	0.02-24 (18 spas < 1 WLM)	/20	[S5]
Japan				
2 caves	0.8 a/			[M23]
Sweden				
Tunnels for water		1.1	11/1	[S13]
Tunnels for cables		0.45	34/2	[S13]
Defence installations		1 - 4 c/		[S13]
Hydro-electric power stations	~ 0.1-1		200/78	[S13]
United States				
6 caves	0.3 - 1	0.1 - 1.5	/6	[Y1,S46]

a/ An equilibrium factor F of 0.5 is assumed.
b/ A fictitious value. An annual occupancy of 2000 h is assumed.
c/ For about 3 % of the staff.

Table 46

Measured values of the concentrations of ^{220}Rn, ^{212}Pb and ^{212}Bi at a gas mantle factory [D6]

Time of measurement (h)	Location	^{212}Pb concentrations (Bq m^{-3})	^{212}Bi concentrations (Bq m^{-3})	Ventilation rate in room air (h^{-1}) a/	^{220}Rn Inferred concentration (Bq m^{-3})	^{220}Rn Measured concentration (Bq m^{-3})	$\frac{^{220}Rn \text{ inferred}}{^{220}Rn \text{ measured}}$	Ratios of the measured concentrations $^{220}Rn:^{212}Pb:^{212}Bi$
First day								
10.50	Impregnating room	270	35	63	7400	22000	0.3	100:1.2:0.75
11.20	Impregnating room	150	23	140	8900	13000	0.7	100:1.1:0.18
12.10	Drying room	140	21	140	8500	6300	1.4	100:2.2:0.33
12.20	Drying room	130	21	33	7400	5900	1.2	100:2.3:0.36
12.40	Drying room	140	19	160	9300	4800	1.9	100:2.8:0.38
12.50	Drying room	110	13	210	10000	5200	1.9	100:2.2:0.24
15.25	Impregnating room	220	28	170	16000	18000	0.9	100:1.2:0.16
15.40	Impregnating room	290	31	210	26000	26000	1.0	100:1.1:0.12
Second day								
11.00	Impregnating room	270	48	120	14000	16000	0.8	100:1.7:0.19
11.25	Thorium nitrate store	100	48	30	1500	3700	0.4	100:2.8:1.3
11.40	Thorium nitrate store	70	22	56	1700	2000	0.8	100:3.5:1.1
12.00	Drying room	130	26	100	5900	3000	2.0	100:4.5:0.89
12.15	Drying room	200	29	150	13000	5600	2.3	100:3.6:0.53

a/ Inferred from the ^{212}Pb and ^{212}Bi concentrations.

Table 47

Typical variations of the potential alpha energy concentration of thoron daughters at different locations in a thorium factory in Trombay, India (1974) [D10]

Location	WL
Evaporator room	0.04
Area around mother liquor tank	0.12
Filling room	0.13
Crushing room	0.40
Area around hydroxide tanks	0.06
Drying room	0.24
Area around chloride filter presses	0.10
Laboratory	0.16
Area around tanks	0.07

Table 48

Increase in collective effective dose equivalents caused by radon daughters per unit of electrical energy conserved by reduction of the ventilation rate (to a rate not less than 0.5 h^{-1}) for Swedish houses built up to 1970

Type of house and building material	Normalized collective effective dose equivalent (10^3 man Sv (GW(e) a)$^{-1}$)		
	Multi-family houses	Single-family houses	Weighted average
Wooden house	2.8	1.4	1.8
Wooden house, cellar walls of concrete based on alum shale	-	11	11
Brick/concrete	8.4	5.7	7.0
Sand based aerated concrete	-	2.9	2.9
Concrete based on alum shale	20	7.5	14
Weighted average	8.7	2.2	5.6

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ANNEX E

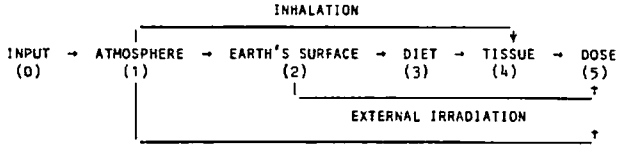
Exposures resulting from nuclear explosions

CONTENTS

Introduction

1. Since the publication of the 1977 report of the Committee [U6], a few additional nuclear tests have occurred in the atmosphere of the northern hemisphere. In this Annex, therefore, the total inventory of radionuclides from nuclear tests has been re-assessed and the consequent changes in the dose commitments have been evaluated.

2. The transfer of radionuclides between compartments of the environment linking the input of radionuclides to the dose in man has been modelled in the same way as in the previous reports of the Committee and can be represented schematically as follows:



Transfers between successive steps in the pathway chains are described by transfer coefficients, which relate infinite time integrals of concentration, dose or other quantities in the relevant compartments (see Annex A of this report and Annex C of the 1977 report [U6]). For example, the transfer coefficient from diet to tissue is the ratio of the integral concentration of activity in tissue to that in diet and is designated P_{34}. Transfers linking input to dose are determined by

sequential multiplication of transfer coefficients. Transfers by parallel pathways are assumed to be independent and are thus additive. For the transfers indicated in the diagram the dose commitment for a specific radionuclide and a given tissue, D^c, due to an input A_o into the atmosphere is given by

$$D^c = P_{01}[P_{12}P_{23}P_{34}P_{45} + P_{14}P_{45} + P_{15} + P_{12}P_{25}]A_o \quad (1)$$

3. In addition to dose commitments, estimates are also made of the collective dose commitments and the collective effective dose equivalent commitments, according to the general methods presented in Annex A. The specific assumptions regarding the global population size are as follows: 3.2 10^9 persons in the early 1960s during the maximum exposures from nuclear explosions, applied to inhalation exposures and to exposures to radionuclides with half-lives less than a few years; an average population size of 4 10^9 persons applied to exposures from radionuclides with half-lives from 10 to 30 years; 6 10^9 persons corresponding to exposures from radionuclides with 50- to 90-year half-lives; and 10^{10} persons for exposures from longer-lived radionuclides.

4. This Annex deals essentially with topics for which new information has become available since the publication of the 1977 report [U6]. The reader is referred to Annex C of that report for a more detailed presentation. Since this Annex incorporates the SI units, a brief summary for each radionuclide is given with converted values for the transfer coefficients. The dose calculations are extended to include estimates of exposures to nuclear tests which have occurred prior to 1981.

I. INPUT AND TRANSPORT OF RADIOACTIVE DEBRIS WITHIN THE ATMOSPHERE

5. Nuclear tests have been conducted in the atmosphere since 1945. Large yield test programmes took place during 1954–1958 and 1961–1962. Continued individual tests have occurred since 1964. Recent deposition of fallout radioactivity has been largely due to the high yield test (4 Mt) which occurred in November 1976. Smaller atmospheric tests (20 kt each) took place in September 1977 and in March and December 1978. No atmospheric tests were conducted during 1979. In October 1980, a test of intermediate yield (0.2 to 1 Mt) occurred.

6. Estimates of the explosive yields of individual nuclear tests have not generally been available. Therefore the estimates of the cumulative amounts of radioactive materials released to the environment have come from measurements of deposition of significant fission nuclides (^{90}Sr, ^{137}Cs). Production of other nuclides can be estimated from observed ratios, taking into account the various radioactive decay times.

7. For some purposes, however, estimates of explosive and fission yields of individual tests or of annual test series are required so that more specific records of concentrations of radionuclides in air or of deposition amounts can be derived. An example is ^{241}Am, which is not directly produced in nuclear tests, but results from decay of ^{241}Pu as it disperses in the atmosphere or after it has been deposited on the ground. Estimates of the total and fission yields for each reported test through 1978 have been made by Bennett [B7]. This compilation makes use of previous listings of dates, locations and types of tests [U8, Z1]. The estimates of individual yields are useful for calculations but cannot yet be verified. The cumulative yields over a one- or two-year period agree with the reported total yields [F3], and these are listed in Table 1. The listing does not include underground nuclear tests, which do not normally release radioactive material to the atmosphere or cause exposure of the public.

8. The production of fission nuclides is proportional to the fission yields of the tests, whereas the production of nuclides formed mainly by neutron activation, such as ^3H and ^{14}C, can be assumed to be proportional to the fusion yields. From Table 1 it may be seen that only about 10% of the fission production has occurred since 1963 and that about 1% is due to explosions carried out between 1976 and 1980.

9. The radioactive debris from a nuclear test is partitioned between the local ground or water surface and tropospheric and stratospheric regions, depending on the type of test, location and yield. Local fallout, which can comprise as much as 50% of the production for surface tests and includes activity present in large aerosol particles which are deposited within about one hundred km of the test site, has not been considered in the Committee's assessments, as tests have generally been conducted in isolated areas.

10. Tropospheric fallout consists of smaller aerosols which are not carried across the tropopause after the explosion and which deposit with a mean residence time of up to 30 d. During this period the debris becomes dispersed, although not well mixed, in the latitude band of injection, following trajectories governed by wind patterns, as illustrated in Figure I. From the viewpoint of human exposures, tropospheric fallout is important for nuclides of a few days to two months half-life, such as ^{131}I, ^{140}Ba or ^{89}Sr.

11. Stratospheric fallout, which comprises the bulk of the production, is due to those particles which are carried to the stratosphere and later give rise to world-wide fallout, the major part of which is in the hemisphere of injection. Stratospheric fallout accounts for most of the world-wide contamination of long-lived fission products.

12. The estimated stratospheric partitioning of nuclear debris is given in Table 2. In this summary from Bennett [B7], partitioning criteria provided by Ferber [F7] and Peterson [P4] have been used. As shown in Figure II, the atmosphere is divided into equatorial and polar regions from 0° to 30° and 30° to 90° latitude, respectively. The lower stratosphere is assumed to range from 9 to 17 km in the polar region and from 17 to 24 km in the equatorial region. The upper stratosphere extends to 50 km altitude. The region above the stratosphere is designated the high equatorial and high polar atmosphere, which extends to several hundred kilometres to include the remainder of the region from which debris will eventually be deposited on the earth's surface. Only a few tests injected debris into this region of the atmosphere. There have been no injections into the south polar atmosphere.

13. The main features of mixing processes and air movements in the atmosphere, illustrated in Figure II,

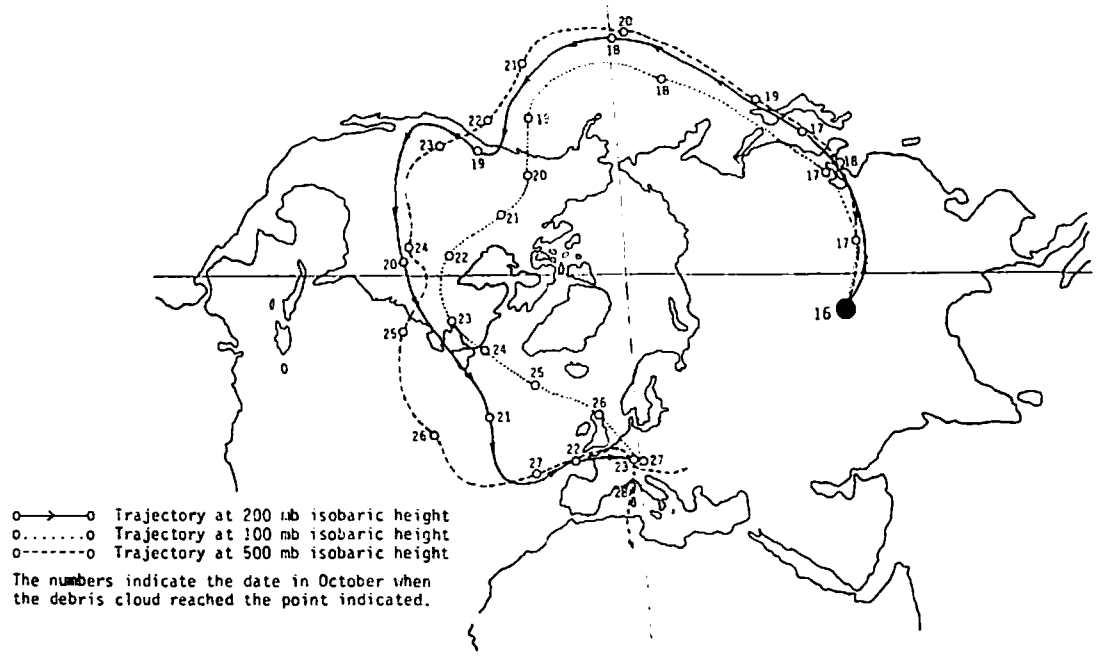


Figure I. Trajectories derived from meteorological data, generally confirmed by activity measurements in ground-level air, of tropospheric fallout from the atmospheric nuclear explosion of 16 October 1980 [I5]

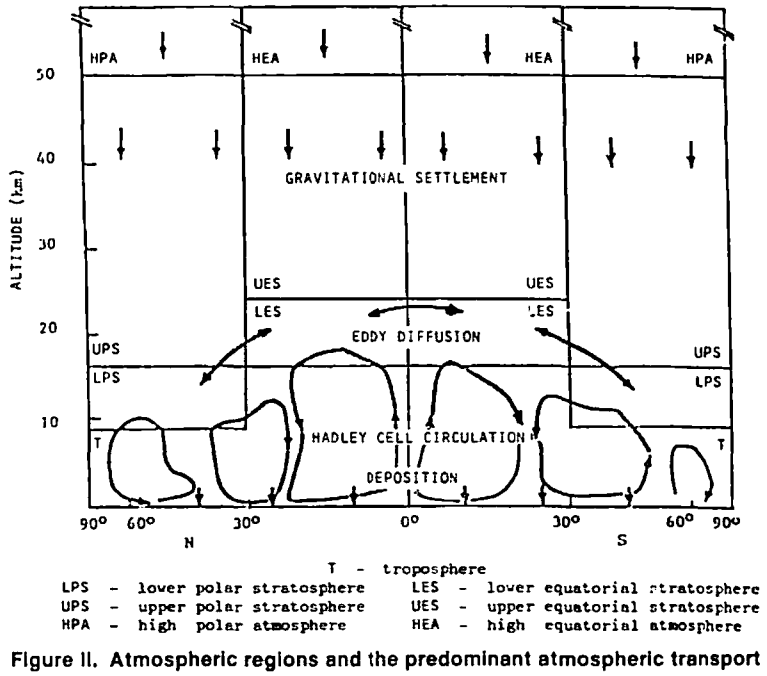


Figure II. Atmospheric regions and the predominant atmospheric transport processes

have been determined largely from the measurements of radionuclide concentrations [B7, D3, F1, F3, K1, K10, M1, P2, P4, R1, S3, T2, U3]. Aerosols descend gravitationally at highest altitudes and move with the general air movements of lower levels. Eddy diffusion in the lower stratosphere and upper troposphere is the irregular migration of air masses in the general directions indicated in Figure II. The circular air flow pattern in the troposphere at lower latitudes is termed Hadley cell circulation. These cells increase or decrease in size and shift latitudinally with season [N11]. The mean residence time of aerosols in the lower stratosphere ranges from 3 to 12 months in the polar regions and 8 to 24 months in the equatorial regions, and the most rapid removal occurs during the spring months. Removal half-time to the next lower region of 6 to 9 months in the upper stratosphere and 24 months in the high atmosphere are considered representative [B7].

14. The estimated total stratospheric injection of nuclear debris given in Table 2, when combined with specific fission yields, is in good agreement with measured deposition. For example, ^{90}Sr production is estimated to be about 3.9 PBq per Mt of fission energy, giving the total production through 1980 of 660 PBq. The estimate from deposition measurements is 600 PBq (see paragraph 37). Representative fission yields and normalized production for past nuclear testing are listed in Table 3. Large deviations are possible for individual tests. It is assumed that 1 Mt fission energy corresponds to 1.45 10^{26} fissions [H8]. This figure times the fission yield times the decay constant ($\lambda = \ln 2 / T_{1/2}$) for the specific nuclide gives the activity production per unit Mt fission energy.

15. Exposure of humans to fallout radioactivity consists of internal irradiation (inhalation of activity in

surface air and ingestion of contaminated foodstuffs) and of external irradiation from activity present in surface air or deposited on the ground.

II. INTERNAL IRRADIATION

A. TRITIUM

16. Tritium, a radioactive isotope of hydrogen, is a pure beta emitter with average energy of 5.69 keV and a half-life of 12.3 years [K7]. It occurs naturally, being produced in the stratosphere in cosmic ray induced reactions [U6]. Man-made tritium, in amounts substantially larger than the natural inventory, has been injected into the stratosphere by thermonuclear explosions. Most of this tritium is in the form of tritiated water. After entering the troposphere, tritium enters the hydrological cycle. The ocean is the ultimate sink for environmental tritium.

17. In Annex C of the 1977 report, the Committee estimated the tritium production from nuclear tests prior to 1970 to be 1.7 10^{20} Bq [U6], based on an assessment by Michel of tritium inventories in the world oceans in 1970 [M5]. An estimate by Miskel [M7], using average tritium production values and an earlier estimate of total fusion yields of nuclear tests conducted through 1962, was 3.0 10^{20} Bq.

18. Using the representative tritium production values per unit fission and fusion yields, as given by Miskel [M7], and the estimates of yields from Table 1, a revised estimate of total tritium production can be obtained:

$$\begin{aligned} \text{Fission } 220 \text{ Mt} \times 2.6\ 10^{13} \text{ Bq/Mt} &= 5.7\ 10^{15} \text{ Bq} \\ \text{Fusion } 330 \text{ Mt} \times 7.4\ 10^{17} \text{ Bq/Mt} &= 2.4\ 10^{20} \text{ Bq} \\ \text{Total} &\quad 2.4\ 10^{20} \text{ Bq} \end{aligned}$$

Production by fusion is far more significant than by fission. About 75% of the production estimate can be associated with stratospheric injection (from Table 2). The tropospheric and local releases can, however, also be expected to have become widely distributed.

19. The United States National Council on Radiation Protection and Measurements [N3], using a seven compartment model to describe the transfer of tritium in the global environment, concluded that the measurements in streams in the United States could be matched closely by approximating the tritium released from weapons testing by a single release of 2.6 10^{20} Bq injected into the atmosphere in 1962 with 90% of this amount, or 2.3 10^{20} Bq, depositing in the northern hemisphere. It was recognized, however, that this overestimates the total injection since levels in the mid-latitude region are enhanced by the general fallout deposition pattern.

20. In this Annex, a value of 2.4 10^{20} Bq is used for the total production of ^{3}H and it is assumed that about 20% of this, that is 0.5 10^{20} Bq, was transferred into or produced in the southern hemisphere, as indicated by the general pattern of fallout deposition measurements (see Table 5).

21. The annual absorbed dose in tissue from natural tritium has been estimated to be 10^{-8} Gy, which results from an annual production per hemisphere of 3.7 10^{16} Bq, corresponding to a global inventory of natural origin of 1.3 10^{18} Bq (see Annex B). Assuming the total release to the atmosphere of the northern hemisphere of 1.9 10^{20} Bq and 0.5 10^{20} Bq in the southern hemisphere from nuclear tests and using the estimation procedure applied previously [U6], the absorbed dose commitments in tissue from fallout tritium are:

$$\text{Northern hemisphere: } \frac{10^{-8} \text{ Gy a}^{-1}}{3.7\ 10^{16} \text{ Bq a}^{-1}}\ 1.9\ 10^{20} \text{ Bq} = 5.1\ 10^{-5} \text{ Gy}$$

$$\text{Southern hemisphere: } \frac{10^{-8} \text{ Gy a}^{-1}}{3.7\ 10^{16} \text{ Bq a}^{-1}}\ 0.5\ 10^{20} \text{ Bq} = 1.4\ 10^{-5} \text{ Gy}$$

The effective dose equivalent commitments are 51 μSv (northern hemisphere), 14 μSv (southern hemisphere) and 47 μSv (world). The global value is the population-weighted estimate, assuming 89% of the population in the northern and 11% in the southern hemisphere.

22. For the appropriate world population of 4 10^{9} people, the collective effective dose equivalent commitment is estimated to be 1.9 10^{5} man Sv. On the basis of the relative intakes of hydrogen in water by the pathway of inhalation, including passage through the skin, and the ingestion pathway [N3], the dose commitments and effective dose equivalent commitments can be apportioned as 7% arising from inhalation and absorption through the skin and 93% from ingestion.

B. CARBON-14

23. Carbon-14 is a pure beta emitter with average energy of 49.5 keV and a half-life of 5730 years [K7]. It is formed in nuclear explosions from the capture of excess neutrons by atmospheric nitrogen. Present in the atmosphere as carbon dioxide, it is taken up by plants during photosynthesis and is subsequently incorporated into the human body. The specific activity in human tissue has been found to come into equilibrium with that in atmospheric CO_2 with a delay time of about 1.4 years [N9].

24. In Annex C of the 1977 report [U6], the Committee estimated that the input of man-made ^{14}C into the atmosphere up to 1972 was 215 PBq. Subsequent injections have increased this amount by less than 1%, based primarily on the increase in total fusion yield of nuclear tests. A rounded estimate of 220 PBq will be assumed for tests through 1980.

25. The dose commitments from ^{14}C from atmospheric explosions can be assessed, as for the case of tritium, by comparison with the natural ^{14}C annual absorbed doses, which are given in Annex B as 5 10^{-6} Gy in the gonads, 5.7 10^{-6} Gy in the lungs, 2.2 10^{-5} Gy in bone lining cells, 2.4 10^{-5} Gy in red bone marrow, 5.9 10^{-6} Gy in the thyroid and 1.3 10^{-5} Gy in other tissues. The natural ^{14}C production rate is 1 PBq a^{-1} (see Annex B). The dose commitments from fallout ^{14}C, assumed to apply uniformly in the world, are thus:

Organ or tissue	*Dose commitment* (mGy)
Gonads	1.1
Lungs	1.3
Bone lining cells	4.8
Red bone marrow	5.3
Thyroid	1.3
Other tissues	2.9

Using ICRP weighting factors, the effective dose equivalent commitment from ^{14}C from atmospheric explo-

sions is thus found to be 2.6 mSv. On the basis of the relative intake and retention of carbon by inhalation and by ingestion, the dose commitments from inhalation are estimated to be about 10^4 times less than those arising from ingestion [K14].

26. The dose commitments from ^{14}C are delivered over a very long time period. The part accumulated up to the year 2000 is 7% of the total dose commitments, 8% to 2020 and 10% to 2050, based on an environmental compartment model for ^{14}C used by the Committee in Annex C of the 1977 report [U6]. The collective dose commitments can be estimated by assuming that the dose commitments apply to an upper limit of the world population, namely 10^{10} people. The collective dose commitments from fallout ^{14}C are:

Organ or tissue	*Collective dose commitment* (10^7 man Gy)
Gonads	1.1
Lungs	1.3
Bone lining cells	4.8
Red bone marrow	5.3
Thyroid	1.3
Other tissues	2.9

The tissue-weighted result, giving the collective effective dose equivalent commitment, is 2.6 10^7 man Sv.

27. This assessment of doses from ^{14}C is based on the assumption that the specific activity of natural ^{14}C will remain constant in the next hundreds and thousands of years. In fact, the combustion of fossil fuel leads to a decrease of the natural $^{14}C/^{12}C$ isotopic ratio in the biosphere and the dose commitments are therefore somewhat over-estimated.

C. MANGANESE-54

28. Manganese-54 has a half-life of 312.7 d, decaying by electron capture with the emission of x rays and a gamma ray of energy 834.8 keV [K7]. It is an activation product which was produced in largest quantities during the test series of late 1961, following which stratospheric measurements indicated a $^{54}Mn/^{90}Sr$ activity ratio of 100 [F5]. It was produced in other tests as well, but in much smaller amounts. Calculations which assume an injection of 5.2 EBq of ^{54}Mn in late 1961 give good agreement with measured surface air concentrations during 1963-1966 [B7].

29. From measurements during 1962-1966, the time integrated ^{54}Mn activity concentrations in surface air were 4.9 10^{-3} Bq a m^{-3} at four sites in the United Kingdom [A7], 5.5 10^{-3} Bq a m^{-3} in Denmark [A8], 6.5 10^{-3} Bq a m^{-3} at three sites in the United States [B7] and 2.8 10^{-4} Bq a m^{-3} at two sites in Chile [B7]. The latter two results were increased by 10% to account for missing data during 1962 [U6]. The average for temperate latitudes of the northern hemisphere is 5.6 10^{-3} Bq a m^{-3}. Concentrations in air have been very low since 1966. In Braunschweig, Federal Republic of Germany, the integral concentration of ^{54}Mn in air during 1971–1977 was 3.6 10^{-5} Bq a m^{-3} [K8, K9], which is negligible when compared to the values obtained for 1962–1966. Since 1970, the ^{54}Mn concentrations measured at Braunschweig and at two other European sites have been about 10 times lower than those of ^{137}Cs [K9].

30. Measurements of ^{54}Mn in grain in localized areas have been reported [A8], but sufficient general data to estimate dose commitments from ^{54}Mn via ingestion are not available. The dose commitments from inhalation of ^{54}Mn are given in Table 4. The doses per unit intake are those estimated by ICRP for oxides of manganese (class W) [13]. The inhalation rate is assumed to be 20 m^3 d^{-1} and the integral air concentration in the temperate latitudes are as given above. Using the latitudinal distribution of ^{90}Sr as a guide (Table 6), it is seen that the temperate latitude levels are a factor of about 1.5 greater than the respective population weighted levels that apply to the entire hemisphere. With this factor, and assuming the population distribution of 89% in the northern hemisphere and 11% in the southern hemisphere, the dose commitments applicable to the global population are derived as in Table 4. The effective dose equivalent commitments, applying the ICRP tissue weighting factors, are 0.07 and 0.0035 μSv in the temperate latitudes of the northern and southern hemisphere, respectively, and 0.042 μSv for the global average. The collective effective dose equivalent commitment for the world population (assumed to be about 3.2 10^9 people averaged over the deposition period) is estimated to be 130 man Sv.

D. IRON-55

31. Iron-55 has a half-life of 2.7 years and decays by electron capture with the emission of several low energy x rays and Auger electrons. It is an activation product and was produced mainly in the nuclear tests of 1961–1962. The concentration of ^{55}Fe in air fell rapidly after 1962–1963 and has been essentially undetectable since 1970. The total production is estimated to be 2 EBq [H11].

32. In Annex C of the 1977 report [U6], the Committee, on the basis of the work of Persson [P3], estimated the dose commitments in the northern hemisphere from fallout ^{55}Fe to be 10 μGy in the gonads and bone lining cells and 6 μGy in the bone marrow. A reduction of 4 was assumed for the southern hemisphere. The dose commitment in the gonads may be taken as representative of that in other soft tissues. As these estimates are based on very limited data, they can be assumed to be only roughly valid. A summary of dose commitments is:

	Dose commitment (μGy)		
Organ or tissue	*Northern hemisphere*	*Southern hemisphere*	*Global*
Gonads	10	2	9
Bone lining cells	10	2	9
Red bone marrow	6	1	5
Other tissues	10	2	9

The effective dose equivalent commitments are 10 μSv (northern hemisphere), 2 μSv (southern hemisphere) and 9 μSv (global). The collective effective dose equivalent commitment to the world population (about 3.2 10^9 persons present at the time of exposure) is estimated to be 3 10^4 man Sv.

E. KRYPTON-85

33. Krypton-85 has a half-life of 10.72 years and is a beta emitter of average energy 250.5 keV [K7]. In 0.4% of the disintegrations a 514 keV photon is emitted. In Annex C of the 1977 report, ^{85}Kr production was

estimated from the $^{85}Kr/^{90}Sr$ fission yield ratio of 0.07 [U6]. On the basis of the total fission yield of atmospheric nuclear tests from Table 1 and of the normalized production of ^{90}Sr from Table 3, production from nuclear tests through 1980 is estimated to be 160 PBq. Most of the ^{85}Kr present in the earth's atmosphere originates in releases from the production and processing of nuclear materials and not from nuclear explosions [R6]. The dose estimates in this Annex refer to ^{85}Kr produced in nuclear explosions.

34. Krypton is an inert gas and most of it remains in the atmosphere until decay. Its concentration becomes fairly uniform throughout the earth's atmosphere within a few years after release [F2]. Assuming a uniform and instantaneous distribution of ^{85}Kr in the atmosphere, which is adequate for dose estimations, the production of 160 PBq results in a time-integrated air concentration of 0.62 Bq a m^{-3}. The dose commitments from 1 Bq a m^{-3} are, in accordance with ICRP [I1], taken to be 4.1 10^{-7} Gy in skin and about 4 10^{-9} Gy in the other tissues (see values below). Therefore the dose commitments to the world population from fallout ^{85}Kr are estimated to be

Organ or tissue	*Dose commitment per unit integrated concentration in air* [nGy/(Bq a m^{-3})]	*Dose commitment* (nGy)
Skin	410	250
Gonads	4.6	2.9
Breast	3.9	2.4
Red bone marrow	5.0	3.1
Lungs	3.8	2.4
Bone lining cells	5.4	3.3
Stomach wall	3.8	2.4
Kidneys	3.5	2.2
Liver	3.3	2.0
Spleen	4.0	2.5
Adrenals	3.5	2.2

The collective dose commitments are obtained by multiplying by the world's population (4 10^9 people). The effective dose equivalent commitment is 0.005 μSv and the corresponding collective quantity is 20 man Sv.

F. STRONTIUM-90

1. Inventory and deposition

35. Strontium-90, a pure beta emitter with average energy of 195.8 keV, decays with a half-life of 28.6 years to ^{90}Y, which has a half-life of 64.1 h and is a beta emitter with average energy of 934.8 keV [K7]. Strontium-90 has been extensively monitored over the years in human tissues and in the environment. Many of the results obtained may be used as a guide to the behaviour of other long-lived radionuclides released by atmospheric tests.

36. The annual deposition of ^{90}Sr in the northern and southern hemispheres for the period 1958–1980 is shown in Table 5, together with the cumulative deposit in each hemisphere and the estimated total injection to January 1981 [T6, U6]. (Deposition is the activity deposited on a specified area. The cumulative deposit is the activity present in a specified area at a given time; it is the result of past depositions and radioactive decay.) The global depositions in 1979 and 1980 were the smallest recorded since the measurements began. In 1977 and 1978 there were increases in the annual deposition in the northern hemisphere as a result of the large test conducted in November 1976 in that hemisphere.

37. The deposition in 1981 may be expected to be slightly increased due to the test of October 1980. Measured data are not yet available. Since 1971, the annual rate of injection has been less than the annual rate of decay and the cumulative deposit has steadily decreased. Total ^{90}Sr production from nuclear tests through 1980 is estimated from these measurements to be 600 PBq. The estimate from cumulative fission yields of ^{90}Sr injected into the stratosphere was 660 PBq (paragraph 14). This estimate, which excludes local fallout, is in good agreement with the global deposition measurements. The global inventory of deposited ^{90}Sr, which is decreasing by radioactive decay, was 400 PBq at the end of 1980 [C1, T6].

38. The distribution of ^{90}Sr deposition by latitude bands is given in Table 6 [T6, U6]. The results are obtained by averaging measurements at sampling sites within the band and by extrapolation to latitudes which no longer contain sampling sites (north of 70°N and south of 60°S). Integrated depositions in the latitude bands are determined by addition of all previous deposition without taking account of radioactive decay. The deposition density (activity per unit area) is determined by dividing by the area of the band. Population weighted integrated deposition densities are useful in exposure assessment and these are also indicated in Table 6.

39. The relationship between input of activity from sources in the atmosphere and deposition onto the earth's surface is given by the transfer coefficient P_{02}, which is defined

$$P_{02} = \frac{\int_0^\infty \dot{U}(t)\,dt}{\int_0^\infty \dot{A}(t)\,dt} = \frac{U_o}{A_o} \qquad (2)$$

where $\dot{U}(t)$ is the deposition density rate and $\dot{A}(t)$ is the input rate. The integral quantities are U_o, the integrated deposition density over the entire fallout period, and A_o, the total injection of ^{90}Sr from all atmospheric tests. Estimates of P_{02} for the past pattern of nuclear tests weighted according to population distribution are, for a total injection of ^{90}Sr through 1980 of 600 PBq:

	P_{02} (10^{-13} Bq m^{-2} per Bq released)
World	3.3
Northern hemisphere	3.6
Southern hemisphere	0.9
North temperate zone (40–50°)	5.4
South temperate zone (40–50°)	1.5

2. Transfer from deposition to diet

40. The deposition of ^{90}Sr on land and the transfer to humans by ingestion is the most important pathway for human exposure. The annual average ^{90}Sr concentrations in milk and whole diet from 1974 onwards are given in Table 7. The practice of expressing results in terms of the $^{90}Sr/Ca$ quotient retains some advantages in minimizing variability in measurements; however, in assuming constant and relatively uniform calcium

levels in diet and humans, there is no need to use the quotients in the assessment models.

41. The relative contributions of different foods to the total ^{90}Sr dietary intake have been indicated previously [A1, B8, K3, U6]. The concentrations in milk and grain products decline fairly rapidly following deposition periods, while fruits and vegetables, reflecting uptake of ^{90}Sr from the slowly varying cumulative deposit in soil, decline much more gradually. It is expected, therefore, that the long-term variation in the ^{90}Sr intake will depend on the composition of the diet.

42. The transfer coefficient from deposition to diet is given by

$$P_{23} = \frac{\int_0^\infty C(t)\,dt}{\int_0^\infty \dot{U}(t)\,dt} \qquad (3)$$

where C(t) is the ^{90}Sr concentration in the diet at time t and $\dot{U}(t)$ is the deposition density rate. For values of C(t) and $\dot{U}(t)$ assessed on a yearly basis, the integrations can be replaced by summation

$$P_{23} = \frac{\sum_{i=1}^{\infty} C(i)}{\sum_{i=1}^{\infty} \dot{U}(i)} \qquad (4)$$

43. In Annex C of the 1977 report, the following model was used to relate ^{90}Sr in food groups or in the total diet to the annual deposition densities [U6]

$$C(i) = b_1 \dot{U}(i) + b_2 \dot{U}(i-1) + b_3 \sum_{m=1}^{\infty} e^{-\lambda_s m} \dot{U}(i-m) \qquad (5)$$

These are contributions to ^{90}Sr concentrations in diet from the annual deposition density in the year considered $\dot{U}(i)$, in the previous year $\dot{U}(i-1)$, and from all preceding years, expressed by the summation, with an exponential term describing the combined physical decay of ^{90}Sr and any decrease in availability to plants of ^{90}Sr in soil. The factors b_1, b_2, b_3, and the effective mean life of available ^{90}Sr, λ_s^{-1}, can be derived from reported data by regression analysis.

44. The combination of equations (4) and (5) leads to

$$P_{23} = b_1 + b_2 + b_3 \frac{e^{-\lambda_s n}}{1 - e^{-\lambda_s n}} \qquad (6)$$

where n = 1 year, a constant in this case. The units for λ_s are a^{-1} and for P_{23}, b_1, b_2 and b_3, Bq a $kg^{-1}/(Bq\ m^{-2})$.

45. Equation (5) has been fitted by regression analysis to the total and component diet data and the deposition data for Argentina, Denmark and New York City. The results are given in Table 8. The contribution of dietary components to the total transfer coefficient is obtained by weighting each food group k by its fractional consumption by weight, w_k, in total diet

$$P_{23} = \sum_k w_k P_{23}^k \qquad (7)$$

The differences in parameter values in Table 8 may be explained by the differences in foods included in the groups, in the amounts of the various foods consumed, and in the actual transfers of ^{90}Sr at the particular locations. The value of the transfer coefficient obtained by summing over the food groups should give a better result than the single exponential fit to total diet. The results are fairly close, however, by both methods in all cases. The fits for ^{90}Sr in total diet of New York and Argentina are shown in Figure III.

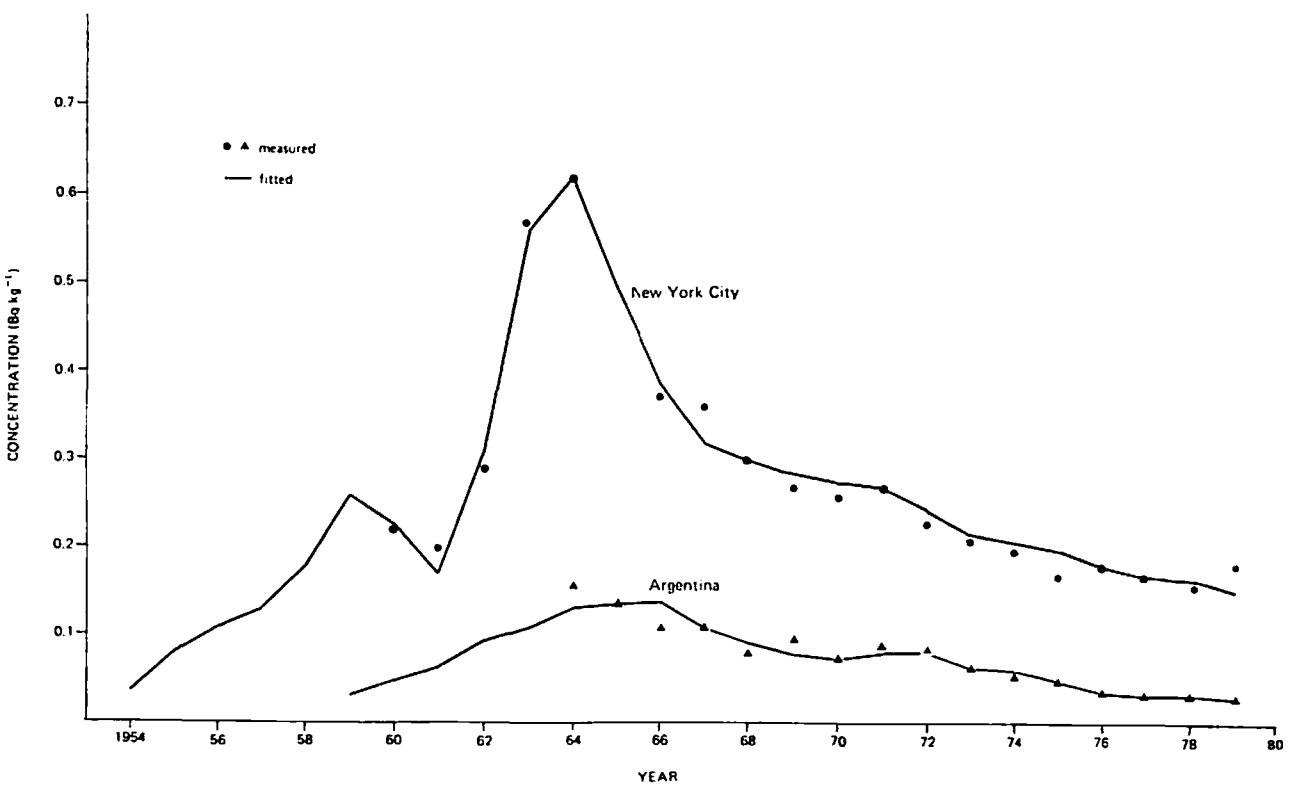


Figure III. Strontium-90 in total diet of Argentina and New York City, United States

46. The average value of the transfer factor P_{23} obtained from data of the three countries is about 4 10^{-3} Bq a kg^{-1}/(Bq m^{-2}). This value is consistent with that in Annex C of the 1977 report of 5 10^{-3} Bq a (g Ca)$^{-1}$/(Bq m^{-2}) for a calcium concentration in diet of 0.8 g kg^{-1}. The same mean value with less variation is obtained by expressing the results per unit calcium intake, using the actual consumption data given in the footnote of Table 8. This result is typical for the diets considered, however, differences could be obtained for other types of diets. In particular, the transfer coefficient would be an underestimate for diets containing less meat and milk and also in areas for which higher than average transfer of ^{90}Sr to milk has been noted [M9, U6].

3. Transfer from diet to bone

47. The annual average ^{90}Sr concentrations in bone from 1974 are given in Table 9 for the various age groups. As a general rule, only the $^{90}Sr/Ca$ quotients are available in the literature. The data may be converted to units of Bq kg^{-1} by assuming 10^3 g Ca in the 5 kg mineral skeleton. Some caution is required, however, as variations may be noted for particular bone types. The ^{90}Sr concentrations for adult bone have varied little in recent years. Typical values are around 40 mBq (g Ca)$^{-1}$, corresponding to 8 Bq kg^{-1}.

48. The transfer coefficient linking diet and human bone, P_{34}, is defined by

$$P_{34} = \frac{\int_0^\infty C_b(t)\,dt}{\int_0^\infty C_d(t)\,dt} \qquad (8)$$

where $C_b(t)$ is the ^{90}Sr concentration in bone at time t and $C_d(t)$ is the concentration in the diet. For values of $C_b(t)$ and $C_d(t)$ assessed as annual averages, equation (8) becomes

$$P_{34} = \frac{\sum_{i=1}^{\infty} C_b(i)}{\sum_{i=1}^{\infty} C_d(i)} \qquad (9)$$

49. In Annex C of the 1977 report, the following model was used to relate ^{90}Sr in bone to concentrations in diet [U6]

$$C_b(i) = c\,C_d(i) + g \sum_{m=0}^{\infty} e^{-\lambda_b m} C_d(i-m) \qquad (10)$$

The parameters c and g may be related to short- and longer-term components of ^{90}Sr retention in bone. The exponential factor accounts for radioactive decay and removal from the body. Combining equations (9) and (10) yields

$$P_{34} = c + \frac{g}{1 - e^{-\lambda_b n}} \qquad (11)$$

where n = 1 year, a constant in this expression.

50. The ^{90}Sr data for diet and adult bone in several countries have been fitted by regression analysis using equation (10). The values of the parameters are given in Table 10, together with the estimates of P_{34} obtained by use of equation (11). The estimates of the transfer coefficient P_{34} vary little from one locality to another, particularly when normalized to dietary calcium intake. The results for Argentina are less certain due to the less specific fit to the data, which show little change from year to year. The results shown in Table 10, along with previously computed estimates of P_{34} [U6], indicate that the most consistent value is 0.15 Bq a (g Ca)$^{-1}$ in bone per Bq a (g Ca)$^{-1}$ in diet, corresponding to 38 Bq a kg^{-1} in bone/(Bq a kg^{-1}) in diet, with the assumptions of 10^3 g Ca in the 5 kg skeleton and 0.8 g Ca per kg diet.

4. Transfer coefficient relating ^{90}Sr concentration in bone to dose

51. The transfer coefficient P_{45} relates the ^{90}Sr time-integrated concentration in bone to the dose commitment. As in Annex C of the 1977 report [U6], the values of P_{45} can be derived for doses to red bone marrow and bone lining cells on the basis of the work of Spiers [S2, S7]. The dose rate $\dot{D}_o$ per unit ^{90}Sr activity in a small tissue-filled cavity in bone from decay of ^{90}Sr–^{90}Y is equal to 6.1 μGy a^{-1}/(Bq kg^{-1}). In order to obtain the dose rates in red bone marrow, $\dot{D}_{RM}$, and in bone lining cells, $\dot{D}_{BLC}$, use is made of the $\dot{D}_{RM}/\dot{D}_o$ and $\dot{D}_{BLC}/\dot{D}_o$ ratios. These values are

	$\dot{D}_{RM}/\dot{D}_o$	$\dot{D}_{BLC}/\dot{D}_o$
Cortical contribution	0.05	0.45
Trabecular contribution	0.26	0.17
Total	0.31	0.62

The value of the latter ratio has been changed in comparison to Annex C of the 1977 report [U6] to account for irradiation of cells on surfaces of both types of bone [I3]. The values of the transfer coefficient obtained in this manner are

P_{45} (red bone marrow) = 1.9 μGy/(Bq a kg^{-1})

P_{45} (bone lining cells) = 3.8 μGy/(Bq a kg^{-1})

52. The dosimetry used by ICRP [I3] for beta emitters uniformly distributed throughout the volume of bone is also based on the work of Spiers [S2, S7]. The absorbed fractions (fractions of energy absorbed in target tissue from radiation originating in a source organ) derived from the $\dot{D}_{RM}/\dot{D}_o$ and $\dot{D}_{BLC}/\dot{D}_o$ ratios given above are:

		Absorbed fraction	
Source	*Target*	*Calculated from the results of Spiers*	*Adopted by ICRP*
Cortical bone	Red bone marrow	0.019	0
Trabecular bone	Red bone marrow	0.42	0.35
Cortical bone	Bone lining cells	0.014	0.015
Trabecular bone	Bone lining cells	0.022	0.025

Instead of using the calculated values appropriate to each beta emitter uniformly distributed throughout the volume of bone, ICRP decided to apply representative nominal values for any radionuclides of that category. These nominal values are presented above in the right-hand column. The results obtained for P_{45} using the nominal values of the absorbed fractions and the distribution of ^{90}Sr in bone adopted by ICRP are found to be

P_{45} (red bone marrow) = 1.9 μGy/(Bq a kg^{-1})

P_{45} (bone lining cells) = 4.2 μGy/(Bq a kg^{-1}).

These values, which are in good agreement with those derived in the previous paragraph, have been adopted by the Committee in this report for reasons of consistency with the dose calculations carried out in this and other Annexes.

5. Dose commitments from strontium-90

53. The dose commitments from ^{90}Sr released by atmospheric nuclear explosions can now be assessed for the ingestion pathway. The relevant part of equation (1) is

$$D^c = P_{02}\, P_{23}\, P_{34}\, P_{45}\, A_o \qquad (12)$$

Using the deposition distribution of ^{90}Sr given in Table 6 from the total production of 600 PBq of ^{90}Sr from nuclear tests conducted through 1980 and values of the transfer factors given in the previous paragraphs, the dose commitments listed in Table 11 are obtained. The doses to other tissues are negligible. Estimates of the collective dose commitments are also included in Table 11. The applicable world population size has been taken to be 4 10^9 persons, distributed as indicated in Table 6. The effective dose equivalent commitments are 110 μSv (world), 170 μSv (North temperate zone), 48 μSv (South temperate zone). The collective effective dose equivalent commitment is 4.4 10^5 man Sv (world).

54. The dose commitment from ^{90}Sr via the inhalation pathway can also be estimated. The average quotient of the integrated concentration in air to the deposition density is 1.8 10^{-6} Bq a m^{-3}/(Bq m^{-2}), as determined from ^{90}Sr measurements over several years in New York City [B7]. The integrated concentrations in air, derived from the deposition estimates of Table 6, are thus estimated to be 5.8 mBq a m^{-3} in the North temperate zone, 1.6 mBq a m^{-3} in the South temperate zone and 3.5 mBq a m^{-3} in the world (population-weighted). For a breathing rate of 20 m^3 d^{-1} and the dose to lungs per unit intake as given by the ICRP [I3] for ^{90}Sr (Class Y) of 2.9 10^{-6} Gy Bq^{-1}, the dose commitments to the lungs from the inhalation pathway are 7.4 10^{-5} Gy (world), 1.2 10^{-4} Gy (North temperate zone), and 3.4 10^{-5} Gy (South temperate zone). The dose commitments to other tissues are negligible. The effective dose equivalent commitments are 8.9 μSv (world), 14 μSv (North temperate zone), and 4.1 μSv (South temperate zone). Since depletion of activity from air is fairly rapid, the inhalation exposures occurred soon after the explosions. The collective effective dose equivalent commitment to the world population (3.2 10^9 persons present at the time of exposure) is estimated to be 2.8 10^4 man Sv.

G. STRONTIUM-89

55. Strontium-89 has a half-life of 50.5 d and decays with the emission of beta particles with average energy of 583.0 keV [K7]. It is one of the main components of fallout activity in the first few months after a nuclear test. As the ratio of activities ^{89}Sr /^{90}Sr at the time of fission is approximately 150 (Table 3), the total atmospheric input of ^{89}Sr is estimated to have been about 90 EBq.

56. Strontium-89 was measured in milk at some 63 cities in the United States between 1961 and 1965 [P6]. The average time integral of the concentration for the period September 1961 to December 1965 was 3.5 Bq a l^{-1} [O1]. Using the measured deposition of ^{90}Sr as a guide (Table 5), it is noted that about 55% of the total deposition in the northern hemisphere occurred during this period. Therefore, the time integral of the ^{89}Sr concentration in milk arising from all tests up to 1980 is estimated to be about 6.4 Bq a l^{-1}. For average milk consumption of 0.3 l d^{-1}, the intake commitment of ^{89}Sr is 700 Bq. The committed doses per unit intake of ingested ^{89}Sr activity as given by the ICRP [I1], are 3.2 10^{-9} Gy Bq^{-1} (red bone marrow), 4.8 10^{-9} Gy Bq^{-1} (bone lining cells), 7.3 10^{-9} Gy Bq^{-1} (upper large intestine) and 2.1 10^{-8} Gy Bq^{-1} (lower large intestine). The dose commitments from fallout ^{89}Sr ingestion are thus

Organ or tissue	*Dose commitment* (μGy)
Bone marrow	2.2
Bone lining cells	3.4
Upper large intestine	5.1
Lower large intestine	15

The effective dose equivalent commitment is 1.6 μSv. These values, being derived from measurements in the United States, apply to the population in the temperate zone of the northern hemisphere. They are somewhat underestimated as other components of the diet, such as leafy vegetables, might have contributed significantly to the intake by ingestion.

57. The dose commitments from inhalation of ^{89}Sr can be assessed from the estimated deposition density. The measured integrated deposition density of ^{89}Sr between 1961 and 1969 in the temperate zone of the northern hemisphere was 1.3 10^4 Bq m^{-2} [H2]. Using measurements of ^{90}Sr deposition as a guide (Table 5), 62% of total deposition in the northern hemisphere occurred in this period. Therefore, the estimated ^{89}Sr deposition in the North temperate zone for the entire fallout period 1951–1980 is about 2.1 10^4 Bq m^{-2}. Using the average quotient of integrated air concentration to deposition density of 1.8 10^{-6} Bq a m^{-3}/(Bq m^{-2}), as for ^{90}Sr [B7], and assuming that the adult person inhales 20 m^3 d^{-1} of air, the intake commitment of ^{89}Sr via inhalation is estimated to be 280 Bq.

58. The committed dose to the lungs per unit intake of inhaled ^{89}Sr (Class Y), as given by the ICRP [I1], is 8.4 10^{-8} Gy Bq^{-1}, the doses to other tissues being negligible. The dose commitment to the lungs from ^{89}Sr inhalation in the North temperate zone is, thus, 2.4 10^{-5} Gy. The effective dose equivalent commitment is 2.9 μSv (North temperate zone).

59. From measurements of ^{90}Sr, it is estimated that the dose commitments which apply to the population of the South temperate latitudes are a factor of about 4 less than the northern hemisphere temperate zone values and that hemispheric values are about 1.5 times less than the temperate zone values (from data in Table 6). Estimates of the effective dose equivalent commitments weighted for the world population are 1.0 μSv from ingestion and 1.8 μSv from inhalation. Most of the dose was delivered in the early 1960s during maximum deposition. Assuming the doses apply to a world population of 3.2 10^9 persons at that time, the collective effective dose equivalent commitments are estimated to be 3.2 10^3 man Sv (ingestion) and 5.8 10^3 man Sv (inhalation).

H. RUTHENIUM-106

60. Ruthenium-106 has a half-life of 368 days and decays to ^{106}Rh by pure beta decay with average energy

of 10 keV. The 29.9 s half-life ^{106}Rh decays with average beta energy of 1.41 MeV and also emits several gamma rays. The total stratospheric injection of ^{106}Ru, assessed from that of ^{90}Sr using the activity ratio of 20 at the time of fission, derived from Table 3, has been about 12 EBq.

61. In Annex C of the 1977 report [U6], the time integral of the concentration of ^{106}Ru in air was estimated to be 5.6 10^{-2} Bq a m^{-3} in the North temperate zone and 1.3 10^{-2} Bq a m^{-3} in the South temperate zone. Assuming ^{106}Ru from fallout to be in the oxide form (Class Y compound), the committed dose per unit inhalation intake is 1.0 10^{-6} Gy Bq^{-1} to the lungs [14]. For a daily intake of air of 20 m^3, the dose commitment to lungs from ^{106}Ru is estimated to be

$$D^c(\text{lungs}) \begin{cases} = 4.1\ 10^{-4}\ \text{Gy (North temperate zone)} \\ = 9.5\ 10^{-5}\ \text{Gy (South temperate zone)} \end{cases}$$

The hemispheric values are less by a factor of 1.5. The value weighted for the world population is 2.5 10^{-4} Gy. Doses to other tissues are negligible. The effective dose equivalent commitments are 49 μSv (North temperate zone), 11 μSv (South temperate zone) and 30 μSv (world). The collective effective dose equivalent commitment to the world's population (about 3.2 10^9 persons on average during the time of exposure) is estimated to be 9.6 10^4 man Sv.

I. IODINE-131

62. Iodine-131 is a beta emitter with a half-life of 8.04 d. The average beta energy is 181.7 keV, and gamma rays of 0.36 MeV and other energies are also emitted [K7]. The total injection of globally dispersed ^{131}I into the atmosphere from nuclear testing is estimated to be about 700 EBq from its yield in test debris (Table 3) and the total explosive yield by fission given in Table 2.

63. Fresh milk dominates as a source of ^{131}I intake in areas where it is a major diet component, because of the large areas scavenged by the grazing animals and also because of the short storage period of milk. Data on ^{131}I concentrations in milk, which have become available since the 1977 report [U6], are given in Table 12. As there were tests only in the northern hemisphere during 1976–1978, ^{131}I in milk has only been detected in that hemisphere.

64. The short half-life of ^{131}I means that it is not well mixed in the atmosphere before deposition or decay. Consequently, concentrations in air or deposition at particular sites vary with meteorological conditions and are not necessarily representative of a larger region nor of a latitude band. There were not widespread measurements of ^{131}I throughout the major fallout period; however a rough estimate of the total activity density deposited, weighted over the population of the world, may be made from the average ratio of measured ^{131}I/^{140}Ba in deposition. The half-life of ^{140}Ba, 12.8 d, is comparable to that of ^{131}I.

65. Data from Argentina [B12, C2] for the years 1966–1973 indicate that the ^{131}I/^{140}Ba ratio of annual deposition densities varied from 0.4 to 1.3, with a median value of 0.6. Data from the stations of the global network of the United Kingdom Atomic Energy Authority [C1] indicate that the ^{131}I/^{140}Ba ratio of annual integrated air activity concentrations at nine stations throughout the world ranged from 0.19 to 3.1, with a median value of 0.46. Since only particulate iodine was sampled, total iodine including the gaseous form in air and deposition would have been higher [P7]. The ^{131}I/^{140}Ba ratio is estimated to be 0.9 from these data, comparable to the value from Argentina of 0.6. An intermediate value of 0.8 will be adopted for the dose estimation.

66. Estimates of population-weighted integrated deposition densities of ^{140}Ba are given in Table 28, the global value being 1.7 10^4 Bq m^{-2}. The corresponding value for ^{131}I is thus estimated to be 1.3 10^4 Bq m^{-2}. The relationship between deposition density and the integrated activity concentration of ^{131}I in milk derived from measurements in Argentina [B12] is 6.3 10^{-4} Bq a l^{-1}/(Bq m^{-2}), showing little variation from year to year. This is the transfer factor P_{23}.

67. Consumption of milk, uptake and retention of ^{131}I in the thyroid and the thyroid size are all age-dependent. Representative values were adopted by the Committee in Annex D of the 1977 report [U6]. A summary of these parameters and the estimated absorbed doses per unit intake is given in Table 13.

68. The product of the milk consumption rate and the dose per unit intake of ^{131}I activity gives the transfer factor P_{35} relating integrated activity of ^{131}I in milk to absorbed dose in the thyroid. Taking the three groups of children to be representative of the age groups 0–1, 1–9 and 10–19 years and that these groups contain respectively 2, 16 and 20% of the population [U6], the population-weighted value of P_{35} is 0.13 mGy per Bq a l^{-1}.

69. From the formula $D^c = P_{23}\ P_{35}\ U_0$ using the values given above, the thyroid dose commitment for the world population arising from ^{131}I fallout is estimated to be 1.1 mGy. Additional estimates, which can be derived in a similar fashion, include for the North temperate zone 1.6 mGy (age-weighted population) and 18 mGy (0–1 year old infants) and in the South temperate zone 0.23 mGy (age-weighted population) and 2.5 mGy (0–1 year old infants). Most of this dose commitment was delivered in the early 1960s. Taking the world population at that time to be 3.2 10^9 persons, the thyroid collective dose commitment would be 3.5 10^6 man Gy. The effective dose equivalent commitments are obtained by multiplying by the weighting factor for thyroid of 0.03 [I3]. Estimates of the effective dose equivalent commitments are 48 μSv (North temperate zone), 6.9 μSv (South temperate zone) and 33 μSv (world). The collective effective dose equivalent commitment to the population of the world is estimated to be 1.1 10^5 man Sv.

J. CAESIUM-137

1. Inventory and deposition

70. Caesium-137 is a beta emitter with average beta energy of 170.8 keV [K7]. Its daughter, ^{137m}Ba of half-life 2.55 min, decays with the emission of a gamma ray of energy 661.6 keV. The half-life of ^{137}Cs is 30.2 a, very close to that of ^{90}Sr, and since the average measured activity ratio of ^{137}Cs/^{90}Sr in deposition at many sites and over a long time has been fairly constant at about 1.6 [C3, U5], the total injection of ^{137}Cs into the stratosphere by past atmospheric tests is about 600 PBq x 1.6 = 960 PBq. The latitudinal distribution of ^{137}Cs can also be estimated from the corre-

sponding data for ^{90}Sr given in Table 6. The population-weighted integrated deposition densities are given below. Also listed are the population-weighted values of the transfer coefficient from input to deposition density, P_{02}, for the past pattern of nuclear testing.

	Integrated deposition density (10^3 Bq m^{-2})	*Transfer coefficient* P_{02} (10^{-15} Bq m^{-2} per Bq released)
World	3.14	3.3
Northern hemisphere	3.42	3.6
Southern hemisphere	0.86	0.9
North temperate zone (40–50°)	5.17	5.4
South temperate zone (40–50°)	1.42	1.5

2. Transfer from deposition to diet

71. As in the case of ^{90}Sr, it has been found that fallout over land is the most important pathway as far as dose commitments to man are concerned. Reported annual average ^{137}Cs activity concentrations in milk and in total diet are shown in Table 14. The transfer of ^{137}Cs from deposition to diet is normally high during the first year and relatively small subsequently.

72. The transfer of ^{137}Cs from deposition to diet can be studied quantitatively using the same approach as for ^{90}Sr. The values of P_{23} obtained in this way for total diet and for milk are summarized in Table 15. Figure IV shows the total diet data for Argentina and Denmark and the fit from regression analysis using equation (5). The parameters of the model and the values for the transfer coefficient also for the component food groups are given in Table 16. The summation of the contributions to the transfer coefficient from the various foods is in agreement with the value obtained from the total diet data. The apparent difference between the two countries in the transfer coefficient P_{23} for total diet disappears when the results are normalized to dietary potassium intake. In both cases the value is 40 mBq a (g K)$^{-1}$ per Bq m^{-2}. This is also the value adopted by the Committee in Annex C of the 1977 report [U6]. For average potassium concentration in diet of the two countries of 2.35 g kg^{-1}, the value of P_{23} is 9 mBq a kg^{-1}/(Bq m^{-2}).

73. The estimated transfer coefficient of ^{137}Cs from deposition to diet and dietary components cannot yet be said to be widely representative and could be underestimated for areas which have shown greater transfer of ^{137}Cs to milk. These are areas where caesium is not strongly adsorbed in soil and, thus, greater uptake by plants from the cumulative deposit in soil occurs.

3. Transfer from diet to human tissues

74. Caesium-137 ingested by man is readily absorbed and becomes relatively uniformly distributed in soft tissues. Uptake by mineral bone is slight and the concentrations in fat tissues are low. The biological half-time of caesium is a function of age and sex. For calculational purposes, representative retention assumptions for the adult are that 10% is excreted with a half-time of 2 d and 90% with a half-time of 110 d [I3].

75. Information on ^{137}Cs activity concentrations in the human body since 1974 is given in Table 17. The measurements are generally reported as $^{137}Cs/K$ quotients. The results may be converted to concentra-

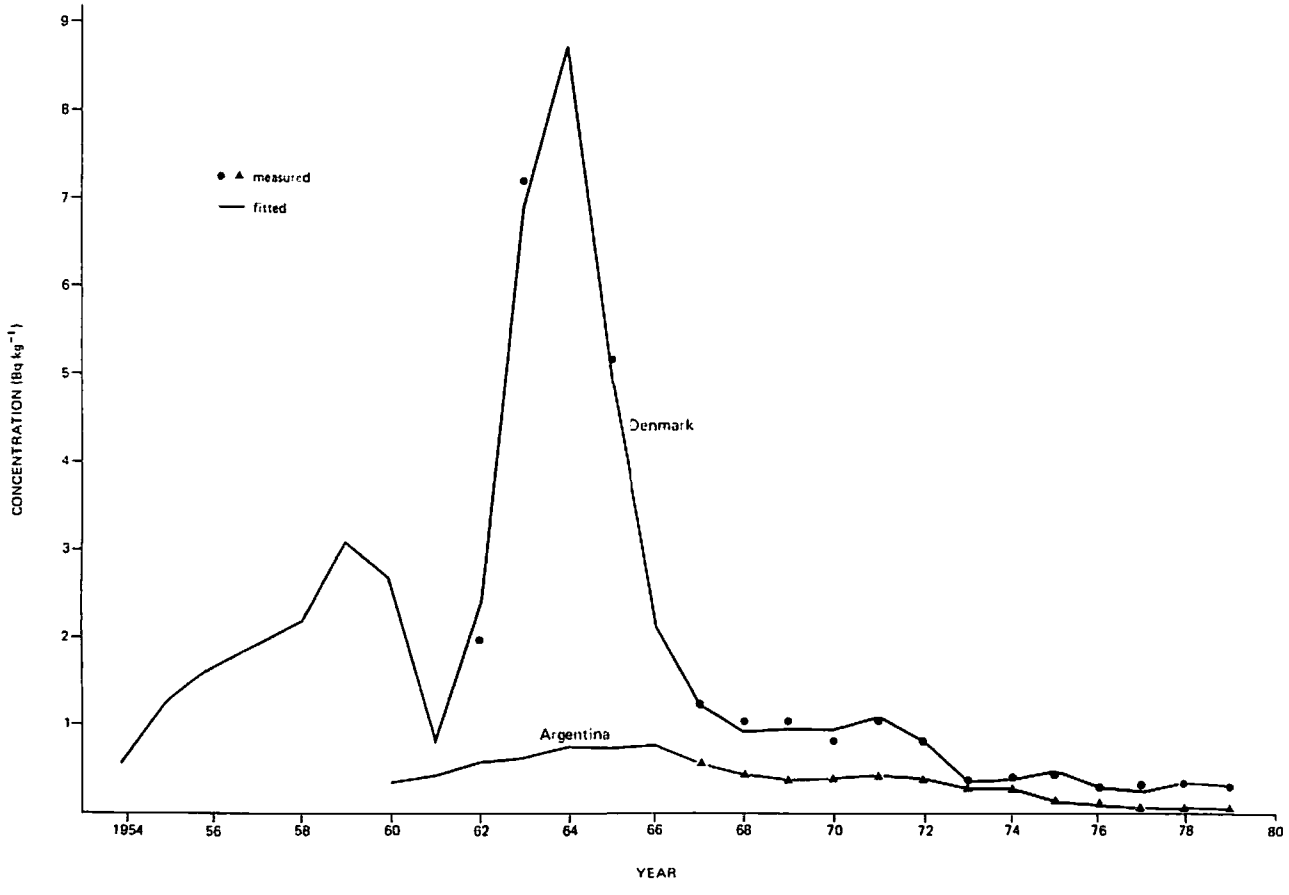


Figure IV. Caesium-137 in total diet of Argentina and Denmark

tions by assuming 140 g K in the 70 kg adult body. For most localities, the ^{137}Cs concentrations have decreased steadily since 1970. The values in subarctic populations are between two and three orders of magnitude higher than those in the middle latitudes, due to higher transfer of ^{137}Cs in the lichen-reindeer (or lichen-caribou) food chain [U5].

76. The short biological half-time of caesium in the body makes it possible to assess the transfer between diet and body, P_{34}, from the quotient of respective ^{137}Cs concentrations integrated over a few years. Using this procedure, an average value of 3 Bq a $(g\ K)^{-1}$ per Bq a $(g\ K)^{-1}$ was derived in Annex C of the 1977 report [U6]. In terms of concentration, the value of the transfer factor becomes 2.6 Bq a kg^{-1} in the body per Bq a kg^{-1} in diet.

4. Dose commitments from caesium-137

77. The combined transfer coefficient, P_{24}, linking deposition density to the ^{137}Cs concentration in the body is the product of P_{23} and P_{34}. From the estimated average values for these two coefficients, the value of the combined coefficient is

$$P_{24} = 0.009 \frac{\text{Bq a kg}^{-1}}{\text{Bq m}^{-2}} \times 2.6 \frac{\text{Bq a kg}^{-1}}{\text{Bq a kg}^{-1}} = 0.023 \frac{\text{Bq a kg}^{-1}}{\text{Bq m}^{-2}}$$

78. An alternative procedure for the assessment of P_{24} is the direct use of the time-integrated ^{137}Cs concentration in the body and the integrated deposition density, both over the same period of several years. The results obtained using this procedure are shown in Table 18. There is general agreement with the value of the previous paragraph except that in the more northern latitudes the greater transfer of ^{137}Cs to diet may contribute to somewhat higher values of P_{24}. The dose commitments will be higher in these areas and, indeed, much higher if reindeer or caribou meat is consumed. It may be assumed, however, that these special situations do not make a large contribution to the collective dose commitments.

79. As was shown in Annex A of the 1969 report of the Committee [U4], the transfer coefficient P_{45}, linking tissue activity and tissue dose, is approximately independent of age if expressed as dose per unit of the time-integrated $^{137}Cs/K$ quotient. The value of P_{45} is $4.9\ 10^{-6}$ Gy per Bq a $(g\ K)^{-1}$. Converting to concentration, the transfer coefficient is

$$P_{45} = 2.4\ 10^{-6}\ \text{Gy/(Bq a kg}^{-1})$$

which is in good agreement with the value derived from ICRP [I1]. It has also been shown directly that this is the appropriate transfer coefficient for the adult [F8, N4]. The transfer coefficient for children is less, due to the partial escape of the photon energy in the smaller body size. For example, Spiers [S2] gave the value for a child weighing 8 kg as $4.1\ 10^{-6}$ Gy per Bq a $(g\ K)^{-1}$.

80. Combining the transfer coefficients P_{24} and P_{45} gives a value of P_{25} of $5.5\ 10^{-8}$ Gy/(Bq m^{-2}). Values of the transfer coefficient P_{02} between input from the nuclear tests and deposition density were given in paragraph 70. Table 19 summarizes the dose commitments which apply to all tissues in the body and the collective dose commitments from ^{137}Cs. The applicable world population size has been taken to be $4\ 10^9$ persons, distributed as indicated in Table 6.

81. The dose commitments from ^{137}Cs via the inhalation pathway can be estimated in a manner similar to ^{90}Sr. The same relationship between deposition density and integrated air concentration may be expected to apply. The integrated concentrations of ^{137}Cs in air, which are 1.6 times the values for ^{90}Sr, are 9.3 mBq a m^{-3} in the North temperate zone, 2.6 mBq a m^{-3} in the South temperate zone and 5.6 mBq a m^{-3} in the world (population-weighted). For the breathing rate of 20 m^3 d^{-1} and dose per unit intake of $8.8\ 10^{-9}$ Gy Bq^{-1}, which is nearly uniform in the various tissues, the dose commitments are 0.6 μGy (North temperate zone), 0.17 μGy (South temperate zone) and 0.36 μGy (world). The collective effective dose equivalent commitment to the world population at the time of exposure ($3.2\ 10^9$ persons) is estimated to be $1.2\ 10^3$ man Sv. These dose estimates from ^{137}Cs inhalation are about 600 times less than those from ^{137}Cs ingestion.

K. CAESIUM-136

82. Caesium-136 is a beta emitter with a half-life of 13.2 d. The average beta energy is 101.1 keV, and several gamma rays with energies up to 1.24 MeV are emitted [K7]. Since it must be produced directly by fission and not by beta decay, because ^{136}Xe is stable, the amount produced in nuclear tests is relatively small (less than 1% of ^{137}Cs on the basis of number of atoms [H8]). The short half-life of ^{136}Cs gives a greater activity, the estimated total production being about $7\ 10^{18}$ Bq.

83. The importance of ^{136}Cs in fallout had at one time been questioned, but the estimated doses have been shown to be very low [O1]. If only the ingestion of fresh milk is considered as a significant pathway, the estimated dose commitment, derived from O'Brien [O1], is about 0.1 μGy to body tissues in general for the population of the temperate region of the northern hemisphere from all tests through 1980. Using the distributional assumptions of levels as before, the dose commitment which applies to the world population ($3.2\ 10^9$ persons) is 0.06 μGy and the collective dose commitment is 190 man Gy.

L. BARIUM-140

84. Barium-140 is a beta emitter with a half-life of 12.8 d and average beta energy of 272 keV [K7]. Several gamma rays are also emitted. Its daughter product, the 40.22 h half-life ^{140}La, decays with 526.9 keV average beta energy and several gamma rays, with energies up to 2.5 MeV. Barium-140 is measurable in fallout only for a few weeks after a nuclear explosion. The activity of ^{140}Ba produced in atmospheric tests is estimated to be 720 EBq, based on globally dispersed ^{90}Sr production and the ratio of fission yields in weapons explosions (Table 3).

85. Barium-140 was measured in the pasteurized milk supply networks of the United States by the Public Health Service between 1961 and 1965 [P6]. The time-integrated concentration in milk was 0.6 Bq a l^{-1} for this period, corresponding to a time integral for all tests of about 1.1 Bq a l^{-1}. For average milk consumption of 0.3 l d^{-1}, the intake commitment of ^{140}Ba is 120 Bq.

86. The committed doses per unit ingested activity of ^{140}Ba are estimated to be 1.0 10^{-9}, 7.7 10^{-9} and 2.6 10^{-8} Gy Bq^{-1} to gonads and walls of the upper large intestine (ULI) and lower large intestine (LLI), respectively [I4]. The dose commitments from ingested fallout ^{140}Ba in the North temperate zone are, thus, 1.2 10^{-7} Gy (gonads), 9.2 10^{-7} Gy (ULI) and 3.1 10^{-6} Gy (LLI). Ingestion of ^{140}Ba in other diet items, such as leafy vegetables, and also direct intake of ^{140}La, have not been taken into account.

87. The same relationship as indicated in paragraph 59 between the North and South temperate zone dose commitments (factor of 4) and between the respective temperate and hemispheric values (factor of 1.5) may be assumed to apply to ^{140}Ba. The dose commitments weighted to the world population are thus estimated to be 7.3 10^{-8} Gy (gonads), 5.6 10^{-7} Gy (ULI) and 1.9 10^{-6} Gy (LLI). The effective dose equivalent commitment to the world population is 0.17 μSv and the collective quantity, applicable to the population of 3.2 10^9 persons in 1961–1962, when most of the ^{140}Ba was released, is 540 man Sv.

88. The dose commitments from inhalation of ^{140}Ba can be calculated using the same method described in paragraph 57 for ^{89}Sr. The integrated deposition density of ^{140}Ba has been evaluated from available measurements and from comparisons with other short-lived radionuclides, as in Annex C of the 1977 report [U6]. The population-weighted values are noted in a subsequent section (Table 28). The estimate for the world population is 1.7 10^4 Bq m^{-2}. This corresponds to a time-integrated concentration in surface air of about 0.03 Bq a m^{-3} during the entire testing period. The intake commitment by inhalation is thus 220 Bq. The corresponding values for the North and South temperate zone are 330 and 46 Bq, respectively.

89. The dose commitments to tissues from inhalation of ^{140}Ba are determined from the product of the intake commitments by the committed doses per unit intake, as given by the ICRP [I4]. The results are listed in Table 20. The effective dose equivalent commitments are 0.32 μSv (North temperate zone), 0.044 μSv (South temperate zone) and 0.21 μSv (world). The collective effective dose equivalent commitment to the applicable world population (3.2 10^9 persons) is 670 man Sv.

M. CERIUM-144

90. Cerium-144 with a half-life of 284 d and its decay product, ^{144}Pr with a half-life of 17.3 min, emit beta particles and several gamma rays [N5]. The average beta decay energies are 82.0 keV from ^{144}Ce and 1.21 MeV from ^{144}Pr [K7]. In comparing with ^{90}Sr fission yield and production (Table 3), the estimated ^{144}Ce production in nuclear tests is 30 EBq.

91. Cerium-144 has been widely measured in air and deposition [C1]. The estimated population-weighted integrated deposition densities are included in Table 28. The corresponding integrated concentrations of ^{144}Ce in air are 8.7 10^{-2} and 2.4 10^{-2} Bq a m^{-3} for the North and the South temperate zones, respectively, and 5.3 10^{-2} Bq a m^{-3} for the global average. Taking the committed dose to the lungs per unit intake of inhaled ^{144}Ce oxide (Class Y compound) to be 7.9 10^{-7} Gy Bq^{-1} [I1], the estimated dose commitments to the lungs are 5.0 10^{-4} Gy (North temperate zone), 1.4 10^{-4} Gy (South temperate zone) and 3.1 10^{-4} Gy (world). The doses to other tissues are negligible. The effective dose equivalent commitment weighted for the world population is 37 μSv. Assuming a world population of 3.2 10^9 in the early 1960s when most of the ^{144}Ce was released in nuclear tests, the estimated collective effective dose equivalent commitment is 1.2 10^5 man Sv.

N. PLUTONIUM AND TRANSPLUTONIUM ELEMENTS

92. Isotopes of plutonium and of transplutonium elements are generated in all weapons tests by activation of ^{238}U or from unfissioned material. Estimates of the production of several isotopes of plutonium, as well as of ^{242m}Am and ^{244}Cm can be inferred from environmental measurements of weapons debris and from the total explosive yield by fission. Such estimates are presented in Table 21. The most important plutonium isotopes are ^{239}Pu, ^{240}Pu, and ^{241}Pu. Since ^{239}Pu and ^{240}Pu are not usually distinguished in environmental measurements, activities reported as ^{239}Pu apply generally to a mixture of ^{239}Pu and ^{240}Pu, containing approximately 60% of ^{239}Pu in terms of activity. The isotope ^{241}Pu is a beta emitter with a half-life of 14.4 a which decays to the alpha emitter ^{241}Am with a half-life of 433 a. Although not produced directly in nuclear explosions, ^{241}Am activity is increasing as ^{241}Pu decays and the total ultimately produced will amount to 5.5 10^{15} Bq of ^{241}Am. Decays of curium isotopes produce plutonium isotopes but in amounts much less significant than direct production. The decay schemes of several transuranium radionuclides are illustrated in Figure V.

93. Plutonium transfer to human tissues can follow the inhalation of airborne plutonium or the ingestion of contaminated food. The available data indicate that for plutonium released by atmospheric tests, the most important pathway to man is the inhalation of contaminated air. Dose commitments have been estimated for each pathway.

1. Dose commitments from inhalation

94. The integrated deposition density of $^{239,240}Pu$ can be inferred from the corresponding values of ^{90}Sr, as it has been observed that the $^{239,240}Pu/^{90}Sr$ activity ratio in stratospheric air samples has been relatively constant throughout the years with a value of about 0.018 [H3]. The ^{90}Sr estimates were given in Table 6. Table 22 gives the results for $^{239,240}Pu$ and for ^{238}Pu and ^{241}Pu from the production ratios (Table 21) and for ^{241}Am from decay of ^{241}Pu.

95. The time-integrated concentrations of the plutonium isotopes in surface air, also presented in Table 22, were estimated from the corresponding deposition densities using the assumption that the value of the apparent deposition velocity of 1.8 10^{-2} m s^{-1} found in New York for ^{90}Sr [B7] can be applied to the plutonium isotopes for large sections of the world. The results agree reasonably well with the values calculated by Bennett [B7] for the New York area, using estimated source terms for each reported nuclear test and a 12-compartment atmospheric model.

96. The time-integrated surface air concentrations of ^{241}Am depend in a significant way on the decay of

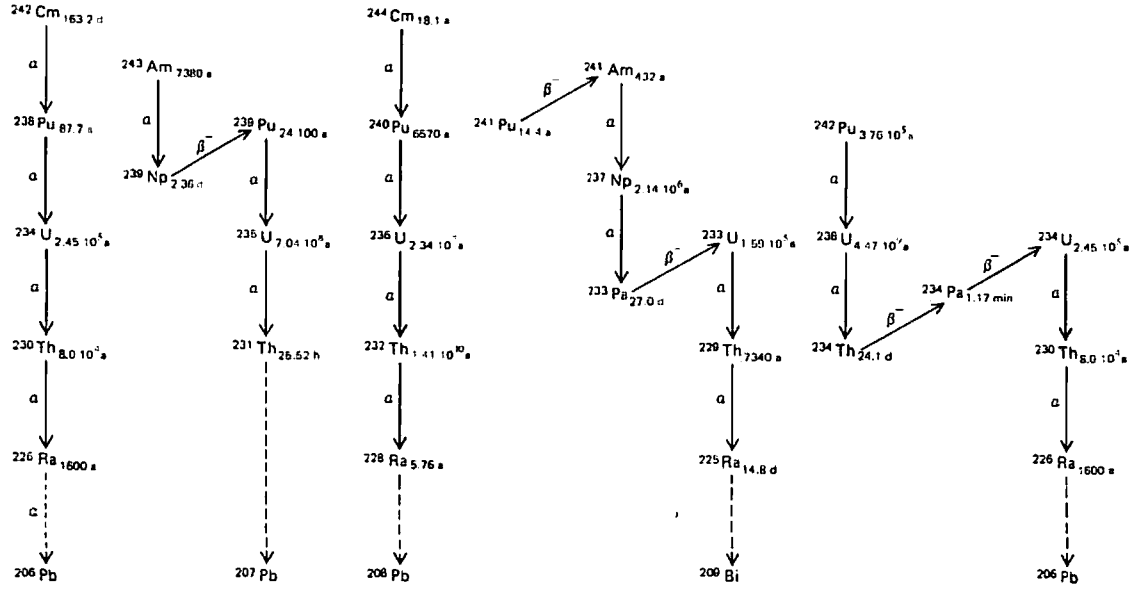


Figure V. Decay schemes of transuranium radionuclides [K7, L3]

^{241}Pu during its residence time in the stratosphere following each nuclear test, and a straightforward comparison with the behaviour of ^{90}Sr or the plutonium isotopes cannot be made. The ^{241}Am surface air concentrations and integrated deposition densities were derived from Bennett's work [B7], using the latitudinal distribution of ^{241}Pu as a guide.

97. It has previously been shown that use of the ICRP lung model with Class Y parameters (appropriate for insoluble aerosol particles) with estimates of ^{239,240}Pu concentrations in air to calculate organ burdens in the general public gives good agreement with measured plutonium concentrations in tissues [B6, U6]. From animal experiments, Class W parameters appear appropriate for americium compounds, including oxides [I3]. Estimates are given in Table 23 of the committed doses per unit intake of plutonium isotopes and ^{241}Am, using the ICRP lung model [I1]. The committed doses per unit intake for ^{239}Pu also apply to ^{240}Pu.

98. Estimates of the dose commitments from inhalation of fallout plutonium and americium are given in Table 24. These results are obtained from the integrated concentrations in air of Table 22, the committed doses per unit inhaled activity of Table 23 and the intake rate of air of 20 m^3 d^{-1}. The effective dose equivalent commitments weighted for the world population are 1.0 μSv (^{238}Pu), 41 μSv (^{239,240}Pu), 8.8 μSv (^{241}Pu) and 1.7 μSv (^{241}Am). The collective effective dose equivalent commitments are obtained by multiplying by the relevant population at the time of exposure (3.2 10^9 persons globally). The results are 3.2 10^3 man Sv (^{238}Pu), 1.3 10^5 man Sv (^{239,240}Pu), 2.8 10^4 man Sv (^{241}Pu), and 5.4 10^3 man Sv (^{241}Am).

99. It is to be noted that inhalation of activity resuspended from the soil surface by winds could add to the long-term intake. However, the Committee in Annex C of its 1977 report [U6] considered this to be insignificant based on a realistic estimate for the resuspension factor of 10^{-9} m^{-1}, applicable to the activity contained in the top centimetre of soil, and considering that plutonium would penetrate into the soil within a few years and then become unavailable for resuspension.

2. Dose commitments from ingestion

100. Information on the dietary intake of ^{239,240}Pu and of ^{241}Am is presented in Table 25 [B7]. Food samples from the New York area were measured for ^{239,240}Pu for 1963, 1964, 1972 and 1974 and for ^{241}Am for 1974 [B7]. The dietary intake of ^{239,240}Pu was found to be about ten times higher in 1963 than in 1974, due to the influence of direct deposition. Clemente [C6] has estimated $^{239,\ 240}$Pu intake in Italian diet to be 0.06 Bq a^{-1} during 1975–1978, in good agreement with the New York data.

101. Using an approach similar to that used for ^{90}Sr and ^{137}Cs, the relationship between ingestion in the year i, $I_{ig}(i)$, and the deposition density rate $\dot{U}(i)$ has been expressed in the following way for the plutonium isotopes

$$I_{ig}(i) = b_1 \dot{U}(i) + b_3 \sum_{m=0}^{\infty} e^{-\lambda_s m} \dot{U}(i-m) \quad (13)$$

where b_1 and b_3 are proportionality constants to be inferred from the measurements and $e^{-\lambda_s m}$ is a factor combining the physical decay and any decrease in the availability to plants of plutonium in soil.

102. The fallout to diet transfer coefficient P_{23} [Bq/(Bq m^{-2})] derived from equation (13) is

$$P_{23} = b_1 + \frac{b_3}{1 - e^{-\lambda_s n}} \approx b_1 + \frac{b_3}{\lambda_s n} \quad (14)$$

where n = 1 year, a constant in this expression.

103. As the number of measurements of the annual ingestion intake, I_{ig}, are very few and cover a time span of only 11 years, the determination of λ_s from equation (13) would be very uncertain as large variations in the value of λ_s result in small variations in the value of I_{ig}. Taking λ_s to be very small, Bennett [B7] found the average solutions for b_1 and b_3 to be 3.3 10^{-2} Bq/(Bq m^{-2}) and 3.5 10^{-4} Bq/(Bq m^{-2}), respectively, for ^{239,240}Pu. The estimation of P_{23} depends on the real value of λ_s. It could be as low as 5 10^{-2} Bq/(Bq m^{-2}) if the availability of plutonium decreases with a mean residence time of 50 a (λ_s = 0.02 a^{-1}) and as high as about 10 Bq/(Bq m^{-2}) for ^{239}Pu and 3 Bq/(Bq m^{-2}) for ^{240}Pu, if the availability

of plutonium decreased only as a result of radioactive decay (λ_s = 3 10^{-5} a^{-1} and 1 10^{-4} a^{-1}). Aarkrog [A4] has estimated transfer of $^{239,240}Pu$ to bread, an important although just one diet component, to be 2 10^{-2} Bq/(Bq m^{-2}). Until additional information becomes available, the geometric mean of the extremes for transfer to total diet will be adopted for the transfer coefficient P_{23}, namely, 0.7 Bq/(Bq m^{-2}). This result corresponds to a mean residence time of $^{239,240}Pu$ in soil of about 100 a, value which is also adopted in Annex C for the mean residence time in soil of long-lived natural radionuclides released from industrial plants.

104. For ^{238}Pu, the above estimate of P_{23} using the 50-year residence time in soil is appropriate, considering the similar radioactive half-life of this isotope. Given the short half-life of ^{241}Pu (14.4 a), the value of P_{23} is dominated by the rate effect and is taken to be equal to 4 10^{-2} Bq/(Bq m^{-2}). In the case of ^{241}Am, the formulation is complicated by the requirement to take the decay of ^{241}Pu into account. Using the equivalent of equation (13) and taking λ_s to be very small and b_1 to have the same value as that obtained for $^{239,240}Pu$, Bennett [B7] estimated b_3 to be equal to 8 10^{-4} Bq/(Bq m^{-2}). This value is very uncertain as only one measurement of annual dietary intake of ^{241}Am has been reported, but it points to the possibility that the americium contained in the soil may be slightly more available to plants than plutonium. The value of P_{23} can be roughly assessed to range from 6 10^{-2} Bq/(Bq m^{-2}) for a residence time of ^{241}Am in soil of 50 years to 0.7 Bq/(Bq m^{-2}) if the availability of ^{241}Am decreases only by radioactive decay. The geometric mean of this range is 0.2 Bq/(Bq m^{-2}).

105. The dose commitments resulting from ingestion intake of plutonium and ^{241}Am are obtained by combining the integrated deposition densities of Table 22 with the values of P_{23} given above and with the committed doses per unit ingested activity of Table 23. The results are presented in Table 26. The dose commitments from ingestion are much lower than those from inhalation, with the exception of ^{241}Am. The dose factors used, however, are those for the soluble form of the elements. If the concentrations do not reflect biologically incorporated forms but simply external contamination, which would seem likely to a large degree, the use of committed doses per unit ingested activity of insoluble forms would be appropriate. The estimates of dose commitments from ingestion would then be lower by a factor of ten.

106. The effective dose equivalent commitments weighted for the world population from ingestion are 0.0047 μSv (^{238}Pu), 2.7 μSv ($^{239, 240}Pu$), 0.04 μSv (^{241}Pu) and 1.8 μSv (^{241}Am). The relevant populations to be used for collective dose estimates may be taken to be 4 10^9 persons for ^{241}Pu, somewhat larger (6 10^9 persons) for ^{238}Pu and the ultimate population size of 10^{10} persons for ^{241}Am and $^{239, 240}Pu$. The collective effective dose equivalent commitments are then roughly 30 man Sv (^{238}Pu), 3 10^4 man Sv ($^{239, 240}Pu$), 200 man Sv (^{241}Pu) and 2 10^4 man Sv (^{241}Am).

III. EXTERNAL IRRADIATION

107. Many radionuclides produced in nuclear testing emit gamma rays and contribute to the dose from external irradiation. The most important from this point of view are a number of short-lived radionuclides, particularly ^{95}Zr and its daughter ^{95}Nb, and long-lived ^{137}Cs.

108. In principle, it is possible to calculate the external doses from the integrated deposition density of each radionuclide. The conversion factors for estimating the absorbed doses in air, 1 metre above the ground, which were used in Annex C of the 1977 report [U6] were based largely on the work of Beck et al. [B1]. A recent compilation provides updated values for specific radionuclides [B14]. These are listed in Table 27. For short-lived radionuclides, a plane source on the surface of the ground is postulated, but for ^{137}Cs an exponential profile is assumed with a mean depth of 3 cm.

109. In order to assess the organ doses from absorbed doses in air, an average combined factor of 0.7 has been used to account for the change of material (air to tissue) and for back-scatter and shielding afforded by other tissues of the body. In addition, the estimation of the organ doses from external radiation due to fallout requires the use of a further factor representing the shielding effect of buildings. The shielding is assumed to reduce the absorbed dose rate in air in the building, on average, to 20 % of its outdoor value. Assuming that on the average 80% of the time is spent indoors, the effective shielding factor of the building is about 0.4. The overall factor used to convert absorbed doses in air to absorbed doses in organs, accounting for indoor occupancy and building shielding, is therefore estimated to be about 0.3. It is assumed to be independent of the gamma energy and thus to apply to all the radionuclides considered. A detailed discussion of the derivation of the values indicated in this paragraph is provided in Annex A.

110. The transfer coefficients P_{25} relating integrated deposition densities of selected gamma-emitting nuclides to the resulting dose commitments in the organs and tissues of interest to the Committee are obtained by multiplying the absorbed dose in air by 0.3. The results are shown in Table 27.

111. Estimates of the population-weighted integrated deposition densities from all atmospheric nuclear tests are given in Table 28 [U6]. The values for ^{137}Cs have already been presented in paragraph 70. With respect to the short-lived radionuclides, the estimates, derived from data contained in Annex C of the 1977 report [U6], are based on the use of quotients of the time-integrated air concentrations and of integrated deposition densities of the relevant nuclides, assessed from measurements at a number of sites, and the known latitudinal distribution of the integrated deposition densities of some nuclides, such as ^{90}Sr, ^{89}Sr and ^{95}Zr. The estimates have been updated to account for the small additional deposition occurring to the end of 1980.

112. The dose commitments, obtained as the products of the P_{25} factors of Table 27 and the population-weighted integrated deposition densities of Table 28, are presented in Table 29. The dose commitment to the world population is estimated to be about 700 μGy, the combined short-lived nuclides and ^{137}Cs each contributing about half of this value. The effective dose equivalent commitment is 680 μSv and the collective effective dose equivalent commitment to the world population, assumed to be 3.2 10^9 persons on average during the time of exposure and 4 10^9 persons for ^{137}Cs, is estimated to be 2.5 10^6 man Sv; the contribution of ^{137}Cs is 1.5 10^6 man Sv.

113. It is interesting to compare the estimated values of Table 29 with actual determinations of the external dose in both hemispheres. At Chilton in the United Kingdom the total gamma absorbed dose in air from fallout has been determined by a combined procedure including direct measurements and computation from measured deposition [G2]. The estimate, for the period 1951–1977, is 1.8 mGy. The corresponding organ absorbed dose, applying the factor 0.3 (paragraph 110), is 500 μGy. In the southern hemisphere, for Buenos Aires up to 1975, an absorbed dose of 150 μGy has been estimated, based upon direct calculation from measured deposition densities of individual short-lived fission products.

IV. SUMMARY OF DOSE COMMITMENTS FROM NUCLEAR EXPLOSIONS

114. Estimates of the dose commitments from nuclear explosions carried out to the end of 1980 are summarized in Table 30. The use of the effective dose equivalent commitments permits a direct comparison of the importance of the various pathways to man and of the importance of the various radionuclides considered. The weighting factors of the ICRP have been applied. The effective dose equivalent commitments are presented in Table 31.

115. For the world population, the contribution of ingestion (3.0 mSv) is found to be about 4 times higher than that of external irradiation (0.7 mSv) which in turn is about 5 times greater than that of inhalation (0.13 mSv). The relative importance of ingestion would be very much reduced if an incomplete effective dose equivalent were calculated up to the year 2000; in that case, external irradiation would be the dominant pathway, as ^{14}C, which is the major contributor to the ingestion dose, delivers in that time span only a small fraction of its total contribution.

116. Of the 21 radionuclides considered, only 7 contribute more than 1% to the effective dose equivalent commitment for the world population (Table 32). Those nuclides are, in decreasing order of importance: ^{14}C, ^{137}Cs, ^{95}Zr, ^{90}Sr, ^{106}Ru, ^{144}Ce, and ^{3}H. For ^{95}Zr, ^{106}Ru and ^{144}Ce, the irradiation to which the world population was committed by nuclear tests to the end of 1980 is already largely completed. For ^{137}Cs, ^{90}Sr and ^{3}H, a large part of their contribution to the effective dose equivalent commitment will have been delivered by the year 2000. If there is no further atmospheric nuclear testing, only ^{14}C will contribute significantly to the dose rate in the third millenium. In the far future, however, the long-lived decay products of the plutonium isotopes may have to be taken into consideration. These have not yet been assessed. A very rough estimate indicates that they could deliver, at a very low rate, an additional contribution of about 0.1% to the total effective dose equivalent commitment.

117. A summary of the collective effective dose equivalent commitments evaluated in this Annex is given in Table 33. The total of $3\ 10^7$ man Sv for nuclear explosions conducted in the atmosphere to the end of 1980 corresponds to about 4 extra years of exposure of the current world population to natural background radiation. The fallout exposure, however, occurs at a much lower rate. The exposure from ^{14}C, which contributes almost 90% to the collective total, will continue for thousands of years to an increasing and then assumed ultimately stabilized large world population size. Other than ^{14}C, only ^{239}Pu, ^{240}Pu and ^{241}Am affect the population of the far future, but their significance is much less, as their long-term contribution amounts to $5\ 10^4$ man Sv, which is less than 0.2% of the collective total.

118. The assessments in this Annex have resulted in minimal adjustments in the absorbed dose commitments to regional or world populations evaluated in Annex C of the 1977 report [U6]. Additional amounts of radioactive material released to the environment from nuclear testing in recent years have been much less than in the past. The estimates of dose commitments have however been extended by consideration of secondary exposure pathways and the various transfer coefficients and dose factors have been re-evaluated. Expressing the doses in terms of effective dose equivalent has allowed a direct comparison of the importance of the various pathways to man and of the various radionuclides to be made. It is expected that continued measurements of fallout activity in the environment will lead to further minor adjustments and improvements in the dose assessments.

Table 1

Estimated yields of atmospheric nuclear tests

Year	Country	Number of tests	Estimated yield (Mt)	
			Fission	Total
1945	USA	3	0.05	0.05
1946	USA	2	0.04	0.04
1948	USA	3	0.10	0.10
1949	USSR	1	0.02	0.02
1951	USA	15	0.50	0.50
	USSR	2	0.04	0.04
1952	USA	10	6.6	12.6
	UK	1	0.02	0.02
1953	USA	11	0.25	0.25
	UK	2	0.04	0.04
1954	USA	6	29.6	47.1
	USSR	1	0.5	0.5
1955	USA	13	0.17	0.17
	USSR	4	1.5	3.0
1956	USA	14	9.7	22.7
	USSR	7	2.5	4.8
	UK	6	0.10	0.10
1957	USA	25	0.34	0.34
	USSR	13	4.7	11.3
	UK	7	5.85	9.25
1958	USA	53	8.2	17.6
	USSR	25	16.2	35.2
	UK	5	4.54	7.24
1960	France	3	0.11	0.11
1961	USSR	50	25.4	122.3
	France	1	0.02	0.02
1962	USSR	39	60.05	180.3
	USA	38	16.5	37.1
1964	China	1	0.02	0.02
1965	China	1	0.04	0.04
1966	France	5	0.68	0.68
	China	3	0.62	0.62
1967	France	3	0.20	0.20
	China	2	1.72	3.02
1968	France	5	4.1	4.9
	China	1	1.2	3.0
1969	China	1	2.0	3.0
1970	France	8	2.55	2.75
	China	1	2.0	3.0
1971	France	5	1.95	1.95
	China	1	0.02	0.02
1972	France	3	0.12	0.12
	China	2	0.12	0.12
1973	France	5	0.05	0.05
	China	1	1.6	2.5
1974	France	7	1.1	1.1
	China	1	0.45	0.60
1976	China	3	2.37	4.12
1977	China	1	0.02	0.02
1978	China	2	0.04	0.04
1980	China	1	0.45	0.6
Summary				
1945-1962	USA	193	72.1	138.6
1949-1962	USSR	142	110.9	357.5
1952-1953	UK	21	10.6	16.7
1960-1974	France	45	10.9	11.9
1964-1980	China	22	12.7	20.7
TOTAL		423	217.2	545.4

Table 2

Stratospheric partitioning of nuclear debris
(Mt fission energy)

Year	Equatorial stratosphere (N)			Polar stratosphere (N)		Equatorial stratosphere (S)		
	Lower	Upper	High	Lower	Upper	Lower	Upper	High
1951	0.009							
1952	1.3	1.8						
1953	0.001			0.12				
1954	7.99	6.76		0.003				
1955				1.13				
1956	4.97	0.15		2.10				
1957	2.32			3.09		2.32		
1958	2.41	0.4	1.5	14.18		1.85		1.51
1961				15.20	7.14			
1962	6.26	0.24	1.2	28.19	30.54	3.79	0.05	0.35
1965				0.003				
1966				0.26		0.17		
1967	1.7					0.10		
1968				0.89	0.31	3.22		
1969				1.5	0.5			
1970				1.5	0.5	2.31		
1971						1.80		
1972				0.02		0.002		
1973	1.6							
1974	0.45					0.14		
1976				1.49	0.78			
1980				0.45				
Total	29.0	9.3	2.7	70.1	39.8	15.7	0.05	1.9

(N) Hemisphere total: 150.9 (S) Hemisphere total: 17.6

Global total: 168.5 (Mt)

Table 3

Fission and production yields of radionuclides in weapons testing

Nuclide (half-life) [K7]	Representative fission yield (%) [H8]	Normalized production (PBq per Mt fission energy)
^{89}Sr (50.5 d)	2.56	590
^{90}Sr (28.6 a)	3.50	3.9
^{95}Zr (64.0 d)	5.07	920
^{103}Ru (39.4 d)	5.20	1500
^{106}Ru (368 d)	2.44	78
^{131}I (8.04 d)	2.90	4200
^{136}Cs (13.2 d)	0.036	32
^{137}Cs (30.2 a)	5.57	5.9
^{140}Ba (12.8 d)	5.18	4700
^{141}Ce (32.5 d)	4.58	1600
^{144}Ce (284 d)	4.69	190

Table 4

Dose commitments from inhalation of ^{54}Mn

Organ or tissue	Committed dose per unit intake (nGy Bq^{-1})	Dose commitment (10^{-8} Gy)		
		Northern temperate zone	Southern temperate zone	Global
Lungs	6.7	27	1.4	16
Liver	2.5	10	0.51	6.1
Red bone marrow	1.1	4.5	0.22	2.7
Breast	0.86	3.5	0.18	2.1
Gonads	0.71	2.9	0.15	1.7
Other tissues	1.8	7.4	0.37	4.4

Table 5

Annual deposition and cumulative deposit of strontium-90

	Annual deposition (10^{16} Bq)			Cumulative deposit (10^{16} Bq)		
	Northern hemisphere	Southern hemisphere	Global	Northern hemisphere	Southern hemisphere	Global
Pre-1958	6.68 a/	2.37 a/	9.05 a/	6.29	2.22	8.51
1958	2.33	0.95	3.28	8.44	3.11	11.55
1959	3.89	0.68	4.57	12.06	3.70	15.76
1960	0.97	0.62	1.59	12.73	4.22	16.95
1961	1.30	0.64	1.94	13.69	4.77	18.46
1962	5.34	0.98	6.32	18.65	5.59	24.24
1963	9.70	1.14	10.84	27.79	6.59	34.38
1964	6.13	1.56	7.69	33.96	7.99	41.95
1965	2.86	1.32	4.18	35.15	9.10	44.25
1966	1.21	0.77	1.98	35.48	9.62	45.10
1967	0.62	0.41	1.03	35.22	9.81	45.03
1968	0.72	0.38	1.10	35.08	9.92	45.00
1969	0.54	0.52	1.06	34.78	10.21	44.99
1970	0.76	0.47	1.23	34.67	10.43	45.10
1971	0.70	0.56	1.26	34.52	10.73	45.25
1972	0.32	0.35	0.67	33.97	10.80	44.77
1973	0.12	0.11	0.23	33.23	10.66	43.89
1974	0.45	0.14	0.59	32.89	10.55	43.44
1975	0.22	0.13	0.35	32.30	10.40	42.70
1976	0.10	0.08	0.18	31.64	10.25	41.89
1977	0.30	0.08	0.38	31.15	10.06	41.21
1978	0.37	0.07	0.44	30.78	9.88	40.66
1979	0.12	0.04	0.16	30.16	9.70	39.86
1980	0.11	0.04	0.15	29.54	9.51	39.05
Integrated deposition (10^{16} Bq)	45.86	14.41	60.27			
Stratospheric inventory b/ (10^{16} Bq)	0.18	< 0.01	0.18			
Total injection through 1980 (10^{16}Bq)	46.0	14.4	60.4			

a/ Estimated from the cumulative deposit.

b/ Measured July 1979 in the northern hemisphere [L1], reduced with a half-time of 10 months to the end of 1980, plus estimated injection in 1980. Estimate only for the southern hemisphere.

Table 6

Latitudinal distribution of strontium-90 deposition[a/]

Latitude band (degrees)	Integrated deposition (10^{16} Bq)	Area of band (10^{12} m^2)	Integrated deposition density (10^3 Bq m^{-2})	Population distribution (%)	Population weighted integrated deposition density (10^3 Bq m^{-2})
NORTHERN HEMISPHERE					
80-90	0.10	3.9	0.26	0	
70-80	0.79	11.6	0.68	0	
60-70	3.29	18.9	1.74	0.4	
50-60	7.39	25.6	2.89	13.7	
40-50	10.16	31.5	3.23	15.5	
30-40	8.53	36.4	2.34	20.4	
20-30	7.12	40.2	1.77	32.7	
10-20	5.09	42.8	1.19	11.0	
0-10	3.57	44.1	0.81	6.3	
Total	46.0			100.0	2.14
SOUTHERN HEMISPHERE					
0-10	2.10	44.1	0.48	54.0	
10-20	1.78	42.8	0.42	16.7	
20-30	2.81	40.2	0.70	14.9	
30-40	2.76	36.4	0.76	13.0	
40-50	2.81	31.5	0.89	0.9	
50-60	1.21	25.6	0.47	0.5	
60-70	0.67	18.9	0.35	0	
70-80	0.25	11.6	0.22	0	
80-90	0.03	3.9	0.08	0	
Total	14.4			100.0	0.54
GLOBAL	60.4			89 (N) 11 (S)	1.96

a/ Through 1980, including projected deposition of stratospheric burden.

Table 7

Strontium-90 concentration in milk and intake rate in total diet

Location	Milk[a/] (Bq l^{-1})							Total diet (Bq d^{-1})							References
	1974	1975	1976	1977	1978	1979	1980	1974	1975	1976	1977	1978	1979	1980	
NORTHERN HEMISPHERE															
Canada	0.2	0.2	0.1	0.2	0.1	0.1	0.08	0.3	0.2	0.2	0.3	0.2			[M4,H10,I2]
Denmark	0.2	0.2	0.2	0.1	0.1	0.1	0.1	0.4	0.3	0.2	0.2	0.3	0.3	0.2	[A1]
Faroe Islands	0.9	0.8	0.7	0.4				0.6	0.6	0.5	0.4	0.4			[A2]
Finland	0.2	0.2	0.2	0.2	0.2										[C4, R3]
France (1)	0.3	0.3	0.2	0.2	0.2	0.2	0.2	0.4	0.4	0.4	0.4	0.4	0.4	0.3	[P1, I2]
France (2)	0.3	0.3	0.2	0.2	0.2	0.2	0.2	0.4	0.4	0.3	0.3	0.3	0.3	0.3	[C10, M10]
German Dem.Rep. (Berlin area)	0.2	0.1	0.1					0.2	0.2	0.2					[K11]
Germany, Fed. Rep.	0.3	0.1	0.1	0.1	0.2	0.2	0.1	0.4	0.3	0.3	0.2	0.3	0.4	0.3	[B11]
Greenland								0.3	0.3	0.2	0.2	0.2			[A3]
India	0.1	0.09	0.06					0.2	0.2	0.1					[L2]
Italy	0.3														[C9]
Japan	0.2	0.1	0.1	0.1	0.1	0.1	0.09	0.3	0.2	0.2	0.2	0.2	0.1	0.1	[N10, I2]
Netherlands	0.2	0.1	0.1	0.1	0.1	0.06	0.06								[M6]
Norway	0.3	0.4	0.3	0.4											[H14]
Poland	0.3	0.2													[J1]
Senegal			0.1												[R2]
Sweden	0.2	0.2	0.1	0.1	0.2	0.2	0.1								[I2]
Switzerland	0.2	0.2	0.2	0.2											[H13]
USSR	0.3	0.3	0.2	0.1	0.07	0.08	0.07	0.5	0.5						[K6, I2, P8]
United Kingdom	0.1	0.1	0.1	0.1	0.09	0.1	0.08								[B10, G3, F6]
United States															
New York City	0.2	0.2	0.2	0.2	0.2	0.2	0.1	0.4	0.3	0.3	0.3	0.3	0.3	0.2	[B8, K3]
San Francisco	0.05	0.07	0.05	0.04	0.05	0.04	0.04	0.1	0.1	0.1	0.09	0.1	0.1	0.09	[B8, K3]
SOUTHERN HEMISPHERE															
Argentina	0.11	0.09	0.08	0.07	0.06	0.06	0.06	0.08	0.07	0.06	0.05	0.04	0.05	0.04	[C7]
Australia	0.2	0.2						0.1	0.1						[A6]
Bolivia	0.04	0.04	0.04	0.04	0.07	0.1	0.1								[R2]
Chile	0.09	0.04	0.1	0.1	0.09	0.09	0.08								[C8, R2]
New Caledonia	0.09	0.04	0.2	0.06	0.04	0.03									[R2]
New Zealand	0.2	0.2	0.1	0.1	0.09	0.09	0.09								[N6, I2]
Peru	0.04	0.09		0.1	0.08	0.06	0.05								[R2]
Réunion	0.1	0.04	0.09	0.1	0.07	0.1	0.07								[R2]
Tahiti	0.2	0.2	0.09	0.1	0.1	0.09	0.08								[R2]

a/ Assumes 1.2 gCa l^{-1}.

Table 8

Parameters of the transfer coefficient for strontium-90 between deposition density and diet

Parameter[a]	Milk products			Grain products			Vegetables		
	Argentina	Denmark	New York[b]	Argentina	Denmark	New York	Argentina[c]	Denmark	New York
b_1	1.2	1.5	0.7	1.6	3.3	0.7	0.02	0.4	0.3
b_2	1.1	0.7	0.3	1.5	8.9	1.5	0	0	0.06
b_3	0.1	0.3	0.2	0.06	0.1	0.2	0.1	0.2	0.3
λ_s	0.10	0.12	0.112	0.02	0.02	0.11	0.26	0.07	0.08
p_{23}^k	3.7	4.8	2.5	6.0	17.4	3.9	0.4	2.5	3.9
w_k	0.26	0.35	0.31	0.20	0.16	0.15	0.24	0.24	0.19
$w_k\ p_{23}^k$	1.0	1.7	0.8	1.2	2.8	0.6	0.09	0.6	0.8

Parameter[a]	Fruit			Meat, etc.			Total diet		
	Argentina[d]	Denmark	New York	Argentina	Denmark	New York	Argentina	Denmark	New York
b_1	0.3	1.0	0.2	0.7	0.4	0.002	1.1	1.3	0.5
b_2	0.2	0.04	0	0.8	0.1	0.09	0.6	1.8	0.4
b_3	0.04	0.04	0.1	0.03	0.04	0.05	0.04	0.1	0.2
λ_s	0.09	0.02	0.03	0.02	0.09	0.17	0.03	0.05	0.08
p_{23}^k	1.0	2.9	4.1	3.0	0.9	0.4	3.0	5.5	3.0
w_k	0.23	0.10	0.15	0.08	0.15	0.19	1.0	1.0	1.0
$w_k\ p_{23}^k$	0.2	0.3	0.6	0.2	0.1	0.07	3.0	5.5	3.0
					Components total		2.7	5.5	2.9

a/ The units of parameters b_1, b_2, b_3 and p_{23}^k for diet group k are 10^{-3} Bq a kg^{-1} / (Bq m^{-2}). The units for λ_s are a^{-1}. The constant w_k is the fractional amount by weight of food group k in the total diet.

b/ New York City.

c/ Root vegetables.

d/ Fruit and leafy vegetables.

NOTE: Data span for regression analysis: Argentina 1964-1979, Denmark 1959-1979, New York 1960-1979 (New York milk 1954-1979). Comsumption data in model diets: Food 558, 498 and 637 kg a^{-1} in Argentina, Denmark and New York, respectively; calcium 256, 620 and 370 g a^{-1} in Argentina, Denmark and New York, respectively.

Table 9

Strontium-90 to calcium quotients in human bone a/

[mBq (g Ca)$^{-1}$]

Location	Year	Age (years)					Ref.
		Newborn or stillborn	< 1	1-4	5-19	> 19	
NORTHERN HEMISPHERE							
Canada	1974		55	(75)	70	60	[M4]
	1975		110	(100)	85	80	[M4]
	1976		110	(120)	65		[M4]
	1977		60	(150)	(65)		[M4]
	1978		95	(200)	65		[M4]
Denmark	1974	(48)		67	52	52	[A1]
	1975	(48)		74	56	56	[A1]
	1976	(33)	41	(37)	37	37	[A1]
	1977	(26)	(52)	(28)	33	33	[A1]
	1978					41	[A1]
	1979					37	[A1]
	1980		(37)		24	30	[A1]
Fiji	1974					37	[H4]
Germany, Fed. Rep. of b/	1977			(48)	52	30	[D2]
	1978			37	52	59	[D3]
India	1975					85	[H5]
	1980					32	[E1]
Japan	1974		49	68	57	41	[T1]
	1975	24	35	48	45	44	[T1]
	1976	24		(20)	45	36	[T1]
	1977	19	30		40	34	[T1]
	1978	19		41	39	38	[T1]
	1979	18		37	37	34	[T1]
	1980	17		34	30	35	[T1]
Nepal	1974					110	[H4]
	1975	(70)		(100)	150	130	[H4]
	1976	(160)	(150)		130	140	[F6]
	1977		(85)	(83)	200	150	[H6,H7]
	1978	(67)		(740)	180	110	[H7]
	1979			70	100	100	[E1]
	1980			(44)	150	56	[E1]
New Guinea	1974					19	[H4]
Norway	1974	63	100	120	110	89	[J2]
	1975	56	96	78	89	100	[J2]
	1976	48	63	70	63	67	[J2]
	1977	48	59	(110)	70	74	[J2]
USSR c/	1974	34	52	(89)	110	53	[M3,B13]
	1975	39	48	(57)	91	56	[M3,B13]
	1976	35	40	(73)	95	56	[B13]
	1977	36	38	(78)	92	56	[B13]
	1978	34	45	57	74	56	[B13]
United States							
New York	1974		63	(56)	63	44	[B2]
	1975		52	(62)	52	41	[B3]
	1976				(59)	41	[B4]
	1977					37	[B5]
	1978					41	[K4]
	1980					33	[K13]
San Francisco	1974		22	(32)	26	26	[B2]
	1975		19	27	30		[B3]
	1976		19	(28)	30	26	[B4]
	1977		19	(32)	22	26	[B5]
	1978		33	34	30	22	[K4]
	1979		15	39	(35)	23	[K12]
	1980		17	(25)	18	21	[K13]
SOUTHERN HEMISPHERE							
Argentina	1974			35			[C7]
	1975	31	33	36	36	36	[C7]
	1976	34	33	35	32	36	[C7]
	1977	33	33	34	34	32	[C7]
	1978	34	32	33	33	31	[C7]
	1979	19	31	31	34	31	[C7]
	1980	22	30	30	27	30	[C7]
Australia	1974	22	37	46	37	37	[A6]
	1975	22	37	62	37	37	[A6]

a/ Samples are vertebrae, unless otherwise indicated. Parentheses indicate averages from sample size less than 5 individuals.

b/ Tibia.

c/ Normalized to whole skeleton.

Table 10

Parameters of the transfer coefficient for ^{90}Sr between diet and bone

Parameter a/	Argentina 1965-1979	Denmark 1960-1979	New York City 1954-1979	San Francisco 1961-1978
c	0.16	0.04	0.02	0.06
g	0.01	0.01	0.02	0.02
λ_b	0.10	0.12	0.27	0.17
P_{34}	0.32	0.16	0.11	0.18

a/ The units for the parameters c, g, and P_{34} are Bq a $(gCa)^{-1}$ in bone per Bq a $(gCa)^{-1}$ and a^{-1} for λ_b.

Table 11

Dose commitments from ingestion of strontium-90

Location	Dose commitment (10^{-4} Gy)		Collective dose commitment (10^5 man Gy)	
	Bone marrow	Bone lining cells	Bone marrow	Bone lining cells
World	5.7	13	23	50
Northern hemisphere	6.2	14	22	49
Southern hemisphere	1.6	3.4	0.7	1.5
North temperate zone (40-50°)	9.4	21	5.2	11
South temperate zone (40-50°)	2.6	5.7	0.01	0.02

Table 12

Iodine-131 in milk

Location	Integrated concentration in milk (Bq d l^{-1})			Ref.
	1976	1977	1978	
Denmark (Risø)	7.4			[A1]
Finland	13	10		[B15]
France	34	7.4		[P1]
Germany, Fed.Rep.of (Kiel)	16	5		[B11]
Japan (Chiba)	13		11	[N10]
United Kingdom (Berkshire)	35	7.4		[B9]
United States (Baltimore) a/	59			[S1]

a/ Inferred from infant thyroid dose, assuming 3 μGy per Bq d l^{-1}.

Table 13

Age-dependent parameters for obtaining absorbed doses in the thyroid gland from ingestion of ^{131}I in milk

Parameter	Age			
	6 months	4 years	14 years	Adult
Mass of thyroid gland (g)	2	4	14	20
Effective half-time in thyroid (d)	6.0	6.3	6.9	7.6
Milk consumption rate (l a^{-1})	330	180	150	90
Absorbed energy per disintegration (MeV)	0.18	0.18	0.19	0.19
Dose per unit intake (μGy Bq^{-1})	4.3	2.0	0.65	0.51
Transfer coefficient P_{35} [mGy/(Bq a l^{-1})]	1.4	0.36	0.098	0.046

Table 14

Caesium-137 concentration in milk and intake in total diet

Location	Milk (Bq l^{-1})							Total diet (Bq d^{-1})							References
	1974	1975	1976	1977	1978	1979	1980	1974	1975	1976	1977	1978	1979	1980	
NORTHERN HEMISPHERE															
Canada	0.3	0.3	0.2	0.3	0.3	0.2	0.1								[H10, I2]
Denmark	0.3	0.2	0.2	0.2	0.3	0.2	0.1	0.6	0.6	0.4	0.5	0.7	0.5	0.3	[A1]
Finland	1.0	0.9	0.7	0.6	0.6										[C4, R3]
France (1)	0.4	0.3	0.2	0.2	0.3	0.2	<0.2	0.6	0.5	0.3	0.5	0.6	0.6	<0.3	[P1, I2]
France (2)	0.4	0.4			0.3	0.1	0.1								[C10, M10]
German Dem.Rep. (Berlin area)	0.3	0.4	0.3					0.6	1.0	0.6					[K11]
Germany, Fed. Rep. of	0.7	0.2	0.4	0.3	0.3	<0.3	<0.2	0.6	0.6	0.4	0.5	0.4	0.4	0.3	[B11]
Japan	0.3	0.4	0.3	0.3	0.4	0.3	0.2	0.3	0.2	0.2	0.2	0.2	0.2	0.1	[N10, I2]
Netherlands	0.3	0.3	0.2	0.2	0.2	0.2	0.1								[M6]
Norway	2.2	1.8	1.9	1.9											[H14]
Poland	0.8	0.8													[J1]
Sweden	0.4	0.4	0.3	0.4	0.4	0.3	0.3								[H1, I2]
Switzerland	0.4														[H13]
USSR	0.7	0.6	0.3	0.3	0.2	0.2	0.1	0.6	0.6						[K6,I2,P8]
United Kingdom	0.3	0.3	0.1	0.2	0.3	0.2	0.1								[B10,G3,F6]
United States	0.1	0.3	0.2	0.2	0.3	0.2		0.5	0.5	0.3	0.3	0.2	0.2	0.2	[H9,K2,I2]
Faroe Islands	9.4	7.3	7.0	6.6	6.6			8.8	10.4	5.4	4.0	5.7			[A2]
Greenland								2.0	1.1	1.0	2.0	2.7			[A3]
SOUTHERN HEMISPHERE															
Argentina	0.4	0.2	0.1	0.06	0.05	0.06	0.06	0.4	0.2	0.1	0.06	0.05	0.05	0.05	[C7]
Australia	0.3	0.2													[A6]
Chile			0.4	0.6	0.4	0.2									[C8, R2]
New Zealand	0.5	0.4	0.3	0.4	0.2	0.3	0.1								[N6, I2]
Peru		0.1	0.1	0.2	0.2	0.2	0.1								[R2]
New Caledonia		0.2													[R2]
Society Islands Tahiti	3.9	3.7	2.6	2.6	2.2	2.0	2.1								[R2]

Table 15

Transfer coefficient for caesium-137 between deposition density and diet or milk

Location	P_{23} (milk) (mBq a kg^{-1} per Bq m^{-2})	P_{23} (diet) (mBq a kg^{-1} per Bq m^{-2})	Ref.
NORTHERN HEMISPHERE			
Denmark (1962-1979)	5.9	12	[K5]
Finland	24	-	[C5]
France	11	-	[M2]
Germany, Fed. Rep. of	12	-	[H15]
Norway (1957-1977)	23	-	[K5]
United States (1960-1973)	5.4	-	[U6]
United Kingdom (1961-1978)	6.5	-	[K5]
USSR	9.3	-	[U6]
Faroe Islands (1962-1977)	34	-	[K5]
SOUTHERN HEMISPHERE			
Argentina a/	12	8.1	[K5]
Australia (1963-1973)	20	-	[U6]
New Zealand (1964-1979)	18	-	[K5]

a/ Milk 1964-1979; diet 1967-1979.

Table 16

Parameters of the transfer coefficient for caesium-137 between deposition density and diet

Parameter a/	Milk products		Grain products		Vegetables	
	Argentina	Denmark	Argentina	Denmark	Argentina	Denmark
b_1	7.7	3.0	2.0	3.3	2.1	2.4
b_2	0	2.0	6.9	23.3	2.3	0
b_3	0.2	0.07	0	0	0	0.02
λ_s	0.14	0.08	-	-	-	0.02
p_{23}^k	8.8	5.9	8.9	26.6	4.4	3.5
w_k	0.26	0.35	0.20	0.16	0.31	0.24
$w_k\ p_{23}^k$	2.3	2.1	1.8	4.3	1.4	0.8

Parameter a/	Fruit		Meat, etc.		Total diet	
	Argentina	Denmark	Argentina	Denmark	Argentina	Denmark
b_1	0.5	1.8	22.1	11.9	6.3	4.0
b_2	2.6	1.2	0	0	1.8	6.4
b_3	0	0.2	3.7	46.9	0	0.03
λ_s	-	0.29	0.65	1.6	-	0.02
p_{23}^k	3.1	3.5	26.2	23.6	8.1	12.0
w_k	0.16	0.10	0.08	0.15	1.0	1.0
$w_k\ p_{23}^k$	0.5	0.4	2.1	3.5	8.1	12.0
			Components total		8.1	11.1

a/ The units of parameters b_1, b_2, b_3 and p_{23}^k for diet group k are mBq a kg^{-1}/(Bq m^{-2}). The units for λ_s are a^{-1}. The constant w_k is the fractional amount by weight of food group k in the total diet.

NOTE: Data span for regression analysis: Argentina 1967-1979; Denmark 1962-1979.
Consumption data in model diets: Food 558, 498 kg a^{-1}; potassium 1.12, 1.37 kg a^{-1} in Argentina and Denmark, respectively.

Table 17

Caesium-137 concentration in the human body

[Bq $(g\ K)^{-1}$]

Location	Sex	1974	1975	1976	1977	1978	1979	1980	Ref.
NORTHERN HEMISPHERE									
Denmark	M,F	0.36	0.42	0.35	0.31				[A1]
Finland	M,F	1.0	1.1	0.85	0.78		0.96		[S5,R4, R5]
France	M,F	0.67	0.63	0.41	0.41	0.48	0.56	0.48	[P1]
Germany, Fed.Rep.									
Karlsruhe	M,F	0.35	0.43	0.38					[B11]
Düsseldorf	M	0.61	0.58	1.2	0.29				[B11]
West Berlin	M,F	0.36	0.42	0.25	0.22	0.22			[B11]
Japan	M	0.4	0.3	0.27	0.23	0.22	0.22		[U1,U9]
Sweden									
Stockholm	M,F	0.82	0.88	0.60	0.45	0.31	0.43	0.37	[E2]
Switzerland									
Geneva	M	0.3	0.4	0.4	0.4				[H13]
Geneva	F	0.3	0.4	0.5	0.4				[H13]
United Kingdom									
Oxfordshire	M	0.33	0.43	0.35	0.30	0.37	0.42	0.35	[N7,N8, F6]
United States									
New Mexico	M,F			0.38	0.31				[T3]
Subarctic region (Reindeer herders)									
Finland (Inari)	M	80	65	60	50				[T4]
USSR (Murmansk)	M	260							[T5]
SOUTHERN HEMISPHERE									
Argentina		0.34	0.13	0.11	0.052	0.037	0.040	0.040	[C7]

Table 18

Values of P_{24} obtained as the quotient of the time-integrated ^{137}Cs concentration in the body and the integrated deposition density

Location	Period	P_{24} (Bq a kg^{-1} per Bq m^{-2})	Ref.
Argentina	1966-1974	0.022	[U6]
Denmark		0.022	[U6]
Finland	1962-1973	0.062	[C5]
Sweden (Stockholm)	1962-1972	0.036	[U6]
United Kingdom (Southern England)	1957-1976	0.015	[N7]

Table 19

Dose commitments from ingestion of caesium-137

Location	Dose commitment (μGy)	Collective dose commitment (10^5 man Gy)
World	170	6.9
Northern hemisphere	190	6.7
Southern hemisphere	47	0.2
North temperate zone (40-50°)	280	1.6
South temperate zone (40-50°)	78	0.003

Table 20

Dose commitments from inhalation of ^{140}Ba

Organ or tissue	Dose per unit intake (10^{-9} Gy Bq^{-1})	Dose commitment (10^{-7} Gy)		
		North temperate zone	South temperate zone	Global
Lower large intestine	4.4	15	2.0	9.7
Bone lining cells	2.4	7.9	1.1	5.3
Lungs	1.7	5.6	0.8	3.7
Upper large intestine	1.5	5.0	0.7	3.3
Red bone marrow	1.3	4.3	0.6	2.9
Small intestine	0.53	1.7	0.2	1.2
Gonads	0.43	1.4	0.2	1.0
Breast	0.29	1.0	0.1	0.6

Table 21

Production of plutonium and transplutonium isotopes by atmospheric nuclear tests

Isotope	Half-life (a) [K7]	Mass ratio relative to ^{239}Pu corresponding to production by nuclear tests [B7, G1, H12]	Production by past nuclear tests (PBq)
^{238}Pu	87.7	0.00016	0.33
^{239}Pu	24100	1	7.8
^{240}Pu	6570	0.18	5.2
^{241}Pu	14.4	0.013	170
^{242}Pu	376000	0.0034	0.016
^{242m}Am	152	0.00000031	0.00037
^{244}Cm	18.1	0.000000025	0.00026

Table 22

Integrated deposition density and concentration in air of ^{238}Pu, $^{239,240}Pu$, ^{241}Pu and ^{241}Am[a/]

Location	Integrated deposition density ($Bq\ m^{-2}$)				Integrated concentration in air (10^{-6} Bq a m^{-3})			
	^{238}Pu	$^{239,240}Pu$	^{241}Pu[b/]/^{241}Am[c/]		^{238}Pu	$^{239,240}Pu$	^{241}Pu	^{241}Am
World	0.90	35	440	15	1.6	62	770	1.7
Northern hemisphere	0.98	39	480	17	1.7	69	840	1.8
Southern hemisphere	0.25	9.7	120	4.2	0.4	17	210	0.5
North temperate zone (40-50°)	1.5	58	730	25	2.6	100	1300	2.8
South temperate zone (40-50°)	0.41	16	200	7.0	0.7	28	350	0.8

a/ Through 1979 from nuclear explosions only. A satellite reentry in 1964 in the southern hemisphere caused additional widespread deposition of ^{238}Pu.

b/ Taking into account a delay of 10 months between production and deposition.

c/ From ^{241}Am deposition plus ^{241}Pu decay.

Table 23

Committed dose per unit intake of Pu and Am radionuclides
Committed dose per unit intake of plutonium and americium radionuclides
($\mu Gy\ Bq^{-1}$)
[11]

	^{238}Pu		^{239}Pu		^{241}Pu		^{241}Am	
	Inhalation (Class Y)	Ingestion (Soluble)	Inhalation (Class Y)	Ingestion (Soluble)	Inhalation (Class Y)	Ingestion (Soluble)	Inhalation (Class W)	Ingestion (Soluble)
Lungs	16	-	16	-	3.2	-	-	-
Red bone marrow	3.3	0.008	3.8	0.008	1.7	0.003	10	0.04
Bone lining cells	42	0.09	48	0.1	21	0.04	130	0.6
Liver	9	0.02	11	0.02	4.4	0.009	28	0.1
Gonads	-	0.001		0.001	0.3	0.0006	1.6	0.007

Table 24

Dose commitments from inhalation of fallout plutonium and americium
(μGy)

	Lungs	Red bone marrow	Bone lining cells	Liver	Gonads
^{238}Pu					
World	0.2	0.04	0.5	0.1	-
Northern hemisphere	0.2	0.04	0.5	0.1	-
Southern hemisphere	0.05	0.01	0.1	0.03	-
North temperate zone	0.3	0.06	0.8	0.2	-
South temperate zone	0.08	0.02	0.2	0.05	-
$^{239,240}Pu$					
World	7.2	1.7	22	5.0	-
Northern hemisphere	8.1	1.9	24	5.5	-
Southern hemisphere	2.0	0.5	6.0	1.4	-
North temperate zone	12	2.8	35	8.0	-
South temperate zone	3.3	0.8	9.8	2.2	-
^{241}Pu					
World	18	9.6	120	25	1.7
Northern hemisphere	20	10	130	27	1.8
Southern hemisphere	4.9	2.6	32	6.7	0.5
North temperate zone	30	16	200	42	2.8
South temperate zone	8.2	4.3	54	11	0.8
^{241}Am					
World	-	0.1	1.6	0.3	0.02
Northern hemisphere	-	0.1	1.7	0.4	0.02
Southern hemisphere	-	0.04	0.5	0.1	0.006
North temperate zone	-	0.2	2.7	0.6	0.03
South temperate zone	-	0.06	0.8	0.2	0.009

Table 25

Dietary intake of fallout $^{239,240}Pu$ and ^{241}Am in the New York region

Year	Annual dietary intake (Bq)	
	$^{239,240}Pu$	^{241}Am
1963	0.55	
1964	0.34	
1972	0.056	
1974	0.048	0.015

Table 26

Dose commitments from ingestion of fallout plutonium and americium

(10^{-8} Gy)

	Red bone marrow	Bone lining cells	Liver	Gonads
^{238}Pu				
World	0.04	0.4	0.09	0.005
Northern hemisphere	0.04	0.4	0.1	0.005
Southern hemisphere	0.01	0.1	0.03	0.001
North temperate zone	0.06	0.7	0.15	0.008
South temperate zone	0.02	0.2	0.04	0.002
$^{239,240}Pu$				
World	20	250	49	2.5
Northern hemisphere	22	270	55	2.7
Southern hemisphere	5.4	68	14	0.7
North temperate zone	32	410	81	4.1
South temperate zone	9.0	110	22	1.1
^{241}Pu				
World	5.3	70	16	1.1
Northern hemisphere	5.8	77	17	1.2
Southern hemisphere	1.4	19	4.3	0.3
North temperate zone	8.8	120	26	1.8
South temperate zone	2.4	32	7.2	0.5
^{241}Am				
World	12	180	30	2.1
Northern hemisphere	14	200	34	2.4
Southern hemisphere	3.4	50	8.4	0.6
North temperate zone	20	300	50	3.5
South temperate zone	5.6	84	14	1.0

Table 27

Conversion factors for the assessment of the effective equivalent dose commitments due to external irradiation

	^{95}Zr a/	^{103}Ru	^{106}Ru a/	^{137}Cs	^{140}Ba a/	^{141}Ce	^{144}Ce a/
Quotient of absorbed dose rate in air to deposition density [10^{-8} Gy a^{-1}/(Bq m^{-2})]	9.5	1.8	0.79	0.89	9.8	0.25	0.17
Mean life (a)	0.253	0.156	1.46	43.6	0.051	0.128	1.12
Quotient of absorbed dose in air to deposition density [10^{-8} Gy/(Bq m^{-2})]	2.4	0.28	1.2	39	0.50	0.032	0.19
P_{25} b/ [(10^{-10} Gy/(Bq m^{-2})]	72	8.4	36	1170	15	0.96	5.7

a/ Including contributions from the daughter radionuclides, assumed in transient equilibrium.

b/ The air-to-tissue conversion factor, taking into account indoor occupancy and shielding by buildings, is assumed to be 0.3 (see Annex A).

Table 28

Integrated deposition densities of the main contributors to external irradiation

(10^3 Bq m^{-2})

Location	^{95}Zr	^{103}Ru	^{106}Ru	^{137}Cs	^{140}Ba	^{141}Ce	^{144}Ce
World	27.2	20.4	14.7	3.14	16.7	15.0	29.4
Northern hemisphere	29.1	21.8	16.0	3.42	18.0	16.0	32.1
Southern hemisphere	12.1	9.1	4.1	0.86	7.5	6.7	8.1
North temperate zone	40.1	30.1	24.2	5.17	24.9	22.1	48.4
South temperate zone	5.6	4.2	6.7	1.42	3.5	3.1	13.4

Table 29

Dose commitments due to external irradiation from radionuclides deposited on the ground

(μGy)

Location	^{95}Zr	^{103}Ru	^{106}Ru	^{137}Cs	^{140}Ba	^{141}Ce	^{144}Ce	Total
World	200	17	53	370	25	1.4	17	680
Northern hemisphere	210	18	58	400	27	1.5	18	730
Southern hemisphere	87	7.6	15	100	11	0.6	4.6	230
North temperate zone	290	25	87	600	37	2.1	28	1070
South temperate zone	40	3.5	24	170	5.3	0.3	7.6	250

Table 30

Summary of dose commitments from radionuclides produced in atmospheric nuclear tests carried out to the end of 1980

(μGy)

Source of radiation	North temperate zone				South temperate zone				World population			
	Gonads	Red bone marrow	Bone lining cells	Lungs	Gonads	Red bone marrow	Bone lining cells	Lungs	Gonads	Red bone marrow	Bone lining cells	Lungs
External												
Short-lived nuclides	470	470	470	470	80	80	80	80	310	310	310	310
^{137}Cs	600	600	600	600	170	170	170	170	370	370	370	370
Internal												
^{3}H	51	51	51	51	14	14	14	14	47	47	47	47
^{14}C a/	77	370	340	91	77	370	340	91	77	370	340	91
^{55}Fe	10	6	10	10	2	1	2	2	9	5	9	9
^{89}Sr		2	3	24		0.6	0.9	6		1	2	15
^{90}Sr		940	2100	120		260	570	34		570	1300	74
^{106}Ru				410				95				250
^{137}Cs	280	280	280	280	78	78	78	78	170	170	170	170
^{144}Ce				500				140				250
^{239}Pu b/	0.04	3	39	12	0.01	0.9	11	3	0.03	2	25	7
^{241}Pu	3	16	20	30	0.8	4	54	8	2	10	120	18
^{241}Am	0.07	0.4	5		0.02	0.1	1		0.04	0.2	3	
TOTAL (rounded)	1500	2700	3900	2600	420	980	1300	720	990	1900	2700	1700

a/ Doses accumulated to the year 2000. The total dose commitments will be delivered over thousands of years; they are estimated in paragraph 25.

b/ Includes dose commitments from plutonium-240.

NOTE: The dose commitments from ^{54}Mn, ^{85}Kr, ^{136}Cs, ^{140}Ba and ^{238}Pu, although discussed in the text, are not shown in this table because they are negligible compared to the values included.
Estimates of age-weighted absorbed doses to the thyroid gland from iodine-131 are: 1.6 mGy (North temperate zone), 0.2 mGy (South temperate zone) and 1.1 mGy (World).
Absorbed doses from alpha particles: plutonium-239, americium-241.

Table 31

Summary of effective dose equivalent commitments from radionuclides produced in atmospheric tests carried out to the end of 1980

(μSv)

Radionuclide	North temperate zone				South temperate zone				World population			
	External irradiation	Inhalation	Ingestion	Total	External irradiation	Inhalation	Ingestion	Total	External irradiation	Inhalation	Ingestion	Total
^{3}H		4	47	51		1	13	14		3	44	47
^{14}C		0.3	2600	2600		0.3	2600	2600		0.3	2600	2600
^{54}Mn		0.07		0.07		0.004		0.004		0.04		0.04
^{55}Fe			10	10			2	2			9	9
^{85}Kr	0.005			0.005	0.005			0.005	0.005			0.005
^{89}Sr		3	2	5		0.7	0.4	1		2	1	3
^{90}Sr		14	170	180		4	48	52		9	110	120
^{95}Zr	290			290	40			40	200			200
^{103}Ru	25			25	4			4	17			17
^{106}Ru	87	49		140	24	11		35	53	30		83
^{131}I			48	48			7	7			33	33
^{136}Cs			0.1	0.1			0.03	0.03			0.06	0.06
^{137}Cs	600	0.6	280	880	170	0.2	78	250	370	0.4	170	540
^{140}Ba	37	0.3	0.3	38	5	0.04	0.07	5	25	0.2	0.2	25
^{141}Ce	2			2	0.3			0.3	1			1
^{144}Ce	28	60		88	8	17		25	17	37		54
^{238}Pu		2	0.008	2		0.4	0.002	0.4		1	0.005	1
^{239}Pu		40	3	43		11	0.7	12		25	2	27
^{240}Pu		26	2	28		7	0.5	8		16	1	17
^{241}Pu		14	0.07	14		4	0.02	4		9	0.04	9
^{241}Am		3	3	6		0.7	0.7	1		2	2	4
Total (rounded)	1100	220	3200	4500	250	60	2750	3100	680	130	3000	3800

Table 32

Contributions to total effective dose equivalent commitment to the world population from nuclear tests

Radionuclide	Effective dose equivalent commitment (μSv)	Contribution to total (%)
^{14}C a/	2600	69
^{137}Cs	540	14
^{95}Zr	200	5.3
^{90}Sr	120	3.2
^{106}Ru	83	2.2
^{144}Ce	54	1.4
^{3}H	47	1.2
^{131}I	33	0.9
^{239}Pu	27	0.7
^{140}Ba	25	0.7
^{103}Ru	17	0.4
^{240}Pu	17	0.4
^{241}Pu	9	0.2
^{55}Fe	9	0.2
^{241}Am	4	0.1
^{89}Sr	3	0.08
^{141}Ce	1	0.03
^{238}Pu	1	0.03
^{136}Cs	0.06	0.002
^{54}Mn	0.04	0.001
^{85}Kr	0.005	0.0001
Total (rounded)	3800	100

a/ The dose commitment from ^{14}C will be delivered over thousands of years. That part delivered up to the year 2000 is 7.7 % of the value listed (see paragraph 26).

Table 33

Summary of global collective effective dose equivalent commitments from atmospheric tests carried out to the end of 1980 a/

(10^4 man Sv)

Radionuclide	External irradiation	Inhalation	Ingestion	Total
^{14}C		0.3 b/	2600 b/	2600
^{137}Cs	150 c/	0.1	69 c/	220
^{95}Zr	64			64
^{90}Sr		3	44 c/	47
^{106}Ru	17	10		27
^{3}H		1 c/	18 c/	19
^{144}Ce	5	12		17
^{131}I			11	11
^{239}Pu		8	2 b/	10
^{140}Ba	8	0.07	0.05	8
^{103}Ru	5			5
^{240}Pu		5	1 b/	6
^{241}Pu		3	0.02 c/	3
^{55}Fe			3	3
^{241}Am		0.5	2 b/	2
^{89}Sr		0.6	0.3	0.9
^{141}Ce	0.4			0.4
^{238}Pu		0.3	0.003 d/	0.3
^{136}Cs			0.02	0.02
^{54}Mn		0.01		0.01
^{85}Kr	0.002 c/			0.002
Total (rounded)	250	44	2750	3000

a/ World population size assumed to be 3.2 10^9 persons unless otherwise specified by a footnote.

b/ Population size 1 10^{10} persons.

c/ Population size 4 10^9 persons.

d/ Population size 6 10^9 persons.

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ANNEX F

Exposures resulting from nuclear power production

CONTENTS

Introduction

1. The use of nuclear reactors to generate electric power has increased since the Committee's previous assessment of the releases of radioactive materials from the nuclear fuel cycle and their resulting dose commitments in Annex D of the 1977 report [U1]. The total installed nuclear generating capacity in the world in 1979 was about 120 GW(e) from some 235 power reactors operating in 22 countries [I1, K12]. This represents an approximate doubling of nuclear generation during the years 1975 to 1979 covered by this Annex. In 1981 the installed electric generating capacity was 144.4 GW(e) from 261 reactors with 209.8 GW(e) (227 reactors) under construction [I12]. Projections of the world nuclear generating capacity in the year 2000 are somewhat speculative, but the figure seems likely to be about 1300 GW(e), or a little over half of the estimate reported by the Committee in Annex D of the 1977 report [U1]. This expectation is based on revised estimates of about 400 GW(e) nuclear generating plant in North America by the year 2000 [I9], towards 350 GW(e) for the Soviet Union and Eastern Europe [U2, I9], and the remainder being made up of perhaps 300 GW(e) in Western Europe [W1, I9], 100 GW(e) for Japan [M8] and 150 GW(e) in developing countries. In the International Nuclear Fuel Cycle Evaluation (INFCE) [I9] a range of 1030–1650 GW(e) was predicted for world installed nuclear capacity in the year 2000.

2. The nuclear fuel cycle includes the mining and milling of uranium ores, conversion to nuclear fuel material, which usually includes enrichment of the isotopic content of ^{235}U, fabrication of fuel elements, production of power in the nuclear reactor, reprocessing of irradiated fuel and recycling of fissile and fertile nuclides recovered, and disposal of radioactive wastes. In addition, nuclear fuel materials are transported between installations at various stages in the cycle. In recent years several reports by the United Nations Environment Programme have assessed the environmental impact of the nuclear fuel cycle [E7, U5] and in the INFCE studies radiation risks were also considered [I9].

3. Almost all of the artificial radionuclides associated with the nuclear fuel cycle are present in the irradiated nuclear fuel, although some neutron activation of structural and cladding materials takes place, and the naturally-occurring radionuclides are present at the uranium mining and milling stage. The majority of irradiated fuel elements are currently stored. However, where reprocessing takes place, the radioactive fission products and transuranium elements are stored as highly active liquors in tanks isolated from the environment. At each step of the fuel cycle releases of small quantities of radioactive material to the environment may occur. Most of the radionuclides released to the environment are only of local or regional concern because of their short radioactive half-lives or limited environmental mobility. Some radionuclides, because of a combination of long radioactive half-lives and rapid dispersal in the environment, become globally distributed.

4. The interest of the Committee is in assessing the overall health detriment and the doses to individual members of the public due to the releases of radioactive materials at each stage of the nuclear fuel cycle. Because of the system of control applied to environmental releases from nuclear power installations, doses to individual members of the public are generally well below the relevant dose limits and correspond to low levels of individual risk. Individual dose levels decrease rapidly with distance from a given source and the doses to most exposed individuals vary widely from installation to installation and between one location and another. In this Annex an indication of the range of doses to the most exposed individuals at each stage of the nuclear fuel cycle is given. To evaluate the total impact of nuclides released at each stage of the fuel cycle, calculated results are first presented in terms of collective absorbed dose commitments to various body organs or tissues, normalized to the production of unit quantity of electric energy generation, expressed as man Gy per GW(e) a. Annex A describes the way in which the absorbed doses may be combined to give the quantity "collective effective dose equivalent" which is assumed to be proportional to health detriment. Values of collective effective dose equivalent commitment per unit of electrical energy actually generated are thus calculated for each stage of the nuclear fuel cycle.

5. The collective dose commitment from nuclear power arises in four population groups: the occupationally exposed, the population within a few hundred km from the site, the population within a few thousand km from the site, and the total world population. This Annex deals only with exposure of the public, as occupational contributions are dealt with in Annex H. Each stage of the nuclear fuel cycle is considered separately and the local and regional dose commitments are given for atmospheric and aquatic discharges. The global contributions from those nuclides which irradiate the world population are then discussed for the fuel cycle as a whole. Finally, the disposal of solid wastes from the nuclear fuel cycle is reviewed.

6. Collective dose commitments to local and regional populations must be estimated by environmental modelling, as the activity concentrations from effluents from the nuclear fuel cycle are very low, both in the general population and in environmental materials. Monitoring of activity concentrations due to effluent releases has concentrated on areas surrounding nuclear facilities to ensure compliance with applicable regulations. In recent years computer models have been developed which enable estimates to be made of doses to large populations over long periods of time [C10, E1, M1]. The values of parameters for the transfer of radionuclides in these models are taken from environmental monitoring results or from experimental observations.

7. The source terms for the releases of radioactive effluents from nuclear installations are usually readily available to the Committee and reflect the operating histories, including abnormal periods of operation. The Committee has reviewed reported discharge data and has produced average releases per GW(e) a generated. These normalized releases do not apply, therefore, to any one plant, but are deemed to be representative of current nuclear power generation. They, therefore, reflect differences in reactor design and changes in release rates between newer and older installations. Future practices may give rise to results considerably different from those derived from past and current experience and any extrapolation to the future must be undertaken with caution. To estimate the collective dose commitments corresponding to these averaged releases, the Committee has decided that a model facility at a representative site be established for each

stage of the fuel cycle: mining and milling, fuel fabrication, reactor operation and reprocessing. The environment receiving the typical releases from each model facility was chosen to represent broad averages containing typical features of existing sites and reflecting the most common environmental pathways. Such generalizations are intended to give dose commitments reflecting the overall impact of the nuclear power programme and will not be applicable to any one given site without due consideration of its own specific environmental pathways and of the particular radioactive release.

8. The calculation of the collective absorbed dose commitment to any organ or tissue requires the integration over infinite time of the collective absorbed dose rate in that organ or tissue. As described in Annex A, it is convenient in evaluating the collective dose commitment, and other similar quantities, to distinguish between external and internal irradiation of the body. For external irradiation the calculation is straightforward, but for internal emitters the integration is complex, particularly for nuclides of long retention times, when detailed knowledge is required of the time variation of dose equivalent rates in body organs and tissues following intake. The Committee, therefore, decided to represent the collective dose commitment for internal radiation as the integral of the collective intake multiplied by the committed dose per unit intake. The collective intake of a nuclide is a quantity readily calculable and tabulations of dose per unit intake are available. The Committee decided to use the committed dose, defined as the 50 year integral of dose rate in any organ or tissue following intake, for the average dose per unit intake in a normal population. This may lead to a slight overestimate of average dose for nuclides of long retention times in the body, since the mean life expectancy of a population is a little less than 50 years. This formulation of collective dose commitment can also lead to slight overestimates of its truncated value for time periods comparable with the mean life expectancy of the population, but the error is small and compensated by the ready availability of tabulations from which committed absorbed dose to the particular body organs of interest may be obtained [I2, A1, C10].

9. In the estimation of collective dose commitments, it is clear that assumptions have to be made about the size and habits of the exposed future populations. For this study it is assumed that the magnitude of the world population remains stable and that no major changes in age structure occur. It is further assumed that the dietary and other habits of the population remain constant, which is a reasonable assumption for short times, although the uncertainties must increase as longer times are considered. Finally, it is assumed that the whole population is represented by adults for the purposes of evaluating doses from inhalation and ingestion. This assumption is valid when estimating collective dose commitments for populations, because children only comprise a fraction of the total, and the difference in their dose per unit level of activity in environmental materials is small, except for a very few nuclides such as those of transuranium elements and ^{90}Sr.

10. Very long-lived nuclides pose a special problem. One example is ^{129}I ($1.6\ 10^7$ a). Another example is radon from mill-tailings containing ^{230}Th ($8\ 10^4$ a) and ^{238}U ($4.5\ 10^9$ a). Assessments of human exposures over such periods of time are obviously hypothetical and their relevance is doubtful. Dose commitments assessed for the purpose of calculating the maximum dose rate in the future, however, should only include integration over periods of time equal to the expected length of the practice that causes environmental pollution. Assuming this period to be 500 years for nuclear power production, the long life-time of some nuclides will not influence the assessment of such truncated dose commitments. The problem therefore only arises when the complete dose commitment is assessed. That assessment will be extremely uncertain for the long-lived nuclides and should therefore not be presented as single figures but preferably in tables or diagrams which indicate when the late dose contributions are expected to occur. One long-lived nuclide, ^{14}C (5730 a), does not pose as great a problem as indicated by its long half-life. The early disappearance of this nuclide from the human environment causes as much as about 10% of the complete dose commitment to be delivered within 70 years.

11. In addition to the small releases of radioactive materials which take place during normal operation, unplanned releases may occur. This Annex also reviews reactor accidents which have led to unplanned releases of activity into the environment, together with estimates of the resulting collective doses.

I. MINING AND MILLING

12. Uranium is obtained from ore mined in several countries of the world, the major producers being Canada, France, South Africa, United States, with Australia soon to join them. Major efforts in uranium exploration and production are also being made in countries such as Algeria, Argentina, Brazil, Gabon, India, Iran and Niger, while many other developing countries are making moderate efforts at uranium exploitation [B25]. World uranium production was 38 000 t in 1979 [H13] and the planned capacity for 1990 is 120 000 t. However, the growth of nuclear power needs to be more predictable in order to provide the incentive and lead times to establish the necessary mining and milling operations. Table 1 shows the 1979 uranium production capability from the major producers and gives for guidance the estimated "reasonably assured" resources in those countries, assuming a price of US $ 130 per kilogram of uranium. The estimates of uranium resources vary widely depending upon the price of uranium assumed; unconventional sources, e.g., coals and lignites, are not included.

13. Uranium mining operations involve the removal from underground of large quantities of ore containing uranium and its daughter products at concentrations up to several thousand times the concentrations of these nuclides in the natural terrestrial environment. The concentration of uranium in mined ores is between 0.1 and about 3% U_3O_8. The mining is carried out either by underground or open pit methods and these techniques accounted for nearly all new uranium production in 1979. Each method produced about the same amount of uranium, although more ore was produced by open pit mining, as it is generally of lower grade. Some underground mines are less than 30 m below the surface and, conversely, some open pit mines operate to depths of 150 m. In recent years in situ solution mining has been carried out, although that, together with heap leaching techniques, only accounted for a few percent of world production. The main radioactive release from underground mining is ^{222}Rn in the mine ventilation air,

while for open pit mining there are also radioactive dust emissions.

14. Uranium milling operations involve the processing of large quantities of ore to extract the partially refined uranium. The uranium concentrate is called yellowcake, which is then used as feed at the fuel fabrication plant, where it is further refined, converted and enriched, if necessary, for use in reactors. Because of the large quantities of ore to be processed, mills tend to be near the uranium mines to minimize transportation. In some cases, where ore is treated locally by heap leaching, precipitated preconcentrates are transported to the mills. In 1979 more than 50 uranium mills were in operation [G1, F5, S16] which processed over 65 million tons of ore. Approximately half of the ore was new and the remainder was tailings from existing operations such as the gold mining industry in South Africa. The process of uranium extraction involves the following steps: crushing, grinding, chemical leaching, separation of the uranium from the leach solution, precipitation, drying and packing of the yellowcake. The mill processes fall into three general types, acid leach solvent extraction, acid leach ion exchange, and alkaline leach; most mills use the acid leach solvent extraction process. The steps in the milling process which lead to the major emissions of radioactive materials are the front end crushing operations and the drying and packaging of yellowcake.

A. EFFLUENTS

15. Gaseous radioactive effluents from mines are almost entirely composed of ^{222}Rn in the ventilation air which is discharged in large quantities. Liquid wastes result from mine drainage and process feed water; they are discharged to ponds for settling of solids and the water is either allowed to evaporate or is released to the environment. Mine drainage water can also be used as process feed for the mill, or may be diluted, treated and discharged [C7]. Leaching of mine tailings may also be a source of liquid waste but generally wastes from the milling process are of more importance. Solid waste is composed of rock and very low grade ore. Only limited information is available on radionuclide emissions from underground uranium mines, and in general only ^{222}Rn emissions are reported, as this gas represents the major airborne radioactive component of the effluent [N21, L8]. Particulate emissions are believed to be far less significant. In a 1978 survey of underground mines in New Mexico, ^{222}Rn emissions per unit mass of ore mined in the range of 0.4 to 8 GBq t^{-1} were reported [J1]. The variation is mainly dependent upon the grade of ore mined, with ores containing up to 1 or 2% uranium at Nabarlek in Australia giving 1–2 GBq t^{-1} [L9] and 0.1% ores at underground Canadian mines giving results 10 times lower [W6].

16. The major airborne radioactive component in effluents from open pit mining is also believed to be ^{222}Rn [E1, C7, W6]. As large areas are involved, it is not possible to directly measure the radon emissions, but they may be inferred from emission rates from particular surfaces of the mine or from ^{222}Rn concentrations downwind of the mine. The results at the Ranger Mine in Australia for radon release per unit mass of ore produced during mining were 0.1 GBq t^{-1} [D7] and the emanation rate per unit ore grade is the same as Nabarlek underground mine. Results for several open pit mines in Canada average 0.2 GBq t^{-1} for ore at about 0.25% uranium [E8]. In a recent study of eight open pit uranium mines in Wyoming, an estimate of the ^{222}Rn emission per unit mass of ore produced was 0.2 GBq t^{-1} [N3]. The grade of ore obtained from open pit mines are typically 0.1–0.2% uranium and thus the radon emission normalized for uranium content seems similar for underground and open pit mines at 1 GBq per tonne and per cent of uranium.

17. Uranium ore requirements per unit of electrical energy generated vary somewhat between the commercial nuclear reactors currently in use. In the recent INFCE studies [I9] the light water reactors (LWRs) are assumed to require 205.4 t of uranium heavy metal to be extracted for the production of 1 GW(e) a of electrical energy, while heavy water reactors (HWRs) operating on the uranium cycle require 178.8 t [GW(e) a]$^{-1}$ of heavy metal. It is estimated by the Committee that gas cooled reactors (GCRs) using natural uranium metal require 270 t [GW(e) a]$^{-1}$ of uranium metal, assuming a mean fuel burnup of 4.5 GW d t^{-1} and a thermal efficiency of 30%, whereas advanced gas-cooled reactors require 219 t [GW(e) a]$^{-1}$ of heavy metal. These uranium requirements are calculated on a "once through" basis in that no recycling of uranium or plutonium is assumed. Were plutonium to be recycled in LWRs or HWRs, the heavy uranium metal requirements would be reduced to 120 and 75 t [GW(e) a]$^{-1}$, respectively. The introduction of fast breeder reactors (FBRs) would reduce the heavy metal input to 1 t [GW(e) a]$^{-1}$ of uranium for plutonium recycle, an improvement of a factor of about 200 in uranium utilization. A heavy water reactor operating on a uranium-thorium cycle breeding ^{233}U would require 7 t [GW(e) a]$^{-1}$ of thorium metal.

18. The grade of ore mined is variable but is usually between 0.1 and about 3.0% U_3O_8. In the United States it is higher from underground mines at an average 0.2% U_3O_8, than from open pit mines with 0.11% U_3O_8 [E1]. Thus the LWR uranium heavy metal requirement of 205 t [GW(e) a]$^{-1}$ corresponds to a mining rate of $1.2\ 10^5$ t of ore from a United States underground mine or $2.2\ 10^5$ t from a United States open pit mine. The Nabarlek mine in Australia produced 2% U_3O_8 ore, so that the LWR requirement is met by an ore production of just over $1.2\ 10^4$ t [L9]. However, since the corresponding normalized ^{222}Rn releases appear to be similar for underground and open pit mines per unit concentration of uranium in ore, the Committee estimates radon releases to be 20 TBq [GW(e) a]$^{-1}$. This compares with the Committee's estimate in Annex D of the 1977 report [U1] of 6.3 TBq [GW(e) a]$^{-1}$ from mining and milling.

19. The activity content of the mined ore is predominantly due to ^{238}U and its daughter products; there is very little, if any, natural thorium in most ores. However, ore from the Elliot Lake region in Canada averages about 0.2% natural thorium. One tonne of ore containing, say, 2 kg of U_3O_8 has an activity of 21 MBq from each of the 14 principal members of the ^{238}U decay chain, a total of about 0.29 GBq [S1]. The operation of uranium mills has thus resulted in the accumulation of large quantities of waste tailings containing significant quantities of uranium daughter nuclides. There are currently known to be some 120 million tonnes of tailings stored at active mill sites mainly in the United States and Canada [N21] and current uranium demand trends would increase this figure to about $5\ 10^8$ t by the year 2000. About 14% of the total activity in the ore feed appears in the uranium concentrate which achieves better than 90% uranium

extraction. In the resulting solid wastes, with the parent nuclides removed and short-lived daughters ^{234}Th ($T_{1/2}$ 24.1 d), ^{234m}Pa ($T_{1/2}$ 1.17 min) and ^{231}Th ($T_{1/2}$ 25.5 h) quickly decaying, some 70% of the original activity remains and is essentially due to ^{230}Th ($T_{1/2}$ 8 10^4 a) and its daughters.

20. Uranium tailings are discharged from the mill usually in slurry form at about 50% solids, to an impoundment area. Tailings piles typically cover areas of between 30 and 60 hectares. The tailings comprise about 70% sand and 30% slimes and about 85% of the activity is contained in the slime fraction [S1, N21]. Although in the early days of uranium mining and milling liquid effluents were discharged to local watercourses [G2], the present practice is to minimize liquid effluent by recycling or evaporation of the water.

21. In dry climates there are essentially no liquid discharges which lead to radiation exposure of the public. This has been confirmed by environmental monitoring which has not detected measurable water contamination beyond plant sites [S2, S3, S4]. Studies on tailings piles in Illinois indicate that thorium and radium concentrations fall off to background levels within 1 m below the bottom of the tailings and that the activity does not migrate into groundwater [N2]. In contrast, Canadian mills operate in a wet environment and the usual practice is to use small lakes and depressions for tailings disposal [W6]. Tailings are contained by dams and the overflows treated with barium chloride to co-precipitate the radium as $Ba(Ra)SO_4$. Further barium chloride addition and settling may be allowed before discharge of effluents to waters available to the public. After treatment, the dissolved ^{226}Ra concentrations are usually less than 0.4 Bq l^{-1} with 0.2–7 Bq l^{-1} suspended ^{226}Ra [M10]. Typical annual releases of ^{226}Ra from tailings into the watershed are of the order of 40 GBq, corresponding to less than 1 GBq [GW(e) a]$^{-1}$.

22. Sources for atmospheric emissions of radionuclides are the ore crushing and grinding circuits, the yellowcake drying and packaging operations, and the tailings. Emission rates from different plants vary widely, owing in part to different process and control technologies. For a typical mill processing about 2000 t of ore per day, the major source of atmospheric dust emissions is from the yellowcake drying and packaging processes; the reported ranges of emissions are 1–4 GBq a^{-1} for ^{238}U; 0.2–2 GBq a^{-1} for ^{230}Th, ^{226}Ra and ^{210}Pb; and 1–7 TBq a^{-1} for ^{222}Rn [N4, N5, N21, E8, D7, N6, N7]. More recent mills may achieve releases from the crushing and storage processes of about 0.04–0.16 GBq a^{-1} particulate emissions [N2, N8]. Atmospheric emissions from the tailings area are in the ranges of 7–500 MBq a^{-1} for ^{238}U and ^{234}U; 0.1–8 GBq a^{-1} for ^{230}TH, ^{226}Ra and ^{210}PB; and 500 GBq to 300 TBq a^{-1} for ^{222}Rn [N2, N3, N4, N5, N6, N7, N8, N21, D7]. The amount of particulate airborne emissions from tailing areas depends upon the size of dry tailings beach areas which are subject to wind and weather erosion, while the radon emission depends on diffusion from the ground. The radon exhalation rate appears to be about 1 Bq m^{-2} s^{-1} per Bq g^{-1} of ^{226}Ra in the tailings [N2], although the figure can vary by an order of magnitude depending on meteorological conditions such as wind speed, atmospheric stability and rainfall [T1]. The release of radon from an uncovered tailings pile containing about 21 Bq g^{-1} of ^{226}Ra will thus be about 21 Bq m^{-2} s^{-1}. Tailings impoundment areas almost completely covered by water will have very low radionuclide emissions [N8].

23. To estimate the environmental releases, a model mill facility has been established based on the data given for the United States [E1, N21, S1]. The model mill processes 600 000 t per year of 0.2% grade ore. Dust from ore crushing is assumed to contain all radionuclides in equilibrium but yellowcake drying and packaging contributes to the uranium release and accounts for the lack of equilibrium in the release. The mill is assumed to produce uranium at a rate equivalent to 5 GW(e) a per year and to operate for 20 years. The normalized atmospheric releases from the milling operations and from the tailings piles are shown in Table 2 together with the mining contribution from ^{222}Rn. The typical tailing impoundment area assumed is 60 hectares with a radon emission rate of 6.7 TBq ha^{-1} a^{-1}. The mill processes ore equivalent to 100 GW(e) a and thus tailings areas amount to 0.6 ha [GW(e) a]$^{-1}$. It is assumed that there is a 2 m covering of earth which reduces the radioactive emissions by a factor of 4. The dust emission data for the tailings disposal area were based on assumptions that average wind speeds produced 0.017 g ha^{-1} s^{-1} of particles smaller than 10 μm; 10–80 μm particles accounted for 0.04 g ha^{-1} s^{-1} with assumed nuclide compositions of 3 Bq g^{-1} for ^{238}U and 60 Bq g^{-1} of all the daughter radionuclides [E1, S1]. Activities of ^{235}U and daughters are some two orders of magnitude below the values for ^{238}U.

24. The tailings remain after the mill has ceased operation and can become a long-term source of radioactive contamination due to wind and water erosion, leaching and radon emanation. Hence the normalized releases quoted in Table 2 for tailings are quoted per year per unit electric generation. Stabilization programmes are generally conducted or planned so that erosion is alleviated using materials which may be native soils, gravel or so-called Rip-rap cover, clays, or even artificial or synthetic covers or sealants such as asphalt or polyvinyl chloride [N2, N21, C7]. Although up to a few per cent of the original uranium isotopes remain in the tailings, the major source of long-lived activity for about 5 10^5 a is ^{230}Th ($T_{1/2}$ 8 10^4 a) which continues to produce ^{226}Ra and corresponding radon releases. The diffusion of radon in the top few metres of tailings is responsible for most of the release and the release rate is independent of the depth of the tailings beyond about 3 m [S5]. The reduction in radon emanation by soil covering depends on the type and depth of cover. In part because of its small particle size, clay can hold moisture and present a more effective barrier to radon diffusion than more common soils. Hence, incorporation of clay can reduce the depth of soil cover required to achieve radon exhalation rates similar to those of normal soils [N2].

B. LOCAL AND REGIONAL COLLECTIVE DOSE COMMITMENTS

25. The uranium mining and milling sites tend to be in areas of low population density. In many areas the conditions are arid and not suitable for farming while those mines in areas of high precipitation are usually remote with again little local farming. In arid areas there is negligible release of radionuclides to the aquatic environment and the radiation doses to the public arise predominantly from airborne effluents. In areas of high precipitation, it is established that the liquid effluent population doses are dominated by ^{226}Ra in drinking water and aquatic foodstuffs [E8, K10, W6]. In a detailed study of Canadian uranium mines and mills which discharged radionuclides to

lakes and water courses, the collective doses resulting from drinking water, fish consumption and external radiation from sediments were in general significantly less than the collective doses due to the atmospheric releases from the mine, mill and tailings areas [E8]. The ^{226}Ra concentrations in surface waters were found to be no higher than 10^{-1} Bq l^{-1}. The levels of maximum individual dose reported were less than 80 μSv a^{-1} [E8].

26. Under the assumption that adequate waste treatment prevents seepage of process liquid effluents directly into rivers, the local and regional collective dose commitments are assumed by the Committee to depend upon the airborne releases which contribute to external exposure from deposited material and to internal irradiation via the inhalation and ingestion pathways. In Annex D of the 1977 report [U1], the Committee has previously used a population density of 3 km^{-2} within a few hundred km of the mine and mill and a uniform population density of 25 km^{-2} from this to 2000 km. These figures still remain suitable on the basis of reported population densities in areas of mining and milling [S1, E1, E2, E8, W6]. The collective dose commitments to the local and regional population from the particulate releases from the model mill (Table 2) were derived using the values presented for the naturally-occurring radionuclides in Annex C, modifying the population density to 25 km^{-2} from the value of 100 km^{-2} used for estimating the impact of coal fired power stations. A deposition velocity of 10^{-2} m s^{-1} was chosen for particulate releases and the majority of the collective dose arises within the first few hundred km.

27. For radon releases an atmospheric dispersion calculation was undertaken to estimate collective doses. The meteorological dispersion characteristics of the representative site are shown in Table 3. They are typical of the local environment in arid areas and are the values chosen in the Rasmussen study as applying to a semi-arid area [R3]. Rainfall occurs for only 0.3% of the time and only in neutral conditions (Pasquill category D); the effective height of release is 10 m. The high incidence of category F conditions is a phenomenon local to the mine environment and the conditions are assumed to persist only up to 100 km. Beyond that distance the meteorological conditions are assumed to become neutral out to 2000 km. The assumption of an equal frequency of all wind directions is considered reasonable for this study since uniform population distributions are assumed. The atmospheric dispersion modelling has been fully described in Annex A and has been utilized here in computer calculations using the methodology developed for the Commission of the European Communities for the assessment of effluent releases [C10]. The dosimetry for radon inhalation was that assumed in Annex D, which gives an average effective dose equivalent per unit inhaled activity of radon daughters of $1.3 \cdot 10^{-8}$ Sv Bq^{-1}. Only effective dose equivalent calculations are presented for radon in this Annex. The equilibrium factor for the short-lived radon daughters is taken as 0.6.

28. The resulting normalized local and regional collective dose commitments from mining and milling are shown in Tables 4 and 5. For the particulate releases inhalation, ingestion and external irradiation all contribute to the dose commitment and a further description of the analysis can be found in Annex C. The resulting collective effective dose equivalent commitment is approximately half that estimated for the radon releases from milling operations. The total normalized collective effective dose equivalent commitment from mining and milling is 0.54 man Sv [GW(e) a]$^{-1}$, of which 93% is from the mining operation. The results are generally similar to those estimated by the Committee in Annex D of the 1977 report [U1]. It is assumed in all these calculations that the indoor air concentrations are the same as outdoors.

29. The estimated doses to most exposed members of the public are highly dependent upon the characteristics of the particular location of the mine and mill. Annual effective dose equivalents between a few hundred μSv to several mSv have been estimated for typical emissions from mines and mills [E1, E8, N21, M10]. For the model mine and mill used by the Committee the annual effective dose equivalent at 500 m from the source is 900 μSv from radon releases, assuming an atmospheric dilution factor of $5\ 10^{-6}$ Bq s m^{-3} per Bq released, and doses from the particulate releases are 50 times lower.

30. As discussed in section I.A., ^{230}Th in tailings piles will provide a long-term source of radon emission. If the release rate were to continue throughout the mean lifetime of $1.1\ 10^{5}$ a, then the emanation rate given in Table 2 for ^{222}Rn would give a normalized collective effective dose equivalent commitment of about 2800 man Sv [GW(e) a]$^{-1}$. The corresponding particulate releases are estimated to give an additional 50 man Sv [GW(e) a]$^{-1}$. A small amount of ^{230}Th would still remain supported by the residual uranium in the tailings. These results must be considered highly speculative because of the assumptions of the duration of the constant release and of the fixed population density and habits. Table 6(a) shows how the normalized collective effective dose equivalent commitment from the tailings varies with the period of time over which the radon and particulate releases are assumed to be released. The results must be extremely uncertain over such geologic time scales and indeed present day tailings management may lead to radon emanation rates no greater than the ambient levels for soils in the mill vicinity, so that almost no long term dose commitment arises.

31. In the INFCE studies [I9] the dose commitment from tailings was estimated on the assumption that the radon emanation continued for 10^{3} a, by which time the tailings are assumed to have been eroded and lead to a further dose commitment from the aquatic environment (freshwater and marine). The dose commitment from the aquatic environment is enhanced by the small percentage of uranium left in the tailings, here assumed to be 10% The regional marine model described in Annex A has been used to estimate the collective dose commitment from the tailings, assuming they are eroded into coastal waters and disperse throughout the world's oceans. The resulting normalized collective effective dose equivalent commitments are shown in Table 6(b) and, because of the nuclide content, these dose commitments are almost independent of the time at which they are released into the marine environment. The normalized radon collective effective dose equivalent commitment for 10^{3} a release is about 25 man Sv [GW(e) a]$^{-1}$ and the uranium figure is 460 man Sv [GW(e) a]$^{-1}$. These figures compare with the INFCE estimates of 10 and 360 man Sv [GW(e) a]$^{-1}$, respectively.

32. Previously the Committee has also used a simplified model for estimating the normalized collective effective dose equivalent commitment from

tailings by comparing with natural radon emanation from soil and the corresponding radon concentration in air. With the model mine and mill data from Table 2 and the normal radon exhalation rate of 20 mBq m^{-2} s^{-1}, leading to a standing equilibrium equivalent radon concentration of 1.8 Bq m^{-3} (Annex D), and an effective dose equivalent per unit of integrated air concentration of 9.2 10^{-5} Sv per Bq m^{-3} a (Annex D), the normalized collective effective dose equivalent commitment from tailings over the mean life of ^{230}Th is calculated to be

$$S^c = (6.7\ \text{TBq ha}^{-1}\ \text{a}^{-1})\,(0.6\ \text{ha [GW (e) a]}^{-1}\,(0.25)$$
$$\left(\frac{1.8\ \text{Bq m}^{-3}}{0.02\ \text{Bq m}^{-2}\ \text{s}^{-1}}\right) \times (25\ 10^{-6}\ \text{man m}^{-2})$$
$$(1.44 \times 80\ 10^{3}\ \text{a})\,(9.2\ 10^{-5}\ \text{Sv Bq}^{-1}\ \text{m}^{3}\ \text{a}^{-1}) \times$$
$$\times\ (3.17\ 10^{-8}\ \text{a s}^{-1}) = 760\ \text{man Sv [GW (e) a]}^{-1}.$$

This is in agreement with the value of 2800 man Sv [GW(e) a]$^{-1}$ calculated using the atmospheric dispersion model (Table 6). The previous estimate by the Committee, in Annex D of the 1977 report [U1], based on the tailings release rate assumptions and radon dosimetry, was equivalent to a collective effective dose equivalent commitment of 2300 man Sv [GW(e) a]$^{-1}$. These values must be extremely uncertain and depend upon future practice, both in the choice of fuel cycle, since plutonium recycle in fast reactors could reduce the uranium ore requirement per unit energy generated by a factor of about 200 with the resulting same reduction in collective dose, and in the management practices of the tailings themselves. Also the downwards migration of radionuclides in soils at rates of 2 10^{-3} m a^{-1} could reduce the collective dose commitment from radon releases by up to two orders of magnitude.

II. URANIUM FUEL FABRICATION

33. The uranium ore concentrate produced at the mills is further processed and purified and often enriched in the isotope ^{235}U before being converted into uranium oxide or metal and fabricated into fuel elements. Natural uranium which contains 0.7% ^{235}U can be utilized in graphite or heavy-water moderated reactors (HWRs). Light water reactors (LWRs) and advanced gas-cooled reactors (AGRs) require enriched fuel of between about 1 and 4% ^{235}U. Before uranium can be enriched it must be converted from the oxide form U_3O_8 to uranium hexafluoride (UF_6), the gaseous form for use in enrichment plants.

34. Conversion takes place, for example, at two UF_6 production facilities in the United States at Sequoyah, Oklahoma and Metropolis, Illinois and in the United Kingdom at Springfields, although other conversion facilities exist. Two industrial processes are used for UF_6 production, dry hydrofluor and solvent extraction and each is responsible for about half the UF_6 production in the United States. The hydrofluor process consists of reduction, hydrofluorination and fluorination of the ore concentrates to produce crude UF_6, followed by fractional distillation to obtain a pure product. The solvent extraction process employs a wet chemical solvent extraction step at the start of the process to produce high purity uranium for the subsequent reduction, hydrofluorination and fluorination steps.

35. Enrichment of the isotopic content of ^{235}U usually takes place at a gaseous diffusion plant, although increasing use is made of centrifuge techniques. At a gaseous diffusion installation the UF_6 is pumped through a series of porous membranes which discriminate against the passage of the heavier isotope of uranium by a factor of 1.0043 at each stage. Some 1700 stages are required to produce an enrichment of 4% [U3]. Centrifuge technology utilizes rapidly rotating cylindrical vessels to separate the isotopes of uranium and utilizes only ten stages to reduce to the normal tailings levels using only 10% of the electricity used by a diffusion plant [C7]. In the final fuel fabrication step the UF_6 is chemically converted to UO_2 or to uranium metal for use in fuel elements. For use in LWRs or AGRs the dioxide powder is sintered into pellets and loaded into zircaloy or stainless steel cladding to produce fuel pins which are filled with helium and welded with end caps. Uranium metal without enrichment is used in Magnox reactors clad in a magnesium alloy (Magnox) can. For HWRs unenriched uranium dioxide is normally used. After the enrichment process large quantities of depleted uranium remain in which the ^{235}U content is 0.3% or more. This uranium may become a source of public exposure if it is disposed of; at present it is stored for possible use in breeder reactors and for other purposes.

A. EFFLUENTS

36. Emissions of radionuclides from the conversion, enrichment and fuel fabrication processes are small. Most of the uranium compounds are solid and conventional equipment may be used to remove particulates from airborne effluents. Liquid wastes are collected in settling tanks or ponds. Estimates of releases from typical installations have been published previously in the United States [U3]. More recently the United States Nuclear Regulatory Commission has reported environmental releases from fuel fabrication plants at six-month intervals [N18].

37. Residual amounts of ^{230}Th and ^{226}Ra are removed from the uranium ore concentrate in the conversion process and small amounts of these nuclides and uranium appear in effluent streams. Atmospheric annual discharges from typical conversion plants in the United States are reported at about 3 GBq for ^{238}U, ^{234}U, ^{234}Th; 33 MBq for ^{230}Th; 3 MBq for ^{226}Ra; and 74 MBq for ^{235}U [E1, N18]. In the United Kingdom, British Nuclear Fuels Ltd. published annual reports on radioactive discharges and monitoring [B2, B22]. The annual atmospheric discharge from Springfields has been about 0.02 TBq of natural uranium from 1977 to 1979. The release of uranium from the Capenhurst enrichment plant in the United Kingdom was reported at 0.2 GBq in 1977 and 1979 and at 0.15 GBq in 1978 [B2, B22]. The Swedish fuel fabrication facility released between 13 and 60 MBq of 2 or 2.3% enriched uranium per year to the atmosphere between 1976 and 1979 [G3].

38. Annual liquid discharges from Capenhurst contain about 1 GBq of uranium and 0.5 GBq of beta activity, and Springfields releases about 1 TBq a^{-1} of uranium. The effluent from Springfields is released into the tidal waters of the river Ribble, while waste from Capenhurst is now discharged through the sewage system. The total beta activity in Springfields liquid effluent discharges greatly exceeds the alpha activity because of the removal and discharge of the short-lived isotopes ^{234}Th (24.1 d) and ^{234m}Pa (1.17 min). Annual

liquid effluent discharges of ^{238}U at United States sites are about 40 GBq for conversion, 67 GBq for enrichment and 17 GBq for fuel fabrication [U3].

39. Table 7 shows discharges from the model fuel conversion, enrichment and fabrication facilities. The atmospheric emissions of the model conversion facility were based on operating data taken from Sears et al. [S6] for plant with low impurity feed. The atmospheric discharges from the model fuel fabrication facility were based on the work of Pechin et al. [P1]. The model enrichment facility is based on the Capenhurst discharges to atmosphere [B2]. The throughput of fuel is assumed to be 10^4 t a^{-1} of uranium at the conversion facility and enrichment plant, which is reduced to 1500 t a^{-1} of enriched fuel for the fabrication plant. The liquid discharges from the model facilities were derived from Capenhurst [B2, B22] and United States data [U3]. The model plant is assumed to be at a site discharging into fresh water. The discharge data for the model facility are about half those used in Annex D of the 1977 report [U1] for airborne releases and the same for liquid effluents.

B. LOCAL AND REGIONAL COLLECTIVE DOSE COMMITMENTS

40. The exposure as a result of liquid effluents from United Kingdom fuel fabrication operations has been reported as mainly due to external irradiation by the sediments on the river bank near the Springfields plant. The annual collective effective dose equivalent has been estimated at less than 10^{-3} man Sv [T4]. For liquid releases into a freshwater environment Pechin has shown that the most exposed individual receives a dose of less than 10% of that received from the gaseous release and has estimated a representative normalized collective effective dose equivalent commitment of about 2 10^{-4} man Sv [GW(e) a]$^{-1}$ to the population exposed to aquatic pathways from the river [P1]. There is great variability in the behaviour of effluents released to the aquatic environments and the collective dose commitment can only be regarded as indicative of the order of magnitude. It seems probable, however, that the major exposure of the population from fuel conversion and fabrication processes arises as a result of the discharges to the atmospheric environment.

41. The location of the model facility has been chosen to be representative of the northern United States and northern Europe. The most significant pathway that emerges, which leads to exposure of the population, is the direct inhalation route, as will be shown below. The population distribution around the model facility is assumed to be constant at 25 km^{-2} and the collective doses for the particulate releases are derived using the results given in Annex C for technologically enhanced releases of radionuclides. The results are modified for the different isotopic composition and population density. The particulate releases are assessed for inhalation from the plume, ingestion of foodstuffs contaminated by activity deposited from the plume and by external irradiation from the ground deposited activity. For the radon releases a meteorological dispersion calculation was performed using an effective dose equivalent per unit inhaled activity of radon daughters of 1.3 10^{-8} Sv Bq^{-1} and an equilibrium factor of 0.6 between radon and its short-lived daughters from Annex D. For the calculation of radon releases the distribution of Pasquill weather categories is typical of a moderate climate in which rain is assumed to occur in near neutral conditions (categories C and D) and accounts for some 10% of the annual frequency distribution (Table 8).

42. The normalized collective absorbed dose equivalent commitments for the particulate releases are shown in Table 9, where it can be seen that inhalation of uranium isotopes is the main route of exposure. These collective dose commitments are estimated on the assumption that the radionuclides deposited onto the ground migrate downwards fairly rapidly and thus become unavailable. In fact, owing to the long half-lives of the nuclides of the uranium decay chain, they may in the far future return to man by various pathways, although the corresponding collective dose commitments are probably small. The estimated collective absorbed dose commitments from ingestion of foodstuffs are estimated to be a factor of about 10 below those due to inhalation.

43. In summary, the normalized collective effective dose equivalent commitment due to uranium fuel fabrication is estimated to be 2 10^{-3} man Sv [GW(e) a]$^{-1}$, as shown in Table 10. The main contribution is inhalation of the isotopes of uranium. Radon releases contribute about 20% of the total. This figure is higher than that estimated in Annex D of the 1977 report [U1] for a similar discharge, but is small compared with the doses from mining and milling. It has been reported that the critical group for uranium fuel fabrication plants are those exposed to sediments on banks of waterways near the site [B22]. For the Springfields site in the United Kingdom this critical group may be exposed at 10^{-9} Sv a^{-1}, but the pathway contributes little to the total collective effective dose equivalent.

III. REACTOR OPERATION

44. Most of the electrical energy generated by nuclear power is produced by thermal reactors in which the fast neutrons produced by the fission process are slowed down to thermal energies by use of a moderator. The smaller the atomic mass of the moderator, the more efficiently it removes energy from the neutrons. The most common materials which have been employed as moderators in thermal power reactors are light water, heavy water and graphite. The choice of moderator greatly affects the design of the reactor, its size and heat removal system.

45. The uranium fuel is contained in discrete pins, both to prevent leakage of produced radioactive fission products into the coolant circuit and also to improve the neutron economy by reducing the parasite neutron captures in the resonance neutron energy region of ^{238}U. The heat generated in the fuel pins by the slowing down of the fission fragments is removed by forced convection. The most usual coolants are light or heavy water and carbon-dioxide gas. In the case of fast-breeder reactors, the neutrons are not moderated and induce fissions with their energies close to those at which they were produced. The usual heat removal system from the core is by means of liquid sodium metal, which is a better heat transfer medium and does not significantly moderate the neutrons.

46. The number of operational reactors of each type and the generating capacity for each country or area utilizing commercial reactors together with the installed capacity per caput are shown in Table 11. There were 235 reactors in 22 countries with an installed capacity

of about 120 GW(e) in 1979 [I1, K12]. The reactor types include the pressurized water moderated and cooled reactor (PWR), the boiling water moderated and cooled reactor (BWR), the Magnox and advanced gas-cooled graphite moderated reactors (GCR), the light-water cooled graphite moderated reactor (LWGR), the heavy-water moderated and cooled reactor (HWR) and the fast breeder reactor (FBR). The average installed capacity per caput was 0.07 kW(e) with the highest value being 0.46 in Sweden and the other developed countries averaging between 0.1 and 0.2 kW(e).

A. EFFLUENTS

47. During the production of power by a nuclear reactor radioactive fission products are formed within the fuel and neutron activation produces radioactive components in structural and cladding materials. Radionuclides are found in the coolant both because the coolant becomes activated, because of diffusion of fission product elements with radioactive nuclides from the small fraction of the fuel with defective cladding, and because of corrosion of the structural and cladding materials. All reactors have treatment systems for the removal of radionuclides from gaseous and liquid wastes which arise from leakage out of the core or from clean-up of the coolant. Low level releases which occur are controlled and monitored.

48. The quantities of different types of radioactive materials released from reactors depend on the particular design and on the specific waste treatment plant installed. Radionuclides released to the atmospheric environment include noble gases from fission (krypton and xenon), activation gases (^{14}C, ^{16}N, ^{35}S, ^{41}Ar), tritium, iodine and particulates. Radionuclides discharged to the aquatic environment in liquid effluents include tritium, fission products and activated corrosion products. Results are presented for annual normalized release, i.e., per unit of electrical energy generated in that year, averaged over all reactors of a given type (PWR, BWR, etc.). Normalized results are not presented for individual sites because releases in any one year often reflect the need for maintenance or irregular procedures which are the result of a number of previous years operation. The total releases of radionuclides between 1975 and 1979 have been divided by the total production of electrical energy over the same years in order to obtain a representative normalized release over the period covered by this Annex. These results are subsequently used to assess collective dose commitments. In the tables which follow open entries mean that no data were available, entries characterized by a dash mean that no releases were reported.

1. Fission noble gases

49. There are at least nine radioactive isotopes of krypton and eleven radioactive isotopes of xenon formed by the fission process. Most of them have very short half-lives (seconds to minutes) and decay before they migrate significantly within the fuel. A fraction of the noble gas inventory of the fuel pins diffuses to the free space between the fuel and the cladding, leading to a build-up of gas pressure. The presence of noble gases in the coolant is generally due to fuel cladding failure.

50. In PWRs the primary coolant is in a sealed loop and off-load refuelling is employed. Short-lived radioactive noble gases, therefore, only appear because of leakages of the primary circuit water. The primary water coolant in a PWR is continually purged for control of chemical composition and purification. Gaseous wastes are released in the process and are held under pressure in tanks for between 30 and 120 days for decay of short-lived nuclides. Other gaseous effluent streams in PWRs originate from the condenser exhaust on the steam circuit, secondary coolant blowdown, reactor building ventilation, including containment purges (about 4 a^{-1}), and turbine plus ancillary building ventilation [N9].

51. Table 12 lists the reported discharges of noble gases from PWRs. The information is taken from Phillips and Gruhlke [P2], Beebe [B23], Luykx and Fraser [L1, L6], Decker [D6], van Daatsellar [D8], Kumatori [K4], Errera [E9], Godas [G3], Norlinder [N19] and Salo [S14]. The releases span more than three orders of magnitude partly because of variation in design and partly because of the need for irregular operations or maintenance. For this reason, the average noble gas release from PWRs was obtained by dividing the total release by the actual total amount of electrical energy generated. The normalized annual release has been similar over the five years 1975 to 1979. The average normalized release over that period was 430 TBq [GW(e) a]$^{-1}$. The composition of the release from PWRs is predominantly from ^{133}Xe ($T_{1/2}$ 5.3 d) but some shorter-lived nuclides are present, particularly ^{135}Xe ($T_{1/2}$ 9.2 h). In Table 13 the nuclide composition of noble gases is presented for United States PWRs in the year 1979 [B23] and the normalized release per unit of electrical energy generated is given. It can be seen that ^{85}Kr ($T_{1/2}$ 10.7 a) represents 5% of the normalized release. Figures for the nuclide composition of noble gases in European PWRs are essentially similar [L1, L6].

52. In BWRs non-condensable gases in the steam flow are continuously removed by the main condenser air-ejector system. This is the main source of noble gas release into the gaseous waste stream. Secondary pathways include the purging system for the turbine gland seals, the condenser mechanical vacuum pump and any leakage of process fluids to ventilated building spaces [N10]. Table 14 lists the discharges reported from BWRs in consecutive years derived from references [B23, D6, D8, E9, G3, K4, L1, L6, N19, P2, S14]. The releases vary by more than six orders of magnitude per unit of installed capacity. The value averaged over all operating experience has been falling year by year from 56 PBq [GW(e) a]$^{-1}$ in 1970, to 37 PBq [GW(e) a]$^{-1}$ in 1974 and to 4.4 PBq [GW(e) a]$^{-1}$ for BWRs in 1979. This consistent reduction in discharges of noble gases from BWRs is partly a result of the commissioning of new plants with lower release rates, but is also due to reductions in discharges from many existing plants for the same annual electrical output. About 85% of the noble gas discharges from BWRs in 1979 came from three plants. The average normalized release from 1975 to 1979 was 8800 TBq [GW(e) a]$^{-1}$.

53. Table 15 gives the nuclide composition of noble gas releases from BWRs in the United States during 1979 [B23]. The release composition varies greatly, depending on the waste treatment hold-up time which varies from less than half an hour on older plants to several hours on newer BWRs. The normalized releases per unit of electricity generated by all United States BWRs is also given and it can be seen that contributions to the total activity released are made by a number of nuclides including ^{138}Xe ($T_{1/2}$ 17 min), ^{135m}Xe ($T_{1/2}$

15 min), ^{135}Xe ($T_{1/2}$ 9.2 h), ^{133}Xe ($T_{1/2}$ 5.3 d), ^{88}Kr ($T_{1/2}$ 2.8 h), ^{87}Kr ($T_{1/2}$ 76 min), ^{85m}Kr ($T_{1/2}$ 4.4 h) and ^{85}Kr ($T_{1/2}$ 10.7 a).

54. In gas-cooled reactors noble gas releases are insignificant. For reactors of the Magnox type utilizing uranium metal fuel, because of the magnesium alloy cladding, temperatures must be kept below 650°C and the reactors are equipped with detection systems for failed fuel pins which are quickly removed from the operating core. The AGR utilizes enriched uranium oxide fuel in stainless steel cladding with CO_2 coolant. Again, early operating experience does not indicate that noble gas releases occur. As with Magnox reactors, AGRs employ on-load refuelling and failed fuel pins are easily removed.

55. Releases of noble gases for heavy water reactors are presented in Table 16 using data from Argentina [B21] and Canada [M10]. The normalized release averaged between 1975 and 1979 is 460 TBq [GW(e) a]$^{-1}$. There is little release reported for fast breeder reactors in France and the United Kingdom [F1]. There has been little exploitation of high temperature reactors in recent years, although one or two experimental facilities remain.

2. Activation gases

56. Although gas-cooled reactors do not generally release noble gas fission products as do BWRs and PWRs, several activation gases are formed in GCR operation. Direct activation of the oxygen in the CO_2 coolant gives rise to ^{16}N by the (n,p) reaction on ^{16}O. Argon-41 arises from (n,γ) reactions in the stable ^{40}Ar content of air, either present as an impurity in the coolant circuit or used for shield cooling in early GCRs with steel pressure vessels.

57. The amount of ^{41}Ar ($T_{1/2}$ 1.8 h) released depends upon the detailed design of the reactor. Release rates of ^{41}Ar are not measured routinely in the United Kingdom, but measurements have been reported by Clarke and Wilson [C1] and give averages of between about 2 and 15 PBq [GW(e) a]$^{-1}$ or between about 20 and 150 MBq s^{-1}. For AGRs the primary source of ^{41}Ar releases is from the leakage of the coolant to atmosphere and releases of the order of about 0.1 PBq [GW(e) a]$^{-1}$ are reported [L6]. The activation gas discharges from GCRs are given in Table 17 for the years 1975–1979. The average normalized release between 1975 and 1979 was 3.2 PBq [GW(e) a]$^{-1}$.

58. Another airborne gaseous effluent of GCRs is ^{35}S ($T_{1/2}$ 87.5 d) arising from (n, γ) reactions on ^{34}S present as an impurity in the graphite core, and from (n,p) reactions on ^{35}Cl also present as an impurity. Discharge rates have been reported in the range of about 1 to 4 GBq d^{-1} [G4] but may reduce as the reactors come to full power. The impurity levels of sulphur and chlorine in the moderator graphite are reported as approximately 50 and 2 ppm, respectively [P3]. Measured releases of ^{35}S from Oldbury and Wylfa (Magnox) and from Hinkley B (AGR) in 1976 were 52, 89 and 81 GBq, while in 1977 they were 17, 200 and 211 GBq, respectively [G4]. In 1978 the values were 28, 174 and 204 GBq, respectively. The average normalized discharge was 170 [GW(e) a]$^{-1}$ and the chemical form was carbonyl sulphide.

59. Nitrogen-16 ($T_{1/2}$ 7 s) provides essentially only direct external irradiation at nuclear power plants. The photons produced in its decay have energies of 6.1 and 7.1 MeV. In BWRs the ^{16}N generated is in part transported with the steam to the turbine buildings producing an external gamma field. External gamma dose rates at the perimeter fence of Central Electricity Generating Board nuclear power stations in the United Kingdom have been reported as being mainly due to ^{16}N [G4].

3. Tritium

60. In LWRs tritium arises from ternary fission in the nuclear fuel and from neutron activation reactions with lithium and boron isotopes dissolved in or in contact with the primary coolant. The normalized tritium production rate has been estimated for LWRs as 0.56 PBq [GW(e) a]$^{-1}$ from ternary fission [E3], assuming a yield of 0.85 10^{-4} per thermal fission in ^{235}U [F2] and 2 10^{-4} per thermal fission in ^{239}Pu and ^{238}U [E3]. The estimate assumes that 55% of the integrated number of fissions have occurred in ^{235}U, 41% in ^{239}Pu and 4% in ^{238}U. Other estimates have given production rates of 0.85 PBq [GW(e) a]$^{-1}$ [O1, K2]. An average value of about 0.75 PBq [GW(e) a]$^{-1}$ is assumed here.

61. Estimated generation rates of tritium from activation reactions depend on the assumed concentrations of the parent nuclide. In PWRs it is thought to be mainly due to reactions with the boron in the coolant water which is used for reactivity control. In BWRs it is mainly from boron in control rods. In GCRs it is due to lithium impurities in the graphite and to the presence of water vapour in the core. For HWRs it is principally due to activation of the deuterium moderator and coolant [K1, S7, T2]. The generation rate from activation only exceeds the ternary fission source for HWRs, where the activation rate is some 30 times higher at about 25 PBq [GW(e) a]$^{-1}$. About 1% of the tritium formed in the fuel elements is usually assumed to appear in the coolant circuit and to find its way to effluent streams.

62. Table 18 gives the reported tritium discharges in airborne effluents for LWRs and HWRs. For BWRs the annual normalized release of tritium to atmosphere is fairly constant and averages 3.4 TBq [GW(e) a]$^{-1}$ for 1975–1979, while for PWRs the value varies between 4 and 15 TBq [GW(e) a]$^{-1}$ and the 1975–1979 average is 7.8 TBq [GW(e) a]$^{-1}$. The atmospheric discharges of tritium are seen to average 540 TBq [GW(e) a]$^{-1}$ for HWRs between 1975 and 1979. The discharges of tritium in liquid effluents are shown in Table 19 and the normalized average release derived for 1975–1979 is 1.4 TBq [GW(e) a]$^{-1}$ for BWRs and 38 TBq [GW(e) a]$^{-1}$ for PWRs. For European PWRs with stainless steel fuel clad, the tritium figure in liquid discharges is 300 TBq [GW(e) a]$^{-1}$. Gas-cooled reactors are seen to release 25 TBq [GW(e) a]$^{-1}$ of tritium in liquid discharges averaged between 1975 and 1979. The highest releases of tritium in liquid effluents are from HWRs with an average normalized release of 350 TBq [GW(e) a]$^{-1}$.

63. Bonka [B5] has recently quoted discharges per unit of electrical energy generated of 4 TBq [GW(e) a]$^{-1}$ to air and 40 TBq [GW(e) a]$^{-1}$ to water for PWRs and normalized rates of 2 TBq [GW(e) a]$^{-1}$ (atmospheric) and 6 TBq [GW(e) a]$^{-1}$ (aquatic) for BWRs. For AGRs the atmospheric discharge rate of tritium amounts to about 10 TBq [GW(e) a]$^{-1}$, about the same as the level in

liquid discharges [G6]. In Magnox reactors, the coolant circuit is continually dried to remove water vapour and tritium produced in the circuit appears primarily in the liquid effluent removed by the humidryers.

64. Gorman and Wong [G7] have estimated ^{3}H normalized production in Canadian HWRs to be up to 89 PBq [GW(e) a]$^{-1}$ in the moderator, compared with 0.74 PBq [GW(e) a]$^{-1}$ in the fuel and the normalized emission is given as 630 TBq [GW(e) a]$^{-1}$ for airborne effluents and 260 TBq [GW(e) a]$^{-1}$ in liquid discharges. These are comparable with the normalized atmospheric and liquid discharges reported here averaged over the years 1975–1979. In HWRs the build-up of tritium in the moderator depends upon the irradiation history and on the leakage rate of deuterium from the core, which will be at least 0.5% and perhaps a few per cent of the inventory per year. These conditions affect the environmental releases, as can be seen from Table 19, where there is a general upward trend in tritium in liquid effluents. However, tritium control and removal systems are being developed and releases could be expected to reduce. Averaged over the years 1975–1979 the reported HWR releases to atmosphere are similar to those to the aquatic environment.

4. Carbon-14

65. Discharges of ^{14}C have been of increasing interest in recent years because of the long half-life (5730 a) of the isotope and its significant contribution to the collective dose commitments. Carbon-14 is produced in LWRs and HWRs by (n,α) reactions with ^{17}O present in the oxide fuel and moderator; by (n,p) reactions with ^{14}N present in the fuel as impurities; and by ternary fission. The production rate by ternary fission is virtually independent of reactor design, while the normalized production of ^{14}C by the other routes depends on the fuel enrichment, the relative masses of fuel and moderator, the concentration of nitrogen in the fuel, and the fuel and moderator temperatures. In gas-cooled graphite moderated reactors, the graphite moderator is a major source of ^{14}C production due to the ^{13}C (n, γ) ^{14}C reaction and the ^{14}N (n,p) ^{14}C reaction on nitrogen impurities. Production of ^{14}C from the CO_2 coolant has been estimated to give only a few per cent of the total contribution from all sources. Because of the large moderator mass, ^{14}C is produced mainly from ^{17}O reactions in the moderator in HWRs.

66. The ^{14}C content of LWR fuels per unit energy generated has been estimated at 0.22 TBq [GW(th) a]$^{-1}$ [K2], i.e., 0.67 TBq [GW(e) a]$^{-1}$, assuming a reactor thermal efficiency of 33%. As noted above, such estimates are dependent upon the assumptions on nitrogen impurity levels in the fuel and values up to 1.9 TBq [GW(e) a]$^{-1}$ have been reported [M2]. More recent estimates by Davis [D2] gave values of 0.74 TBq [GW(e) a]$^{-1}$ for both PWRs and BWRs and a study carried out for the Swedish power reactors [L2] estimates 0.52 TBq [GW(e) a]$^{-1}$ for PWRs. Hayes and MacMurdo have estimated ^{14}C normalized production to be 0.22 and 0.55 TBq [GW(e) a]$^{-1}$ for PWRs and BWRs, respectively [H2]. Bonka et al. [B4] gave values of 0.9 TBq [GW(e) a]$^{-1}$ for PWRs and 1.1 TBq [GW(e) a]$^{-1}$ for BWRs. It was estimated in Annex D of the 1977 report [U1] that approximately 30% of the ^{14}C total production is in the moderator for both PWRs and BWRs. This is the likely source of release to the environment from the reactor while, based on experimental studies, most of the content of the fuel appears to be released during reprocessing [S8].

67. In gas-cooled reactors a normalized production within the fuel of 0.96 TBq [GW(th) a]$^{-1}$ has been estimated [K2] which, assuming a thermal efficiency from Magnox reactors of 30%, gives a normalized production of 3.2 TBq [GW(e) a]$^{-1}$. The primary source of ^{14}C is the graphite moderator in which a normalized production of 9.3 TBq [GW(e) a]$^{-1}$ has been estimated. The normalized production in the carbon dioxide coolant by the ^{17}O (n,α) ^{14}C has been estimated at 0.11 TBq [GW(e) a]$^{-1}$ for Magnox and 0.37 TBq [GW(e) a]$^{-1}$ for AGRs [K2]. For HWRs the normalized ^{14}C production is estimated at 0.74 TBq [GW(e) a]$^{-1}$ in the fuel and at 21 TBq [GW(e) a]$^{-1}$ in the moderator [W3].

68. A programme of measurements have been made in the Federal Republic of Germany by the Bundesgesundheitsamt [R1, S15], the results of which are given in Table 20. In European PWRs only a small fraction of the ^{14}C is in the form of CO_2; it is mostly present in methane or other hydrocarbons. The normalized discharge is about 220 GBq [GW(e) a]$^{-1}$ [L1, S15, R1]. For European BWRs the release of ^{14}C appears to be more than 95% as CO_2 and the normalized release rate is about 520 GBq [GW(e) a]$^{-1}$. In a detailed study of the Oyster Creek (United States) BWR Blanchard has measured ^{14}C normalized releases of 220 GBq [GW(e) a]$^{-1}$ from the condenser air ejector and 74 GBq [GW(e) a]$^{-1}$ from building ventilation air [B3]. The same study revealed liquid discharges of ^{14}C at 0.74 GBq [GW(e) a]$^{-1}$. For a PWR, Kahn et al. have reported ^{14}C measured atmospheric discharges of 37 GBq [GW(e) a]$^{-1}$ [K3].

69. Carbon-14 discharges from gas-cooled reactors result from the leakage of the primary coolant (typically a few per cent per day) which contains radionuclides released to the coolant by corrosion of the graphite moderator; estimated normalized releases are 0.22 TBq [GW(e) a]$^{-1}$ for Magnox and 0.63 TBq [GW(e) a]$^{-1}$ for AGRs [P3]. Groome has reported [G6] that the total ^{14}C discharge from Magnox reactors is 3.7 TBq, corresponding to 1.1 TBq [GW(e) a]$^{-1}$, and that AGRs are expected to give similar normalized release.

70. For HWRs it is reported that about half the ^{14}C moderator production is released to atmosphere, giving a normalized release of 10 TBq [GW(e) a]$^{-1}$ [W3], while other reported normalized releases are about 17 TBq [GW(e) a]$^{-1}$ [B21].

5. Iodine

71. The volatile element iodine is produced in the fission process. Its yield is almost independent of whether uranium or plutonium isotopes are undergoing fission. The isotopes of iodine of interest in radiological assessments are ^{129}I ($T_{1/2}$ 1.6 10^{7} a), ^{131}I ($T_{1/2}$ 8.04 d), ^{132}I ($T_{1/2}$ 2.3 h), ^{133}I ($T_{1/2}$ 21 h), ^{134}I ($T_{1/2}$ 53 min) and ^{135}I ($T_{1/2}$ 6.6 h). Owing to the short half-lives of all the isotopes except ^{129}I, equilibrium activity concentrations are achieved quickly and releases depend on the number of fuel cladding failures and coolant leakage rate. Iodine-131 has been studied for many years in view of its mobility in the environment and selective human organ irradiations. In recent years ^{129}I has received more attention, although its release rate is extremely low, because of its contribution to the collective dose commitment through its long availa-

bility in the environment. Of particular interest in fuel reprocessing, ^{129}I is not generally reported in routine discharges from nuclear power plants.

72. Table 21 gives the year by year reported atmospheric discharges of iodines from power reactors in various countries. There are wide differences both in the quantities and in the nuclide composition of the releases due to different waste treatment systems. Table 22 gives the isotopic composition of atmospheric releases of iodine from United States PWRs and BWRs in 1979, together with the normalized release rates. The annual iodine normalized discharge for PWRs has been fairly constant and averages 5.0 GBq [GW(e) a]$^{-1}$ between 1975 and 1979. For BWRs the 1975–1979 averaged normalized discharge is 410 GBq [GW(e) a]$^{-1}$. The comparable figures for HWRs are between 0.08 and 3.1 GBq [GW(e) a]$^{-1}$ [M10]. It is clear from Table 22 that while for PWRs ^{131}I contributes about one third of the total iodine discharge, for BWRs it represents less than 10% of the iodine release. The normalized releases are not typical of any one reactor but reflect the average for the nuclear power industry. Few data are available on the proportions of organic and inorganic forms of the iodine released to the atmosphere, but analysis for power stations in the Federal Republic of Germany shows that usually less than 1% of the iodine released in gaseous effluent is in particulate form [W2].

73. Measurements at six power reactors in the United States indicated that on average 73% of the iodine in the reactor off-gases was in the organic form, 22% was hypoiodous acid and 5% elemental [P7]. All forms were also present in ventilation exhaust air, though the release rate from this source is usually much less than from the reactor off-gas system. The release of iodine isotopes depends strongly on the filtration system used at the plant.

6. Particulates in airborne effluents

74. Radionuclides in particulate form can arise directly or as decay products of fission noble gases or may arise from corrosion of materials in the primary coolant circuit. Aerosols are generated because of primary coolant leaks or because of maintenance work on active components removed from the primary circuit. The air in all areas where aerosols might arise is continually purged and the plenum activity is filtered through high efficiency particulate (HEPA) filters which retain all but the finest aerosols. Releases of particulate activity are very low and the nuclide composition is essentially unique to each operating plant; it depends on the particular impurities in cladding and structural materials, coolant chemistry and fuel failure modes. The releases also vary from time to time because of different operational and maintenance needs and practices.

75. As a consequence, the range of reported nuclides in particulate atmospheric discharges is very large, up to several tens of nuclides at any one plant [D3, B23, B24]. Radionuclides identified and reported at various plants include: ^{7}Be, ^{22}Na, ^{24}Na, ^{51}Cr, ^{54}Mn, ^{56}Mn, ^{59}Fe, ^{57}Co, ^{58}Co, ^{60}Co, ^{63}Ni, ^{65}Zn, ^{76}As, ^{88}Rb, ^{89}Sr, ^{90}Sr, ^{91}Sr, ^{95}Zr, ^{97}Zr, ^{95}Nb, ^{99}Mo, ^{99m}Tc, ^{103}Ru, ^{105}Ru, ^{106}Ru, ^{108m}Ag, ^{110m}Ag, ^{113}Sn, ^{115}Cd, ^{122}Sb, ^{124}Sb, ^{125}Sb, ^{123m}Sn, ^{123m}Te, ^{134}Cs, ^{136}Cs, ^{137}Cs, ^{139}Ce, ^{140}Ba, ^{140}La, ^{141}Ce, ^{144}Ce, ^{182}Ta.

76. It is thus clear that averaging the nuclide composition of particulate releases by reactors is difficult and may mean little. There is no indication in current discharge data of any one nuclide dominating the release for any given reactor type. In Table 23, the average particulate discharges from reactors year by year are given as the reported sum of activity. Over the period 1975–1979 normalized releases of particulates from PWRs averaged 2.2 GBq [GW(e) a]$^{-1}$, while the BWR normalized releases to atmosphere were 53 GBq [GW(e) a]$^{-1}$. The normalized release from GCRs was 1.0 GBq [GW(e) a]$^{-1}$, from the Argentinan HWR was 0.044 GBq [GW(e) a]$^{-1}$, from the Canadian HWRs 0.9 GBq [GW(e) a]$^{-1}$ [M10] and from the fast reactor Phénix was 4.8 MBq [GW(e) a]$^{-1}$ [L6].

7. Liquid effluents

77. The sources of radionuclides other than tritium in liquid effluents are essentially the same as those described for particulate releases to the atmosphere and the discharges reported are equally as varied. The amount and composition of the discharge depends upon the design and operating practice of the reactor, impurity levels and trace quantities of materials in structural and cladding components. The available discharge data for 1975–1979 are given in Table 24 for operating reactors. Table 25 shows the isotopic composition of liquid effluent discharges for reactors in the United States in 1979. The isotopic composition of liquid effluents from GCRs in the United Kingdom for 1979 is shown in Table 26.

78. The normalized release levels based on the reported discharges for each reactor type using the actual reported generation of electrical energy averaged between 1975 and 1979 are approximately (Table 24):

PWR: 180 GBq [GW (e) a]$^{-1}$
BWR: 290 GBq [GW (e) a]$^{-1}$
GCR: 4800 GBq [GW (e) a]$^{-1}$
HWR: 470 GBq [GW (e) a]$^{-1}$.

Canadian HWR averaged results are some 10 times lower [M10]. The elevated levels for GCRs in the United Kingdom reflect the fact that discharges are made (with the exception of Trawsfynydd) to the marine environment. Swedish reactors also discharge to the sea and have slightly higher normalized liquid effluent release rates than LWRs of the United States or Europe. In Annex D of its 1977 report [U1], the Committee quoted normalized releases for PWRs, BWRs and GCRs of 296, 2220 and 5550 GBq [GW(e) a]$^{-1}$. The average normalized aquatic releases for BWRs over the 5-year period 1975–1979 have been reduced by about an order of magnitude and normalized discharges in the last few years have been even lower. This reduction does not appear to have been due to removal of specific nuclides from the liquid waste streams, but appears to be applicable to all the nuclides constituting the release.

79. In 1979 the isotopes ^{134}Cs and ^{137}Cs represented 10% and 35% of the activity concentration in liquid discharges from the United States PWR and BWR systems, respectively. In Annex D of the 1977 report [U1], the Committee found that caesium isotopes contributed 70% of the discharged activity concentration for BWRs and GCRs, and 30–50% for PWRs. For LWRs the remaining contributions to activity in aqueous discharges arise from a number of nuclides; cobalt isotopes ^{58}Co and ^{60}Co contribute about 65% of the

activity in PWRs and iodine isotopes some 6%. For BWRs cobalt isotopes contributed 10% of the liquid effluent activity concentration in 1979 and iodines 5%.

80. The isotopic ratio of ^{134}Cs to ^{137}Cs from GCRs was 0.28 in 1977, compared with 0.2 found by the Committee in Annex D of the 1977 report [U1]. The increase in ^{134}Cs level probably reflects the increasing fuel irradiation time achieved in Magnox reactors (now approximately 4.5 GW d t^{-1}). As fuel burnup increases, the amount of the long half-life isotope ^{137}Cs increases almost linearly, whereas ^{134}Cs is produced primarily from neutron captures in the stable fission product ^{133}Cs, and, since the amount of ^{133}Cs increases linearly with burnup, the production of ^{134}Cs increases nearly as the square of the fuel burnup. Its radioactive half-life (2.1 a) means that some radioactive decay takes place, but the $^{134}Cs/^{137}Cs$ ratio should increase nearly linearly with burnup. For BWRs the $^{134}Cs/^{137}Cs$ ratio is 0.77 and for PWRs it is 0.57.

81. The release of ^{131}I into liquid effluents contributed about 4.7 GBq [GW(e) a]$^{-1}$ for BWRs in the United States in 1979. In the same year, ^{131}I normalized releases from PWRs average out at 4.6 GBq [GW(e) a]$^{-1}$ in the United States, 4.8 GBq [GW(e) a]$^{-1}$ in Sweden and 6.7 GBq [GW(e) a]$^{-1}$ in western Europe. The liquid discharges of ^{131}I are therefore similar for BWRs and PWRs and compare with the atmospheric normalized releases of ^{131}I of 42 GBq [GW(e) a]$^{-1}$ from BWRs, and 1.9 GBq [GW(e) a]$^{-1}$ from PWRs. The normalized releases of other iodine isotopes in liquid effluents amount to about 3 GBq [GW(e) a]$^{-1}$ from ^{133}I and ^{135}I in PWRs, and 2 GBq [GW(e) a]$^{-1}$ in BWRs.

82. There is a wide range of activation products and fission products reported in liquid discharges and results vary widely from reactor to reactor. It is apparent that one or two nuclides consistently contribute to the discharge from LWRs. Amongst these, ^{24}Na is widely reported and contributes to radionuclide discharges from both BWRs and PWRs. Also ^{58}Co discharges are as high or higher than ^{60}Co discharges and ^{89}Sr contributes to BWR liquid effluents.

83. For GCRs the next most significant contributions to aqueous releases after caesium are from ^{35}S and ^{90}Sr. The ^{35}S is collected in the humidryers which remove water from the gas circuit and appears in the liquid effluent stream at a normalized release of 547 GBq [GW(e) a]$^{-1}$, compared with 170 GBq [GW(e) a]$^{-1}$ in gaseous releases (paragraph 58).

B. LOCAL AND REGIONAL COLLECTIVE DOSE COMMITMENTS

84. National authorities usually require an environmental monitoring programme in the vicinity of a nuclear power plant to be carried out either by the operator, or by another competent agency, or both. Detailed investigative studies have been reported [K3, E4, B3] and, in general, levels of radioactive contamination are not readily detectable except in the immediate vicinity of the plant. Dose assessments for the population, therefore, rely on modelling the environmental transport and transfer of radioactive materials. In recent years trajectory modelling has been developed for long-range atmospheric dispersion calculations in which historical meteorological data is used to calculate the paths of discrete masses of air [Z1]. The Committee has felt these models are not yet sufficiently developed to offer advantages over the models described in Annex A.

85. The object of the Committee in making its present assessment is to give a representative value of the collective dose commitments per unit electric energy generated by nuclear power stations and to reflect the levels of dose received by most exposed individuals. The results will not apply to any one reactor or location and the collective dose commitments should not be applied to the known discharge rate of a given reactor to obtain estimates of total health detriment. To undertake such a study the values of parameters in the models used would need to be specific to that site (for example, for the meteorological dispersion) and to the particular local terrestrial pathways.

86. In the following sections, the normalized discharges of radionuclides found in the previous sections are assessed at a model reactor site using the methodologies outlined in Annex A. The site is most representative of the areas of Europe and the North-Eastern United States, as those areas contain the majority of the power producing reactors. Agricultural production patterns and population distribution are most typical of those areas. The parameter values in the models necessary for the assessment of each of the source terms are described in turn below.

1. Fission noble gases

87. The exposure of the population from noble gas discharges to the atmosphere is by external β- and γ-radiation. For β-irradiation a semi-infinite cloud model is adequate, but for γ-exposure, because of the long mean free path of γ rays in air, a finite cloud model must be used. The models are described in Annex A. The finite cloud-γ calculation integrates contributions to the photon fluence from radioactive source terms throughout the volume of the plume. For the present calculations the computer code ESCLOUD has been used [J2] which is essentially similar to other codes developed in the Federal Republic of Germany by Vogt [V1] and Rohloff [R2] and in the United States at the Oak Ridge National Laboratory [M1].

88. The energy deposition build-up factors for the γ-exposure at each downwind distance of interest were taken from Chilton [C2]. The absorbed dose in air is calculated using values of absorbed dose in air per unit fluence [H1] and the ratios of the absorbed doses in human body organs and tissues per unit absorbed dose in air have been obtained from Poston and Snyder [P4]. The effective dose equivalent is calculated using the procedure outlined in Annex A for presentation of summary results. The absorbed doses in skin have been taken into account using a weighting factor of 0.01. The nuclear decay schemes have been taken from Nichols [N11, N12], Nair [N13] and Despres et al. [D9]. These same data sources were used for the β-energies for skin dose equivalent calculations.

89. The meteorological data applicable to the model site are given in Table 27. The frequency distribution of Pasquill meteorological categories is assumed to be the same in each sector, which is an approximation to observations. A representative frequency distribution of wind directions has been taken. Rain is only assumed to occur for 3.5% of the time and only in near neutral conditions. A typical population distribution for Northern Europe and North-Eastern United States has

been taken and the summary of individuals in distance bands and cumulative population all round the site are also given in Table 27. The cumulative population within a radius of 2000 km from the site is 260 million people, giving an average population density of about 20 km^{-2}. The population density within 50 km of the site is an average of about 400 km^{-2}. An effective height of release of 30 m has been chosen for collective dose calculations, although the choice of height has only a secondary influence on the results. The individual dose to a member of a critical group is of course highly dependent upon stack height.

90. Using the normalized releases for PWRs from Table 12 for noble gas atmospheric releases and the nuclide composition from Table 13, the normalized collective absorbed dose commitments averaged between 1975 and 1979 from the model PWR facility have been calculated and are shown in Table 28. The normalized release term is 430 TBq [GW(e) a]$^{-1}$ and only those isotopes which contribute significantly to the collective absorbed doses are presented. The growth of daughter nuclides, e.g., $^{88}Kr \rightarrow {}^{88}Rb$ has been included in the calculations.

91. The normalized collective effective dose equivalent commitment totals 4.2 10^{-2} man Sv [GW(e) a]$^{-1}$, compared with the Committee's previous assessment in Annex D of the 1977 report [U1] of 2.5 10^{-2} man Sv [GW(e) a]$^{-1}$, even though releases have been reduced by about a factor of 2. About 80% of the collective dose commitment is given by the single isotope ^{133}Xe. Xenon-135 is responsible for about 11% of the collective dose commitment and ^{88}Kr for a further 4% of the total. The difference in the assessment is mainly due to the somewhat higher population density within the first few hundred km of the site (towards 300 km^{-2}) as compared with a value of 100 km^{-2} used previously. This reflects the closer siting of reactors to centres of population in the last decade. In Table 29 the spatial distribution of collective dose for the PWR is shown; of the collective dose, 90% is accumulated within 500 km, and the bulk of the contribution (nearly 60%) arises between 100 and 500 km. There is little contribution from inhalation of radioactive daughter products. The estimates made here include an allowance for the shielding from buildings and fraction of time spent outdoors.

92. For BWR normalized releases for the years 1975–1979, a value of 8800 TBq [GW(e) a]$^{-1}$ was taken from Table 14, together with the isotopic composition shown in Table 15, and the resulting collective dose commitments are shown in Table 30. The normalized collective effective dose equivalent commitment is 1.9 man Sv [GW(e) a]$^{-1}$, compared with the Committee's previous estimate in Annex D of the 1977 report [U1] of 5.5 man Sv [GW(e) a]$^{-1}$. The main isotope contributing to the normalized collective effective dose equivalent commitment is ^{88}Kr ($T_{1/2}$ 2.8 h) giving about 50% of the total with its daughter isotope ^{88}Rb ($T_{1/2}$ 15.4 min). This ^{88}Rb component is only due to the decay of the ^{88}Kr in the atmosphere. Most of the remainder of the normalized collective effective dose equivalent commitment arises from: ^{135}Xe ($T_{1/2}$ 9.2 h), 21%; ^{138}Xe ($T_{1/2}$ 17 min), 14%; ^{87}Kr ($T_{1/2}$ 1.3 h), 7% and ^{133}Xe ($T_{1/2}$ 5.27 d), 5%. The growth of ^{138}Cs ($T_{1/2}$ 32.2 min) from decays of ^{138}Xe is included in the dose calculations in Table 30. The collective dose commitments due to noble gases include a contribution from inhalation of the ^{88}Rb isotope. Only those isotopes contributing significantly to the collective dose commitments are included in Table 30.

93. The spatial distribution of the normalized collective effective dose equivalent commitment over distance for the model BWR is shown in Table 31. More than 80% of the collective dose is accumulated within 50 km of the site, and 40% within 10 km. This behaviour is caused by the dominant contribution of ^{88}Kr which decays by a half-life about every 40 km of travel distance, and by the fact that all the shorter-lived nuclides decay within the first tens of kilometres.

94. Martin and Nelson computed the collective doses to populations within 80 km of eight BWRs in the United States [M3]. The collective absorbed whole-body dose was 9 man Gy from 1.85 GW(e) a of power generation, corresponding to 5 man Gy [GW(e) a]$^{-1}$. There has been a very marked tendency for releases to be reduced partly as newer plants come into operation, and Martin's estimate is consistent with the assessment made here when allowance is made for the reduction in releases.

95. In summary, the normalized collective effective dose equivalent commitment from noble gas releases is 0.63 man Sv [GW(e) a]$^{-1}$, based on the weighted electricity production by PWRs and BWRs as a fraction of total nuclear generation over the years 1975–1979. The annual effective dose equivalents to most exposed individuals of hypothetical critical groups have been calculated at 40 μSv for the model BWR and more than 100 times lower for PWRs, taking an average over the first 2 km from the site. Reported levels of annual dose equivalent rates to most exposed individuals are generally a few tens of μSv, although one or two plants can give figures of a few hundred μSv [L1, L6].

2. Activation gases

96. The primary interest has been in the release of ^{41}Ar which, because of its short half-life (1.83 h), contributes most of its dose within a few tens of kilometres of the site, although the exact result is clearly highly dependent upon the close-in population density. The normalized release of ^{41}Ar from GCRs between 1975 and 1979 is taken from Table 17 as 3240 TBq [GW(e) a]$^{-1}$ and the associated normalized collective effective dose equivalent commitment from the model site is 0.95 man Sv [GW(e) a]$^{-1}$. Clarke and Wilson [C1] have reported collective doses in the United Kingdom which correspond to values between 0.3 and 1.0 man Gy [GW(e) a]$^{-1}$ and individual dose equivalents of up to a few hundred μSv for early GCRs, depending on the site, all of which are fairly remote. The weighted normalized dose commitment, allowing for GCR nuclear generation as a fraction of all electricity produced over the years 1975–1979, is about 0.1 man Sv [GW(e) a]$^{-1}$. For reasons of convenience, the doses arising from releases of ^{41}Ar from LWRs were included with the doses due to the fission noble gases (paragraphs 87 to 95).

97. The consequences of the release of ^{35}S from GCRs have been studied in some detail by environmental monitoring. The isotope is released in the form of carbonyl sulphide (COS) which has a very low deposition velocity and a slow reaction rate in air. The major route of exposure of the population is through the ingestion of milk; estimates of collective whole-body dose per unit activity released have been

made by Linsley [L7] which yield 2.2 10^{-4} man Gy $(GBq)^{-1}$ for typical United Kingdom conditions. Taking a normalized release rate of 0.17 TBq [GW(e) a]$^{-1}$ thus gives rise to 3.7 10^{-2} man Gy [GW(e) a]$^{-1}$ and the contribution to collective effective dose equivalent commitment weighted by the fraction of nuclear electricity from GCRs is 3.8 10^{-3} man Sv [GW(e) a]$^{-1}$.

3. Tritium

98. The transfer of tritium between the atmosphere and the terrestrial environment is particularly complex because of the hydrogen cycle in biological systems. Tritium released to the environment will make a contribution to the collective dose commitment by becoming globally dispersed and this is considered in chapter V. The assessment of the local and the regional collective doses from atmospheric discharges of tritium is performed slightly differently from the method outlined in the introduction to this Annex.

99. To assess the collective dose, a specific activity model has been assumed for transfer through the terrestrial environment. It is assumed that tritium in man and in the terrestrial environment rapidly achieves equilibrium with the tritium in the atmosphere. The specific activity of tritium taken into the body is equal to that in atmospheric water vapour at the point of interest. The specific activity of tritium in atmospheric water vapour is determined by the atmospheric dispersion to the point of interest and the concentration of water vapour in the atmosphere (8 g m^{-3} annual average value).

100. This specific activity approach assumes that all water taken in by humans, whether by inhalation and absorption through the skin or by ingestion of water or foodstuffs in normal diet, is contaminated at the specific activity appropriate to the point of interest. This is a conservative assumption. It also fails to distinguish any temporal distribution in the dose which may be extended over some considerable time. The dose is, therefore, only assessed on a specific activity model for the period of discharge. The annual intake of water has been obtained from the data given by ICRP in its publication 23 [I5]. The total water intake rate by all routes is assumed to be 3 kg d^{-1} for men and 2.1 kg d^{-1} for women; the respective inhalation and ingestion intake rates have been assessed assuming an annual average concentration of water vapour in air of 8.1 g m^{-3} and a mean adult inhalation rate of 20 m^3 d^{-1}. The intake by inhalation is assumed to be accompanied by an equal intake by skin absorption so that the net annual intakes of H_2O become 130 kg inhaled and 800 kg ingested.

101. The collective whole-body absorbed dose commitment to the local and regional population on this basis is evaluated, assuming normalized atmospheric discharges taken from Table 18 of 3.4 TBq [GW(e) a]$^{-1}$ for BWRs, 7.8 TBq [GW(e) a]$^{-1}$ for PWRs, 11 TBq [GW(e) a]$^{-1}$ for GCRs and 540 TBq [GW(e) a]$^{-1}$ for HWRs. The local and regional collective doses per unit electrical energy generated are shown in Table 32. The ingestion pathway appears to be more important by a factor of about 6 than the inhalation pathway and the collective absorbed doses to all body organs may be regarded to be the same as the collective effective dose equivalent because of the assumption of the models.

102. The collective effective dose commitment varies between 0.04 and 5.6 man Sv [GW(e) a]$^{-1}$. The previous estimation in Annex D of the 1977 report [U1] gave a normalized collective dose commitment of 4 10^{-4} man Gy [GW(e) a]$^{-1}$ for PWRs and a normalized discharge of 7.4 TBq [GW(e) a]$^{-1}$. The reason for the difference in collective dose commitment per unit discharge of a factor of about 200 higher in the present estimate is due to the previous estimate being given only for the local population within 100 km (about 25% of the local and regional collective dose); to the fact that the previous estimation only considered inhalation (about 15% of total intake); and to the greater by a factor of about 4 population density. In summary, the normalized collective effective dose equivalent commitment for atmospheric releases of tritium, weighted by the proportion of electricity generated, is 0.46 man Sv [GW(e) a]$^{-1}$. For the model site taken by the Committee, individual annual effective dose equivalents from LWRs and GCRs are about 10^{-6} Sv, while the HWR model results are about 10^{-4} Sv.

103. For tritium in liquid effluents the model river site (Table 38) gives a collective whole-body dose commitment per unit activity discharged of 8.1 10^{-4} man Gy TBq^{-1} on the assumption that the river is used as a source of drinking water. Using the normalized discharges for 1975–1979 in Table 19 (1.4 TBq [GW(e) a]$^{-1}$ for BWRs, 38 TBq [GW(e) a]$^{-1}$ for PWRs and 350 TBq [GW(e) a]$^{-1}$ for HWRs) leads to collective effective dose equivalent commitments of 1.1 10^{-3} man Gy [GW(e) a]$^{-1}$ for BWRs, 3.1 10^{-2} man Gy [GW(e) a]$^{-1}$ for PWRs and 0.28 man Gy [GW(e) a]$^{-1}$ for HWRs. The models indicate dose commitments 10 times lower for aquatic effluents than for atmospheric effluents per unit release, while the reported release data indicate the atmospheric pathways as the more significant. The contribution to the normalized collective effective dose equivalent commitment from liquid releases of tritium weighted by generation of each reactor type is 0.04 man Sv [GW(e) a]$^{-1}$.

4. Carbon-14

104. The local and regional collective doses due to ^{14}C releases from reactors only represent a small proportion of the total dose commitments. The main significance of ^{14}C is due to its entry into the carbon cycle and resulting global dispersion, leading to long-term irradiation which is considered in chapter V. The assessment of the first pass regional collective dose commitments may be made using the same specific activity approach that was used for tritium in the preceding subsection. For a release to atmosphere the specific activity will be determined by the atmospheric dispersion and the carbon concentration in the atmosphere, taken as 0.16 g m^{-3}. The intake of carbon is assumed to be that given by ICRP in publication 23 [I5], that is, 93 kg a^{-1} by ingestion and 1.2 kg a^{-1} by inhalation, based on the average level of carbon in the atmosphere and assuming a breathing rate of 20 m^3 d^{-1}. As with tritium, it is assumed that all components of the diet are contaminated at the specific activity applicable to the downwind distance of interest from the source.

105. The form of release of carbon-14 is taken to be as CO_2. The collective whole-body absorbed dose commitment, corresponding to the production of 1 GW(e) a, for the model site and discharges of 518 GBq for the model BWR, 222 GBq (PWR), 1100 GBq (GCR) and 17 TBq (HWR) are given in Table 33. The results range from 0.9 to 30 man Gy, and it is clear that the inhalation pathway accounts for little of the dose. The

study of the Nuclear Energy Agency of the OECD [N14] has given a regional collective effective dose equivalent commitment per unit activity associated with the release of ^{14}C of 0.68 man Sv TBq^{-1}. However, the majority of the collective effective dose equivalent commitment from the release will arise from the global contribution. The present estimates must be qualified for two reasons. Firstly, the figures will be overestimates because of the assumption of a specific activity model; and, secondly, the assumption of all components of diet being contaminated at the specific activity corresponding to that point means that the time distribution in the delivery of the dose is ignored. The normalized collective effective dose equivalent commitment, weighted by generation of electric energy, is 2.8 man Sv [GW(e) a]$^{-1}$. For the model site, the annual effective dose equivalents to most exposed individuals would be 2 μSv for the PWR, 5 μSv for the BWR, 10 μSv for the GCR and 200 μSv for the HWR.

5. Iodine

106. Releases of radioactive iodine from nuclear power plants are small and there is only a small contribution to the total local and regional collective dose commitments from reactor discharges. Iodine-129 because of its long half-life enters the global cycle for iodine and potentially irradiates the global population for many millions of years. The release of ^{131}I contributes only to the local and regional collective doses but its assessment is complicated by the chemical form in which the iodine is released, i.e., elemental, organic or particulate. Elemental iodine readily deposits on vegetation and enters the terrestrial foodchains. The deposition rate of organic iodine is between 200 and 100 times less per unit air concentration than that of the elemental form [H3, S9]. The exact value of deposition velocity for a particular circumstance depends upon the size of particles, the reactivity of the vapour, the nature of the underlying surface and the meteorological conditions. In this assessment 75% of the iodine released is assumed to be in organic form and 25% elemental (subsection III.A.5).

107. A representative deposition velocity of 5 10^{-3} m s^{-1} is used here for elemental iodine and is also applicable for particulates with mean aerodynamic diameters of a few micrometres depositing on a wide variety of surfaces. In particular circumstances with defined physico-chemical forms and specific vegetation, more appropriate values would be needed. In fact, elemental iodine becomes absorbed onto aerosols in the atmosphere and its behaviour is then governed by that of the aerosol. For organic iodine a deposition velocity of 5 10^{-5} m s^{-1} has been chosen as typical. These deposition velocities refer to removal from the plume and once the activity is removed, only a certain fraction is found on the surface of the vegetation.

108. Hoffman has shown that care must be taken to distinguish between the total removal from the air, and the fraction intercepted by the vegetation [H4] and that many experiments have been misinterpreted. Considerable variation has been observed in the measured values of interception factors and removal rates from plant surfaces [B6, G8, H4]. An interception fraction of 0.2 is used here as a compromise between the somewhat higher fraction for dry deposition and the lower one for wet deposition. The remaining fraction of the deposit, 0.8, is transferred directly to the ground surface. The removal of the radionuclides from plant surfaces due to the actions of wind and rain and plant growth is taken to occur with a half-life of 14 days for pasture grass [B6] and 30 days for all other plants [G8].

109. Calculations have been performed for iodine releases from the model PWR and BWR reactors into the model environment, using the computer codes developed by Simmonds et al. [S10] which provide a methodology for dealing with the assessment of the intakes of radionuclides by grazing animals and the transfer to human diet. The concentration factor for iodine in root vegetables, pasture and grain is assumed to be 0.02 and the translocation fractions to the edible portions are 0.1 for vegetables and grain [N15, F3].

110. The consumption rate of grass (dry weight) by cows is taken as 5.1 10^3 kg a^{-1}, the half-time in the bovine GI tract is 15 h, the mean-life of milk cows is taken as 6 a, the weight of meat 230 kg and the milk production rate 10 l d^{-1} [S11]. The time integrals of activity in animal products derived from cows grazing on contaminated pasture have been given [C10]. Assuming a unit deposition rate (1 Bq m^{-2} s^{-1}), the time-integrated concentrations of ^{131}I in beef, liver and milk are 4.4 10^4, 4.4 10^4 and 7.5 10^4 Bq a kg^{-1}, respectively.

111. The dosimetric and metabolic data for ^{131}I have been derived from Adams [A1] and ICRP publication 30 [I2]. The model site has production rates of foodstuffs typical of Europe and North-Eastern United States at the typical densities of production. The density of cattle in grazing areas is over 200 km^{-2} and averages out at about 15 km^{-2} over an area of radius 2000 km, similar to the average of values given by Eckerman et al. for the states of New York, Pennsylvania, Washington, Virginia, Illinois and Ohio [E2]. Vegetable production is given as a fraction of land, leading to 2 10^{-2} km^2 per km^2 averaged over the same area. The collective absorbed dose commitments are shown in Tables 34 and 35 for 1975–1979 normalized emissions to atmosphere of iodine: 410 GBq [GW(e) a]$^{-1}$ for BWRs and 5.0 GBq [GW(e) a]$^{-1}$ for PWRs, respectively (Table 21). HWR normalized releases appear to be similar to those for PWRs. The isotopic composition of the iodine released was assumed to be that averaged over United States PWRs and BWRs (Table 22).

112. For PWRs the normalized collective effective dose equivalent commitment is assessed at 6.6 10^{-4} man Sv [GW(e) a]$^{-1}$ and the collective thyroid dose at 2.1 10^{-2} man Gy. The largest component of the collective dose comes from inhalation, with ingestion contributing almost equally; most of the ingestion dose arises from milk. In the case of BWRs the normalized collective effective dose equivalent commitment is 1.9 10^{-2} man Sv [GW(e) a]$^{-1}$ and the normalized collective thyroid dose is 5.9 10^{-1} man Gy [GW(e) a]$^{-1}$. The fractional contributions by the ingestion pathways are smaller than for the PWR. The main route of exposure for ^{133}I and ^{135}I is, as expected, inhalation although these isotopes contribute about 22% to the collective thyroid dose for BWRs and 4% for PWRs. The normalized collective effective dose commitment averaged over the proportions of electricity generated is 6.5 10^{-3} man Sv [GW(e) a]$^{-1}$. Representative annual effective dose equivalents for individuals at about 1 km from the model site are 10 μSv for BWRs and some 30 times lower for PWRs.

6. Particulates in airborne effluents

113. As reported in subsection III.A.6, the quantities of radionuclides in particulate releases are highly variable between reactors of the same type and indeed for the same reactor from year to year. Also, there are several tens of nuclides identified which contribute significantly to the releases. The approach adopted here is to release the normalized discharge rate from PWRs and BWRs and assume that the rate is composed of equal amounts of activity concentration from a range of the nuclides most frequently reported to be present in atmospheric discharges. Again the releases take place from the model facility and the collective dose commitments evaluated via all the pathways. The transfer data for the nuclides in environmental materials have been taken from the work of Ng et al. [N15, N16], Fletcher and Dotson [F3] and Linsley et al. [L3].

114. Much of the external contamination on plants when harvested is removed before consumption by man (e.g., washing or milling of grain). There is recent evidence that 90% of the external contaminant is removed during preparation and processing before consumption by man, based on the observations on values for the transfer of plutonium from the outside surfaces of grain to flour [A2]. Other pathways which need to be considered are the root uptake of radionuclides migrating downwards through the soil, their resuspension from the ground onto plant surfaces, and their translocation from the surfaces of plants to the internal tissues. In addition, account must be taken of the regular removal of radionuclides by harvesting crops. A mean growing period of 100 days is assumed here.

115. The nuclides considered were: ^{51}Cr, ^{54}Mn, ^{59}Fe, ^{58}Co, ^{60}Co, ^{65}Zn, ^{89}Sr, ^{90}Sr, ^{90}Y, ^{95}Zr, ^{95}Nb, ^{124}Sb, ^{134}Cs, ^{136}Cs, ^{137}Cs, ^{140}Ba, ^{140}La, ^{141}Ce, and ^{144}Ce. The normalized total particulate release for PWRs was 2.2 GBq [GW(e) a]$^{-1}$, and that for BWRs was taken as 53 GBq [GW(e) a]$^{-1}$ corresponding to the 1975–1979 averaged discharges for release (Table 23). The resulting collective absorbed dose commitments per unit electrical energy generated are shown in Table 36. For both BWR and PWR the highest collective organ dose commitments are to bone lining cells, although most organs and tissues receive similar doses. In the case of GCRs, the normalized releases and resulting doses are similar to those for PWRs, while those for HWRs are about an order of magnitude lower.

116. For PWR releases the sum of the collective effective dose equivalent commitments by all routes is 0.012 man Sv [GW(e) a]$^{-1}$, most of which arises from the external dose and ingestion from ground deposits of activity. Results for GCR releases are essentially the same. The major contributions to this ground-γ dose are ^{137}Cs and ^{60}Co (80%) most of the remaining dose coming from ^{134}Cs and ^{54}Mn. The dose distribution through all the body organs is similar because it is from penetrating external radiation. Some 95% of the collective effective dose equivalent commitment is received in the first 50 years following ground deposition. The nuclides contributing to the collective effective dose equivalent commitment via grain are ^{90}Sr (30%), ^{134}Cs (30%), ^{137}Cs (30%) and ^{60}Co (5%). For the green and root vegetable routes, 80% of the collective effective dose equivalent commitment arises from ^{90}Sr and the remainder from ^{137}Cs. For beef, the two caesium isotopes and ^{90}Sr contribute equally to the collective effective dose equivalent commitment. In the case of the BWR releases the time distribution of the collective effective dose equivalent commitment is the same as for the PWR and the same isotopes and routes are important; the collective effective dose equivalent commitment is 0.29 man Sv [GW(e) a]$^{-1}$. The normalized result for all reactors thus becomes 0.1 man Sv [GW(e) a]$^{-1}$. Individual annual effective dose equivalents amount to 1 nSv for BWRs at typically 1 km; corresponding values for exposures to PWR releases are 10 times lower.

7. Liquid effluents

117. For releases of radionuclides into fresh water the receiving medium is usually a river or a lake, and the pathways leading to human exposures are drinking water, ingestion of fish, irrigation leading to contamination of foodstuffs, and external irradiation from sediments. For discharges to the marine environment it is usually sufficient to consider the ingestion of foodstuffs, including ocean fish and crustacea. Other pathways exist, such as swimming in contaminated waters and the consumption of unusual foodstuffs, but these contribute little to the collective dose commitments [P1, B7].

118. The collective doses resulting from discharges to the aquatic environment are more difficult to estimate using generalized models than are those from atmospheric releases. This is because the local dispersion from the discharge point is very dependent upon particular site characteristics, such as sedimentation and water volume flow patterns. The collective dose from a reactor discharge is, therefore, highly variable depending upon how much activity is transferred to the areas where foodstuffs are significantly harvested. Site-specific assessments have identified the critical pathways to man and estimated doses to critical groups for reactor liquid discharges. The reported annual doses to the critical group are estimated to be in general less than 5 μGy [H5, M4, B7, M10, W3].

119. Mitchell suggests that the annual collective dose to the United Kingdom from radioactive liquid effluents into the sea had come into equilibrium in 1976 [M5]. On this basis the collective whole-body absorbed dose to the United Kingdom population in 1976 resulting from the discharge of about 8 TBq of ^{137}Cs each year from all the coastal nuclear stations during the period 1974–1976 can be estimated at about 0.2 man Gy. Hetherington has estimated [H5] that the collective whole-body dose per unit discharge to the population of Europe is 0.16 man Gy TBq^{-1} at equilibrium for a continuous discharge of ^{137}Cs. This leads to an estimate of 1.0 man Gy as the collective absorbed whole-body dose to the United Kingdom and Europe for 1979 total ^{137}Cs discharges from United Kingdom reactor liquid effluents and corresponds to 0.24 man Gy [GW(e) a]$^{-1}$.

120. The Committee, in Annex D of the 1977 report [U1], discussed the difficulty of assigning values to parameters in assessing liquid effluents, in particular, the water utilization rate and flow rates for rivers, the fish production rates and sedimentation rates. Any assessment of a given site must, therefore, utilize site-dependent values of parameters and even models developed specifically to model the movements of activity in the local aquatic environment. Generalized models for a river and a typical marine environment have been described in Annex A and these models are

now applied to a model site either discharging into a river or into local coastal waters.

121. For the present assessment, the site environmental characteristics are chosen to be representative of the receiving media in northern Europe and the northern states of the United States and do not refer to any one particular site. The results are intended to be indicative of the collective dose commitments per unit of electricity generated by nuclear power stations and, therefore, the collective dose per unit discharge should not be combined with the discharges reported for a specific site in an attempt to estimate the collective dose commitment from that site.

122. The 1975–1979 normalized releases for PWRs, BWRs and GCRs given in Table 24 with the isotopic composition shown in Tables 25 and 26 are used as source terms for the model sites and shown in Table 37. Only those nuclides which contribute significantly to the collective dose from each installation are shown. Also shown in Table 37 are the concentration factors assumed for the freshwater and marine environments. The concentration factor is the quotient of the activity per unit weight of the animal considered (fish, crustacea, etc.) and the activity per unit volume of filtered water [Bq t^{-1}/(Bq m^{-3})]. The factors are based on dry weight of sediments and wet weight of the edible fraction of other materials. The marine concentration factors are taken from Ancellin et al. [A3] and the International Atomic Energy Agency work on models for use in sea dumping of radioactive wastes [I6].

123. The freshwater concentration factors for fish were taken from Thompson et al. [T3] and those for sediments from Booth's model [B8]. The quantities of fresh water extracted from the model river site for drinking purposes have been estimated assuming that populations bordering the river take their water at a rate per individual of 1.5 10^{-8} m^3 s^{-1}, given for a study of the Rhine-Meuse region by Bayer [B9]. The model river has three sections below the point of discharge and the relevant model data are given in Table 38.

124. Values in Table 38 are selected to be representative values and many vary by several orders of magnitude in both directions for any given site. Nevertheless they are deemed to reflect the situation averaged over several countries [B9]. The population along the sides of the river is assumed to be 20 km^{-1} for the purpose of calculating external exposure from sediments. This population is assumed to spend 200 h a^{-1} on average on the river bank [B9]. The doses per unit activity ingested were again consistent with Adams [A1] and ICRP publication 30 [I2].

125. The collective absorbed dose commitments for normalized releases to the freshwater receiving medium, the model river, are shown in Table 39 for PWR and BWR systems. The total normalized collective effective dose equivalent commitment for the BWR is estimated at 2.8 10^{-3} man Sv [GW(e) a]$^{-1}$; two-thirds of this dose comes from drinking water and one-third from fish consumption. For drinking water 20% of the collective effective dose equivalent commitment is from ^{131}I and nearly all the dose from ingestion arises from caesium isotopes. For the PWR the total normalized collective effective dose equivalent commitment is 1.0 10^{-3} man Sv [GW(e) a]$^{-1}$ with drinking water giving 78% of the total. The contribution from drinking water is given almost equally by ^{131}I, ^{60}Co, ^{134}Cs and ^{137}Cs. For ingestion, the caesium isotopes give more than two-thirds of the total normalized collective effective dose equivalent commitment. The normalized collective effective dose equivalent commitment, weighted for electricity generated, is 1.4 10^{-3} man Sv [GW(e) a]$^{-1}$.

126. For releases to salt water it is necessary to consider the dispersion close to the site where the effects of sedimentation may lead to a reduction in the activities which become available for dispersion on a regional scale. Using the local marine model described in Annex A, the values of parameters adopted for the model site are as follows: volume, 2 km^3; water depth, 15 m; rate of sedimentation, 100 g m^{-2} a^{-1}; suspended sediment load, 5 g m^{-3}; rate of renewal of water in the compartment, 50 a^{-1}. These values have been taken as typical of a coastal marine site from the data detailed by Booth et al. [B7] and the study for the Commission of the European Communities by the National Radiological Protection Board of the United Kingdom jointly with the Commissariat à l'Energie Atomique of France [C10]. In general, from 50% to 90% of the activity released to the local marine environment becomes available for the regional dispersal.

127. In the regional dispersal model the sedimentation rates in coastal waters on the continental shelf vary in the range of about 10 to 100 g m^{-2} a^{-1} [A3, I6] and the suspended sediment loads are of the order of 0.1 to 6 g m^{-3} [A3, I6, C10], with the lower values applying to the ocean compartments. At any given time the activity in the water column is partitioned between the water phase and the suspended sediment material. The fraction of activity remaining in solution will be high for elements such as caesium which do not concentrate on sediments, but for other nuclides such as ruthenium or plutonium the fraction remaining in the water phase can be reduced by a factor of 10 for suspended sediment loads approaching 100 g m^{-3} [H6].

128. Fish-catch data and production of other marine foodstuffs vary greatly from location to location. Reported landings of fish have been obtained from the Conseil International pour l'Exploitation de la Mer [C3]. Typical values from the Baltic Sea are 4.6 10^5 t a^{-1} and the North Sea catch is 2 10^6 t a^{-1}, while some 3 10^5 t a^{-1} are taken from the Arctic ocean. Catches of molluscs and crustacea vary in the range of 8 10^3 t a^{-1} for the Baltic and perhaps 2 10^5 t a^{-1} for the Bay of Biscay and the southern North Sea.

129. Using the normalized discharge rates given in Table 37, the collective effective dose equivalent commitments from the notional BWR, PWR and GCR on the model coastal site have been computed using the regional marine model prepared for the Commission of the European Communities [C10, C8]. The notional release was into the receiving waters of the eastern English Channel. This area is representative of many sites both in Europe and North America.

130. The resulting collective absorbed dose commitments are shown in Table 40. The dose per unit intake was again derived from the ICRP 30 models and metabolic data [I2] and the results presented by Adams which uses the same basic data [A1]. The collective doses were estimated by taking the time integrals of the activity in the filtrate fraction of the water in each compartment and multiplying by the concentration factors already listed for the marine environment in Table 37. The edible fraction of the marine foodstuffs has been taken as 50% for fish, crustacea and molluscs [C10].

131. A large proportion of the collective dose commitment for GCRs arises from isotopes of caesium. The radionuclide releases from the gas-cooled reactors are higher because they are essentially all coastal sited, whereas the normalized discharge figures for LWRs are based largely on inland siting experience. The collective effective dose equivalent commitment for gas-cooled reactors is 0.18 man Sv [GW(e) a]$^{-1}$ which can be compared with the estimate by Hetherington [H5] of 0.24 man Sv [GW(e) a]$^{-1}$. For BWRs the corresponding collective effective dose equivalent commitment is 4.2 10^{-2} man Sv [GW(e) a]$^{-1}$, mainly coming from ^{65}Zn in molluscs, and the remainder from fish, with the largest contributions from caesium and ^{65}Zn. The collective effective dose equivalent commitment for PWRs is 6.0 10^{-3} man Sv [GW(e) a]$^{-1}$, about one-third coming from caesium in fish and many of the isotopes contributing to the mollusc component. The normalized collective effective dose equivalent commitment, weighted by electricity production of each reactor type is 3.5 10^{-2} man Sv [GW(e) a]$^{-1}$ for marine discharges.

132. The collective effective dose equivalent commitment from caesium isotopes is not very dependent upon the location at which they enter northern European waters, the variation for unit discharge being between 150 Bq (integrated intake) for releases into the eastern Irish Sea, 130 Bq for the English Channel (east), 120 Bq for the southern North Sea and 27 Bq for a release into the Bay of Biscay. These results are per unit release into the relevant regional compartment from the local model. The results obtained may certainly be taken as typical of Europe and the collective effective dose equivalent commitment is essentially all delivered over the first few years after discharge.

133. Again it must be emphasized that the figures given in Tables 39 and 40 are representative of the generation of unit quantity of electricity and should not be applied to a specific site where particular environmental pathways exist which have not been considered here and might lead to significant changes of the collective dose contributions. The normalized collective effective dose equivalent commitment due to aquatic discharges has been estimated on the assumption that half the discharges are to freshwater and half to marine environments. The result amounts to about 0.02 man Sv [GW(e) a]$^{-1}$.

C. REACTOR ACCIDENTS

Collective dose commitments due to releases of radioactive materials in accidents

134. There have only been two reactor accidents which are known to have caused measurable irradiation of the public: Three Mile Island in March 1979 and the Windscale reactor accident in October 1957. The latter accident was at a military reactor, but the collective dose commitments have been included here on the grounds that the reactor contributed partly to the development of gas-cooled civil reactors.

135. It is impossible, on the basis of these two accidents, to retrospectively calculate a component of the collective dose commitments due to accidents involving public exposure from nuclear power. The Committee has decided that the probabilistic approaches, which predict the risk of reactor programmes by extrapolating into the future, while useful for other purposes, should not be used as a basis for estimating any speculative future component of collective dose commitment. Contributions from accidents to occupational exposures are dealt with in Annex H.

136. The accident at Three Mile Island has been the subject of many reports, particularly from the United States Nuclear Regulatory Commission and the President's Commission [K9]. The basic form of the accident was very simple, but the details were extremely complicated. The pumps providing feed water to the boilers stopped and the safety system shut down the turbine. A relief valve in the reactor primary cooling circuit opened correctly and the reactor was shut down automatically. A second fault was the failure of the relief valve to close when the reactor primary circuit pressure fell, while the control room instrumentation indicated closure. As the primary circuit pressure fell, high pressure emergency core cooling was automatically injected into the circuit but this flow was stopped by the operators in the mistaken belief that the reactor was too full of water. This action was caused by instrument readings correctly showing high water levels in part of the system, although it was caused by water being forced out of the core by the generation of steam. At this point severe damage to the fuel elements occurred.

137. Steam and fission products released from the damaged fuel are now thought to have left the reactor by a relief valve in the primary water makeup system which was kept running to maintain the boron concentration. The condensed water was retained in the containment building. This building is designed to seal automatically in the event of a pressure rise, but none occurred and it took four hours before the building was sealed. During this time fission product gases escaped to the atmosphere, and gave rise to irradiation of the public. Further releases took place later when contaminated waste water was discharged from the containment building. Most fission products were retained in the water but a release of about 370 PBq of noble gases, mainly ^{133}Xe, and some 550 GBq of ^{131}I were released to the atmosphere.

138. The accident released large amounts of activity from failed fuel in the core but the environmental releases and the resulting exposure of the public was small. The collective whole-body dose commitment was mainly due to the ^{133}Xe release and has been estimated at between 16 and 35 man Gy within 50 miles [B19]. The corresponding mean value and the value given in the Kemeney report [K9] is 20 man Gy. Individual levels of dose averaged 1.5 10^{-5} Gy within 50 miles of the plant and the maximum absorbed dose which any number of the public could have received has been estimated at 85 10^{-5} Gy [K9] from external gamma-irradiation. The contribution to the collective whole-body dose commitment due to ^{133}Xe dispersion beyond 50 miles can be estimated roughly from the results in Table 29 for the model PWR, where ^{133}Xe dominates the release. Over all distances the whole-body dose commitment might be expected to be twice that within 50 miles.

139. In the 1957 Windscale reactor fire, the accident began during a routine release of the Wigner Energy stored in the graphite (a phenomenon caused in low temperature graphite by neutron bombardment, leading to the creation of interstitials and the stressing of the moderator). Due to errors in operation, the fuel became overheated and, in the once-through air cooled system,

caught fire. The fire lasted for about three days and major releases of iodine occurred on two occasions; once when air flow was started through to core in an attempt to cool it, and secondly when water was pumped into the reactor which finally extinguished the fire. The Windscale reactor has never been utilized since.

140. A theoretical re-analysis of the Windscale accident has been given by Clarke [C6] who estimated the activities released and dosimetric consequences out to 50–100 km. Extensive environmental measurements were undertaken at the time of the accident, which can be used to evaluate the collective doses. Individual doses were re-examined by Baverstock and Vennart [B20]. The release of ^{131}I has been estimated at some 740 TBq accompanied by 44 TBq ^{137}Cs, 12 TBq ^{106}Ru and 1.2 PBq of ^{133}Xe. Collective dose estimates were not made at the time, but measurements of activity in the thyroids of adult individuals in Leeds and London indicated thyroid dose commitments of 10^{-3} and $4\ 10^{-4}$ Gy, respectively [B20], with young children receiving doses of twice this value. Maximum doses to local individuals close to the site were estimated to be of the order of 10^{-2} Gy to the thyroid of adults and perhaps 10^{-1} Gy to children's thyroids [C6, L10].

141. The contamination of pasture land was widespread, the majority of the released activity passing south-south-east from Windscale, passing directly towards London, and eventually passing over Belgium before turning northwards to Norway. In a new evaluation of the accident to assess the collective doses the principal route for irradiation was shown to be iodine in milk [C9]. Although other nuclides did not deposit as readily on pasture they have been shown to contribute significantly to the collective dose. The estimate given by Crick et al. [C9] for the collective thyroid dose commitment is $1.8\ 10^4$ man Gy of which about 25% was derived from inhalation and 75% from ingestion. The corresponding collective effective dose equivalent commitment is $6\ 10^2$ man Sv. The collective effective dose equivalent commitment from all isotopes and pathways was estimated to have been $1.3\ 10^3$ man Sv, of which somewhat less than 50% was due to iodine isotopes and thyroid irradiation. External irradiation from ground deposits of activity was estimated to contribute another 40%, while the remaining 10% arose mainly from ingestion of foodstuffs contaminated by nuclides other than iodine [C8].

IV. FUEL REPROCESSING

142. At the fuel reprocessing stage of the nuclear fuel cycle the elements uranium and plutonium in the irradiated nuclear fuel are recovered for use again in fission reactors. The spent fuel elements are stored under water (which serves both for radiation shielding and for cooling) while waiting for reprocessing. Fuel elements are usually left until all the short-lived isotope ^{131}I has decayed to insignificant amounts (usually at least 120 days). One reprocessing plant can serve a whole nuclear reactor programme, so that the quantities of the nuclides significant from the health point of view which pass through the plant will be rather high in absolute terms, but may be small per unit of electrical energy generated. When the fuel elements are reprocessed the irradiated fuel is first taken out from its canning material and then dissolved in nitric acid. This is known as the head-end process.

143. A solvent extraction process is next used for the separation of uranium and plutonium from the fission products, and the remaining transuranic elements. Nearly all reprocessing facilities employ the PUREX process which uses the organic complexing compound tributyl phosphate to extract both the uranium and the plutonium into the organic phase. The uranium and plutonium can be separately recovered from the organic phase using nitric acid. The resulting nitrates are further purified and then converted to oxides suitable for storage until they are refabricated into fuel elements.

144. The only reprocessing plants operating commercially in the world are at Windscale (United Kingdom), La Hague and Marcoule (France). In addition, there are several small experimental reprocessing facilities, such as the one at Karlsruhe in the Federal Republic of Germany. The capacity of the Windscale plant is $2\ 10^3$ t a^{-1} and that of La Hague is 900 t a^{-1} for GCR fuel and 400 t a^{-1} LWR fuel. The capacity of the La Hague plant for LWR is thought likely to increase to 800 t a^{-1} in 1983/84, when essentially all the French GCR fuel will be reprocessed at Marcoule, except for some 150 t a^{-1} which will be used at La Hague to dilute the fast reactor fuel from Phenix when it is reprocessed at La Hague [L1]. The assessment performed here considers first the commercial reprocessing plants and then establishes a model facility for representative calculations of collective and individual dose assessment.

A. EFFLUENTS

145. The design and operation of reprocessing plants to avoid releases of large amounts of radionuclides is complex. The gaseous and volatile fission products (I, ^3H, C, Kr, Xe, Ru, Tc and Cs) are largely separated from the fuel solution at the dissolution stage. The dissolver off-gas is treated for nitric acid recovery and for iodine removal before being blended with the other off-gases from other vessels in the process. The vessel off-gas is usually treated by caustic scrubbing, drying and filtering through high efficiency filters before discharge from a tall stack. The aqueous wastes, containing almost all the fission products and transuranium elements are concentrated by evaporation and stored in double-containment stainless steel tanks to await further treatment before disposal.

146. The radionuclides of principal concern in reprocessing plants effluents are primarily the long-lived nuclides, ^3H, ^{14}C, ^{85}Kr, ^{90}Sr, ^{106}Ru, ^{129}I, ^{134}Cs, ^{137}Cs and isotopes of transuranium elements. There have been many publications on the releases, environmental pathway analysis and dosimetric consequences of reprocessing plant effluents [B2, B10, B11, K2, N17, P5, P6, V2]. Many other papers are to be found dealing with the specific nuclides of interest, particularly ^3H, ^{14}C, ^{85}Kr and ^{129}I, which have also been the subject of a special study group sponsored by the Nuclear Energy Agency of the OECD [N14].

147. In Tables 41 and 42 the annual discharges for Windscale, La Hague and Marcoule are presented for atmospheric and liquid effluent discharges, respectively. The amount of activity in effluents depends not only upon the specific waste treatment and processing systems of the reprocessing plant, but also on the type of fuel reprocessed, its irradiation history and storage (cooling) time. The discharges of liquid effluents from Marcoule are controlled to lower amounts of radio-

nuclides than from the other two sites because Marcoule discharges into a river, the Rhone, which flows into the Mediterranean Sea. The other two sites are coastal and discharge to the sea. The sources of data for the discharges were Luykx [L1, L6] and British Nuclear Fuels [B2, B22]. For the liquid discharges from Windscale an isotopic breakdown of the discharge in successive years is given in Table 43.

148. The throughput of fuel at each reprocessing plant has been calculated on the basis of its reported ^{85}Kr discharges and the Committee's estimate of the ^{85}Kr content of fuels from different reactor types as given in the following paragraphs. These figures imply that at Windscale the throughput of fuel in 1978 corresponded to less than 2 GW(e) a and the ^{85}Kr discharges have fallen from the levels in previous years. The figures for 1979 imply an increase in fuel throughput; however the corresponding amounts of electricity generated by nuclear power stations do not agree with reported electrical energy production in the United Kingdom [C4]. The implication is that there is a time lag in reprocessing fuel and that there is a growing backlog of fuel committed for reprocessing.

1. Krypton-85

149. Krypton-85 is the only noble gas of interest released from reprocessing plants. It is essentially always totally released from the fuel at the dissolution stage and, consequently, knowledge of the ^{85}Kr discharge from a plant can be used to assess the throughput of fuel. The production of ^{85}Kr per unit energy generated in typical reactor fuels have been taken from White [W4] as 4.1 PBq [GW(th) a]$^{-1}$ for GCRs and 3.6 PBq [GW(th) a]$^{-1}$ for LWRs, on the basis of 3.5 GW d t^{-1} and 33 GW d t^{-1} fuel burnups. Assuming the average thermal efficiency of a GCR is 30% and that of the LWRs is 31% leads to an inventory of 14 PBq [GW(e) a]$^{-1}$ for GCRs and 11.5 PBq [GW(e) a]$^{-1}$ for PWRs. Bernero et al. [B10] have estimated for reprocessing fuel from LWRs in the United States that 45 GW(e) a generates 520 PBq of ^{85}Kr to be released to the atmosphere, corresponding to 11.5 PBq [GW(e) a]$^{-1}$ which is similar to the value derived here.

2. Tritium

150. It was estimated in paragraph 60 that the normalized production of tritium in LWR fuel totalled some 0.75 PBq [GW(e) a]$^{-1}$. Using these figures for GCR fuel, the total tritium inventory passing through Windscale in 1979 was about 1.9 PBq. In Table 42 it is seen that for the same year liquid effluent discharges totalled 1.2 PBq, while Table 1 indicates that 0.29 PBq were released to atmosphere. Thus, most of the tritium in the fuel appears in the effluent streams during reprocessing and perhaps about 20% is emitted to atmosphere. A recent retrospective study on the WAK reprocessing plant in the Federal Republic of Germany reveals that 2% of the tritium in LWR fuel is released to atmosphere [H7]. Releases of tritium to atmosphere per unit of electrical energy generated, averaged between 1975 and 1979, are 3.2 TBq [GW(e) a]$^{-1}$ (La Hague) 46 TBq [GW(e) a]$^{-1}$ (Marcoule) and 133 TBq [GW(e) a]$^{-1}$ (Windscale).

151. A portion of the tritium in LWR zircaloy clad fuel elements is immobilized as a solid zirconium compound. This has been estimated to account for 15% of tritium production [K5]. An analysis by Luykx and Fraser for European reprocessing plants [L1] indicated that for 1973–1974 at Eurochemic (Belgium, no reprocessing since 1974) tritium discharges were 0.48 PBq [GW(e) a]$^{-1}$, which corresponds to about 65% of the Committee's estimated throughput; 26% of this was to atmosphere. For the WAK Karlsruhe plant in the Federal Republic of Germany (1973–1976) the discharges were 0.44 PBq [GW(e) a]$^{-1}$, 60% of throughput, with 3% being discharged to atmosphere.

3. Carbon-14

152. Routine measurements of discharges of ^{14}C from the Windscale reprocessing plants are now available and reported in Table 41 [B22]. Schuettelkopf and Herrmann [S8] have reported that for a 2-year period, when PWR and BWR fuel was being reprocessed at Karlsruhe, normalized atmospheric discharges of ^{14}C in the form $^{14}CO_2$ were at a level of between 0.46 and 0.51 TBq [GW(e) a]$^{-1}$. The ^{14}C content of such fuels is taken as 0.66 TBq [GW(e) a]$^{-1}$ based on the results of Kelly [K2], assuming a thermal efficiency of 31% at the reactor, so that about 75% of the inventory was released to atmosphere. The ^{14}C levels in fuel are highly sensitive to nitrogen impurity levels in fuel.

153. For GCRs a normalized production rate within the fuel of 0.96 TBq [GW(th) a]$^{-1}$ is assumed [K2], and taking a reactor efficiency of 30% leads to a normalized production rate of 3.2 TBq [GW(e) a]$^{-1}$. The potential discharges from GCRs fuel are greater than those for the quantity of LWR fuel for the same electricity production. The throughput of ^{14}C at Windscale in 1979 can be assumed to be about 8 TBq on this basis and from Table 41 it can be seen that the reported atmospheric release was 3.5 TBq, i.e., 44% of throughput.

4. Iodine

154. The ^{131}I content of irradiated nuclear fuel varies depending upon the cooling time and the final power rating of the fuel before discharge. The ^{131}I normalized content of LWR fuel cooled to 180 days is estimated to be 2.8 TBq [GW(e) a]$^{-1}$, falling to 1.4 GBq [GW(e) a]$^{-1}$ at 270 days and to 550 kBq [GW(e) a]$^{-1}$ at 1 year. For ^{129}I the arisings depend on burnup and are assessed to be between 37 GBq and 74 GBq [GW(e) a]$^{-1}$. Since fuel is generally cooled to about a year before reprocessing, ^{131}I discharges are generally extremely small. For 1975–1978 at Windscale atmospheric releases of ^{131}I were averaging 1.7 GBq [GW(e) a]$^{-1}$, while La Hague averaged 32 GBq [GW(e) a]$^{-1}$ and Marcoule 144 GBq [GW(e) a]$^{-1}$.

155. Atmospheric discharges of ^{129}I are now reported for Windscale and average 2.2 GBq [GW(e) a]$^{-1}$. Discharge data for the WAK reprocessing plant in the Federal Republic of Germany indicate that in 1975–1976 the ^{129}I normalized releases averaged 11 and 0.4 GBq [GW(e) a]$^{-1}$, representing 25% and 1% of the ^{129}I throughput in fuel [B12]. The reduction in 1976 resulted from the installation of a new filtration system for the dissolver off-gases. In a series of measurements from November 1975 to August 1977 the average value for the components of ^{129}I discharges were reported as 74% inorganic, 23% organic, 2% aerosol [B12]. These averages conceal a wide variation composition, the

inorganic form having a range of 21–97%, organic 2–54% and elemental 0.04–14%. Annual liquid discharges of ^{129}I from Windscale are about 0.1 TBq, corresponding to about 40 GBq [GW(e) a]$^{-1}$.

5. Radioactive aerosols

156. In Table 41 figures are given for total α activity discharged to atmosphere. Although a wide variety of α-emitting nuclides are present, United States experience of a particular plant there suggests that the majority of the α activity will be from plutonium isotopes [F4]. Windscale reports [B2] that in 1978 of the activity associated with the α-emitting radionuclides released, 71% was from plutonium isotopes and the remainder was from ^{241}Am and ^{242}Cm. The percentage isotopic composition of the plutonium α emitters will roughly be as follows:

	^{238}Pu	^{239}Pu	^{240}Pu	^{242}Pu
GCR	16	44	40	0.1
LWR	78	9	13	0.04

The normalized release rate for α aerosols from Windscale in 1979 was 0.4 GBq [GW(e) a]$^{-1}$.

157. The beta aerosol results are also given in Table 41, the largest component at Windscale being ^{137}Cs discharges in aerosols. In addition, ^{90}Sr is separately identified, the remaining activity comprising the following nuclides: $^{95}Zr/Nb$, ^{106}Ru, ^{125}Sb, ^{134}Cs, ^{144}Ce. The discharges of ^{137}Cs and ^{90}Sr have been substantially higher since 1974 compared with previous years, reflecting higher discharges from the solid waste site used primarily for the storage of Magnox fuel cladding and these discharges are expected to be reduced in the near future [L4]. Of these discharges about half are released from high stacks. Approximately 50% of the ^{137}Cs and ^{90}Sr discharges took place from stacks of height less than 46 m [H8] and are associated with high active silos and cooling pond water. Site discharges of α activity to atmosphere mainly arise from the research and development laboratories and from the plutonium recovery plant [L4].

6. Liquid effluents

158. The liquid effluents discharged from Windscale, La Hague and Marcoule are shown in Table 42 for total α, total β and the releases of tritium, ^{90}Sr and ^{106}Ru. A wide range of nuclides appears in waste streams and the isotopic composition of Windscale liquid effluent discharges for 1977, 1978 and 1979 are shown in Table 43. The α-isotopic composition in Windscale liquid effluents largely reflects the isotopic composition of GCR fuel [H9]. Americium-241 has also contributed significantly to Windscale releases, although the percentage has been decreasing from over 50% of the total α-discharges in 1972 to about 10% of this value since 1977; this reduction is due to more efficient removal of ^{241}Am from waste streams prior to discharge [W5]. The normalized release rate of α activity from Windscale into liquid effluents is currently 25 TBq [GW(e)a]$^{-1}$, and the figures for Marcoule and La Hague are 0.016 and 0.24 TBq [GW(e) a]$^{-1}$, respectively. The Marcoule discharges are to the river Rhone.

159. The liquid discharges of β activity shown in Table 42 give normalized release rates of 3.7, 0.52 and 0.04 PBq [GW(e) a]$^{-1}$ for Windscale, La Hague and Marcoule, respectively, in 1978. The isotopic composition of the release varies between La Hague and Windscale. In liquid effluents from La Hague up to 1976, 65% of the total β activity concentration was from ^{106}Ru with 13% from ^{137}Cs, 12% from ^{144}Ce and 7.6% from ^{90}Sr. The isotopic composition for Windscale is 63% ^{137}Cs and ^{134}Cs, 11% ^{106}Ru, 8.3% ^{90}Sr, the remainder being composed of a number of nuclides. The Windscale caesium discharges which began to rise in 1974 are not due to reprocessing as such but are the result of the corrosion of Magnox fuel cans by water in the storage pond. Corrective action has now been undertaken to reduce the discharge levels by the use of ion exchange resins in the effluent treatment plant. The result has been that in 1979 the liquid effluent discharge was reduced to 1.6 PBq [GW(e) a]$^{-1}$.

B. LOCAL AND REGIONAL COLLECTIVE DOSE COMMITMENTS

160. The evaluation of the collective dose commitments from reprocessing nuclear fuel requires a study both of the local and regional effects and of the global consequences of the releases. Estimates of the local and regional contribution to collective dose commitments are given here and the global contribution in chapter V. Monitoring of the local environment and regional distribution of activity from Windscale is extensive and widely reported in annual reports [B2, B22, H5, M4, M5] and in the open literature [H8, H9, P5, P6, W5]. Studies on the fate of liquid effluents from La Hague have also recently been published [V2]. In this section the collective absorbed dose commitments are evaluated for normalized discharges from Windscale and La Hague. However, since there are only three known operating commercial reprocessing plants, their contributions of collective dose per unit of electrical energy generated may not be representative of that which will be made by other installations when they commence processing irradiated fuel. Therefore a summary of collective dose commitments is given for typical discharge figures quoted for new designs of reprocessing plant. The characteristics of the population data and meteorological conditions used for the model plant are those applicable to the Windscale site in the United Kingdom and are shown in Table 44.

1. Krypton-85

161. The assessment of the averaged ^{85}Kr discharges from Windscale between 1975 and 1979 has been performed using the methodology provided for the Commission of the European Communities [C10]. The average annual release of ^{85}Kr was 35 PBq and the resulting collective absorbed dose commitments are shown in the summary Table 46. The collective effective dose equivalent commitment is estimated to be 0.074 man Gy from the cloud γ-irradiation, using the dose conversion factors of Poston and Snyder [P4]. A further contribution from the cloud-β irradiation amounts to 19 man Sv collective absorbed dose in skin, which contributes 0.19 man Sv to the collective effective dose equivalent commitment. The normalized local and regional collective effective dose equivalent commitment for the ^{85}Kr annual discharge from Windscale averaged from 1975 to 1979 is 0.1 man Sv [GW(e) a]$^{-1}$.

2. Tritium and carbon-14

162. In this case a specific activity model is used as described in paragraphs 99 and 100. The average

annual release of tritium to atmosphere from Windscale between 1975 and 1979 was 0.33 PBq, or 0.13 PBq [GW(e) a]$^{-1}$. The associated normalized collective dose commitments are shown in Table 45. The specific activity model chosen with the dosimetric results of Adams [A1] suggests that the individual organ doses (thyroid, gonad, etc.) expressed in gray are essentially the same as the effective dose equivalent expressed in sievert. The normalized release of ^{3}H to atmosphere leads to a local and regional collective effective dose equivalent commitment of 0.35 man Sv [GW(e) a]$^{-1}$. Releases to the regional marine environment lead to lower dose commitments: the normalized tritium release from Windscale in the period 1975–1979 was 0.45 PBq [GW(e) a]$^{-1}$ (Table 42) leading to a collective effective dose equivalent commitment of about 8 10^{-4} man Sv [GW(e) a]$^{-1}$, using the distributions of marine foodstuffs, water movements and sedimentation rates taken from chapter III.

163. For ^{14}C atmospheric releases the normalized collective effective dose equivalent commitment in the local and regional population is 0.69 man Sv [GW(e) a]$^{-1}$ for the population distribution within 2000 km of the Windscale site. The average annual throughput of fuel at Windscale from 1975 to 1979 corresponds to 2.6 GW(e) a, leading to a collective effective dose equivalent commitment per year of release of 1.8 man Sv. If the same discharge took place to the marine environment the regional model suggests the integrated activity found in foodstuffs would be 2.5 10^{-4} Bq a per Bq discharged. Thus the same annual release in the marine environment would lead to 2.7 man Sv, essentially the same figure as for the release to atmosphere.

3. Other atmospheric releases

164. Of the other nuclides released to the atmosphere, apart from ^{129}I which makes a significant contribution to the global collective dose commitment because of its long half-life (1.6 10^{7} a) and is considered in detail in chapter V, the remainder contribute only to the local and regional dose commitment. Again, the spatial patterns of population distribution and of agricultural production applicable to the United Kingdom and Europe were taken from Simmonds and Linsley [S12] and the study undertaken for the Commission of the European Communities [C10]. The release rates of the various isotopes discharged to atmosphere from Windscale given in Table 41 were used and the resulting collective dose commitments for those nuclides contributing are shown in Table 46. The total collective effective dose equivalent commitment comes to 6.2 man Sv as a result of one year of average atmospheric discharges between 1975 and 1979. The result is dominated by the collective effective dose equivalent commitment from ingestion (4.4 man Sv). Of the remainder, 1 man Sv arises from ground deposition (^{137}Cs), 0.48 man Sv from inhalation (^{3}H, ^{239}Pu, ^{240}Pu, ^{241}Am) and 0.26 man Sv from ^{85}Kr doses in the local and regional population.

4. Liquid effluents

165. In Table 47 the collective absorbed dose commitments are presented for releases of the nuclides in liquid effluents from both the Windscale and La Hague sites averaged from 1975 to 1979. The dose commitments include doses from the consumption of all marine foodstuffs from the areas of northern European waters, as described in Annex A and paragraphs 126–128. The releases occur to a local marine model and then subsequently into the regional model. The experimental evidence strongly suggests that a large proportion of the plutonium discharges into the eastern Irish Sea is rapidly fixed on to sediments in the local dispersion and only a small fraction is available for transfer into the regional waters. The large suspended sediment load in the Irish Sea accounts for the considerable difference in plutonium dose commitments per unit discharge between the Channel site and the eastern Irish Sea site.

166. In Table 47 the annual average releases from Windscale and La Hague from 1975 to 1979 have also been used with the Committee's models to obtain collective effective dose equivalent commitments. For Windscale the result is 311 man Sv of which 90% is due to ^{137}Cs discharges and the remainder nearly all due to ^{106}Ru. The normalized collective dose commitment is thus 124 man Sv [GW(e) a]$^{-1}$. For the La Hague discharges the collective effective dose equivalent commitment is 84 man Sv with 86% due to ^{106}Ru and the remainder due to ^{137}Cs discharges. The normalized collective dose commitment for La Hague is 53 man Sv [GW(e) a]$^{-1}$, although this is probably an overestimate because of the assumptions in the models used. The normalized results for La Hague and Windscale are seen to be similar. From Table 43 it is seen that in 1979 the releases of caesium and ruthenium from Windscale to the marine environment were half those in 1978, so that the collective effective dose equivalent commitment will be reduced to 62 man Sv [GW(e) a]$^{-1}$. Annual effective dose equivalents to most exposed individuals near Windscale were probably less than 0.5 mSv from 1979 discharges of ^{137}Cs.

5. Atmospheric and liquid effluents from a notional plant

167. There are significant uncertainties in predicting dose commitments over the long periods of time during which the long-lived isotopes may be available in the environment. Furthermore, the collective dose commitments derived from present day releases from Windscale and La Hague are probably not representative of future reprocessing practices if all LWR fuel currently stored were reprocessed. Notional reprocessing plant designs exist, some of which are sited inland, with very low discharges to the aquatic environment. Consideration is also being given to retention of ^{85}Kr, ^{3}H, ^{14}C and ^{129}I, nuclides which are currently released into the atmosphere. In order to obtain a more representative set of collective dose commitments, a model oxide fuel reprocessing facility is assumed which discharges into a marine environment. The discharges are based on the implied discharges of the British Nuclear Fuels Ltd. thermal oxide reprocessing plant (THORP) as reported at the Windscale Inquiry [P8]. Table 48 gives a summary of the notional discharges per unit energy generated for the model facility assuming a fuel throughput equivalent to 40 GW(e) power and the associated collective effective dose equivalent commitments. It has been assumed that there is no retention of ^{14}C or ^{85}Kr in atmospheric discharges and in this case ^{14}C is the main contributor to the collective effective dose equivalent commitment from atmospheric releases, although the ^{14}C content of LWR fuels is much less than for Magnox (paragraphs 66–67). On the basis of the very notional

discharges assumed here, the liquid effluents are as significant as the atmospheric releases with ^{137}Cs and ^{106}Ru being the main contributors. Iodine-129 releases contribute to the global collective dose and this is considered in chapter V. The representative local and regional normalized collective effective dose equivalent commitment from reprocessing is thus 1 man Sv [GW(e) a]$^{-1}$.

168. The representative values of doses to critical groups from the discharges at the model facility are presented in Table 49. For atmospheric releases the largest single contribution to individual effective dose equivalent is from ^{14}C and a representative annual effective dose equivalent to the critical group is 25 μSv. The liquid effluents contribute more to the total effective dose equivalent, with ^{137}Cs being the most important nuclide. The results must only be used to indicate the order of magnitude of doses foreseen in designs of reprocessing plants. The annual effective dose equivalent to the most exposed group amounts to 200 μSv for marine discharges. These doses for critical group exposures are similar to those from the proposed Barnwell Nuclear Fuel Plant in South Carolina, United States [P9].

V. COLLECTIVE DOSE COMMITMENTS FROM THE GLOBAL DISPERSION OF RADIONUCLIDES

169. The radionuclides that contribute to the global collective dose commitment are those which are sufficiently long-lived and readily migrate through the environment, thereby achieving widespread distribution. Those of primary interest are ^{3}H, ^{14}C, ^{85}Kr and ^{129}I and assessments of the global collective doses from the release of these nuclides have appeared in several reports [C10, K2, N14]. The environmental transfer of ^{3}H and ^{85}Kr is becoming fairly well established and more reliable estimates of collective dose commitments can be made. Long-lived nuclides such as ^{137}Cs and ^{239}Pu are less mobile in the environment and become far less dispersed after deposition onto soil or onto sediments, following release into the local region. Some other nuclides are considered which are released in the nuclear fuel cycle in a mobile form and have sufficiently long half-lives to irradiate populations beyond the regional area.

170. The very long-lived nuclides, for example, ^{129}I ($1.6\ 10^{7}$ a) pose a special problem because extrapolation far into the future is required to estimate the dose commitment. This introduces uncertainties because of the unknown population size, its dietary habits and, amongst other things, environmental changes. This implies that little weight can be placed on dose commitments for decision-making purposes. Estimates of the incomplete collective dose commitment from these nuclides is useful firstly in demonstrating the time distribution of the dose commitment, and secondly to calculate an estimate of the per caput annual doses resulting from a finite continuing practice. Thus, if electrical energy production by nuclear fission has a finite duration, of the order of a few hundred years, the incomplete collective dose commitment to that time divided by the mean population size will indicate the maximum per caput dose rate that may be experienced in the future from that practice. Collective dose commitments must be treated with caution since the significance of the results must be carefully interpreted. This topic is fully discussed in Annex A.

171. In the following paragraphs collective dose commitments (and incomplete values where of interest) have been estimated for those nuclides which become globally dispersed and irradiate the world population. This dose is received in addition to that received during the local and regional dispersion, the so-called first pass dose, from the point of discharge. Recently a report has been published by the Nuclear Energy Agency of the OECD which discusses the collective dose commitments from releases of ^{3}H, ^{14}C, ^{85}Kr [N14]. In this chapter extensive reference is made to the results obtained by the study group who produced the report for the Nuclear Energy Agency.

A. KRYPTON-85

172. The collective dose commitments from ^{85}Kr generated during nuclear power production arise almost entirely from the release at reprocessing plants, as reactor releases are small in comparison. Since krypton is an inert gas it disperses through the atmosphere and achieves a uniform concentration in a period of about two years. Although the assumption of instantaneous dilution in the world's atmosphere, as used in Annex E, gives a reasonable estimate of time integral of concentration, a two-compartment model similar to that proposed by Kelly et al. [K2] is used in which the released krypton is assumed to be instantaneously dispersed throughout the troposphere of the northern hemisphere which is assumed to have a height of 10 km and a mass of $1.9\ 10^{21}$ g. Exchanges take place between the troposhere of the two hemispheres with a half time of about 2 years. Within a few years the ^{85}Kr becomes uniformly dispersed and the sole removal mechanism is radioactive decay.

173. The concentration in air and the time integral of activity concentration of ^{85}Kr for a discharge of 1 Bq s^{-1} for a year is shown in Figure I. The whole-body absorbed dose commitment per unit time integral of air concentration of ^{85}Kr has been taken as $4.3\ 10^{-9}$ Gy (Bq a kg^{-1})$^{-1}$ [C10], and the collective skin dose commitment due to the β^{-}-irradiation as $5.4\ 10^{-7}$ Gy (Bq a kg^{-1})$^{-1}$. These values are in good agreement with the dose rates per unit air concentration of ^{85}Kr as given by ICRP publication 30 [12]. The collective absorbed dose commitment from the gamma contribution is $5.5\ 10^{-19}$ man Gy for a release of 1 Bq s^{-1} for one year, while the collective absorbed dose in skin for the same release is $7.4\ 10^{-17}$ man Gy.

174. The normalized ^{85}Kr discharges from reprocessing of nuclear fuel have been given in paragraph 149 as 11 PBq [GW(e) a]$^{-1}$ for a typical LWR and 14 PBq [GW(e) a]$^{-1}$ for a GCR. The corresponding collective effective dose equivalent commitments are calculated, assuming a world population of $4\ 10^{9}$ during the irradiation period, to be 0.81 man Sv [GW(e) a]$^{-1}$ of reprocessed LWR fuel and 0.98 man Sv [GW(e) a]$^{-1}$ for GCR fuel for the external gamma irradiation. The collective absorbed dose commitment to skin is 110 man Gy [GW(e) a]$^{-1}$ for LWR and 130 man Gy [GW(e) a]$^{-1}$ for GCR fuel, which adds 1.1 and 1.3 man Sv [GW(e) a]$^{-1}$ to the collective effective dose equivalent commitments, respectively. The total collective effective dose equivalent commitment weighted for energy produced is 1.9 man Sv [GW(e) a]$^{-1}$. All of the dose commitment is delivered within the first 50 years following the year of release. These results compare with the Committee's previous estimate in Annex D of the 1977 report [U1] of a gonadal dose commitment of

0.9 man Sv [GW(e) a]$^{-1}$. The results of the Nuclear Energy Agency expert group report give a collective effective dose equivalent commitment for ^{85}Kr global dispersion of 0.81 man Sv [GW(e) a]$^{-1}$ for LWR fuel, if the same world population is assumed as used here.

B. TRITIUM

175. The collective dose to the global population from reactor and reprocessing plant releases of tritium can be estimated from the evidence concluded from fallout measurements following atmospheric weapons testing. The absorbed dose commitment has been estimated to be 5 10^{-4} man Sv per TBq released (see Annex E).

176. In recent years a number of models have been proposed to describe the global circulation of tritium for predicting dose commitments [B13, B14, B15, C10, K2, N20]. In a very simple model emissions to atmosphere or to hydrosphere are not distinguished, since the exchange of water between the atmosphere and the remaining circulating waters of the globe is rapid. In such models it has been usual to assume that the released tritium is immediately and uniformly distributed in the circulating waters of the northern hemisphere to a depth of 75 m [B14, B15, U1]. More recent models [C10, K2] still assume that discharged tritium, whether to atmosphere or hydrosphere, is immediately dispersed and exchanged with the hydrogen content of the circulating waters of the hemisphere into which the discharge is made.

177. The subsequent circulation of tritium is determined, however, by the exchange of waters between the two hemispheres and the deep oceans. The model is described in Annex A and the exchange rates taken are shown below. The mass transfer rates are obtained by multiplying the exchange rates by the relevant mass of each component.

Circulating waters (N. hemisphere) → circulating waters (S. hemisphere)	0.1	a^{-1}
Circulating waters (S. hemisphere) → circulating waters (N. hemisphere)	0.05	a^{-1}
Exchange between deep oceans (N. hemisphere ⇄ S. hemisphere)	0.005	a^{-1}
Exchange between circulating surface waters and deep oceans	0.1	a^{-1}
Exchange between deep oceans and circulating waters	0.0014	a^{-1}

Using this model, the time integral of activity concentration in the circulating waters of the Northern hemisphere is shown in Figure I to be 1.4 10^{-11} Bq a kg^{-1} for a release of 1 Bq s^{-1} for a year. Assuming an individual

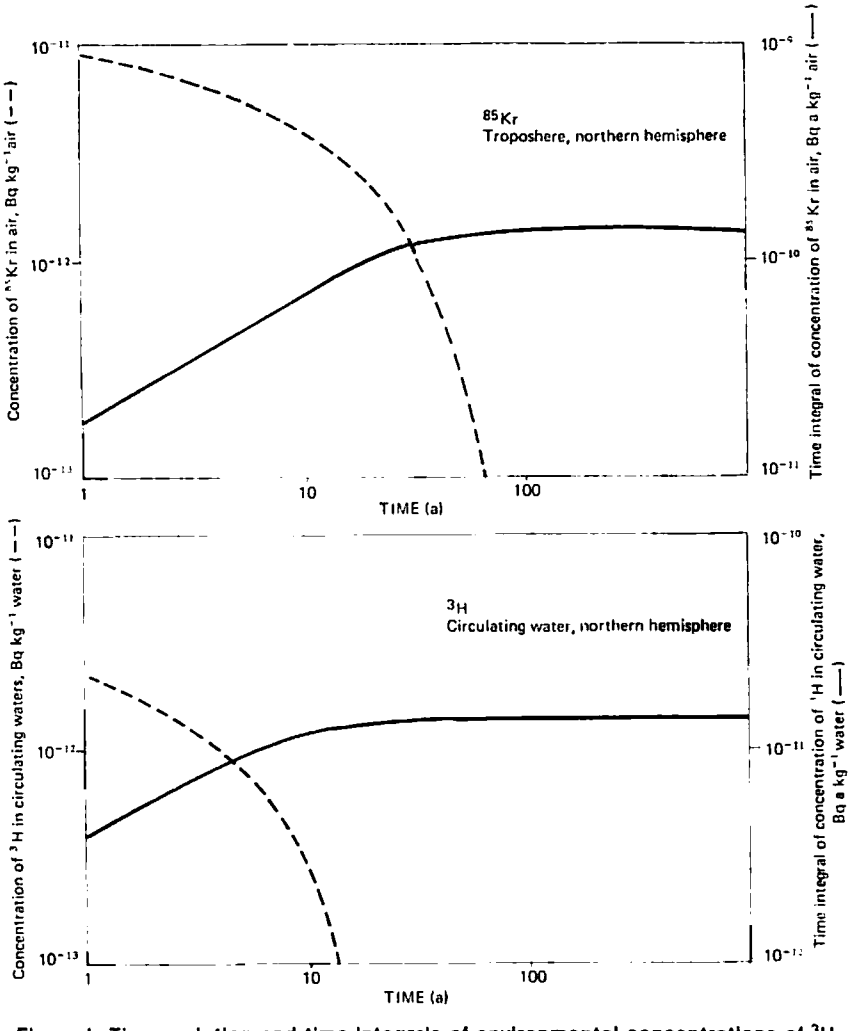

Figure I. Time variation and time integrals of environmental concentrations of ^{3}H and ^{85}Kr for releases of 1 Bq s^{-1} during one year [C10]

intake of water of 930 kg a^{-1}, as given by ICRP in publication 23 [15], a population of 4 10^9, and a dose per unit intake of 1.7 10^{-11} Gy Bq^{-1} [A1, I2], the collective effective dose equivalent commitment per unit release is estimated to be 2.8 10^{-5} man Gy TBq^{-1}. Assuming the normalized release of tritium in reprocessing to be 0.6 PBq [GW(e) a]$^{-1}$ plus about 40 TBq [GW(e) a]$^{-1}$ for the average of reactor discharges, gives a total of 0.64 PBq [GW(e) a]$^{-1}$ and a normalized collective effective dose equivalent commitment of 1.8 10^{-2} man Sv [GW(e) a]$^{-1}$. The result is directly proportional to the assumed population size.

178. The Nuclear Energy Agency expert group assumed a population of 10^{10} so the present model would predict 6.8 10^{-5} man Gy TBq^{-1}. The expert group derived a value of 4.6 10^{-4} man Gy TBq^{-1} and the Committee, in Annex D of its 1977 report [U1], gave a value of 8.1 10^{-4} man Gy TBq^{-1}. The figure derived from the comparison of the natural dose rate and production of tritium (see Annexes B and E) would be about 5 10^{-4} man Gy TBq^{-1} for a uniform production over the world, assuming a global population of 4 10^9. One reason for the smaller value obtained in this Annex is the inclusion of the removal rates of tritium to deep oceans which leads to a reduction of a factor of 4 to 5 in integrated tritium intakes. The local and regional effective dose equivalent commitment per unit energy generated for atmospheric releases of tritium amount to about 0.5 man Sv [GW(e) a]$^{-1}$, so that the global contribution is found to be small in comparison (paragraph 102).

C. CARBON-14

179. The global dose commitment from ^{14}C releases from the nuclear industry is estimated by constructing compartment models which reflect the environmental distribution and behaviour of naturally-produced ^{14}C. Models of varying degrees of complexity have been produced using between 2 and 20 compartments [H2, K2, K6, M2, S13, U1]. In the two-compartment model the stratosphere, troposphere and ocean surface are considered as one compartment which exchanges with the deep ocean [H2]. In the 20-compartment model there are four latitude bands each with compartments in the stratosphere, troposphere, terrestrial biosphere, mixed ocean and deep ocean [M6]. An additional input to some models is the increased stable carbon in the atmosphere due to the combustion of fossil fuels, which tends to decrease the specific activity of ^{14}C. It is not easy, therefore, to evaluate the various estimates of dose commitment. However, there is evidence [K6] that, owing to the long half-life of ^{14}C compared with the rate of environmental transport of carbon, estimates of dose commitment are fairly insensitive to the details of the environmental models except for the rate of transfer to the deep ocean which affects the result.

180. The model chosen for the present estimates has been described in Annex A and is an 8-compartment model allowing for two hemispheres comprising humus, circulating carbon, surface ocean and deep ocean. The circulating carbon compartment represents carbon in the troposphere and those parts of the terrestrial biosphere which are subject to rapid cycles of growth and decomposition. The humus compartment represents the carbon content of the terrestrial biosphere which circulates more slowly. Carbon-14 discharged to atmosphere or hydrosphere is assumed to be instantaneously mixed with the carbon in the compartment to which it is released. The subsequent circulation between compartments governs the specific activity of ^{14}C in all carbon inhaled or ingested by man, which is assumed to be taken from the circulating carbon in the northern hemisphere. The mass of circulating carbon in the northern hemisphere has been estimated at 3.6 10^{14} kg by Ekdahl et al. [E5] and this value is assumed to remain constant.

181. In Figure II the airborne concentration and the time integrals of activity concentration in carbon are shown for a release of 1 Bq s^{-1} for a year to either the atmospheric or aquatic environments. The doses in all

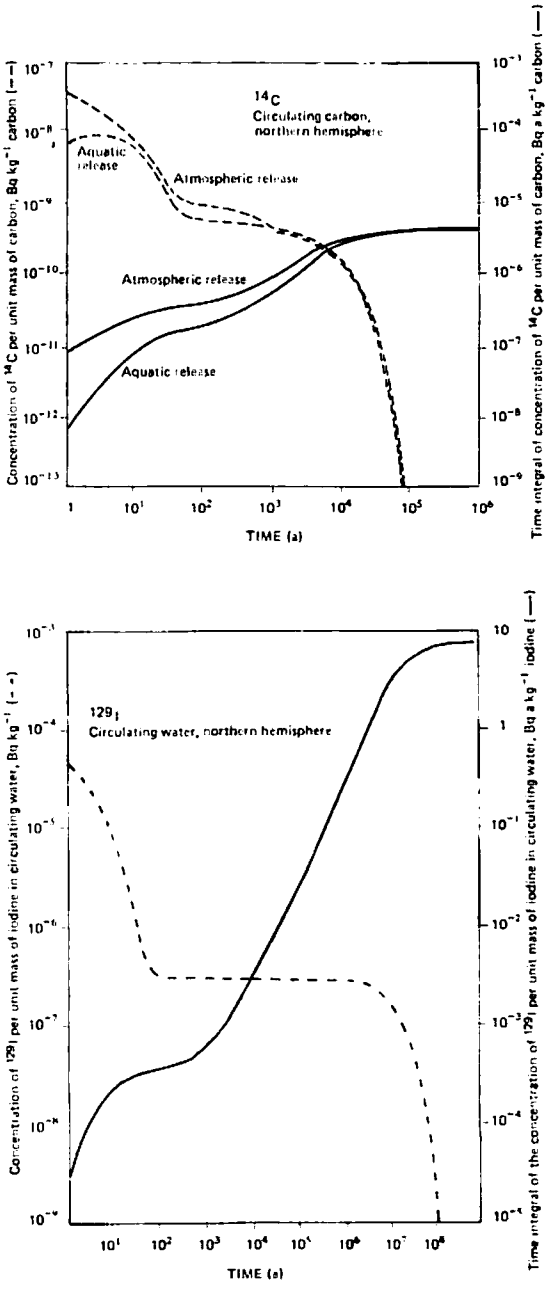

Figure II. Time variation and time integrals of environmental concentrations of ^{14}C and ^{129}I for releases of 1 Bq s^{-1} during one year [C10]

organs and tissues are assumed to be equal and the effective dose equivalent per unit intake is taken as 5.7 10^{-10} Sv Bq^{-1} for ingestion and 6.4 10^{-12} Sv Bq^{-1} for inhaled CO_2. The Reference Man [15] annual intakes of carbon are taken as 93 kg a^{-1} ingested and 1.2 kg a^{-1} inhaled. A population of 10^{10} is assumed for this calculation and is taken to be constant during the integration

period. This figure represents an estimated equilibrium population figure during the irradiation.

182. The collective effective dose equivalent commitment per unit release is estimated at 67 man Sv TBq^{-1} as an average for both atmospheric and aquatic releases. This compares with an estimate of the incomplete effective dose equivalent commitment per unit release given by the Nuclear Energy Agency expert group of 70 man Sv TBq^{-1} for the same population figure used here. The expert group, incomplete collective effective dose equivalent commitment was to 10^4 years, during which time they expected 67% of the dose commitment to have been delivered [N14]; thus their estimate of the complete collective effective dose equivalent commitment per unit release is about 105 man Sv TBq^{-1}. The answers are thus in good agreement given the assumptions made and the associated uncertainties over long time periods. Based on the dose rates due to natural ^{14}C production (Annex B), the collective effective dose equivalent commitment per unit release is 120 man Sv TBq^{-1}, confirming the results of the models.

183. The estimated local and regional collective effective dose equivalent commitments given in Tables 33 and 45 correspond to 2.0 or 0.5 man Sv TBq^{-1}, depending upon site, and thus represents a few per cent of the total collective effective dose equivalent commitment per unit release for ^{14}C. The normalized release of ^{14}C is given as 0.4 TBq $[GW(e)\,a]^{-1}$ from the model reprocessing plant handling LWR fuel (Table 48), and LWR reactor releases can be expected to contribute about the same amount (Table 33). The normalized collective effective dose equivalent commitment is thus 54 man Sv $[GW(e)\,a]^{-1}$ for LWRs, only half of which arises from atmospheric discharges at the reprocessing plant. HWR reactor operation leads to 17 TBq $[GW(e)\,a]^{-1}$ (Table 33) and reprocessing would give little addition; the global collective effective dose equivalent commitment per unit energy generated in HWRs is thus $1.1\ 10^3$ man Sv $[GW(e)\,a]^{-1}$. The 1000-year incomplete values are about 20% of the infinite values, 11 man Sv $[GW(e)\,a]^{-1}$ for LWR releases and 200 man Sv $[GW(e)\,a]^{-1}$ for HWR operation. The 1000-year incomplete collective effective dose equivalent commitment is 21 man Sv $[GW(e)\,a]^{-1}$ averaged over electricity production by each reactor type, and the infinite value is 110 man Sv $[GW(e)\,a]^{-1}$.

D. IODINE-129

184. Iodine-129 emitted to the atmosphere, because of its mobility in the environment, becomes rapidly incorporated in foodstuffs ingested by individuals. Iodine in the environment is not uniformly distributed and the highest concentrations are found in sea water. Models proposed for the environmental transport of ^{129}I have been discussed in Annex A, and range from simple assumptions of instantaneous mixing in the oceans with stable iodine, as in Annex D of the 1977 report [U1], to multicompartment models taking account of transfer between surface waters and the deep ocean [K7] and between these waters and the land and atmosphere [B16]. The most important feature to be included appears to be the transfer to the deep oceans [K7]. The model utilized here probably leads to an overestimate of collective dose commitment since effects such as sedimentation are not taken into account. It is extremely difficult to estimate dose commitments for periods of tens of millions of years. The increasing uncertainty with which doses can be predicted in the far future means that less weight can be placed on them for decision making.

185. In Figure 11 the integrated activity concentrations of ^{129}I are given for a 1 Bq s^{-1} for a year's discharge whether to atmospheric or aquatic environments. Once more an equilibrium population of 10^{10} is assumed and held constant throughout the irradiation time. These integrated concentrations are per kg of stable iodine so that collective dose commitments are found by multiplying the integral of activity concentration by the population size, the individual rate of intake of iodine and the committed dose per unit intake. The thyroid dose equivalent is $3.3\ 10^{-6}$ Sv Bq^{-1} ingested, giving an effective dose equivalent per unit intake of $9.9\ 10^{-8}$ Sv Bq^{-1} ingested [A1, I2]. The intake of iodine is $7\ 10^{-5}$ kg a^{-1} [I5]. The collective effective dose equivalent commitment per unit release is thus found to be $1.4\ 10^4$ man Sv TBq^{-1}, while the value truncated to 10^4 years would be 4.1 man Sv TBq^{-1}. The answers must clearly be very uncertain for this nuclide because most of the dose commitment is delivered beyond 10^6 years into the future.

186. The incomplete collective effective dose equivalent commitment per unit ^{129}I release for the same population as used here was estimated by the Nuclear Energy Agency expert group for an integration time of 10^4 years as 8.1 man Sv TBq^{-1} [N14]. The NEA group calculated 10^4 year incomplete collective dose equivalent commitments because they assumed this to be a feasible containment period and thus they were interested in detriment averted. The value here is just over half that value at 10^4 years, but the collective dose is increasing steeply with time at this point and the results are very sensitive to parameter values. The NEA group comment that the complete collective effective dose equivalent commitment per unit ^{129}I release is some 3500 times the 10^4 year value, i.e., $2.8\ 10^4$ man Sv TBq^{-1}, compared with the Committee's current estimate of $1.4\ 10^4$ man Sv TBq^{-1}. A factor of about 3400 has been found here between the 10^4 year incomplete value and the complete dose commitment. The normalized release for the model reprocessing plant discharge was 0.2 GBq $[GW(e)\,a]^{-1}$ (Table 48) to atmosphere and 40 GBq $[GW(e)\,a]^{-1}$ in liquid effluents, giving a total of 40 GBq $[GW(e)\,a]^{-1}$.

187. The resulting normalized global collective effective dose equivalent commitment for ^{129}I releases is thus 560 man Sv $[GW(e)\,a]^{-1}$ from reprocessing plant discharges, reactor releases being insignificant by comparison. The collective thyroid dose equivalent commitment is about 19 000 man Sv $[GW(e)\,a]^{-1}$. The local and regional collective effective dose equivalent commitment has been estimated as $4\ 10^{-3}$ man Sv $[GW(e)\,a]^{-1}$ for atmospheric releases and $8\ 10^{-3}$ man Sv $[GW(e)\,a]^{-1}$ for liquid discharges (Table 48). The local and regional collective dose commitments are delivered over a relatively short time scale due to environmental removal processes (less than 500 a) and over the same time period the normalized global collective effective dose equivalent commitment is about $3\ 10^{-2}$ man Sv $[GW(e)\,a]^{-1}$.

E. SUMMARY

188. A summary of the normalized releases of the nuclides of global significance, together with their

collective effective dose equivalent commitments, are shown in Table 50. Incomplete values of collective dose commitment are shown to illustrate their time dependence. It should be noted that, in addition to ^{3}H, ^{14}C, ^{85}Kr and ^{129}I, a fraction of those radionuclides released into the atmosphere with half-lives greater than a few days and deposition velocities of less than about 10^{-3} m s^{-1} will leave the regional area and potentially become globally dispersed. Their contribution to the collective dose commitment beyond the regional area has been estimated using the ^{85}Kr model and results. It may be deduced that the global dose commitment increases with increasing half-life and equals that from the regional area when the half-life is about 0.5 a. Short-lived nuclides such as ^{133}Xe ($T_{1/2}$ 5.3 d) and ^{131}I (8.05 d) in organic form can thus only be expected to add a few per cent to the regional dose commitment by becoming globally dispersed. The release of ^{35}S ($T_{1/2}$ 87.5 d) however would contribute an extra 50% of the local and regional dose commitment. These three nuclides contribute 2 10^{-3} man Sv $[GW(e)\,a]^{-1}$ from global dispersion which is 0.05% of the collective dose commitment from reactor operation.

VI. RADIOACTIVE WASTE STORAGE AND DISPOSAL

189. Only a small fraction of the artificial activity generated in the nuclear fuel cycle is released to the environment during normal operations. Except for the uranium, plutonium, and certain other nuclides present in spent fuel, the radionuclides generated by the nuclear fuel cycle are generally considered as waste which must be subjected to suitable treatment followed by storage or disposal. Storage is taken to mean any arrangement intended to enable retrieval of the waste at some future time; the waste may be temporarily inaccessible, but there is an intent, by surveillance and documentation, to retrieve. Disposal implies that control over the waste has been relinquished. It is useful to distinguish between high-level wastes, which may consist of unreprocessed fuel or may arise in liquid form following reprocessing of nuclear fuel and contain more than 99% of the fission product and actinide radionuclides in the fuel, and the low and intermediate level wastes which arise both in reprocessing and in reactor operation. The latter are, for example, used ion exchange resins, air and liquid filters, in-reactor components (control rods, instrumentation), contaminated clothing and equipment. A further category of waste is known as plutonium contaminated material, which is a low-level waste but because of the long half-lives of the α-emitting nuclides covered in this category, needs to be treated similarly to intermediate level wastes.

A. LOW AND INTERMEDIATE LEVEL WASTES

190. The tailings from uranium milling are one example of low-level solid waste, the radiological exposures from which have been considered in chapter I. Solid wastes may be treated by compaction or incineration to reduce their volume before being placed in storage or disposed of in shallow land or deep burial sites. Most nuclear sites have provision for the storage of solid wastes generated through the reactor lifetime and the final disposition of these wastes probably will depend upon the decision as to the final method of disposal of the reactor itself.

191. It is common practice to dump low-activity solid wastes untreated into trenches and to cover with earth. In the United States there were six commercial low-level waste burial facilities and five major active sites operated by the Department of Energy in 1978 [A4]. Three of the commercial facilities are currently inoperative, three of the sites are closed indefinitely and responsibility for perpetual care is expected to be placed upon the respective States. In general the wastes are placed as received into trenches excavated in the existing soil and the removed material used to cover the wastes once the trench is filled to capacity. The overburden is sometimes compacted and usually mounded to promote water run-off. The capacity of the currently open commercial sites is between 10^{5} and 10^{6} m^3 and typical areas would be of the order of 1.5 km^2, in low population density often semi-arid areas. A recent review of the radioactive waste inventory at the Maxey Flats site [G10] revealed the following radionuclides which are attributable to the nuclear fuel cycle:

^{3}H	20 PBq	^{137}Cs	0.93 PBq
^{14}C	1.3 PBq	^{226}Ra	0.18 PBq
^{60}Co	3.0 PBq	^{238}Pu	1.6 PBq
^{90}Sr	0.56 PBq	^{239}Pu	0.14 PBq

192. Emissions from waste handling operations have been studied at Maxey Flats [A4] and also at other waste disposal sites [D4, L5, M7, S17]. Atmospheric releases from normal waste handling and from leachate evaporators have been studied by Blanchard et al. [B17] and assessments made by the United States Environmental Protection Agency [E1] give estimates of collective effective dose equivalent commitment arising from one year of release of 4.2 10^{-2} man Sv per facility, leading to normalized collective effective dose equivalent commitments of less than 4 10^{-5} man Sv $[GW(e)\,a]^{-1}$.

193. Disposal of low-level packaged radioactive waste in the deep ocean is governed by the International Convention on the Prevention of Marine Pollution by Dumping of Wastes and Other Matter (the London Convention). The special permits granted by the appropriate national authorities for radioactive waste should take into account the relevant IAEA definition of high-level waste unsuitable for disposal at sea and recommendations for the purpose of the London Convention. In addition, sea disposal operations undertaken by NEA member countries are required to conform to the terms of the Multilateral Consultation and Surveillance Mechanism which was established in 1979 by a decision of the OECD Council. This mechanism was set up to further the objectives of the London Convention and provides a framework for cooperation between participating countries. It provides for the development of standards, guidelines, practices and procedures for sea disposal operations and for international consultation on and surveillance of operations to verify that these are carried out in accordance with internationally established rules.

B. HIGH-LEVEL WASTES

194. The majority of irradiated nuclear fuel which has been removed from reactors is currently stored awaiting national decisions on whether to dispose of the fuel directly or to reprocess and recycle fissile nuclides. When reprocessing takes place, high-level wastes are currently stored as liquids. The intent is to solidify in some manner to facilitate further handling, storage and

eventually disposal. In France a decision has been made about the process for solidifying high-level wastes and a vitrification plant was commissioned at Marcoule in 1978. After about a year's operation during 1979 some 250 glass blocks had been produced and stored in air-cooled facilities. Other countries are pursuing research into the most appropriate form for solidifying high-level wastes, for containing the wastes, and to find the most suitable location for disposal. Assuming a world nuclear generating capacity of 1300 GW(e) by the year 2000, it might be expected that some 5000 GW(e) a will have been generated and assuming the waste is vitrified in a cylindrical form similar to those developed in the French AVM process several tens of thousands of cylinders will be required.

195. The procedures for disposal being studied widely are either disposal in deep geological formations, or disposal on or under the ocean bed. International studies are being undertaken on research needs to assess ocean disposal and many countries are actively investigating geologic disposal in either salt or hard rock (granite, gneiss or basalt). In addition, there is the possibility of using argillaceous rock as a repository. The main barriers which can prevent the return of activity to man's environment from a geologic repository or can influence the rate at which activity returns are: the waste form and its container; geologic containment of the waste within the rock formation; retardation of activity during transport through geologic media; and dispersion and dilution of activity in the biosphere.

196. Assessments of geologic disposal have been undertaken in many countries [E6, K8, K11]. In the United Kingdom [H11, H12], assessments estimate not only public health consequences but are performed with the intention of using the theoretical models to perform sensitivity analysis so that those parameters whose uncertainties have a significant effect on the overall result can be identified for further research. In the United States a number of studies have been undertaken on a range of geologic media and the present emphasis is also on the identification of areas of uncertainty, so that research needs and priorities can be properly co-ordinated in the development of the overall strategy for high-level waste disposal [E6]. In Sweden a comprehensive study of the radiological consequences of geological disposal of unreprocessed nuclear fuel and vitrified high-level waste has been undertaken [K8].

197. Disposal of high-level wastes from nuclear power production has not yet taken place. There has only been storage under surveillance by national authorities, awaiting a final decision on processing. Therefore the Committee has to make its estimate of the potential collective dose commitments from high-level waste disposal on the basis of theoretical studies. For normal operations in the preceding steps in the nuclear power cycle, truncated dose commitments per unit of electrical energy generated have been used as a tool for the assessment of the maximum dose rate in the future, if the practice were continued at constant rate. The integration period was taken to be equal to the expected length of the practice. For high-level waste contained over periods which are longer than the assumed period of practice, such truncated dose commitments are not needed, since the dose rate at the time when the radioactive material may reach the biosphere can be calculated directly and there would be no continued practice that would add to it in later years. The potential collective dose commitments given below have been based on the INFCE analysis of waste disposal [I9], as this was an exercise involving many countries active in the development of nuclear power. No assessment is made by the Committee of dose commitments, but rather the INFCE values are quoted. The INFCE analysis of geologic repositories assumes that the lifetime of stainless steel containers is 10^3 a and the retention time of wastes in a vitreous matrix is 10^4 a, although these figures have little influence on the overall result as the time scale of the subsequent geologic transfer is much greater. For a salt repository the waste is only exposed to groundwater due to a disruptive event which is assumed to have a probability of occurrence approaching unity in 10^5–10^6 a. A detailed analysis of this scenario showed that the mean arrival times of the nuclides of significance, ^{99}Tc, ^{129}I, ^{135}Cs and the actinides, in fresh water was of the order of several million years. In the repository in nominal hard rock, the canisters would be in contact with water which has a low flow velocity. Transport of dissolved species through the buffer material surrounding the canisters will be governed by diffusion which is extremely slow. Further retardation of many nuclides is expected by chemical interactions with the buffer material and the host rock. The INFCE study assumes that because of these processes it will be between 10^5 and 10^6 a before radionuclides from the waste arrive in fresh surface waters and the radiological consequences are calculated following the different pathways to humans [I10].

198. Dose commitments are first evaluated assuming the radionuclides are released to fresh water for which simple assumptions are made about turnover time (10 a), fractions of water drunk ($2.7\ 10^{-5}$ of the available volume per year) and fractions of fish content consumed ($3\ 10^{-8}\ a^{-1}$). These figures are global averages. It is assumed that all the long-lived nuclides released from a repository eventually reach the ocean where sedimentation processes become an important removal mechanism for radionuclides from the biosphere. In the consideration of population exposure, in addition to consumption of fish and other sea foods, resuspension of sediments provides inhalation doses and external exposure to sediments occurs along the shoreline.

199. The dose commitments due to waste disposal depend upon whether unreprocessed fuel or high-level reprocessing wastes are considered and from which fuel cycle they arose. The doses would not be received until after 10^5 or 10^6 a, so they will be subject to considerable uncertainty and the absolute numerical values should be used with caution. Their main virtue is in providing the ability to compare the cycles. Table 51 shows the collective effective dose equivalent commitments for the major fuel cycles under consideration for the future where the contribution from the uranium isotopes and their radioactive daughters are separately identified from other elements in the waste. Results are presented assuming both 10^5 and 10^6 a migration times through the geosphere to show the range to be expected for dose commitments. The once-through fuel cycles give higher values of collective dose commitment and the fast breeder reactor gives lower values because of its more efficient use of uranium. Assuming LWR fuel is reprocessed, then whether the plutonium is recycled through LWRs or in FBRs, the normalized collective effective dose equivalent commitment is between 20 and 50 man Sv [GW(e) a]$^{-1}$, regardless of the actual time chosen for migration through geologic media.

200. As regards the levels of individual dose associated with a geologic repository, studies on a salt medium [U5] and on hard rock [110, K8] have been undertaken, assuming wastes from 100 GW(e) a of electrical energy production are disposed of. For the salt repository the annual whole-body dose equivalent was between 5 10^{-8} and 3 10^{-5} Sv, some 3.5 10^{6} a after the event initiating ground water ingress. For hard rock, maximum individual annual dose equivalents were predicted some 4 10^{8} a after disposal and ranged from 10^{-8} to 10^{-6} Sv. These doses should be regarded as indicative rather than definitive and the conclusion to be drawn is that either disposal option for any fuel cycle will probably lead to very low levels of individual annual dose in the far distant future.

VII. MISCELLANEOUS CONTRIBUTIONS

201. Other aspects of the nuclear fuel cycle which contribute to the collective dose commitment from the use of nuclear power are transportation of irradiated nuclear fuel and the operation of nuclear research facilities.

A. TRANSPORTATION

202. Unirradiated nuclear fuel is transported to reactor sites from fuel fabrication facilities and irradiated nuclear fuel is transported from the reactor sites to reprocessing or fuel storage facilities. The transport of radioactive materials is subject to national regulations generally based on the IAEA regulations [17]. Shipments occur by road, rail and sea, and the number of shipments and distances travelled vary widely from country to country. Typical studies have been carried out in the United Kingdom [B18] and in the United States [U4] and for the Commission of the European Communities [C5].

203. Calculations can be performed knowing the dose rate distribution as a function of distance from the irradiated fuel flask and the population density along the routes used for transportation and up to a distance of perhaps 1 km away from the pathway. Estimates of the normalized collective effective dose equivalent commitment associated with irradiated fuel transport is in the range 10^{-3} to 10^{-2} man Sv [GW(e) a]$^{-1}$. This does not include any contribution from flask accidents which could lead to radiation exposures of the public. It is difficult to add any meaningful component to total health detriment from accidents since there is a probability distribution of a whole range of accidents leading to different releases, for each of which there are probability distribution functions representing the chance of different meteorological conditions (weather category and wind direction), and widely different population distributions depending upon the location of the incident and meteorology.

B. NUCLEAR RESEARCH INSTALLATIONS

204. A proportion of the radioactive materials released to the environment from nuclear research facilities may be attributed to support for continued operation or future development of nuclear power. However, other activities at nuclear facilities such as radioisotope production and processing and other types of research are usually responsible for a large fraction of the environmental releases. Since the fraction of the releases to the environment which may be attributed to the generation of electricity by nuclear power is unknown, it is not possible for the Committee to assess their contributions to overall dose.

205. Reported estimates of discharges have been used to calculate the associated collective doses in 1977–1978 from 27 nuclear research and operational institutions in the United States [E1]. The annual collective dose equivalents ranged from 10^{-10} man Sv up to 2 man Sv and the total value was about 6 man Sv from all installations, over half of this being due to ^{3}H releases from two sites (Savannah River and Ames Laboratory). One-third of the total was due to ^{41}Ar discharges from the Argonne National Laboratory. The collective doses from nuclear research facilities in the United Kingdom have been estimated [T4] based on reported discharge data. The only significant contribution is from the tritium discharged to the river Thames by the United Kingdom Atomic Energy Authorities' Research Establishment at Harwell, for which the annual collective dose equivalent via the drinking water pathway to the population of Greater London is estimated to be 1 man Sv. Data on radioactive materials released from the nuclear research centres Jülich and Karlsruhe and from research reactor sites in the Federal Republic of Germany have been reported and the collective doses associated with nuclear power production are negligible.

VIII. SUMMARY OF NORMALIZED COLLECTIVE EFFECTIVE DOSE EQUIVALENT COMMITMENTS TO THE PUBLIC FROM NUCLEAR POWER PRODUCTION

206. The preceding chapters contain the results of the Committee's assessments of collective dose commitments and collective effective dose equivalent commitments, excluding the contributions from occupational exposure, associated with nuclear power production. The collective effective dose equivalent commitments, which have been averaged over reactor types according to their total contribution to electrical power production, are summarized in normalized form, i.e., per unit of electrical energy generated, in Table 52. Normalized collective effective dose equivalent commitments are presented, so that different steps in the cycle may be compared and appropriate estimates of the health detriment may be estimated using the procedures outlined in Annex A. For releases during the operational phase in the nuclear fuel cycle, i.e., excluding waste disposal, the normalized collective effective dose equivalent commitment is 5.7 man Sv [GW(e) a]$^{-1}$, of which some 90% is delivered in the year the wastes are discharged and some 98% within 5 years. This estimate is made using the notional reprocessing plant effluents. Present day reprocessing may give normalized collective effective dose equivalent commitments 10–20 times higher; however, since less than 10% of fuel is reprocessed, the weighted contribution would be similar to that here.

207. For those long-lived nuclides which become globally dispersed incomplete normalized collective effective dose equivalent commitments are also given in Table 52. The incomplete dose commitments give an indication of the time distribution of the dose commitment and can also be used to derive the maximum annual per caput effective dose equivalents

by dividing by the mean population size, assuming the production of electricity by nuclear power continues throughout the period chosen for the integration time, and that the release rates remain constant. The normalized collective effective dose equivalent commitment due to global dispersion of nuclides released during fuel cycle operations is 670 man Sv [GW(e) a]$^{-1}$, 90% of which is delivered in the time period 10^4-10^8 a after release. The incomplete value to 500 a, which might be taken as the duration of the practice of generation of electricity by fission power is 18 man Sv [GW(e) a]$^{-1}$. If this figure is used to derive an annual per caput effective dose equivalent, it is comparable with that obtained from the local and regional normalized collective effective dose equivalent commitment.

208. Considerable caution must be exercised in extrapolation of doses into the future because the trend over the last five years has been for reactor releases to the environment to decrease despite the increasing electrical output of plants. This has been due partly to improvements in control technology and partly to the development of new concepts in radiation protection. Also, the collective doses due to global dispersion of radionuclides may not be typical of future practices; for example, in the model reactor and reprocessing facilities assumed here for LWR assessments, it was taken that long-lived nuclides such as ^{85}Kr and ^{14}C were emitted untreated to the atmosphere, whereas they may be contained and immobilized. Finally, when extrapolating thousands or millions of years into the future it is difficult to predict the population size, its dietary and other habits as well as medical services so that the estimation of global collective dose commitments must be regarded as highly speculative.

209. The results in Table 52 indicate that the largest contributions to the normalized collective effective dose equivalent commitments arise from mining and milling tailings. The incomplete dose commitments are proportionally less and depend entirely on the assumptions made about the amount and type of covering on tailings and the time before the activity either migrates downwards into the ground and becomes unavailable, or is eroded into the aquatic environment. If the tailings are immobilized by use of polyvinylchloride or asphalt coverings, the radon emanation rate can be reduced to ambient levels and the contribution to dose commitment is essentially zero; similarly downwards migration of uranium and thorium with a rate of $2\ 10^{-3}$ m a^{-1} would lead to a normalized collective effective dose equivalent commitment of the order of 30 man Sv [GW(e) a]$^{-1}$. Assuming that the tailings are eroded into the aquatic environment, leads to a normalized collective effective dose equivalent commitment of 460 man Sv [GW(e) a]$^{-1}$, of which 76% is contributed by ^{210}Po. The results will be highly dependent upon the local site characteristics and the answer given here must be uncertain by at least an order of magnitude. Finally, it must be recognized that any decision to use fast-breeder reactors, by more efficient utilization of uranium resources, could reduce the normalized collective effective dose equivalent commitment from tailings by two orders of magnitude.

210. In order to estimate the maximum per caput annual effective dose equivalent in the future as a result of nuclear power production, an incomplete collective effective dose equivalent commitment truncated over the expected duration of the practice of generation of electricity by fission power, taken here as 500 a, must be used. The releases during the operational stage of the nuclear fuel cycle lead to a local and regional normalized collective effective dose equivalent commitment of 5.7 man Sv [GW(e) a]$^{-1}$ of which 98% is received in the first few years after discharge. For those nuclides which become globally dispersed, the incomplete normalized collective effective dose equivalent commitment to 500 a is about 18 man Sv [GW(e) a]$^{-1}$. The choice of 500 a as a mean duration of the practice of producing power by nuclear fission implies the use of breeder reactors and the rate of mining would decrease. The normalized incomplete collective effective dose equivalent commitment from mining and milling, based on the present fuel cycle, is therefore to 100 a and is likely to be due mainly to radon releases giving 2.5 man Sv [GW(e) a]$^{-1}$. Thus, on the pessimistic assumption that no technological improvements are made and current levels of discharge continue for 500 a, the maximum annual collective effective dose equivalent would be about 25 man Sv [GW(e) a]$^{-1}$. The annual collective and per caput effective dose equivalents for a notional nuclear programme to the year 2500 are shown in Table 53, again assuming that present release levels are not reduced and that the annual generation of electric energy reaches 1 kW a per caput, i.e., some 10^4 GW(e) a in 2500. It can be seen that even with the maximizing assumptions made here, the level of annual per caput effective dose equivalent rises to the equivalent of 1% of natural background radiation. The annual per caput effective dose equivalent would reduce after the end of the practice, to about 1% of the final values after 100 a.

211. Normalized collective effective dose equivalent commitments from mill tailings, waste disposal and the global dispersion of the long-lived nuclides ^{14}C and ^{129}I must be uncertain because of difficulties in predicting future practices, population sizes and habits, environmental pathways and human metabolism. At present the estimate is of the order of $4\ 10^3$ man Sv [GW(e) a]$^{-1}$, mainly delivered in the time period starting 10^5 years from now. Such figures should not be relied upon for decision-making purposes and the Committee therefore recommends that little significance be attached to these complete collective effective dose equivalent commitment estimates. The Committee however recommends that more research be undertaken in order to better quantify the incomplete collective effective dose equivalent commitments.

Table 1

Attainable production capability of uranium in 1979 and estimated reserves [113]

Country or area	Production capability in 1979 (t)	Estimated reserves a/ (t)
Argentina	135	37000
Australia	600	354000
Brazil	103	164000
Canada	6900	1,029000
France	2950	100000
Gabon	1000	35000
India	200	13000
Namibia	3700	175000
Niger	3350	210000
South Africa	5240	525000
Spain	339	19000
Sweden	0	304000
United States	19000	1,831000

a/ Reasonably assured reserves, assuming a price of US$ 130 per kilogram of uranium.

Table 2

Estimated radioactive airborne effluents from the model mine and operations at the model mill

Radionuclide	Normalized release from mine [GBq (GW[e] a)$^{-1}$]	Normalized release from milling [GBq (GW[e] a)$^{-1}$]	Normalized annual release from tailings area [GBq (GW[e] a)$^{-1}$]
^{238}U	-	0.66	0.0007
^{234}U	-	0.66	0.0007
^{230}Th	-	0.074	0.015
^{226}Ra	-	0.04	0.015
^{210}Pb	-	0.04	0.015
^{210}Po	-	0.04	0.015
^{222}Rn	20000	880	1000

Table 3

Population and atmospheric dispersion parameters at the model mine and mill site a/

	Pasquill category						
	A	B	C	D	E	F	D + rain
Frequency (%)	3.8	5.1	6.5	25.5	22.6	36.2	0.3
Height of atmospheric mixing depth (m)	2000	2000	1000	1000	200	200	1000
Wind speed (m s^{-1})	1	2	5	5	3	2	5

a/ The effective height of release is 10 m. The population density is 3 km^{-2} for 0-100 km and 25 km^{-2} for 100-200 km.

Table 4

Estimated normalized collective absorbed dose commitments from particulate airborne releases from uranium milling

	Normalized collective absorbed dose commitment [10^{-5} man Gy (GW[e] a)$^{-1}$]								
	Gonads	Breast	Lungs	Red bone marrow	Bone lining cells	Thyroid	Kidneys	Liver	Remainder tissues
Cloud passage: Inhalation									
^{238}U	-	-	210	0.2	2	-	0.9	0.006	-
^{234}U	-	-	250	0.2	3	-	1	0.006	-
^{230}Th	-	-	26	15	200	-	0.04	0.3	-
^{226}Ra	-	-	0.9	0.03	0.4	-	0.006	0.006	-
^{210}Pb	-	-	0.5	0.2	2	-	0.4	0.8	-
^{210}Po	-	-	1.2	0.02	0.02	-	0.6	0.2	-
Total (rounded) (α)	-	-	490	16	210	-	3	1	-
Activity deposited: Internal irradiation									
^{238}U	2	2	2	5	29	2	17	2	2
^{234}U	2	2	2	3	26	2	16	2	2
^{230}Th	0.01	0.01	0.7	0.8	11	0.01	0.4	0.01	0.01
^{226}Ra	0.1	0.1	0.1	0.4	4	0.1	0.1	0.1	0.1
^{210}Pb-^{210}Po	4	4	2	4	26	4	4	4	4
Total (rounded) (α)	8	8	7	13	96	9	37	8	8
Activity deposited: External irradiation (γ)	23 to all organs and tissues								

Table 5

Normalized collective effective dose equivalent commitments from particulate and gaseous airborne releases from mining and milling

	Collective effective dose equivalent commitment (10^{-2} man Sv [GW(e) a]$^{-1}$)			
	Inhalation during the passage of the cloud	Internal irradiation due to the activity deposited	External irradiation due to the activity deposited	Total
Milling				
Particulates	1.3	0.2	0.02	1.5
Gaseous radon-222 and daughters	2.3	0.1		2.4
Mining				
Gaseous radon-222 and daughters	50	-	-	50
Total				54

Table 6

Normalized collective effective dose equivalent commitment to the local and regional population from tailings at the model mine and mill

(a) Atmospheric releases of radon and airborne particulates as a function of the time for which the erosion continues

	Normalized collective effective dose equivalent commitment (man Sv [GW(e) a]$^{-1}$)		
Release duration (a)	1	10^3	10^5
^{238}U	0.000005	0.005	0.5
^{234}U	0.000006	0.006	0.6
^{230}Th	0.0004	0.44	44
^{226}Ra	0.000009	0.009	0.9
^{210}Pb	0.00002	0.02	2
^{210}Po	0.00002	0.02	2
^{222}Rn	0.025	25	2500
Total (rounded)	0.026	26	2600

(b) Releases of tailings into the marine environment

	Normalized collective effective dose equivalent commitment (man Sv [GW(e) a]$^{-1}$)
^{238}U	0.15
^{234}Th	8.8
^{234}U	0.17
^{230}Th	0.54
^{226}Ra	18.6
^{210}Pb	79.7
^{210}Po	350
Total	460

Table 7

Normalized effluent discharges from the model fuel conversion, enrichment and fabrication facilities

(MBq [GW(e) a]$^{-1}$)
[E1, B2, B22, P1, S6]

Isotope	Atmospheric			Aquatic		
	Con-version	En-richment	Fabri-cation	Con-version	En-richment	Fabri-cation
^{238}U	74	3.7	0.74	814	370	370
^{235}U	2.0	0.07	0.22	20	7.4	7.4
^{234}U	74	3.7	7.4	814	370	370
^{234}Th	74	3.7	0.74	-	-	370
^{230}Th	0.74	-	-	56	-	-
^{226}Ra	0.07	-	-	126	-	-
^{222}Rn	8140	-	-	-	-	-

Table 8

Meteorological characteristics and population distribution around the model fuel fabrication facility used for assessing radon releases a/

Quantity	Pasquill weather category							
	Dry						Rain	
	A	B	C	D	E	F	C	D
Frequency (%)	0.3	4.5	12.1	63	5	4.6	1.7	8.4
Wind speed ($m\ s^{-1}$)	1	2	5	5	3	2	5	5
Depth of mixing layer (m)	2000	2000	1000	1000	200	200	1000	1000

a/ The assumed stack height is 60 m.
The assumed population distribution is uniform at 25 km^{-2}.

Table 9

Normalized collective absorbed dose commitments by inhalation for airborne releases from fuel fabrication

	Normalized collective absorbed dose commitment [10^{-6} man Gy $(GW[e]\ a)^{-1}$]								
	Gonads	Breast	Lungs	Red bone marrow	Bone lining cells	Thyroid	Kidneys	Liver	Remainder tissues
Cloud passage: Inhalation									
^{238}U	-	-	250	0.2	3	-	1	-	-
^{234}U	-	-	320	0.2	3	-	1	-	-
^{230}Th	-	-	3	2	20	-	0.004	-	-
^{226}Ra	-	-	0.02	-	0.007	-	-	-	-
Total (rounded) (α)	-	-	570	2	30	-	2	-	-
Activity deposited: Internal irradiation									
^{238}U	2	2	2	6	35	2	20	2	2
^{234}U	2	2	2	4	34	2	20	2	2
^{230}Th	0.001	0.001	0.07	0.08	1	0.001	4	0.001	0.001
^{226}Ra	0.002	0.002	0.002	0.008	0.08	0.002	0.002	0.002	0.002
Total (rounded) (α)	4	4	4	10	70	4	40	4	4
Activity deposited: External irradiation (γ)	0.4 to all organs and tissues								

Table 10

Normalized collective effective dose equivalent commitment from the model fuel fabrication facility

Radionuclide	Normalized collective effective dose equivalent commitment [10^{-4} man Sv (GW[e] a)$^{-1}$]		
	Cloud passage: Inhalation	Activity deposited: Internal irradiation	Activity deposited: External irradiation
^{238}U	6	0.7	0.004
^{234}U	7	0.9	
^{230}Th	0.2	0.01	
^{226}Ra	0.0004	0.001	
^{222}Rn	4	0.02	
Total (rounded)	20	2	0.004

Table 11

World nuclear generating capacity in 1979
[Net values in GW(e) and numbers of units in parentheses]
[I1, K12]

Country or area	Reactor type: PWR	BWR	GCR	HWR	LWGR	FBR	Total capacity	kW(e) per caput
Argentina				0.34 (1)			0.34	0.015
Belgium	1.66 (3)						1.66	0.17
Bulgaria	0.82 (2)						0.82	0.10
Canada				5.49 (11)			5.49	0.25
Czechoslovakia	0.38 (1)						0.38	0.024
Finland	0.42 (1)	0.66 (1)					1.08	0.23
France	5.71 (7)		2.13 (7)	0.07 (1)		0.25 (1)	8.16	0.15
German Dem. Rep.	1.29 (4)						1.29	0.074
Germany, Fed.Rep.of	5.37 (6)	3.16 (5)	0.01 (1)	0.05 (1)		0.02 (1)	8.61	0.14
India		0.40 (2)		0.20 (1)			0.60	0.001
Italy	0.24 (1)	0.15 (1)	0.15 (1)				0.54	0.01
Japan	6.44 (9)	7.72 (12)	0.16 (1)	0.15 (1)			14.47	0.16
Republic of Korea	0.56 (1)						0.56	0.17
Netherlands	0.45 (1)	0.05 (1)					0.50	0.038
Pakistan				0.13 (1)			0.13	0.002
Spain	0.15 (1)	0.44 (1)	0.48 (1)				1.07	0.031
Sweden	0.80 (1)	2.90 (5)					3.70	0.46
Switzerland	1.62 (3)	0.32 (1)					1.94	0.31
USSR	2.49 (7)	0.09 (5)			7.89 (16)	0.15 (2)	10.62	0.043
United Kingdom			6.75 (32)			0.23 (1)	6.98	0.13
United States	31.88 (42)	17.78 (26)	0.33 (1)				49.99	0.24
Other Asia	1.21 (2)						1.21	0.084
Total	61.49 (92)	33.67 (60)	10.01 (44)	6.43 (17)	7.89 (16)	0.65 (6)	120.14	0.07

Table 12

Noble gases discharged in airborne effluents from PWRs in various countries 1975-1979
[B23, D6, D8, E9, G3, K4, L1, L6, N19, P2, S14]

Country and reactor	Startup year	Electrical capacity [GW(e)]	Release (TBq)				
			1975	1976	1977	1978	1979
Belgium							
Doel 1,2	1974/75	0.79	7.7	30	28	17	44
Tihange	1975	0.87	17	170	55	58	14
Finland							
Loviisa	1977	0.42	-	-	2.2	1.4	1.6
France							
Fessenheim	1977	1.78	-	-	70	73	
Chooz	1967	0.30	100	183	103	120	
Bugey 2,3	1978	1.85	-	-	-	4.1	
Germany, Fed. Rep. of							
Obrigheim	1968	0.33	296	12	14	17	3.8
Stade	1972	0.63	47	389	132	18	8.5
Biblis A,B	1974/76	2.39	62	54	156	79	43
Neckarwestheim	1976	0.81	-	19	70	4.3	12
Unterweser	1978	1.23	-	-	-	1.9	38
Italy							
Trino	1964	0.25	17	6.6	2.2	20	
Japan							
Mihama 1	1970	0.34	2.7	2.1	2.7	1.7	2727
Mihama 2	1972	0.50	7.0	30	14	6.7	0.59
Mihama 3	1976	0.83	-	10	6.3	0.9	0.26
Takahama 1	1974	0.83	4.8	3.6	4.4	3.1	3.0
Takahama 2	1975	0.83	3.0	3.3	2.3	2.1	2.4
Ohi 1	1977	1.17	-	-	0.4	9.3	3.0
Ohi 2	1978	1.17	-	-	-	0.33	2.3
Ikata 1	1977	0.57	-	-	2.2	3.0	3.4
Genkai 1	1975	0.57	1.5	1.8	2.0	1.6	1.0
Netherlands							
Borssele	1973	0.45	97	144	37	15	8
Sweden							
Ringhals 2	1975	0.80	-	8.5	11	5.4	22
United States							
Arkansas 1	1974	0.84	38	210	514	277	315
Arkansas 2	1979	0.95	-	-	-	-	168
Beaver Valley	1976	0.80	-	-	2	14	65
Calvert Cliffs 1,2	1974	1.62	3.2	286	825	1020	378
Cook 1,2	1975	2.14	-	36	141	1795	403
Crystal River	1977	0.80	-	-	112	254	2802
Davis Besse	1977	0.92	-	-	47	77	62
Farley	1978	0.83	-	-	-	131	118
Fort Calhoun	1973	0.46	16	80	141	50	26
R.E. Ginna	1969	0.47	389	204	118	36	28
Haddam Neck	1968	0.55	18	18	115	79	204
Indian Point	1973/76	1.77	303	392	592	551	343
Kewaunee	1974	0.52	91	59	90	16	5.6
Maine Yankee	1972	0.77	152	48	11	53	73
Millstone Point 2	1975	0.80	-	57	84	28	13
North Anna	1978	0.90	-	-	-	559	232
Oconee	1973/74	2.64	562	1628	1317	1612	1772
Palisades	1971	0.64	97	1.1	2.2	12	2.5
Point Beach 1,2	1970/72	0.99	1676	74	42	19	36
Prairie Island	1973/74	1.01	81	64	25	47	26
Rancho Seco	1974	0.87	4.4	4.7	74	263	326
H.B. Robinson	1970	0.66	43	29	18	33	56
St. Lucie	1976	0.78	-	-	940	1084	570
Salem 1	1976	1.08	-	-	7.3	0.38	9.2
San Onofre	1967	0.44	66	15	5.6	67	24
Surry 1,2	1972/73	0.55	298	710	703	161	66
Three Mile Island 1	1974	0.79	134	102	614	581	83
Trojan	1975	1.08	-	-	113	11	34

Table 12, continued

Country and reactor	Startup year	Electrical capacity [GW(e)]	Release (TBq) 1975	1976	1977	1978	1979
Turkey Point	1972/73	1.32	496	577	862	870	392
Yankee Rowe	1960	0.17	1	1	4.6	24	6.7
Zion 1,2	1973/74	2.08	1676	5254	1191	2505	1262
Total annual energy generated [GW(e) a]			16.9	19.2	23.8	29.4	27.5
Normalized release [TBq (GW[e] a)$^{-1}$]			402	570	388	432	370
		Average 1975-1979			430 TBq [GW(e) a]$^{-1}$		

Table 13

Isotopic composition of noble gases discharged from PWRs in the United States during 1979 [B23]

Reactor	Startup year	Energy generated [GW(e) a]	Release (TBq) ^{41}Ar	^{85m}Kr	^{85}Kr	^{87}Kr	^{88}Kr	^{131m}Xe	^{133m}Xe	^{133}Xe	^{135m}Xe	^{135}Xe	^{138}Xe
Arkansas 1	1974	0.397	0.30	3.2	0.20	0.49	1.7	0.11	2.8	289	-	24	-
Arkansas 2	1979	0.916	5.3	-	-	-	-	0.001	-	143	-	19	-
Beaver Valley	1976	0.221	-	-	0.52	-	0	18	1.6	45	-	0.027	-
Calvert Cliffs 1,2	1975/77	1.161	0.005	1.3	0.036	-	0.045	0.048	0.14	363	-	13	-
Cook 1,2	1975/78	1.373	0.019	0.007	326	-	-	-	0.88	70	-	7.8	-
Crystal River	1977	0.453	17	25	-	7.8	19	36	49	2290	21	212	125
Davis Besse	1977	0.381	0.02	0.26	56	0.61	0.43	0.019	0.023	3.3	0.51	0.24	1.2
Joseph M. Farley	1978	0.211	11	0.001	0.78	0.062	0.007	3.5	1.4	95	-	5.1	0.01
Fort Calhoun	1973	0.440	0.078	0.01	0.48	0.004	0.016	-	0.19	25	-	0.24	-
R.E. Ginna	1969	0.355	0.033	0.11	0.74	-	-	0.036	0.018	25	-	1.9	-
Haddam Neck	1967	0.493	-	0.051	37	0.13	0.12	1.5	0.29	155	0.027	1.1	0.13
Indian Point	1973	1.142	-	0.92	24	0.29	1.0	3.8	3.6	297	0.38	11	0.84
Kewaunee	1974	0.412	0.31	0.016	1.0	-	0.013	-	0.007	1.1	-	0.41	-
Maine Yankee	1972	0.537	-	-	1.0	-	-	2.4	-	67	-	1.4	-
Millstone Point 2	1975	0.520	0.068	-	0.36	-	-	-	-	648	-	0.64	-
North Anna	1978	0.507	0.007	0.67	0.05	0.01	0.02	0.12	0.58	224	0.02	7.3	0.01
Oconee 1,2,3	1973/74	1.708	1.0	3.4	40	0.26	1.1	14	27	1646	1.4	29	0.15
Palisades	1971	0.415	-	-	0.090	-	-	0.021	0.002	2.4	-	0.007	-
Point Beach 1,2	1970/72	0.808	2.1	2.3	1.2	1.2	3.6	-	0.11	11.3	0.78	12	1.2
Prairie Island 1,2	1973/74	0.865	0.1	0.03	0.048	0.09	-	-	0.068	25	-	0.71	-
Rancho Seco	1974	0.687	0.06	0.52	0.27	0.007	0.041	0.085	0.92	300	-	24	-
H.B. Robinson	1970	0.482	0.05	-	-	-	-	-	-	56	-	0.87	-
Salem	1976	0.250	0.011	0.043	0.050	-	0.04	-	0.12	8.4	-	0.56	-
St. Lucie	1976	0.592	0.92	4.9	2.9	5.0	10	31	4.9	492	0.41	9.4	4.7
San Onofre	1967	0.401	0.40	0.08	2.3	0.019	0.084	0.10	0.073	19	-	0.53	-
Surry 1,2	1972/73	0.343	0.083	0.029	0.013	0.041	0.02	-	0.36	63	-	2.5	-
Three Mile Island 1	1974	0.266	0.67	-	0.007	-	0.007	0.093	0.26	81	-	0.95	-
Trojan	1975	0.631	0.016	0.042	0.038	0.034	0.058	0.092	0.28	32	0.13	1.4	0.016
Turkey Point	1972/73	0.811	2.0	0.050	0.035	0.0099	0.036	0.075	0.25	389	0.068	1.1	0.026
Yankee Rowe	1960	0.149	0.062	0.060	0.060	0.050	0.093	0.012	0.069	4.3	0.82	0.94	0.028
Zion	1973	1.238	0.28	0.062	0.097	-	1.5	8.8	0.63	1132	-	118	-
Total annual energy generated [GW(e) a]		19.165											
Normalized release [TBq (GW[e] a)$^{-1}$]			2.1	2.2	25	0.84	2.0	6.3	5.0	469	1.3	26	6.9

Table 14

Noble gases discharged in airborne effluents from BWRs in various countries 1975-1979
[B23, D6, D8, E9, G3, K4, L1, L6, N19, P2, S14]

Country and reactor	Startup year	Electrical capacity [GW(e)]	Release (TBq) 1975	1976	1977	1978	1979
Finland							
Olkiluoto	1978	0.660	-	-	-	0.25	0.014
Germany, Fed. Rep.of							
Gundremmingen	1966	0.237	274	195	9.2	8.5	-
Lingen	1968	0.182	1295	237	4.9	-	-
Würgassen	1971	0.640	4.5	18	29	121	159
Brunsbüttel	1976	0.770	-	36	116	280	46
Isar	1977	0.870	-	-	0.9	40	85
Italy							
Garigliano	1964	0.152	8456	8861	3328	2886	
Caorso	1978	0.548	-	-	-	-	
Japan							
Tsuruga	1970	0.357	85	70	23	16	8.1
Tokai 2	1978	1.100	-	-	-	-	-
Fukushima 1	1971	0.460	196	1070	17	740	133
Fukushima 2	1974	0.784					
Fukushima 3	1976	0.784	0.63	0.25	1.1	0.77	0.67
Fukushima 4	1978	0.784					
Fukushima 5	1978	0.784	-	-	0.0026	0.024	0.0025
Hamaoka 1	1976	0.540	-	-	-	-	-
Hamaoka 2	1978	0.840	-	-	-	-	-
Shimane	1974	0.460	-	-	-	-	-
Netherlands							
Dodewaard	1968	0.052	78	230	481	159	119
Sweden							
Oskarshamn 1	1970	0.460	-	5402	5217	4613	4700
Oskarshamn 2	1974	0.590	-	1.4	31	44	290
Ringhals 1	1974	0.780	-	1712	78	2900	19300
Barsebäck 1	1975	0.590	-	0.78	3	2.9	0.97
Barsebäck 2	1976	0.590	-	-	0.37	2.0	3.3
United States							
Big Rock Point	1963	0.075	1872	562	496	699	323
Browns Ferry	1973/77	3.195	932	2974	6142	5809	10027
Brunswick	1975/76	1.580	6.8	685	9102	3381	3184
Cooper	1974	0.764	729	1420	47	151	1125
Dresden 1	1960	0.200	19240	17020	19240	31450	6.8
Dresden 2,3	1971/72	1.545	13653	1199	11581	1502	2557
Duane Arnold	1975	0.515	57	195	143	58	342
J.A. Fitzpatrick	1975	0.300	151	1709	862	218	125
Edwin I. Hatch	1975	0.717	57	115	70	60	142
Humboldt Bay	1963	0.065	10952	3441	-	-	-
Lacrosse	1969	0.048	2109	4588	1573	312	385
Millstone Point 1	1971	0.652	109890	18759	22940	20942	762
Monticello	1971	0.536	5735	422	254	238	149
Nine Mile Point	1969	0.610	48100	6512	131	112	38
Oyster Creek	1969	0.520	7622	6142	6549	36926	37470
Peach Bottom	1974	2.086	480	7730	2631	1425	4592
Pilgrim	1972	0.664	3885	6771	15281	1210	514
Quad Cities	1973	1.538	4070	1166	947	1199	1644
Vermont Yankee	1972	0.514	124	106	131	183	299
Total annual energy generated [GW(e) a]			9.53	13.04	13.24	18.1	20.0
Normalized release [TBq (GW[e] a)$^{-1}$]			25447	7104	8103	6500	4407

Average 1975-1979 8800 TBq [GW(e) a]$^{-1}$

Table 15

Isotopic composition of noble gases discharged from BWRs in the United States during 1979 [B23]

Reactor	Startup year	Energy generated [GW(e) a]	Release (TBq)							
			^{41}Ar	^{83m}Kr	^{85m}Kr	^{85}Kr	^{87}Kr	^{88}Kr	^{89}Kr	^{90}Kr
Big Rock Point 1	1962	0.013	-	9.9	12	0.037	31	17	24	26
Browns Ferry 1,2,3	1973/77	2.393	44	-	50	8140	73	101	-	-
Brunswick 1,2	1975/77	0.810	41	-	88	-	316	281	-	-
Cooper	1974	0.591	-	25	74	3.9	100	188	-	-
Dresden 1	1959	1.013	-	-	-	-	-	-	-	-
Dresden 2,3	1970/71		-	54	-	-	69	136	-	-
Duane Arnold	1974	0.352	3.8	-	32	13	3.2	21	-	-
J.A. Fitzpatrick	1974	0.349	1.5	-	4.7	0.13	2.4	4.1	-	-
Edwin I Hatch	1974	0.401	2.0	-	5.8	-	0.37	2.8	0.06	-
Lacrosse	1967	0.024	-	-	6.8	0.36	41	25	0.49	-
Millstone Point 1	1970	0.505	-	-	14.	-	8.4	2.2	-	-
Monticello	1970	0.522	-	0.37	0.31	0.74	1.9	1.0	36	1.2
Nine Mile Point	1969	0.354	-	-	-	-	-	16	-	-
Oyster Creek	1969	0.541	-	-	1613	-	5217	5032	1.1	-
Peach Bottom 2,3	1973/74	1.740	-	-	16	-	4.1	3.1	-	-
Pilgrim	1972	0.574	-	-	96	0.002	83	204	-	-
Quad Cities 1,2	1971/72	1.075	-	-	121	-	488	190	-	-
Vermont Yankee	1972	0.414	-	-	1.3	-	3.8	3.2	-	-
Total annual energy generated [GW(e) a]		11.670								
Normalized release [TBq (GW[e] a)$^{-1}$]			7.9	7.6	180	690	550	530	5.2	2.3

Reactor	Startup year	Energy generated [GW(e) a]	Release (TBq)							
			^{131m}Xe	^{133m}Xe	^{133}Xe	^{135m}Xe	^{135}Xe	^{137}Xe	^{138}Xe	^{139}Xe
Big Rock Point 1	1962	0.013	0.11	0.32	5.8	40	20	38	64	35
Browns Ferry 1,2,3	1973/77	2.393	-	-	319	121	38	-	610	-
Brunswick 1,2	1975/77	0.810	-	29	84	888	1217	-	240	-
Cooper	1974	0.591	1.7	11	310	9.4	358	0.23	45	-
Dresden 1	1959	1.013	-	-	6.8	-	-	-	-	-
Dresden 2,3	1970/71		-	-	219	250	466	-	1365	-
Duane Arnold	1974	0.352	-	-	212	9.4	42	-	5.1	-
J.A. Fitzpatrick	1974	0.349	4.6	1.2	70	0.6	29	-	3.3	-
Edwin I Hatch	1974	0.401	14	1.2	110	0.74	2.1	-	2.4	-
Lacrosse	1967	0.024	0.35	3.0	27	33	120	2.9	120	-
Millstone Point 1	1970	0.505	81	-	12	119	74	269	182	-
Monticello	1970	0.522	0.07	0.02	10	2.8	2.1	47	41	3.7
Nine Mile Point	1969	0.354	-	-	-	6.0	5.1	-	12	-
Oyster Creek	1969	0.541	-	-	1298	3648	8362	23	12284	-
Peach Bottom 2,3	1973/74	1.740	5.0	72	3922	3.2	566	-	0.97	-
Pilgrim	1972	0.574	-	-	71	7.6	19	-	32	-
Quad Cities 1,2	1971/72	1.075	-	-	481	33	97	-	235	-
Vermont Yankee	1972	0.414	-	-	164	36	8.1	-	81	-
Total annual energy generated [GW(e) a]		11.670								
Normalized release [TBq (GW[e] a^{-1}]			9.1	10	630	450	980	33	1300	3.3

Table 16

Noble gases discharged in airborne effluents from HWRs in various countries 1975-1979 [B21, M10]

Country and reactor	Startup year	Electrical capacity [GW(e)]	Release (TBq) 1975	1976	1977	1978	1979
Argentina							
Atucha	1974	0.320	9.3	160	71	311	252
Canada							
Bruce A	1976/79	4 x 0.755	-	-	1254	1550	3084
Pickering A	1971/73	4 x 0.514	162	104	159	152	218
Total annual energy generated [GW(e) a]			2.2	2.6	3.2	4.1	4.3
Normalized release [TBq (GW[e] a)$^{-1}$]			86	102	464	491	827

Average 1975-1979: 460 TBq [GW(e) a]$^{-1}$

Table 17

Activation gases released from GCRs in various countries 1975-1979

Country and reactor	Startup year	Electrical capacity [GW(e)]	Release (TBq) 1975	1976	1977	1978	1979
France							
Chinon 1	1963	0.070					
Chinon 2	1965	0.210	224	182	145	94	
Chinon 3	1966	0.400					
St. Laurent des Eaux 1	1969	0.460	129	107	155	250	
St. Laurent des Eaux 2	1971	0.515					
Bugey 1	1972	0.540	195	114	89	107	
Italy							
Latina	1963	0.153	96	92	89	97	
Japan							
Tokai	1966	0.166	207	229	289	307	333
United Kingdom							
Calder	1956	0.200		548	962	1073	1100
Chapelcross	1959	0.192		1184	1184	1184	1200
Berkeley	1962	0.276		592	555	444	444
Bradwell	1962	0.250		555	666	592	555
Hunterston A	1964	0.300			555	740	
Hunterston B	1976	1.240		74			
Trawsfynydd	1964	0.390		5550	5550	4810	5180
Hinkley Point A	1965	0.460		2960	2960	2960	2590
Hinkley Point B	1976	1.240					
Dungeness A	1965	0.410		1110	1110	1110	444
Sizewell	1965	0.420		2220	2220	2220	2220
Oldbury	1967	0.416					
Wylfa	1971	0.840					
Total annual energy generated [GW(e) a]			4.42	4.59	5.10	5.07	4.4
Normalized release [TBq (GW[e] a)$^{-1}$]				3381	3241	3153	3194

Average 1976-1979: 3240 TBq [GW(e) a]$^{-1}$

Table 18

Tritium discharged in airborne effluents from reactors 1975-1979
[B21, B23, D6, D8, E9, G3, K4, L1, L6, M10, N19, P2, S14]

Country and reactor	Release (TBq)				
	1975	1976	1977	1978	1979
P W R					
France					
Bugey 2,3	-	-	-	44	
Chooz	-	-	-	-	
Fessenheim	-	-	-	-	
Germany, Fed.Rep.of					
Obrigheim	0.99	2.3	0.85	0.96	0.63
Stade	0.56	0.78	0.59	0.99	1.2
Biblis, A,B	0.48	0.48	1.26	2.29	2.4
Neckarswestheim		0.074	0.92	1.04	1.1
Unterweser		-	-	-	0.21
Italy					
Trino	0.14	0.60			
Netherlands					
Borssele	0.44	0.33	0.37	0.93	0.9
United States					
Arkansas 1	0.019	0.25	7.0	0.22	0.47
Arkansas 2	-	-	-	-	0.15
Beaver Valley		138	7.9	14	0.82
Calvert Cliffs	0.046		4.3	0.06	0.19
Cook 1	0.0007	0.004	0.007	0.72	0.5P
Crystal River	-	-	4.5	0.96	1.1
Davis Besse	-	-	0.0014	1.2	0.4
Joseph M. Farley	-	-	-	2.9	0.54
Fort Calhoun	0.088	0.093	0.11	0.14	0.054
R.E. Ginna	0.21	0.89	1.90	1.6	3.6
Haddam Neck	2.59	27	0.0004	2.5	6.4
Indian Point	0.48	0.89	0.44	0.38	0.48
Kewaunee	1.37	0.026	0.14	0.46	0.26
Maine Yankee	0.17	0.14	0.078	0.041	0.11
Millstone Point II	0.063	0.56	0.070	1.5	3.8
North Anna	-	-	-	0.66	0.070
Oconee	62.9	18.5	2.31	2.5	0.98
Point Beach	15.5	14.8	7.22	6.3	29.7
Prairie Island	0.37	1.22	3.24	5.3	5.8
Rancho Seco		0.34	0.78	8.9	5.3
H.B. Robinson	7.14	5.85	2.26	1.6	0.38
Salem	-	-	1.9	5.3	108
St. Lucia		0.074	11.8	19.8	12.6
San Onofre	1.26	1.74	2.81	1.1	1.0
Surry	1.18	13.7	32.5	8.1	3.0
Three Mile Island	1.48	26.6	4.77	7.9	2.4
Trojan	-	0.056	0.11	0.15	0.39
Turkey Point	0.13	0.19	0.14	0.13	0.035
Yankee Rowe	0.074	0.074	0.12	0.11	0.13
Total annual energy generated [GW(e) a]	15.7	16.8	21.3	24.4	22.8
Normalized release [TBq (GW[e] a)$^{-1}$]	6.2	15.2	4.5	5.9	8.5
	Average 1975-1979		7.8 TBq [GW(e) a]$^{-1}$		
B W R					
Germany, Fed. Rep.of					
Gundremmingen	3.7	1.0	0.26	0.037	0.014
Lingen	1.1	0.22	0.20	0.078	-
Würgassen	0.07		0.89	0.28	0.33
Brunsbüttel		0.0074	0.18	0.24	0.34
Isar				0.056	0.25
Italy					
Garigliano	0.026	0.55			
Netherlands					
Dosewaard	-	-	-	-	-
United States					
Big Rock Point	0.27	0.31	0.40	0.31	0.12
Browns Ferry	0.19	0.021	0.87	1.1	1.3
Brunswick	0.07	0.81	0.052	0.37	0.88
Cooper	1.6	2.5	1.9	0.21	0.92
Dresden 1	1.3	2.3	0.56	3.3	0.25
Dresden 2,3	8.1	5.2	18	12	6.8

Table 18, continued

Country and reactor	Release (TBq)				
	1975	1976	1977	1978	1979
Duane Arnold	0.70	0.59	0.56	0.22	0.33
J.A. Fitzpatrick	0.011	0.56	0.26	0.28	0.24
Edwin I. Hatch	0.066	0.052	0.085	0.22	0.54
Humboldt Bay	0.093	0.048	0.0024	0.0015	0.002
Lacrosse	0.63	0.48	0.32	0.29	0.17
Millstone Point I	0.63	1.1	2.4	1.8	2.2
Monticello		2.8	5.1	8.7	8.1
Nine Mile Point	3.4	0.70	1.7	3.2	1.5
Oyster Creek	0.10	0.041	0.044	1.4	1.4
Peach Bottom	0.011	1.0	3.7	0.74	1.0
Pilgrim	2.7	1.4	0.023	3.5	5.8
Quad Cities	1.4	11.0	1.5	3.7	5.4
Vermont Yankee	0.26	0.52	0.85	0.45	0.61
Total annual energy generated [GW(e) a]	7.1	9.6	10.6	13.1	13.2
Normalized release [TBq (GW[e] a)$^{-1}$]	3.8	3.5	3.8	3.2	2.9
	Average 1975-1979		3.4 TBq [GW(e) a]$^{-1}$		
H W R					
Argentina					
Atucha	38	220	224	222	237
Canada					
Bruce	-	-	315	481	1399
Pickering	918	891	1628	962	1147
Total annual energy generated [GW(e) a]	2.0	2.6	3.2	4.1	4.3
Normalized release [TBq (GW[e] a)$^{-1}$]	478	427	677	406	647
	Average 1975-1979		540 TBq [GW(e) a]$^{-1}$		

Table 19

Tritium discharged in liquid effluents from reactors 1975-1979
[B21, B23, D6, D8, E9, G3, G4, K4, L1, L6, M10, N19, P2, S14]

Country and reactor	Release (TBq)				
	1975	1976	1977	1978	1979
P W R					
Finland					
Loviisa	-	-	1.2	5.0	
France					
Bugey 2,3	-	-	-	3.3	
Chooz	92	71	96	65	
Fessenheim	-	-	3.1	31	
Germany, Fed. Rep.of					
Obrigheim	6.2	4.7	5.5	4.8	5.0
Stade	3.9	1.6	4.8	4.9	5.4
Biblis A,B	4.1	13	13	28	18
Neckarwestheim	-	0.19	3.1	5.0	3.8
Unterweser	-	-	-	0.0081	4.0
Italy					
Trino	44	27	64	77	
Japan					
Mihama 1,2	2.4	5.2	4.1	8.1	7.4
Mihama 3	-	1.7	3.7	5.2	3.6
Takahama 1,2	13	13	11	17	8.5
Ohi 1,2	-	-	0.014	4.4	16
Ikata 1	-	-	3.3	11	4.1
Genkai	2.3	1.1	11	6.7	11

Table 19, continued

Country and reactor	Release (TBq) 1975	1976	1977	1978	1979
Netherlands					
Borssele	2.1	1.5	1.5	8.4	8.3
Sweden					
Ringhals 2	-	10	8.8	11	8.9
United States					
Arkansas 1	17	7.8	9.1	10.8	6.2
Arkansas 2	-	-	-	-	1.95
Beaver Valley	-	0.32	4.0	12.9	3.5
Calvert Cliffs	9.7	10	21	16.8	19
Cook 1	2.1	7.1	11	23	45
Crystal River	-	-	6.1	5.7	6.1
Davis Besse	-	-	0.33	8.0	9.1
Joseph M. Farley	-	-	-	2.2	3.5
Fort Calhoun	4.1	4.5	5.8	5.6	9.5
R.E. Ginna	9.6	8.9	4.4	8.9	8.9
Haddam Neck	210	179	247	146	131
Indian Point	2.9	12	14	28.4	18.2
Kewaunee	10	6.7	11	10.9	9.2
Maine Yankee	6.5	14	5.7	11.7	7.5
Millstone Point 2	0.28	10	7.8	7.4	9.4
North Anna	-	-	-	10.4	11.6
Oconee	131	81	71	43	33
Palisades	1.5	0.36	2.1	3.7	4.7
Point Beach	33	27	37	48	33
Prairie Island	0.017	0.0037	50	20	23.3
Rancho Seco	4.9	0	0.0031	-	-
H.B. Robinson	23	36	25	17.5	15.9
Salem	-	0.0015	11	16.5	86
St. Lucie	-	0.49	9.0	4.7	4.7
San Onofre 1	148	125	66	92.5	85.8
Surry	16	29	15	27.6	13.2
Three Mile Island 1	17	7.0	7.1	5.7	2.1
Trojan	-	1.3	12	5.9	2.5
Turkey Point	29	29	34	43	35
Yankee Rowe	9.1	5.8	5.1	7.2	6.5
Zion	38	28	27	27	22
Total annual energy generated [GW(e) a)]	16.9	19.2	23.8	29.4	25.8
Normalized release, [TBq (GW[e] a)$^{-1}$]	52.9	38.7	40.0	33.0	30.0
	Average 1975-1979 38 TBq [GW(e) a]$^{-1}$				
B W R					
Finland					
Olkiluoto	-	-	-	0.0086	0.46
Germany, Fed.Rep.of					
Gundremmingen	4.7	1.9	0.81	0.093	0.026
Lingen	0.63	0.56	0.092	0.070	0.028
Würgassen	0.15	1.1	1.3	2.0	1.5
Brunsbüttel	-	-	0.34	0.70	0.085
Isar	-	-	0.0015	0.17	0.80
Italy					
Garigliano	0.19	0.67	0.56	0.37	
Japan					
Tsuruga	1.5	1.9	1.0	0.78	1.4
Tokai 2	-	-	-	0.14	0.31
Fukushima 1	-	-	0.14	0.067	0.13
Fukushima 2	-	-	0.0017	0.13	0.16
Fukushima 3	-	-	0.13	0.19	0.0052
Fukushima 4	-	-	-	0.034	0.000027
Fukushima 5	-	-	0.0073	0.10	0.078
Hamaoka 1	-	-	0.24	0.037]	0.63
Hamaoka 2	-	-	-	0.085]	
Shimane	0.14	0.24	0.18	0.19	0.16
Sweden					
Oskarshamn		1.3	1.3	1.6	2.7
Ringhals 1		0.85	0.56	0.32	1.7
Barsebäck		0.52	0.74	1.3	1.1
United States					
Big Rock Point	0.22	0.074	0.33	0.15	0.20
Browns Ferry	0.37	0.15	0.89	1.1	0.49
Brunswick	0.11	0.22	0.33	0.52	1.1

Table 19, continued

Country and reactor	Release (TBq)				
	1975	1976	1977	1978	1979
Cooper	0.30	0.30	0.33	0.28	0.25
Dresden 1	0.01	0.0007	0.0033	0.49	0.056
Dresden 2,3	2.0	0.74	0.19	0.71	0.71
Duane Arnold	0.012	0.013	0.0078	4.4	0.010
J.A. Fitzpatrick	0.18	0.16	0.12	0.070	0.056
Edwin I. Hatch	0.22	0.33	0.44	0.33	0.46
Humboldt Bay	0.74	0.48	0.020	0.001	0.002
Lacrosse	4.7	1.5	1.8	1.7	1.3
Millstone Point 1	3.0	0.74	0.16	0.12	0.29
Monticello	-	-	-	-	-
Nine Mile Point	1.0	0.093	0.092	-	0.25
Oyster Creek	0.67	1.4	0.70	0.73	0.052
Peach Bottom	1.1	2.7	2.6	1.2	1.6
Pilgrim	0.67	1.7	1.2	0.11	0.50
Quad Cities	2.0	1.8	0.98	0.64	0.63
Vermont Yankee	-	0.059	0.031	-	0.15
Total annual energy generated [GW(e) a]	9.53	13.04	13.24	18.1	20.0
Normalized release, [TBq (GW[e] a)$^{-1}$]	2.6	1.6	1.3	1.1	1.0
	Average 1975-1979		1.4 TBq [GW(e) a]$^{-1}$		
G C R					
France					
Chinon	-	3.9	4.1	4.8	
St. Laurent	-	19	13	25	
Bugey 1	9.0	7.2	8.9	14	
Japan					
Tokai	-	-	-	0.0006	0.033
United Kingdom					
Calder	-	-	-	-	-
Chapelcross	0.26	0.33	0.074	1.2	2.8
Bradwell	3.3	11	7.4	3.8	4.4
Berkeley	2.6	1.1	1.9	0.59	1.6
Hunterston A	2.0	2.4	2.0	2.0	
Hunterston B		1.6	2.0	85	
Trawsfynydd	3.3	0.59	0.48	0.56	2.1
Hinkley Point A	2.0	0.89	1.2	2.0	3.6
Hinkley Point B		0.11	27	59	160
Dungeness A	0.93	1.3	0.96	1.2	0.78
Sizewell	1.8	2.3	1.6	1.1	1.6
Oldbury	0.52	0.70	0.56	0.27	0.22
Wylfa	4.8	7.3	11	39	4.6
Total annual energy generated [GW(e) a]	4.42	4.59	5.10	5.07	4.4
Normalized release, [TBq (GW[e] a)$^{-1}$]	6.91	13.0	16.0	47.2	41.0
	Average 1975-1979		25 TBq [GW(e) a]$^{-1}$		
H W R					
Argentina					
Atucha	31	76	218	229	259
Canada					
Bruce	-	-	36	152	546
Pickering	540	224	703	1188	1421
Total annual energy generated [GW(e) a]	2.0	2.6	3.2	4.1	4.3
Normalized release, [TBq (GW[e] a)$^{-1}$]	286	115	299	383	518
	Average 1975-1979		350 TBq [GW(e) a]$^{-1}$		

Table 20

Carbon-14 discharges from LWRs
in the Federal Republic of Germany 1976-1978
[R1, S15]

Reactor	Release (GBq)		
	1976	1977	1978
PWR a/			
Obrigheim		111 (15)	33 (19)
Stade		111(111)	55 (55)
Biblis A		178 (15)	78 (22)
Biblis B		181 (4.4)	168 (15)
Neckarwestheim		148 (4.1)	144 (6)
Normalized release [GBq (GW[e] a)$^{-1}$]			222
BWR b/			
Gundremmingen	137	37	3.7
Lingen	42	7.4	-
Würgassen	-	229	229
Brunsbüttel		159	167
Normalized release [GBq (GW[e] a)$^{-1}$]			518

a/ CO_2 bound values in parentheses.
b/ CO_2 values only.

Table 21

Iodine releases to atmosphere from reactors 1975-1979
[B21, B23, D6, D8, E9, G3, K4, L1, L6, N19, P2, S14]

Country and reactor	Release (GBq)				
	1975	1976	1977	1978	1979
PWR					
Belgium					
Doel	0.089	0.19	0.089	-	0.33
Tihange	0.021	0.74	0.081	0.37	0.11
Finland					
Loviisa	-	-	0.04	-	0.0021
Germany, Fed. Rep. of					
Obrigheim	0.41	0.074	0.022	0.026	0.03
Stade	0.37	0.74	0.96	0.14	0.086
Biblis A,B	0.19	0.37	0.15	0.59	0.68
Unterweser	-	-	-	0.00074	0.045
Neckarwestheim	-	0.074	1.7	0.26	0.032
Italy					
Trino	0.0017	0.00003	0.0033		
Japan					
Mihama 1	-	0.012	0.014	0.0089	0.0048
Mihama 2	-	0.18	0.078	0.093	0.037
Mihama 3	-	0.0052	0.0082	0.010	0.0078
Takahama 1,2	0.048	0.0074	0.070	0.010	0.014
Ohoi 1	-	-	0.00067	0.078	0.041
Ohoi 2	-	-	-	0.0022	0.089
Ikata 1	-	-	-	0.00056	0.028
Netherlands					
Borssele	0.52	0.31	0.13	0.0078	-
Sweden					
Ringhals 2	-	0.27	0.81	0.69	0.27
United States					
Arkansas 1	0.81	1.5	0.41	0.11	0.16
Arkansas 2	-	-	-	-	0.17
Beaver Valley	-	0.0081	0.0056	0.63	0.015
Calvert Cliffs	1.3	18.0	14.0	7.4	15.5
Cook 1	0.0063	0.052	3.7	0.48	0.55
Fort Calhoun	0.26	27.0	4.8	0.30	0.47
Crystal River	-	-	0.058	31.0	58.0
Davis Besse	-	-	0.0041	0.11	0.20

Table 21, continued

Country and reactor	Release (GBq)				
	1975	1976	1977	1978	1979
Joseph M. Farley	-	-	-	0.0017	0.0005
R.E. Ginna	2.4	1.3	0.96	0.32	0.71
Haddam Neck	0.033	0.027	0.030	0.11	1.8
Indian Point	15.0	10.0	5.2	3.0	6.1
Kewaunee	0.74	0.12	0.76	0.15	0.043
Maine Yankee	0.22	0.059	0.21	0.074	4.8
Millstone Point 2	0.0017	1.8	0.22	0.53	0.62
North Anna	-	-	-	1.1	1.4
Oconee	0.41	5.9	14.0	6.3	7.4
Palisades	16.0	1.1	0.89	1.6	1.0
Point Beach	7.0	0.23	0.23	0.56	0.78
Prairie Island	0.78	0.93	0.30	0.74	0.16
Rancho Seco	0.007	0.04	0.096	18	0.20
H.B. Robinson	0.85	9.3	0.44	0.070	0.006
Salem	-	-	-	0.20	0.30
St. Lucie	-	0.074	3.0	38	7.4
San Onofre	9.3	0.17	0.0066	0.0078	0.0045
Surry	4.8	20.0	18.0	2.2	0.23
Three Mile Island 1	0.035	0.32	0.78	0.96	0.41
Trojan	-	-	0.97	0.89	1.7
Turkey Point	17.0	19.0	52.0	18.0	1.7
Yankee Rowe	0.1	0.048	0.0085	0.014	0.014
Zion	-	3.3	1.6	2.6	0.45
Total annual energy generated [GW(e) a]	16.9	19.2	23.8	29.4	27.5
Normalized release [GBq (GW[e] a)$^{-1}$]	4.70	6.41	5.32	4.68	4.18
	Average 1975-1979 5.0 GBq [GW(e) a]$^{-1}$				
B W R					
Finland					
Olkiluoto	-	-	-	0.017	0.023
Germany, Fed.Rep. of					
Gundremmingen	9.3	13	0.19	0.0028	-
Lingen	48	1.9	0.052	0.00074	-
Würgassen	0.052	1.7	1.0	4.1	2.5
Brunsbüttel	-	0.00074	0.56	1.8	0.018
Isar	-	-	-	-	0.003
Italy					
Garigliano	0.59	1.3	0.56		
Japan					
Tsuruga	1.2	1.0	0.37	0.19	0.17
Tokai 2	-	-	-	0.012	0.028
Fukushima 1,2	0.48	8.9	1.0	32.0	5.9
Fukushima 3,4	-	0.0037	0.18	0.048	0.096
Fukushima 5					-
Hamaoka 1,2					0.0052
Shimane					-
Sweden					
Ringhals 1		0.67	0.32	1.2	23
Oskarshamn		2.7	8.9	5.5	5.0
Barsebäck		0.070	0.031	0.089	0.10
United States					
Big Point Rock	10.0	5.9	7.4	5.4	0.24
Browns Ferry	22.0	22.0	5.9	14.4	5.8
Brunswick	0.10	17.0	78.0	38.0	28.0
Cooper	16.0	3.3	1.7	5.4	8.0
Dresden 1	211.0	85.0	2020.0	997.0	0.12
Dresden 2,3	4.1	4.8	4.8	2110.0	1298.0
Duane Arnold	15.0	4.1	4.1	1583.0	569.0
J.A. Fitzpatrick	0.67	215.0	7.0	9.4	0.86
Edwin I. Hatch	0.24	0.13	0.27	0.084	0.92
Humboldt Bay	41.0	14.0	0.00044	-	-
Lacrosse	4.8	3.7	9.3	1.5	0.82
Millstone Point 1	2331.0	1332.0	2257.0	1417.0	141.0
Monticello	555.0	37.0	20.0	15.0	10.3
Nine Mile Point	222.0	318.0	52.0	44.0	5.8
Oyster Creek	1517.0	1702.0	1517.0	2294.0	2868.0
Peach Bottom	1.3	70.0	63.0	52.0	49.0

Table 21, continued

Country and reactor	Release (GBq)				
	1975	1976	1977	1978	1979
Pilgrim	229.0	74.0	126.0	61.0	52.0
Quad Cities	107.0	159.0	222.0	407.0	523.0
Vermont Yankee	15.0	2.6	0.81	11.0	21.0
Total annual energy generated [GW(e) a]	9.53	13.04	13.24	18.1	20.0
Normalized release [GBq (GW[e] a)$^{-1}$]	561	314	484	501	280
	Average 1975-1979 410 GBq [GW(e) a]$^{-1}$				
G C R					
France					
Chinon	0.78	0.081			
Bugey	0.81	0.070			
St. Laurent	0.59	0.41			
Japan					
Tokai				0.0041	0.0030
H W R					
Argentina					
Atucha [GBq (GW[e] a)$^{-1}$]	0.16	1.2	0.24	5.4	8.7
	Average 1975-1979 3.1 GBq [GW(e) a]$^{-1}$				

Table 22

Isotopic composition of iodine releases from reactors in the United States in 1979 [B23]

Reactor	Release (GBq)				
	^{131}I	^{132}I	^{133}I	^{134}I	^{135}I
P W R					
Arkansas 1	0.16	-	0.0067	-	-
Arkansas 2	0.17	-	0.0003	-	-
Beaver Valley	0.015	-	0.0015	-	0.0018
Calvert Cliffs	11.1	0.28	4.0	-	0.14
Cook 1	0.53	-	0.026	-	-
Crystal River	0.69	-	0.15	-	58.0
Davis Besse	0.18	-	0.023	-	0.0041
Fort Calhoun	0.048	-	0.067	0	0.35
Joseph M. Farley	0.0005	-	-	-	-
R.E. Ginna	0.35	0.044	0.32	-	-
Haddam Neck	1.7	-	0.093	-	0.14
Indian Point	4.3	-	0.46	-	1.3
Kewaunee	0.020	0.0078	0.011	0.00035	0.0039
Maine Yankee	2.0	-	2.6	-	0.23
Millstone Point 2	0.53	-	0.036	-	0.059
North Anna	1.3	-	0.052	-	-
Oconee	5.1	0.10	1.8	0.033	0.37
Palisades	0.70	-	0.31	-	0.083
Point Beach	0.16	0.36	0.26	0.008	0.0029
Prairie Island	0.14	-	0.023	-	-
Rancho Seco	0.17	-	0.030	-	-
H.B. Robinson	0.0014	-	0.0021	-	0.004
St. Lucie	3.7	-	3.7	-	0.004
Salem	0.20	-	0.10	-	-
San Onofre	0.045	-	-	-	-
Surry 1,2	0.23	0.0044	0.0029	-	-
Three Mile Island 1	0.41	-	-	-	-
Trojan	0.53	0.001	0.47	-	0.70

Table 22, continued

Reactor	Release (GBq)				
	^{131}I	^{132}I	^{133}I	^{134}I	^{135}I
Turkey Point	1.2	-	0.58	-	0.065
Yankee Row	0.0067	-	0.0028	-	0.0048
Zion 1,2	0.23	-	0.22	-	-
Total annual energy generated [GW(e) a]	19.165				
Normalized release, [GBq (GW[e] a)$^{-1}$]	1.9	0.042	0.78	0.0017	3.2
B W R					
Big Rock Point	0.011	-	0.11	-	0.13
Browns Ferry 1,2,3	1.0	-	1.1		3.7
Brunswick 1,2	4.7	1.3	17,8	-	4.2
Cooper	2.5	-	0.76	-	4.7
Dresden 1	0.12	-	-	-	-
Dresden 2,3	75	-	390	-	834
Duane Arnold	0.35	-	2.7	-	566
J.A. Fitzpatrick	0.21	-	0.44	-	0.21
Edwin I. Hatch	0.88	-	0.043	-	-
Lacrosse	0.41	0.011	0.28	0.030	0.088
Millstone Point	15	-	59	-	67
Monticello	0.89	-	3.4	-	6.0
Nine Mile Point	1.0	-	1.5	-	3.3
Oyster Creek	326	-	1095	-	1447
Peach Bottom 2,3	9.5	-	23	-	16
Pilgrim	3.7	-	5.7	-	43
Quad Cities 1,2	35	-	210		278
Vermont Yankee	15	-	4.4	-	1.8
Total annual energy generated [GW(e) a]	11.670				
Normalized release, [GBq (GW[e] a)$^{-1}$]	42	0.11	155	0.0026	281

Table 23

Particulate releases from reactors in various countries 1975-1979
[B23, D6, D8, E9, G3, K4, L1, L6, N19, P2, S14]

Country and reactor	Release (GBq)				
	1975	1976	1977	1978	1979
P W R					
Belgium					
Doel	6.7	7.8	6.3	6.7	
Tihange	-	0.0018	1.1	3.2	
Finland					
Loviisa	-	-	-	0.042	0.037
France					
Chooz	0.089	0.063	3.4	0.44	
Fessenheim	-	-	-	0.67	
Bugey 2,3	-	-	-	0.059	
Germany, Fed. Rep.of					
Obrigheim	0.93	0.30	0.24	0.16	0.075
Stade	1.1	0.26	0.33	0.37	0.025
Biblis A,B	0.22	0.11	0.20	0.0013	0.016
Neckarwestheim	-	0.019	0.45	0.19	0.025
Italy					
Trino	-	-	0.0037		
Netherlands					
Borssele	0.67	0.052	0.025	0.00052	0.004
Sweden					
Ringhals 2	-	0.30	0.26	0.083	0.009
United States					
Arkansas 1	0.41	0.63	0.0044	0.044	0.00074
Arkansas 2	-	-	-	-	0.0074
Beaver Valley	-	0.00005	0.0002	0.00074	0.00059
Calvert Cliffs	0.41	0.59	5.2	0.50	0.18

Table 23, continued

Country and reactor	Release (GBq)				
	1975	1976	1977	1978	1979
Cook 1,2	-	0.0002	0.52	3.6	2.2
Crystal River	-	-	0.037	0.0006	0.16
Davis Besse	-	-	0.0088	0.0083	0.033
Joseph M. Farley	-	-	-	1.5	0.81
Fort Calhoun	0.0041	0.01	0.0027	0.0045	0.0059
R.E. Ginna	0.0016	0.001	0.0026	0.0048	0.34
Haddam Neck	0.078	0.0063	0.036	0.081	0.11
Indian Point	46	1.0	0.56	6.9	12
Kewaunee	24	0.012	0.021	0.059	0.003
Maine Yankee	0.0093	0.078	0.012	0.0081	0.037
Millstone Point 2	0.0004	0.11	0.014	0.029	3.0
North Anna	-	-	-	0.036	0.81
Oconee	0.010	3.7	7.8	1.9	3.7
Palisades	0.022	0.56	0.041	0.15	0.059
Point Beach	3.5	0.59	0.067	0.37	0.35
Prairie Island	0.13	0.0089	0.041	0.0015	0.003
Rancho Seco	0.0029	0.002	0.093	0.52	0.048
H.B. Robinson	0.050	0.021	0.093	0.013	0.015
St. Lucie	-	0.00056	2.8	10	3.7
Salem	-	-	0.00001	1.3	0.081
San Onofre	1.3	0.00067	0.00018	0.093	0.00074
Surry	2.9	3.0	0.56	0.13	0.052
Three Mile Island 1	0.0037	0.16	0.44	3.7	0.04
Trojan	-	0.37	0.95	0.24	0.74
Turkey Point	2.2	2.8	1.9	2.9	1.7
Yankee Rowe	0.30	0.00081	0.0012	0.0002	0.003
Total annual energy generated [GW(e) a]	15.7	17.3	21.8	24.8	23.6
Normalized release, [GBq (GW(e) a)$^{-1}$]	5.77	1.27	1.54	1.85	1.28
	Average 1975-1979 2.15 GBq [GW(e) a]$^{-1}$				
B W R					
Finland					
Olkiluoto	-	-	-	0.0059	0.33
Germany, Fed.Rep.of					
Gundremmingen	0.30	0.19	0.27	0.15	0.004
Lingen	3.7	0.019	0.070	0.056	0.0013
Würgassen	4.0	0.63	1.4	2.1	1.4
Brunsbüttel	-	0.26	2.7	1.4	7.4
Isar	-	-	0.0011	0.16	0.79
Italy					
Garigliano		1.2	0.74		
Netherlands					
Dodewaard	0.22	0.12	0.11	0.035	
Sweden					
Oskarshamm	-	15	8.3	1.2	1.6
Ringhals 1	-	4.9	20	11	94
Barsebäck	-	0.096	0.72	1.6	0.30
United States					
Big Rock Point	3.6	1.5	0.32	0.22	0.059
Browns Ferry	2.2	2.0	2.4	3.7	4.8
Brunswick	0.14	0.70	5.2	4.1	25
Cooper	1.1	0.41	0.17	0.081	0.11
Dresden 1	13.0	17.0	22.0	41	0.77
Dresden 2,3	153.0	167.0	1561.0	89.0	185.0
Duane Arnold	0.33	0.25	0.27	0.85	0.89
J.A. Fitzpatrick	0.67	0.70	1.1	2.0	0.32
Edwin I. Hatch	0.01	0.017	0.031	0.085	0.078
Humboldt Bay	31.0	1.0	0.015	0.026	0.004
Lacrosse	0.48	0.85	0.41	0.12	0.48
Millstone Point 1	7.0	5.6	7.4	50	7.0
Monticello	24.0	1.9	0.74	0.50	0.37
Nine Mile Point	16.0	3.7	1.8	1.0	0.74
Oyster Creek	6.7	8.1	48.0	296.0	19.0
Peach Bottom	0.14	1.4	1.0	0.46	0.30
Pilgrim	24.0	12.0	7.8	2.1	2.0

Table 23, continued

Country and reactor	Release (GBq) 1975	1976	1977	1978	1979
Quad Cities	15.0	20.0	27.0	41.0	23.0
Vermont Yankee	0.074	0.21	0.28	0.20	1.1
Total annual energy generated [GW(e) a]	7.1	10.9	11.9	15.5	15.5
Normalized release [GBq (GW[e] a)$^{-1}$]	43.0	24.4	144.0	35.5	24.2
	Average 1975-1979 52.7 GBq [GW(e) a]$^{-1}$				
G C R					
France					
Chinon	0.37	0.67	0.48	0.48	
Bugey	0.063	0.30	0.28	0.67	
St. Laurent	0.048	0.070	0.23	0.16	
Japan					
Tokai	-	-	-		
United Kingdom					
Bradwell	0.11	0.096	0.11	0.15	0.15
Berkeley	0.14	0.11	0.11	0.074	0.15
Hunterston A	-	-	0.37	0.37	-
Hunterston B	-	0.27	0.26	0.019	-
Trawsfynydd	0.41	0.48	0.67	0.37	0.41
Hinkley Point A	0.41	0.48	0.37	0.41	0.74
Hinkley Point B	-	0.70	0.67	1.1	1.1
Dungeness A	2.0	0.70	0.41	0.52	0.33
Sizewell	0.37	0.41	0.56	0.48	0.45
Oldbury	1.3	0.067	0.11	0.074	0.10
Wylfa	0.15	0.31	0.37	0.37	0.26
Total annual energy generated [GW(e) a]	4.42	4.59	5.10	5.07	4.3
Normalized release [GBq (GW[e] a)$^{-1}$]	1.19	1.02	0.98	1.03	0.86
	Average 1975-1979 1.0 GBq [GW(e) a]$^{-1}$				
H W R					
Argentina					
Atucha [GBq (GW[e] a)$^{-1}$]	0.018	0.037	0.028	0.060	0.078
	Average 1975-1979 0.044 GBq [GW(e) a]$^{-1}$				

Table 24

Liquid effluent discharges other than tritium from reactors 1975-1979
[B23, D6, D8, E9, G3, K4, L1, L6, N19, P2, S14]

Country and reactor	Release (GBq) 1975	1976	1977	1978	1979
P W R					
Belgium					
Doel	381	1840	625	696	
Tihange	14	31	132	72	
Finland					
Loviisa	-	-	4	18	15
France					
Chooz	318	95	4.1		
Fessenheim	-	-	256	174	
Bugey 2,3	-	-	-	364	
Germany, Fed. Rep.of					
Obrigheim	64	36	9.6	6.3	6.3
Stade	10	12	14	3.7	9.7
Biblis A	27	8.1	3.8	4.7	1.9

Table 24, continued

Country and reactor	Release (GBq) 1975	1976	1977	1978	1979
Biblis B	-	11	1.1	4.4	7.8
Neckarswestheim	-	8.9	5.6	1.1	2.1
Unterweser	-	-	-	-	0.07
Italy					
Trino	54	100	52	48	
Japan					
Mihama 1	0.74	0.22	0.28	0.32	0.34
Mihama 2					
Mihama 3		0.01	0.044	0.048	0.078
Takahama 1	0.16	0.14	0.31	0.074	0.063
Takahama 2					
Ohi 1		0.0014	0.041	0.06	
Ohi 2					
Ikata 1		0.037	0.048	0.007	
Genkai 1	0.033	-	-	-	-
Netherlands					
Borssele	60	31	16	11	11
Sweden					
Ringhals	-	225	427	209	115
United States					
Arkansas 1	115	485	167	223	114
Arkansas 2	-	-	-	-	48
Beaver Valley 1	-	6.3	24	9.7	4.5
Calvert Cliffs 1	53	44	129	227	289
Cook 1	9.6	69	56	55	95
Crystal River	-	-	0.57	1.1	15
Davis Besse	-	-	0.96	3.3	1.6
Joseph M. Farley	-	-	-	3.7	2.2
Fort Calhoun	13	20	13	22	9.0
R.E. Ginna	16	26	2.4	2.2	3.2
Haddam Neck	44	4.8	63	35	32
Indian Point	182	184	112	111	87
Kawaunee	27	105	47	26	33
Maine Yankee	119	105	16	3.8	17
Millstone Point 2	0.74	9.6	57	103	180
North Anna	-	-	-	9.9	22
Oconee 1,2,3	187	293	1340	241	34
Palisades	128	16	3.4	3.6	4.7
Point Beach 1,2	87	120	56	25	27
Prairie Island 1,2	17	3.7	0.49	0.18	0.33
Rancho Seco	0.37	-	-	-	-
H.B. Robinson	17	14	12	6.6	11
St. Lucie	-	3.0	215	104	99
Salem 1	-	0.37	107	148	147
San Onofre 1	45	275	364	437	407
Surry 1,2	343	1246	2424	89	94
Three Mile Island 1	2.6	3.7	7.2	23	18
Trojan	-	102	155	26	21
Turkey Pt. 3,4	114	320	329	123	15
Yankee Rowe	0.74	0.37	0.67	3.0	0.43
Zion 1,2	0.37	5.9	35	35	26
Total annual energy generated [GW(e) a]	16.9	19.2	23.8	29.4	27.5
Normalized release, [GBq (GW!e] a)$^{-1}$]	145	310	306	126	74
	Average 1975-1979 184 GBq [GW(e) a]$^{-1}$				
B W R					
Finland					
Olkiluoto	-	-	-	1.2	7.7
Germany, Fed. Rep.of					
Gundremmingen	47	43	64	20	8.3
Lingen	1.5	9.6	0.37	0.37	0.93
Würgassen	69	41	58	20	16
Brunsbüttel	-	83	61	52	17
Isar	-	-	1.5	7.8	9.7
Italy					
Garigliano	116	139	152	111	
Japan					
Tsuruga	1.5	1.9	1.0	0.78	1.4
Tokai 2	-	-	-	0.14	0.31
Fukushima 1	-	-	0.14	0.067	0.13

Table 24. continued

Country and reactor	Release (GBq) 1975	1976	1977	1978	1979
Fukushima 2	-	-	0.017	0.13	0.16
Fukushima 3	-	-	0.13	0.19	0.0052
Fukushima 4	-	-	-	0.034	0.000027
Fukushima 5	-	-	0.0073	0.10	0.078
Hamaoka 1	-	-	0.24	0.037	0.63
Hamaoka 2	-	-	-	0.085	
Shimane	0.14	0.24	0.18	0.19	0.16
Sweden					
Oskarshamn 1,2		903	485	158	155
Ringhals 1		232	249	148	223
Barsebäck 1,2		64	68	140	58
United States					
Big Rock Point 1	74	28	14	10	33
Browns Ferry 1,2,3	100	146	44	488	66
Brunswick 1,2	70	122	230	129	189
Cooper	64	2.6	28	113	92
Dresden 1	31	13	22	12	0.98
Dresden 1,2	30	45	16	15	9.8
Duane Arnold	3.7	3.7	0.085	10	0.02
J.A. Fitzpatrick	197	222	33	58	24
Edwin I. Hatch	2.2	1.5	925	1.5	1.8
Humboldt Bay	140	37	34	7.2	3.5
Lacrosse	525	214	788	328	124.7
Millstone Point 1	7360	357	19	6.5	7.8
Monticello	-	-	-	-	-
Nine Mile Point	780	79	11	-	70
Oyster Creek	15	8.1	3.6	0.55	0.25
Peach Bottom 2,3	34	125	83	189	722
Pilgrim	296	86	126	65	19
Quad Cities	633	258	50	83	48
Vermont Yankee	0.37	0.37	5.7	-	0.01
Total annual energy generated [GW(e) a]	9.53	13.04	13.24	18.1	20.0
Normalized release, [GBq (GW[e] a)$^{-1}$]	1100	251	273	121	96
	Average 1975-1979	290 GBq [GW(e)a]$^{-1}$			
G C R					
France					
Chinon	24	21	8.5	13	
Bugey 1	511	133	144	401	
St. Laurent	174	110	181	300	
Japan					
Tokai					
United Kingdom					
Chapelcross	640	1200	337	2830	9100
Bradwell	4400	2420	2450	2000	1576
Berkeley	2000	4140	5480	1180	1687
Hunterston A	4260	5880	5440	2220	-
Hunterston B	-	22	44	220	-
Trawsfynydd	629	740	500	648	289
Hinkley Point A	5880	5110	4440	4070	2812
Hinkley Point B	-	41	44	189	600
Dungeness	2940	1710	1680	1410	1110
Sizewell	740	1090	1590	910	1420
Oldbury	1010	1860	2440	1120	706
Wylfa	125	241	688	977	600
Total annual energy generated [GW(e) a]	4.42	4.59	5.10	5.07	4.3
Normalized release, [GBq (GW[e] a)$^{-1}$]	5280	5390	4990	3650	4628
	Average 1975-1979	4767 GBq [GW(e) a]$^{-1}$			
H W R					
Argentina					
Atucha [GBq (GW[e] a)$^{-1}$]	520	750	530	230	390
	Average 1975-1979	473 GBq [GW(e) a]$^{-1}$			

Table 25

Radionuclide composition of liquid discharges other than tritium from reactors in the United States in 1979

Reactor	Release (GBq)									
	^{131}I	^{132}I	^{133}I	^{134}I	^{135}I	^{24}Na	^{51}Cr	^{54}Mn	^{56}Mn	^{57}Co
P W R										
Arkansas 1	10	0.0004	0.012	-	-	0.002	11	1.5	-	0.11
Arkansas 2	8.9	0.0033	1.7	0.0037	0.19	2.5	0.67	1.4	0.0037	0.12
Beaver Valley 1	0.032	-	0.030	-	-	-	0.048	0.27	-	-
Calvert Cliffs 1	24	0.46	14	-	1.3	-	24	4.1	0.024	0.24
Cook 1	0.44	-	0.024	-	-	0.52	5.2	2.9	-	0.085
Crystal River	2.2	0.0063	0.070	-	0.0056	0.0033	0.63	0.20	-	-
Davis Besse	0.13	-	0.0074	-	-	0.0037	0.034	0.24	-	-
Joseph M. Farley	0.049	0.0048	0.0037	-	0.00026	0.056	0.093	0.11	-	0.0036
Fort Calhoun	0.78	-	0.10	-	-	-	0.57	0.13	-	0.089
R.E. Ginna	0.34	-	-	-	-	-	0.13	0.048	-	-
Haddam Neck	2.5	-	-	-	-	-	0.31	0.093	-	0.00015
Indian Point	5.1	0.00096	0.0037	-	-	-	2.9	1.3	-	0.0002
Kawaunee	0.022	-	-	-	-	0.052	1.9	0.63	-	0.0018
Maine Yankee	15	-	0.21	-	-	-	0.0023	0.014	-	0.0023
Millstone Point 2	4.4	0.0059	0.19	-	-	3.0	8.2	5.9	0.0016	-
North Anna	5.9	-	0.89	-	-	0.012	0.033	0.048	-	0.74
Oconee 1,2,3	5.3	0.019	0.36	0.074	0.096	0.0096	0.36	0.27	0.0017	0.018
Palisades	0.014	-	-	-	-	-	0.47	0.46	-	0.00019
Point Beach 1,2	0.33	0.36	6.3	0.78	3.1	-	0.020	0.27	-	0.0059
Prairie Island 1,2	0.028	-	-	-	-	-	0.016	0.0013	-	-
Rancho Seco	-	-	-	-	-	-	-	-	-	-
H.B. Robinson	0.14	-	-	-	-	-	-	1.1	-	0.0042
St. Lucie	1.8	0.0057	0.35	0.0037	0.091	0.0032	5.2	2.1	1.6	0.054
Salem 1	0.70	-	0.11	-	-	0.16	3.5	15	-	-
San Onofre 1	0.93	-	-	-	-	-	8.3	0.28	-	-
Surry 1,2	2.4	5.2	4.9	4.3	7.1	8.9	7.4	1.5	-	0.074
Three Mile Island 1	5.3	-	-	-	-	-	0.25	0.054	-	-
Trojan	0.47	-	0.071	0.0037	0.026	0.0067	2.7	1.3	-	0.048
Turkey Pt. 3,4	0.74	0.49	2.1	0.11	1.2	0.19	0.18	0.041	-	0.005
Yankee Rowe	0.15	-	0.015	-	-	-	0.015	0.004	-	-
Zion 1,2	0.43	-	0.00057	-	-	0.39	2.2	0.61	-	0.024
Total annual energy generated [GW(e) a]	19.165									
Normalized release [GBq (GW[e] a)$^{-1}$]	4.6	0.31	1.7	0.24	0.68	1.1	4.6	2.2	0.085	0.084

Table 25, continued

Reactor	Release (GBq)										
	^{58}Co	^{59}Fe	^{60}Co	^{65}Zn	^{89}Sr	^{90}Sr	^{95}Zr	^{97}Zr	^{95}Nb	^{97}Nb	^{99}Mo
P W R											
Arkansas 1	58	0.74	17	0.013	0.11	0.015	1.1	0.01	2.0	0.16	0.11
Arkansas 2	30	0.56	0.81	0.0013	0.24	-	0.031	-	0.047	0.022	0.031
Beaver Valley 1	1.6	0.033	2.3	-	0.0007	0.0016	0.0033	-	-	-	-
Calvert Cliffs 1	141	1.1	12	-	0.085	0.096	5.6	0.019	0.59	-	0.45
Cook 1	33	0.70	20	0.21	0.0096	0.0044	3.0	0.11	3.0	-	-
Crystal River	4.3	0.093	1.3	0.034	1.8	0.26	0.26	-	-	-	0.52
Davis Besse	0.85	0.0093	0.093	0.01	0.0014	0.0017	0.012	-	-	-	0.036
Joseph M. Farley	0.96	0.019	0.81	0.0011	-	0.00074	0.0074	-	0.023	-	0.0013
Fort Calhoun	0.41	0.074	0.15	0.089	0.018	0.0048	0.079	-	0.046	-	0.032
R.E. Ginna	0.081	0.0074	1.5	-	-	-	0.033	-	0.024	-	0.041
Haddam Neck	0.52	0.00015	3.6	0.00015	0.25	0.13	5.4	-	-	-	0.00015
Indian Point	11	0.56	5.9	1.8	0.18	0.33	0.52	-	-	-	6.3
Kawaunee	11	0.085	6.7	-	0.030	0.0063	0.11	-	0.13	-	-
Maine Yankee	0.67	-	0.052	-	-	0.0017	-	-	-	-	0.0024
Millstone Point 2	60	0.67	58	0.0044	0.048	0.0063	1.1	0.0015	2.6	3.3	0.037
North Anna	4.8	0.0033	0.47	-	0.18	0.13	0.033	-	-	-	-
Oconee 1,2,3	6.7	0.019	1.8	-	3.0	0.27	0.37	0.011	0.15	1.0	0.059
Palisades	2.4	0.047	0.46	-	-	-	0.021	-	0.054	-	-
Point Beach 1,2	1.8	0.0033	0.59	-	0.0026	0.00063	0.081	-	0.046	-	0.070
Prairie Island 1,2	0.11	0.015	0.035	-	-	-	0.00034	-	-	-	0.0025
Rancho Seco	-	-	-	-	-	-	-	-	-	-	-
H.B. Robinson	3.7	0.085	2.9	-	-	-	-	-	-	-	-
St. Lucie	37	0.37	7.0	0.12	0.028	0.00004	0.67	0.0095	-	-	0.0074
Salem 1	52	0.98	70	-	-	-	0.37	-	-	-	-
San Onofre 1	343	7.3	25	-	0.60	0.025	-	-	0.59	-	-
Surry 1,2	67	0.0060	61	-	0.052	0.016	-	-	0.71	-	-
Three Mile Island 1	2.3	0.0049	0.54	0.015	3.4	0.27	0.0011	-	0.34	-	0.00032
Trojan	5.2	0.15	6.4	0.0097	0.065	0.0037	0.48	-	0.78	-	0.00078
Turkey Pt. 3,4	1.8	0.0063	3.1	-	0.29	0.048	0.029	-	0.012	-	0.0044
Yankee Rowe	0.015	-	0.0069	0.0036	0.0006	0.0021	-	-	-	-	0.0083
Zion 1,2	5.2	0.041	7.1	-	0.021	0.016	0.14	-	0.50	-	-
Total annual energy generated [GW(e) a]	19,165										
Normalized release, [GBq (GW(e) a)$^{-1}$]	46	0.71	17	0.12	0.54	0.086	1.0	0.0084	0.60	0.23	0.38

Table 25, continued

Reactor	Release (GBq)											
	^{99m}Tc	^{103}Ru	^{106}Ru	^{110m}Ag	^{124}Sb	^{125}Sb	^{134}Cs	^{136}Cs	^{137}Cs	$^{140}Ba/La$	^{141}Ce	^{144}Ce
P W R												
Arkansas 1	-	0.12	0.040	1.1	-	-	3.6	-	5.6	0.25	-	0.037
Arkansas 2	-	0.0051	-	0.061	-	-	0.057	0.0081	0.95	0.018	-	-
Beaver Valley 1	-	-	-	-	-	-	0.023	-	0.10	-	0.0090	-
Calvert Cliffs 1	-	0.93	0.47	3.5	1.0	10	14	0.12	21	0.70	0.21	-
Cook 1	-	-	-	-	-	-	0.048	-	0.15	0.016	-	-
Crystal River	0.014	-	-	0.0074	-	-	1.7	-	2.5	0.013	0.022	0.17
Davis Besse	0.0033	-	-	-	-	-	0.048	-	0.12	0.016	0.0074	-
Joseph M. Farley	0.00004	-	0.0013	0.0063	-	-	0.0052	0.00019	0.016	0.0037	0.00019	0.0033
Fort Calhoun	0.016	0.059	-	-	0.070	-	2.3	0.070	0.37	0.14	0.12	-
R.E. Ginna	-	0.011	0.05	0.028	-	-	0.12	0.049	0.48	0.013	0.0025	0.0070
Haddam Neck	0.00015	2.4	1.4	0.002	-	0.00015	1.5	-	1.8	0.017	2.0	10
Indian Point	0.22	0.0004	-	-	0.0074	0.011	5.2	-	16	1.7	0.50	0.0096
Kawaunee	-	-	-	1.2	2.1	2.4	2.9	-	3.2	0.059	-	-
Maine Yankee	-	-	-	-	-	-	0.12	-	0.78	-	-	-
Millstone Point 2	-	-	-	2.4	-	-	12	1.6	14	0.035	0.018	0.13
North Anna	0.0028	0	0	0	0	-	3.3	-	4.6	-	-	-
Oconee 1,2,3	0.036	0.0020	0.25	0.37	-	0.061	4.6	0.37	8.9	0.12	-	0.17
Palisades	-	-	-	-	-	-	0.074	-	0.29	-	-	-
Point Beach 1,2	-	0.081	-	-	0.0085	0.019	0.56	0.00048	2.0	1.1	-	0.074
Prairie Island 1,2	0.0034	-	-	-	0.027	-	-	-	-	-	-	-
Rancho Seco	-	-	-	-	-	-	-	-	-	-	-	-
H.B. Robinson	-	-	-	-	0.031	0.041	0.13	1.7	1.1	-	0.00070	0.019
St. Lucie	0.036	0.027	-	1.2	1.5	1.0	10	0.12	14	0.013	0.030	0.11
Salem 1	-	-	-	-	0.45	-	2.1	0.019	1.6	-	-	-
San Onofre 1	1.2	0.50	-	1.1	-	-	0.87	-	1.7	-	-	-
Surry 1,2	-	-	-	-	-	-	16	0.0042	36	0.015	0.0060	0.12
Three Mile Island 1	-	0.011	-	0.057	0.016	0.098	0.86	0.058	3.7	0.84	0.0019	0.0013
Trojan	0.008	0.22	-	0.63	0.16	0.37	0.078	0.0032	0.19	0.54	0.074	0.14
Turkey Pt. 3,4	0.0044	0.010	-	0.12	0.58	0.63	1.1	-	1.8	-	-	-
Yankee Rowe	0.0013	-	-	0.0011	0.0016	-	0.075	-	0.098	0.0061	0.0021	0.0083
Zion 1,2	0.029	-	-	0.24	0.80	-	4.4	-	5.3	0.070	-	-
Total annual energy generated [GW(e) a]	19.165											
Normalized release, [GBq (GW[e] a)$^{-1}$]	0.087	0.23	0.12	0.63	0.35	0.76	4.4	0.21	7.7	0.29	0.16	0.57

Reactor	Release (GBq)									
	^{131}I	^{132}I	^{133}I	^{134}I	^{135}I	^{24}Na	^{51}Cr	^{54}Mn	^{56}Mn	^{57}Co
B W R										
Big Rock Point	-	-	0.010	-	-	0.0014	0.21	2.2	-	-
Browns Ferry 1,2,3	1.4	-	0.78	-	-	10	17	3.7	0.10	-
Brunswick 1,2	8.0	0	0.65	-	-	60	13	18	0.024	-
Cooper	3.4	-	-	-	-	0.046	2.1	5.5	0.0053	-
Dresden 1	-	-	-	-	-	-	-	0.037	-	-
Dresden 2,3	0.18	-	-	-	-	-	0.012	1.1	-	-
Duane Arnold	-	-	-	-	-	-	-	0.0037	-	-
J.A. Fitzpatrick	0.023	-	0.010	-	0.0023	1.8	0.14	5.3	-	-
Edwin I. Hatch	0.18	0.0002	0.0019	-	0.0007	0.11	0.12	0.035	0.00037	-
Humboldt Bay	-	-	-	-	-	-	-	0.18	-	-
Lacrosse	1.8	0.17	0.94	0.009	0.33	-	0.16	2.4	0.0037	2.5
Millstone Point 1	0.20	0.0004	0.028	0.0008	0.014	-	0.29	1.0	0.0006	-
Monticello	-	-	-	-	-	-	-	-	-	-
Nine Mile Point	-	-	-	-	-	-	-	0.81	-	-
Oyster Creek	0.052	-	0.027	-	0.023	0.0009	0.096	0.0024	-	0.00015
Peach Bottom 2,3	36	0.12	17	-	4.4	343	2.4	0.27	-	-
Pilgrim	0.0007	-	0.005	-	-	-	0.25	0.48	-	-
Quad Cities	4.2	-	-	-	-	-	-	0.26	-	-
Vermont Yankee	0.0002	-	-	-	-	-	0.0019	0.0022	-	-
Total annual energy generated [GW(e) a]	11.670									
Normalized release, [GBq (MW[e] a)$^{-1}$]	4.7	0.025	1.7	0.0008	0.41	36	3.1	3.5	0.011	0.22

Table 25, continued

Reactor	Release (GBq)										
	^{58}Co	^{59}Fe	^{60}Co	^{65}Zn	^{89}Sr	^{90}Sr	^{95}Zr	^{97}Zr	^{95}Nb	^{97}Nb	^{99}Mo
B W R											
Big Rock Point 1	0.063	0.19	4.8	0.034	0.016	0.042	-	-	-	-	-
Browns Ferry 1,2,3	0.85	0.47	7.9	11	0.32	0.14	4.9	-	-	-	0.35
Brunswick 1,2	3.6	1.1	18	0.68	0.014	0.008	-	0.17	-	0.035	0.11
Cooper	1.3	0.37	11	6.5	3.6	0.27	0.21	-	0.18	-	0.21
Dresden 1	0.051	0.0037	0.46	-	0.072	0.0074	0.011	-	0.013	-	-
Dresden 1,2	0.24	0.012	5.7	-	0.30	0.07	0.07	-	0.17	-	-
Duane Arnold	-	-	0.0096	-	0.0021	0.0021	-	-	-	-	-
J.A. Fitzpatrick	2.1	0.061	8.9	0.25	0.0074	0.0056	0.0024	-	-	-	0.019
Edwin I. Hatch	0.089	0.0052	0.29	0.30	0.012	0.0031	0.0013	0.00015	0.0033	0.0011	0.0025
Humboldt Bay 3	-	-	0.44	-	-	0.078	-	-	-	-	-
Lacrosse	18	0.061	33	1.1	11	0.43	3.7	-	6.0	0.19	0.062
Millstone Point 1	0.15	0.070	3.6	0.006	0.032	0.0067	0.016	0.0003	0.067	0.002	0.0009
Monticello	-	-	-	-	-	-	-	-	-	-	-
Nine Mile Point	0.22	-	17	-	0.037	0.12	-	-	-	-	-
Oyster Creek	-	-	0.012	-	0.0011	0.00012	-	-	-	-	-
Peach Bottom 2,3	2.9	-	6.0	17	0.74	0.030	-	-	0.017	-	0.0059
Pilgrim	0.059	0.013	3.1	0.025	0.078	0.019	0.0052	-	-	-	0.0074
Quad Cities	0.089	-	7.0	0.17	19	0.20	-	-	-	-	-
Vermont Yankee	0.0004	0.001	0.00056	0.0011	0.0002	0.0001	0.00085	-	-	-	0.00011
Total annual energy generated [GW(e) a]	11.670										
Normalized release [GBq (GW[e] a)$^{-1}$]	2.5	0.20	11	3.2	3.0	0.12	0.76	0.015	0.023	0.019	0.066

Reactor	Release (GBq)									
	^{99m}Tc	^{103}Ru	^{110m}Ag	^{124}Sb	^{134}Cs	^{136}Cs	^{137}Cs	$^{140}Ba/La$	^{144}Ce	^{239}Np
B W R										
Big Rock Point 1	-	-	-	0.16	1.9	-	18	0.059	-	0.047
Browns Ferry 1,2,3	0.35	-	-	0.41	1.9	0.43	2.8	0.19	-	0.41
Brunswick 1,2	0.41	-	0.052	0.003	12	0.014	21	-	-	-
Cooper	0.19	-	0.60	0.11	11	0.042	14	0.70	-	-
Dresden 1	-	0.0037	-	-	0.076	-	0.21	-	0.037	-
Dresden 2,3	-	0.069	0.23	0.0015	0.41	-	1.1	-	0.033	-
Duane Arnold	-	-	0.0003	-	0.0009	-	0.0003	-	-	-
J.A. Fitzpatrick	0.0013	-	0.0022	-	1.6	-	3.4	0.00059	0.0026	-
Edwin I. Hatch	0.0021	-	0.00052	-	0.20	0.01	0.22	0.001	0.0005	0.0022
Humboldt Bay 3	-	-	-	-	0.27	-	2.2	-	0.074	-
Lacrosse	1.3	1.1	-	0.0048	4.5	0.026	18	3.7	12	3.1
Millstone Point 1	-	-	0.0013	0.0048	0.037	-	0.17	0.12	0.026	-
Monticello	-	-	-	-	-	-	-	-	-	-
Nine Mile Point	-	-	-	-	13	-	37	0.023	-	0.059
Oyster Creek	0.014	-	-	-	0.0001	-	0.026	-	-	0.007
Peach Bottom 2,3	3.7	0.0067	0.0037	0.020	145	-	121	0.89	-	1.1
Pilgrim	0.0074	-	-	-	0.22	-	1.1	0.30	0.023	-
Quad Cities	-	-	0.027	-	7.4	0.37	12	6.1	-	-
Vermont Yankee	0.00011	-	-	-	0.00032	-	0.00041	0.0012	-	-
Total annual energy generated [GW(e) a]	11.670									
Normalized release [GBq (GW[e] a)$^{-1}$]	0.51	0.10	0.023	0.060	17	0.076	22	1.0	1.0	0.40

Table 26

Liquid effluents other than tritium discharged from GCRs in the United Kingdom in 1979 [H14]

Reactor	Release (GBq)									
	^{35}S	^{55}Fe	^{60}Co	^{89}Sr	^{90}Sr	^{106}Ru	^{125}Sb	^{134}Cs	^{137}Cs	^{144}Ce
Bradwell	250	79	14	14	150	2	2	120	670	17
Berkeley	350	2	2	2	78	2	30	190	860	15
Trawsfynydd	120	3	0.6	0.1	27	6	10	9	49	3
Hinkley A	210	8	1	11	350	67	140	150	1160	67
Dungeness	46	4	0.6	3	95	1	2	120	730	2
Sizewell	140	4	6	4	91	0.7	4	170	870	7
Oldbury	260	18	3	7	52	4	7	18	200	8
Wylfa	12	4	0.6	0.6	23	1	2	37	480	1
Total annual energy generated	4.3 GW(e) a									
Normalized release [GBq (GW[e] a)$^{-1}$]	320	28	6	10	200	19	46	190	1170	28

Table 27

Population distribution around the model reactor site and meteorological characteristics of its location

METEOROLOGICAL CHARACTERISTICS

Quantity	Pasquill weather category							
	Dry						Rain	
	A	B	C	D	E	F	C	D
Frequency (%)	1	11	19	32	16	18	1	25
Wind speed (m s^{-1})	1	2	5	5	3	1	5	5
Depth of mixing layer (m)	2000	2000	1000	1000	200	200	1000	1000

Distribution of wind direction frequencies (30° sectors)
0.079, 0.08, 0.1, 0.1, 0.044, 0.023, 0.024, 0.061, 0.12, 0.16, 0.13, 0.074

Stack height: 30 m

POPULATION DISTRIBUTION

Distance (km)	0 - 1	1 - 2	2 - 5	5 - 10	10 - 20	20 - 50
Population	1300	3000	26000	90000	430000	2800000
Cumulative	1300	4300	30000	120000	550000	3300000

Distance (km)	50-100	100-200	200-500	500-1000	1000-2000
Population	6100000	20000000	70000000	140000000	17000000
Cumulative	9400000	29000000	99000000	240000000	260000000

Table 28

Normalized local and regional collective dose commitments for noble gases from the model PWR

Radionuclide	Normalized collective absorbed dose commitment (10^{-4} man Gy [GW(e) a]$^{-1}$)									Normalized collective effective dose equivalent commitment (10^{-4} man Sv [GW(e) a]$^{-1}$)
	Gonads	Breast	Red bone marrow	Lungs	Thyroid	Bone lining cells	Liver	Skin	Remainder tissues	
^{41}Ar	4.3	5.3	5.7	5.0	4.8	5.7	5.0	9.8	5.3	5.1
^{85m}Kr	1.2	1.3	2.2	1.3	1.5	2.2	1.3	6.4	1.4	1.5
^{85}Kr	1.2	1.7	2.0	1.6	1.4	2.0	1.6	410	1.7	5.7
^{87}Kr	0.7	0.9	1.0	0.9	0.9	1.0	0.9	3.9	0.9	0.9
^{88}Kr	12	15	16	22	15	16	15	41	15	16
^{131m}Xe	0.8	0.8	1.2	0.6	0.7	1.2	0.6	47	0.9	1.3
^{133m}Xe	2.4	2.6	4.2	2.4	2.7	4.2	2.4	44	2.8	3.2
^{133}Xe	220	270	560	250	350	560	250	2700	310	340
^{135m}Xe	0.2	0.2	0.3	0.2	0.2	0.3	0.2	0.5	0.2	0.2
^{135}Xe	40	43	64	42	42	64	42	180	46	48
^{138}Xe	1.8	2.2	2.4	2.1	2.1	2.4	2.1	4.8	2.2	2.2
Total (rounded)	280	350	660	330	420	660	320	3450	380	420

Table 29

Normalized collective effective dose equivalent commitment for noble gases from the model PWR as a function of distance

Distance (km)	Normalized collective effective dose equivalent commitment [10^{-4} man Sv (GW[e] a)$^{-1}$]	Percentage distribution
0-2	5	1.2
2-5	12	2.9
5-10	18	4.2
10-20	27	6.5
20-50	40	9.6
50-100	55	13.2
100-200	114	27.2
200-500	122	29.0
500-1000	20	4.8
1000-2000	6.3	1.5
Total (rounded)	420	100

Table 30

Normalized local and regional collective dose commitments for noble gases from the model BWR

Radionuclide	Normalized collective absorbed dose commitment (man Gy [GW(e) a]$^{-1}$)									Normalized collective effective dose equivalent commitment (man Sv [GW(e) a]$^{-1}$)
	Gonads	Breast	Red bone marrow	Lungs	Thyroid	Bone lining cells	Liver	Skin	Remainder tissues	
^{41}Ar	0.003	0.004	0.005	0.004	0.004	0.005	0.004	0.008	0.004	0.004
^{85m}Kr	0.02	0.02	0.04	0.02	0.03	0.04	0.02	0.11	0.03	0.03
^{85}Kr	0.007	0.01	0.01	0.009	0.008	0.01	0.009	2.5	0.01	0.034
^{87}Kr	0.10	0.13	0.14	0.12	0.13	0.14	0.12	0.56	0.13	0.13
^{88}Kr	0.69	0.87	0.92	1.2	0.88	0.92.	0.83	2.3	0.87	0.90
^{131m}Xe	0.001	0.001	0.001	0.001	0.001	0.002	0.001	0.02	0.001	0.001
^{133}Xe	0.06	0.08	0.16	0.07	0.10	0.16	0.07	0.79	0.09	0.10
^{135m}Xe	0.13	0.02	0.02	0.02	0.01	0.02	0.02	0.04	0.02	0.02
^{135}Xe	0.32	0.35	0.52	0.34	0.34	0.52	0.34	1.5	0.37	0.39
^{138}Xe	0.21	0.26	0.28	0.35	0.25	0.28	0.25	0.55	0.26	0.26
Total (rounded)	1.4	1.7	2.2	2.2	1.8	2.1	1.7	9.1	1.8	1.9

Table 31

Normalized collective effective dose equivalent commitment for noble gases from the model BWR as a function of distance

Distance (km)	Normalized collective effective dose equivalent commitment [man Sv (GW[e] a)$^{-1}$]	Percentage distribution
0-2	0.19	10
2-5	0.27	14
5-10	0.30	16
10-20	0.34	18
20-50	0.46	24
50-100	0.18	9.3
100-200	0.10	5.4
200-500	0.04	2.2
500-1000	0.01	0.5
1000-2000	0.01	0.5
Total	1.9	100

Table 32

Normalized local and regional collective absorbed dose commitments from tritium in airborne discharges from the model reactor

Reactor	Normalized discharge [TBq (GW[e] a)$^{-1}$]	Normalized collective whole-body absorbed dose commitment [man Gy (GW[e] a)$^{-1}$]		
		Ingestion	Inhalation	Total
BWR	3.4	0.03	0.005	0.04
PWR	7.8	0.07	0.01	0.08
GCR	11	0.1	0.02	0.1
HWR	540	4.8	0.8	5.6

Table 33

Normalized local and regional collective absorbed dose commitments from carbon-14 releases to atmosphere

Reactor	Normalized discharge [TBq (GW[e] a)$^{-1}$]	Normalized collective whole-body absorbed dose commitment [man Gy (GW[e] a)$^{-1}$]		
		Ingestion	Inhalation	Total
BWR	0.5	0.92	0.001	0.92
PWR	0.2	0.39	0.00006	0.39
GCR	1.1	2.2	0.0003	2.2
HWR	17	30	0.005	30

Table 34

Normalized local and regional collective dose commitments for iodine releases from the model PWR

Pathway	Normalized collective absorbed dose commitment (10^{-4} man Gy [GW(e) a]$^{-1}$)									Normalized collective effective dose equivalent commitment (10^{-4} man Sv [GW(e) a]$^{-1}$) a/
	Gonads	Breast	Red bone marrow	Lungs	Thyroid	Bone lining cells	Liver	Skin	Remainder tissues	
Direct cloud irradiation	0.04	0.05	0.06	0.05	0.04	0.06	0.05	0.11	0.02	0.05
Inhalation	0.01	0.04	0.03	0.42	120	0.03	0.02	0.03	0.04	3.7
Ingestion b/	0.006	0.02	0.02	0.02	84	0.02	0.009	0.01	0.02	2.6
External dose from ground deposits	0.18	0.22	0.32	0.13	0.19	0.35	0.11	0.27	0.22	0.22
Resuspension	0.000005	0.00002	0.00001	0.0002	0.07	0.00001	0.000009	0.00001	0.00002	0.002
Total (rounded)	0.24	0.33	0.42	0.62	210	0.45	0.19	0.42	0.32	6.6

a/ Percentage contribution by iodine isotopes to collective effective dose equivalent commitment: ^{131}I 96 %; ^{133}I 2 %; ^{135}I 2 %.

b/ Percentage contribution of each pathway to ingestion doses: milk 90 %; beef 5 %, green vegetables 5 %.

Table 35

Normalized local and regional collective dose commitments for iodine releases from the model BWR

Pathway	Normalized collective absorbed dose commitment (10^{-4} man Gy [GW(e) a]$^{-1}$)									Normalized collective effective dose equivalent commitment (10^{-4} man Sv [GW(e) a]$^{-1}$) a/
	Gonads	Breast	Red bone marrow	Lungs	Thyroid	Bone lining cells	Liver	Skin	Remainder tissues	
Direct cloud irradiation	3.5	4.4	5.1	4.2	3.8	5.1	4.2	9.8	4.4	4.2
Inhalation	0.91	1.7	1.5	32	3900	1.4	1.4	1.2	1.7	120
Ingestion b/	0.16	0.55	0.38	0.44	2000	0.36	0.22	0.35	0.50	62
External dose from ground deposits	7.2	9.0	12	6.8	7.8	13	5.9	11	8.7	8.7
Resuspension	0.0002	0.0005	0.0003	0.006	1.6	0.0003	0.0003	0.0003	0.0005	0.05
Total (rounded)	12	16	19	43	5900	20	12	22	15	190

a/ Percentage contribution by iodine isotopes to collective effective dose equivalent commitment: ^{131}I 78 %; ^{132}I 0.001 %; ^{133}I 17 %; ^{135}I 5 %.

b/ Percentage contribution of each pathway to ingestion doses: milk 90 %; beef 5 %, green vegetables 5 %.

Table 36

Normalized local and regional collective dose commitments for particulate releases from the model PWR and BWR

Pathway	Normalized collective absorbed dose commitment (10^{-3} man Gy [GW(e) a]$^{-1}$)									Normalized collective effective dose equivalent commitment (10^{-3} man Sv [GW(e) a]$^{-1}$)
	Gonads	Breast	Red bone marrow	Lungs	Thyroid	Bone lining cells	Liver	Skin	Remainder tissues	
PWR										
Direct cloud irradiation	0.001	0.002	0.002	0.002	0.002	0.002	0.002	0.003	0.002	0.002
Inhalation	0.04	0.06	0.41	1.4	0.05	0.82	0.11	0.04	0.06	0.27
Ingestion a/	2.1	1.9	14	1.9	1.9	28	2	1.9	1.9	4.4
External dose from ground deposits	5.9	7.7	8.3	7.2	6.4	8.6	6.6	9.6	7.3	7.3
Resuspension	0.001	0.002	0.02	0.04	0.002	0.04	0.004	0.001	0.002	0.009
Total (rounded)	8.1	9.7	23	11	8.4	37	8.9	11	9.2	12
BWR										
Direct cloud irradiation	0.03	0.04	0.05	0.04	0.04	0.05	0.04	0.07	0.04	0.04
Inhalation	0.93	1.4	10	35	1.3	20	2.8	0.91	1.4	6.6
Ingestion a/	52	47	350	45	48	680	52	36	46	110
External dose from ground deposits	150	190	200	180	160	210	160	240	180	180
Resuspension	0.03	0.05	0.42	1.1	0.04	0.85	0.09	0.03	0.05	0.22
Total (rounded)	200	240	560	260	210	910	220	270	230	290

a/ The pathways contributing to the ingestion dose are: grain 30 %; green vegetables 25%; milk 15 %; milk products 10 %; root vegetables 10 %; beef 5 %; others 5 %.

Table 37

Radionuclides considered for liquid effluent calculations from the model reactor site, normalized releases and concentration factors for marine and freshwater media

Radionuclide	Normalized release [GBq/(GW[e] a)]			Marine concentration factor ($m^3\ t^{-1}$)					Freshwater concentration factor ($m^3\ t^{-1}$)	
	BWR	PWR	GCR	Fish	Crustacea	Molluscs	Sediments	Seaweed	Sediments	Fish
^{54}Mn	10	4.0	-	500	10000	10000	10000	10000	10000	300
^{58}Co	6.9	90		100	1000	1000	10000	1000	30000	300
^{60}Co	30	34	25	100	1000	1000	10000	1000	30000	300
^{65}Zn	8.8	-	-	2000	5000	100000	10000	1000	1000	1000
^{89}Sr	8.2	1.0	-	1	10	10	500	10	2000	30
^{90}Sr	0.33	0.2	420	1	10	10	500	10	2000	30
^{106}Ru	-	-	34	1	500	2000	10000	2000	40000	10
^{110m}Ag	-	1.2	-	1000	5000	50000	10000	1000	200	3
^{125}Sb	-	-	80	500	300	100	10000	100	300	1000
^{131}I	13	9	-	10	100	100	100	1000	200	30
^{134}Cs	46	9	392	50	30	30	500	30	30000	1000
^{137}Cs	60	16	2600	50	30	30	500	30	30000	1000
^{144}Ce	-	-	50	10	1000	1000	10000	1000	30000	1000

Table 38

Parameters for the river model used to assess reactor releases

Section	Water velocity ($m\ s^{-1}$)	Sediment velocity ($m\ s^{-1}$)	Suspended sediment load ($g\ m^{-3}$)	Drinking water extraction ($m^3\ a^{-1}$)	Fish production ($t\ a^{-1}$)
1	0.8	0.0002	40	100000	100
2	0.75	0.00015	45	140000	66
3	0.7	0.0001	50	31000	600

Table 39

Normalized collective dose commitments from liquid reactor effluents discharged into the model river

Reactor type and pathway	Normalized collective absorbed dose commitment (10^{-4} man Gy [GW(e)a]$^{-1}$)							Normalized collective effective dose equivalent commitment (10^{-4} man Sv [GW(e) a]$^{-1}$)
	Gonads	Breast	Red bone marrow	Lungs	Thyroid	Bone lining cells	Remainder tissues	
PWR								
Drinking water								
^{131}I	0.008	0.02	0.02	0.02	94	0.02	-	2.8
^{58}Co	0.58	0.33	0.39	0.29	0.27	0.29	0.79	0.53
^{60}Co	1.4	0.70	0.82	0.56	0.49	0.59	3.1	1.6
^{90}Sr	0.009	0.009	1.2	0.009	0.009	2.6	-	0.21
^{134}Cs	1.2	1.1	1.2	1.1	1.2	1.1	1.3	1.2
^{137}Cs	1.6	1.5	1.5	1.5	1.5	1.5	1.4	1.5
Total	4.8	3.7	5.1	3.5	97	6.1	6.5	7.8

Table 39, continued

Reactor type and pathway	Normalized collective absorbed dose commitment (10^{-4} man Gy [GW(e)a]$^{-1}$)							Normalized collective effective dose equivalent commitment (10^{-4} man Sv [GW(e) a]$^{-1}$)
	Gonads	Breast	Red bone marrow	Lungs	Thyroid	Bone lining cells	Remainder tissues	
Fish								
^{131}I	0.0006	0.002	0.001	0.002	6.7	0.001	-	0.20
^{58}Co	0.11	0.06	0.07	0.06	0.05	0.06	0.14	0.10
^{60}Co	0.26	0.13	0.15	0.11	0.09	0.11	0.59	0.30
^{90}Sr	0.0003	0.0003	0.05	0.0003	0.0003	0.10	-	0.008
^{134}Cs	0.76	0.68	0.76	0.68	0.72	0.68	0.81	0.75
^{137}Cs	1.0	0.93	0.93	0.93	0.93	0.93	0.91	0.94
Total	2.1	1.8	2.0	1.8	8.5	1.9	2.4	2.3
External								
^{58}Co	0.0014		to all organs and tissues					0.0014
^{60}Co	0.033		to all organs and tissues					0.033
^{134}Cs	0.0023		to all organs and tissues					0.0023
^{137}Cs	0.0079		to all organs and tissues					0.0079
Total	0.045		to all organs and tissues					0.045
B W R								
Drinking water								
^{131}I	0.01	0.03	0.02	0.03	130	0.02	-	4.0
^{60}Co	1.3	0.63	0.75	0.53	0.46	0.55	3.3	1.6
^{65}Zn	1.0	1.0	1.4	0.88	0.88	1.4	1.2	1.1
^{89}Sr	0.06	0.06	0.75	0.06	0.06	1.1	1.1	0.49
^{90}Sr	0.01	0.01	1.9	1.3	1.3	3.9	-	0.34
^{134}Cs	5.8	5.2	5.8	5.2	5.4	5.2	5.3	5.4
^{137}Cs	5.6	5.2	5.2	5.2	5.2	5.2	5.2	5.6
Total	14	12	16	12	140	18	18	19
Fish								
^{131}I	0.08	0.002	0.002	0.002	10	0.002	-	0.29
^{60}Co	0.24	0.12	0.14	0.10	0.10	0.10	0.62	0.30
^{65}Zn	1.2	1.2	1.7	1.2	1.1	1.7	1.6	1.4
^{89}Sr	0.002	0.002	0.03	0.002	0.002	0.04	0.05	0.02
^{90}Sr	0.0005	0.0005	0.07	0.0005	0.0005	0.15	-	0.01
^{134}Cs	3.6	3.2	3.6	3.2	3.4	3.2	4.7	3.8
^{137}Cs	3.5	3.3	3.3	3.3	3.3	3.2	3.8	3.5
Total	8.8	7.5	8.8	7.5	18	8.1	11	9.3
External								
^{60}Co	0.033		to all organs and tissues					0.033
^{134}Cs	0.012		to all organs and tissues					0.012
^{137}Cs	0.030		to all organs and tissues					0.030
Total	0.075		to all organs and tissues					0.075

Table 40

Normalized collective dose commitments for the model PWR, BWR and GCR on a notional site in the eastern English Channel

Reactor type and pathway	Normalized collective absorbed dose commitment (10^{-4} man Gy [GW(e) a]$^{-1}$)								Normalized collective effective dose equivalent commitment (10^{-4} man Sv [GW(e) a]$^{-1}$)
	Gonads	Breast	Red bone marrow	Lungs	Thyroid	Bone lining cells	Upper large intestine	Lower large intestine	
PWR									
Fish									
^{54}Mn	0.29	0.14	0.25	0.11	0.06	0.30	0.72	1.1	0.37
^{58}Co	0.48	0.15	0.21	0.071	0.05	0.10	1.7	3.3	0.64
^{60}Co	4.0	2.0	2.4	1.6	1.4	1.7	11	20	4.9
^{110m}Ag	0.45	0.20	0.25	0.22	0.05	0.13	1.6	2.9	0.77
^{134}Cs	3.8	3.4	3.8	3.4	3.6	3.4	4.2	4.4	4.0
^{137}Cs	8.2	7.6	7.6	7.6	7.6	7.6	8.8	8.8	8.2
Total	17	13	15	13	13	13	28	41	19
Crustacea									
^{54}Mn	0.29	0.14	0.25	0.11	0.06	0.30	0.72	1.1	0.37
^{58}Co	0.28	8.6	0.12	0.04	0.03	0.06	0.96	1.9	0.37
^{60}Co	1.5	0.73	0.87	0.59	0.51	0.62	3.9	7.3	1.8
^{110m}Ag	0.11	0.05	0.06	0.05	0.01	0.03	0.37	0.68	0.18
^{134}Cs	0.09	0.08	0.09	0.08	0.09	0.08	0.10	0.10	9.5
^{137}Cs	0.17	0.16	0.16	0.16	0.15	0.16	0.18	0.18	0.17
Total	2.4	1.2	1.5	1.0	0.86	1.2	6.2	11	3.0
Molluscs									
^{54}Mn	2.5	1.2	2.1	0.98	0.49	2.6	6.2	9.8	3.2
^{58}Co	2.8	0.89	1.2	0.42	0.32	0.59	9.9	23	3.8
^{60}Co	11	5.3	6.3	4.3	3.7	4.5	28	53	13
^{110m}Ag	9.4	4.2	5.1	4.6	1.0	2.7	33	61	16
^{134}Cs	0.70	0.63	0.70	0.63	0.67	0.63	0.78	0.81	0.74
^{137}Cs	1.1	1.0	1.0	1.0	1.0	1.0	1.2	1.2	1.1
Total	28	13	16	12	7.2	12	79	150	38
Grand total	47	28	32	26	21	26	110	200	60

Table 40, continued

Reactor type and pathway	Normalized collective absorbed dose commitment (10^{-4} man Gy [GW(e) a]$^{-1}$)								Normalized collective effective dose equivalent commitment (10^{-4} man Sv [GW(e) a]$^{-1}$)
	Gonads	Breast	Red bone marrow	Lungs	Thyroid	Bone lining cells	Upper large intestine	Lower large intestine	
B W R									
Fish									
^{54}Mn	0.62	0.30	0.54	0.25	0.12	0.65	1.6	2.5	0.81
^{60}Co	3.7	1.8	2.2	1.5	1.3	1.5	9.7	18	4.5
^{65}Zn	13	13	18	12	12	18	16	19	15
^{134}Cs	19	17	19	17	18	17	21	22	20
^{137}Cs	31	29	29	29	29	29	33	33	31
Total	67	61	69	60	60	66	81	95	71
Crustacea									
^{54}Mn	0.62	0.30	0.54	0.25	0.12	0.65	1.6	2.5	0.81
^{60}Co	1.3	0.65	0.77	0.53	0.46	0.55	3.4	6.5	1.6
^{65}Zn	1.1	1.2	1.6	1.0	1.0	1.6	1.4	1.6	1.3
^{134}Cs	0.47	0.42	0.47	0.42	0.44	0.42	0.51	0.54	0.49
^{137}Cs	0.64	0.59	0.59	0.59	0.59	0.59	0.69	0.69	0.64
Total	4.1	3.1	4.0	2.8	2.6	3.8	7.6	12	4.8
Molluscs									
^{54}Mn	5.4	2.6	4.7	2.1	1.1	5.6	13	21	7.0
^{60}Co	9.8	4.9	5.8	4.0	3.4	4.1	26	49	12
^{65}Zn	280	270	390	250	250	390	340	400	320
^{134}Cs	3.6	3.2	3.6	3.2	3.4	3.2	4.0	4.2	3.8
^{137}Cs	4.1	3.8	3.8	3.8	3.8	3.8	4.4	4.4	4.1
Total	300	280	410	260	260	410	390	480	350
Grand total	370	350	480	330	320	480	480	580	420

Table 40, continued

Reactor type and pathway	Normalized collective absorbed dose commitment (10^{-4} man Gy [GW(e) a]$^{-1}$)								Normalized collective effective dose equivalent commitment (10^{-4} man Sv [GW(e) a]$^{-1}$)
	Gonads	Breast	Red bone marrow	Lungs	Thyroid	Bone lining cells	Upper large intestine	Lower large intestine	
G C R									
Fish									
^{60}Co	3.0	1.5	1.8	1.2	1.1	1.3	7.9	15	3.7
^{90}Sr	0.39	0.39	55	0.39	0.39	120	1.7	6.1	10
^{106}Ru	0.02	0.01	0.01	0.01	0.01	0.01	0.23	0.66	5.4
^{125}Sb	6.1	2.1	4.6	1.3	0.96	20	48	130	14
^{134}Cs	160	140	160	140	150	140	180	190	170
^{137}Cs	1300	1200	1200	1200	1200	1200	1400	1400	1300
^{144}Ce	0.004	0.001	0.009	0.0006	0.0005	0.13	2.2	6.4	0.51
Total	1500	1300	1400	1300	1400	1500	1600	1700	1500
Crustacea									
^{60}Co	1.1	5.3	0.63	0.43	0.37	0.45	2.8	5.3	1.3
^{90}Sr	0.14	0.14	20	0.14	0.14	42	0.62	2.2	3.6
^{106}Ru	0.33	0.29	0.31	0.29	0.29	0.29	5.2	15	1.2
^{125}Sb	0.15	0.51	0.11	0.03	0.02	0.49	1.2	3.0	0.34
^{134}Cs	4.0	3.6	4.0	3.6	3.8	3.6	4.4	4.6	4.2
^{137}Cs	27	25	25	25	25	25	29	29	27
^{144}Ce	0.02	0.006	0.04	0.003	0.002	0.06	11	31	2.5
Total	33	34	50	29	30	72	54	90	39
Molluscs									
^{60}Co	8.1	4.1	4.8	3.3	2.9	3.4	0.00002	41	10
^{90}Sr	0.91	0.91	130	0.91	0.91	260	3.9	14	23
^{106}Ru	12	10	11	10	10	10	190	530	43
^{125}Sb	0.37	0.13	0.28	0.08	0.06	1.2	3.0	7.7	0.86
^{134}Cs	30	27	30	27	29	27	34	35	32
^{137}Cs	180	170	170	170	170	170	190	190	180
^{144}Ce	0.20	0.06	0.45	0.03	0.03	0.64	110	320	26
Total	230	210	350	210	210	470	530	1100	310
Grand total	1700	1600	1800	1600	1600	2000	2200	3000	1800

Table 41

Radionuclides discharged to the atmosphere from fuel reprocessing plants 1975-1979
[B2, B22, L1, L6]

Year	Energy [GW(e) a]	Activity released (TBq)									
					Particulate release		Isotopic composition of particulate release (total β)					
		^{3}H	^{14}C	^{85}Kr	Total α	Total β	^{90}Sr	^{106}Ru	^{129}I	^{131}I	^{134}Cs	^{134}Cs
						WINDSCALE (United Kingdom)						
1975	3.2	444		44000	0.0028	0.070						
1976	3.2	444		44000	0.0019	0.13						
1977	2.1	296		33000	0.0010	0.28	0.041		0.0059	0.0026		0.23
1978	1.8	222	4.1	26000	0.00089	0.34	0.048	0.0078	0.0026	0.015	0.027	0.24
1979	2.5	290	3.5	35000	0.0010	0.31	0.009	0.003	0.006	0.03	0.025	0.24
1975-1979 Normalized release [TBq (GW[e] a)$^{-1}$]		133	1.8	14000	0.0006	0.088						
						LA HAGUE (France)						
1975	1.6	3.3		24000	$5.9\ 10^{-10}$	0.0006						
1976	0.84	1.8		13000	$7.4\ 10^{-10}$	0.0003						
1977	1.8	11		25000	$1.1\ 10^{-7}$	0.0001						
1978	2.1	4.1		29000	$1.1\ 10^{-6}$	0.0001						
1975-1979 Normalized release [TBq (GW[e] a)$^{-1}$]		3.2		14000	$1.9\ 10^{-7}$	0.0002						
						MARCOULE (France)						
1975	0.24	4.4		3700	$8.1\ 10^{-7}$	0.001						
1976	0.22	4.4		3500	$6.7\ 10^{-7}$	0.001						
1977	0.32	2.8		4400	$3.2\ 10^{-6}$	0.0002						
1978	0.83	63		11000	$1.7\ 10^{-6}$	0.0003						
1975-1978 Normalized release [TBq (GW[e] a)$^{-1}$]		46		14000	$4.0\ 10^{-6}$	0.002						

Table 42

Radionuclides released to the aquatic environment from fuel reprocessing
[B2, B22, L1, L6]

Year	Activity released (TBq)				
	Total α	Total β (other than ^{3}H)	^{3}H	^{90}Sr	^{106}Ru
		WINDSCALE (United Kingdom)			
1975	85	9065	1400	466	762
1976	60	6771	1200	381	766
1977	46	7129	910	427	816
1978	68	7124	1050	597	810
1979	62	4100	1200	250	390
1975-1979 Normalized release [TBq (GW[e] a)$^{-1}$]	25	2671	450	166	277
		LA HAGUE (France)			
1975	0.49	1180		75	829
1976	0.37	714		40	555
1977	0.67	765	331	73	540
1978	0.51	1092	728	140	801
1975-1978 Normalized release [TBq (GW[e] a)$^{-1}$]	0.32	592	272	52	430
		MARCOULE (France)			
1975	0.019	42		0.93	33
1976	0.011	23		0.41	20
1977	0.013	30	117	0.37	27
1978	0.013	35	270	0.88	25
1975-1978 Normalized release [TBq (GW[e] a)$^{-1}$]	0.035	81	337	1.6	65

Table 43

Isotopic composition of liquid effluents from the Windscale reprocessing plant [D2, D22]

Radionuclide	Annual discharge (TBq)		
	1977	1978	1979
^{35}S		1.8	1.4
^{54}Mn		0.22	0.037
^{55}Fe		2.3	1.8
^{60}Co		1.0	0.52
^{63}Ni		1.5	0.18
^{65}Zn		0.037	0.022
^{89}Sr		9.9	7.5
^{90}Sr	427	597	250
^{95}Zr	92	82	60
^{95}Nb	203	148	98
^{99}Tc		179	43
^{103}Ru		8.5	5.8
^{106}Ru	816	810	390
^{110m}Ag		0.33	0.033
^{125}Sb		29	14
^{129}I	0.11	0.074	0.12
^{134}Cs	594	404	240
^{137}Cs	4480	4090	2600
^{144}Ce	152	104	83
^{152}Eu		10	3.7
^{154}Eu		38	1.9
^{155}Eu		7.8	4.0
Uranium		10936 (kg)	6000 (kg)
^{237}Np		0.60	0.33
^{238}Pu		12	12
$^{239+240}Pu$	36	46	37
^{241}Pu	981	1773	1500
^{241}Am	3.6	7.9	7.9
^{242}Cm		0.55	0.37
$^{243+244}Cm$		0.33	0.15
Electricity production from fuel reprocessed [GW(e) a]	2.1	1.8	2.5

Table 44

Population distribution around the Windscale reprocessing plant and meteorological characteristics of its location

METEOROLOGICAL CHARACTERISTICS

Quantity	Pasquill weather category							
	Dry						Rain	
	A	B	C	D	E	F	C	D
Frequency (%)	0.3	4.5	12.1	63	5	4.6	1.7	8.4
Wind speed ($m\ s^{-1}$)	1	2	5	5	3	1	5	5
Depth of mixing layer (m)	2000	2000	1000	1000	200	200	1000	1000

Distribution of wind direction frequencies (30^{o} sectors): 0.091, 0.089, 0.096, 0.11, 0.098, 0.069, 0.049, 0.034, 0.056, 0.10, 0.11, 0.094

Stack height: 100 m (effective)

POPULATION DISTRIBUTION

Distance (km)	0 - 1	1 - 2.5	2.5 - 6	6 - 12.5	12.5-17.5
Population	36	230	1100	12000	17000
Cumulative	35	220	1400	14000	31000

Distance (km)	17.5-60	60-150	150-375	375-900	900-2700
Population	71000	20000000	36000000	110000000	82000000
Cumulative	74000	21000000	57000000	170000000	260000000

Table 45

Averaged local and regional normalized whole-body absorbed dose commitments from tritium and carbon-14 discharges to the atmosphere from Windscale (United Kingdom)

Radio-nuclide	Normalized collective absorbed whole-body dose commitment [man Gy (GW[e] a)$^{-1}$]		
	Ingestion	Inhalation	Total
^{3}H	0.30	0.049	0.35
^{14}C	0.69	0.0001	0.69

Table 46

Collective dose commitments from atmospheric annual discharges from Windscale (United Kingdom) averaged between 1975 and 1979

Pathway	Collective effective dose equivalent commitment (man Sv)	Collective absorbed dose commitment (man Gy)								
		Gonads	Breast	Red bone marrow	Lungs	Thyroid	Bone lining cells	Liver	Skin	Remainder tissues
CLOUD										
^{85}Kr	0.26	0.058	0.078	0.095	0.074	0.065	0.095	0.074	19	0.078
DEPOSIT										
^{137}Cs	1.1	0.87	1.2	1.4	1.1	0.97	1.4	1.0	1.4	1.1
INHALATION										
^{3}H	0.3	0.13	0.3	0.13	0.13	0.13	0.13	0.13	0.13	0.13
^{239}Pu	0.11	0.00074	-	0.0043	0.02	-	0.059	0.012	-	-
^{240}Pu	0.10	0.00068	-	0.0044	0.018	-	0.054	0.011	-	-
^{241}Am	0.08	0.000095	-	0.0056	0.00052	-	0.075	0.016	-	-
^{238}Pu	0.04	0.00022	-	0.0015	0.0071	-	0.019	0.0041	-	-
^{129}I	0.007	-	-	-	-	0.24	-	-	-	-
^{137}Cs	0.006	0.006	0.005	0.006	0.0056	0.005	0.005	0.0054	0.0041	0.005
Total	0.47									
INGESTION										
^{3}H	0.78	0.78	0.78	0.78	0.78	0.78	0.78	0.78	0.78	0.78
^{134}Cs	0.13	0.13	0.11	0.13	0.11	0.11	0.11	0.13	0.11	0.086
^{137}Cs	1.1	1.1	0.98	0.98	0.98	0.98	0.98	1.1	0.98	0.76
^{14}C	1.8	1.8	1.8	1.8	1.8	1.8	1.8	1.8	1.8	1.8
^{90}Sr	0.24	-	-	1.3	-	-	2.8	0.0096	0.0096	0.0096
^{129}I	0.34	-	-	-	-	11	-	-	-	-
Total	4.4									
GRAND TOTAL	6.2									

Table 47

Collective absorbed dose commitments for average releases between 1975 and 1979 into the Eastern Irish Sea from Windscale (United Kingdom) and into the Eastern English Channel from La Hague (France)

Pathway		Collective absorbed dose commitment (man Gy)							
		Gonads	Breast	Red bone marrow	Lungs	Thyroid	Bone lining cells	Liver	Lower large intestine
		WINDSCALE (United Kingdom)							
Fish									
^{137}Cs		270	250	250	250	250	250	250	270
Mollusc and crustacea									
^{106}Ru		8.7	7.4	8.1	7.4	7.4	7.4	-	380
Fish, crustacea, mollusc									
^{90}Sr		-	-	25	-,	-	54	-	-
Mollusc									
^{239}Pu and ^{240}Pu		0.024	-	0.16	-	-	2	0.42	0.50
^{241}Pu		0.46	-	2.7	-	-	36	5.9	2.3
Total	βγ	280	260	290	260	260	350	260	650
	α	0.024	-	0.16	-	-	2	0.42	0.50
		Collective effective dose equivalent commitment: 311 man Sv							
		LA HAGUE (France)							
Fish									
^{137}Cs		9.5	8.8	8.8	8.8	8.8	8.8	8.8	9.5
Mollusc and crustacea									
^{106}Ru		20	17	19	17	17	17	-	880
Mollusc									
^{239}Pu and ^{240}Pu		0.005	-	0.036	-	-	0.42	0.09	0.11
^{241}Pu									
Total	βγ	30	26	28	26	26	26	11	890
	α	0.005	-	0.036	-	-	0.42	0.09	0.11
		Collective effective dose equivalent commitment: 84 man Sv							

Table 48

Local and regional collective effective dose equivalent commitments for normalized discharges from the model reprocessing facility to atmospheric and marine environments

Radionuclide	Normalized release [TBq (GW!e! a)$^{-1}$]	Normalized collective effective dose equivalent commitment [man Sv (GW!e! a)$^{-1}$]
ATMOSPHERIC		
^{3}H	60	0.1
^{14}C	0.4	0.2
^{85}Kr	10000	0.03
^{90}Sr	0.0007	0.006
^{129}I	0.0002	0.004
$^{238,239,240}Pu$	0.00001	0.002
	Total	0.3
AQUATIC		
^{137}Cs	7	0.4
^{106}Ru	10	0.3
^{90}Sr	2	0.02
^{129}I	0.04	0.008
$^{238,239,240}Pu$	0.5	0.0006
	Total	0.7

Table 49

Representative annual effective dose equivalents to most exposed individuals from reprocessing LWR fuel at the model facility

Radionuclide	Annual effective dose equivalent (μSv)
ATMOSPHERIC	
^{3}H	5
^{14}C	10
^{85}Kr	5
^{90}Sr	2
^{129}I	2
α emitters	1
Total	25
AQUATIC	
^{90}Sr	2
^{106}Ru	50
^{137}Cs	150
^{129}I	1
α emitters	0.5
Total (rounded)	200

Table 50

Summary of normalized releases of radionuclides of global significance and of the corresponding collective effective dose equivalent commitments

Radionuclide	Normalized release [TBq (GW[e] a)$^{-1}$]	Normalized collective effective dose equivalent commitment [man Sv (GW[e] a)$^{-1}$]				
		Integration time (a)				
		10^1	10^2	10^4	10^6	10^8
^{3}H	640	0.015	0.02	0.02	0.02	0.02
^{85}Kr	11000	0.9	1.9	1.9	1.9	1.9
^{14}C	17	3	10	70	110	110
^{129}I	0.04	-	0.02	0.2	28	560

Table 51

Collective effective dose equivalent commitments from high-level waste disposal per unit electrical energy generated for different fuel cycles [111]

	Normalized collective effective dose equivalent commitment [man Sv (GW[e] a)$^{-1}$]				
	LWR	HWR			
DISPOSAL OF UNREPROCESSED FUEL					
Uranium content of fuel					
Migration time 10^6 a	62	300			
Migration time 10^5 a	71	170			
All other elements					
Migration time 10^6 a	27	10			
Migration time 10^5 a	200	280			
Total (rounded) (10^6 a)	89	310			
(10^5 a)	270	450			
	LWR (Plutonium recycle)	FBR	HWR		HTR
			Uranium Plutonium	Uranium Thorium	Uranium Thorium
DISPOSAL OF REPROCESSING WASTES					
Uranium content of fuel					
Migration time 10^6 a	22	0.8	130	22	1.1
Migration time 10^5 a	23	1.1	72	120	6.0
All other elements					
Migration time 10^6 a	9	18	6	14	24
Migration time 10^5 a	27	51	45	140	110
Total (rounded) (10^6 a)	31	19	140	36	25
(10^5 a)	50	52	120	260	120

Table 52

Summary of normalized collective effective dose equivalent commitments to the public from nuclear power production

	Normalized collective effective dose equivalent commitment [man Sv (GW[e] a)$^{-1}$]		
LOCAL AND REGIONAL CONTRIBUTION			
Mining			
Radon	0.5	Total	0.5
Milling (excluding releases from tailings)			
Uranium, thorium, radium	0.015		
Radon	0.02		
		Total	0.04
Fuel fabrication			
Uranium	0.002	Total	0.002
Reactor releases			
Atmospheric			
- Noble gases	0.6		
- Tritium	0.5		
- Carbon-14	2.8		
- Iodines	0.06		
- Particulates (caesium, ruthenium, cobalt)	0.1		
		Total	4.1
Aquatic			
- Tritium	0.04		
- Other (caesium, ruthenium, cobalt)	0.02		
		Total	0.06
Fuel reprocessing			
Atmospheric			
- Tritium	0.1		
- Krypton-85	0.03		
- Carbon-14	0.2		
- α emitters	0.002		
		Total	0.3
Aquatic			
- Caesium 134, 137	0.4		
- Ruthenium-106	0.3		
- Strontium-90	0.02		
- α emitters	0.0006		
- Iodine-129	0.008		
		Total	0.7
Transportation	0.003	Total	0.003
TOTAL for operations in the nuclear fuel cycle		5.7 man Sv [GW(e) a]$^{-1}$	

	Complete and incomplete normalized collective effective dose equivalent commitment [man Sv (GW[e] a)$^{-1}$]				
	Integration period (a)				
	10^1	10^2	10^4	10^6	10^8
GLOBAL CONTRIBUTION FROM OPERATIONS IN THE NUCLEAR FUEL CYCLE					
Tritium	0.015	0.02	0.02	0.02	0.02
Krypton-85	0.9	1.9	1.9	1.9	1.9
Carbon-14	3	10	70	110	110
Iodine-129	-	0.02	0.2	28	560
TOTAL (rounded)	3.9	12	72	140	670
WASTE DISPOSAL (assuming LWR fuel reprocessed and plutonium utilization in LWRs and FBRs)					
Mill tailings (radon) a/	0.25	0.25	250	2800	2800
(uranium) b/			460	460	460
High-level wastes	-	-	-	30	30

a/ Assuming radon emanation continued at the same rate as at disposal with 2 m earth covering.

b/ Assuming that at 10^3 a the tailings are eroded into fresh water, then marine environments.

Table 53

Annual per caput doses from the continued generation of nuclear electric power to the year 2500

	Year			
	1980	2000	2100	2500
Annual projected nuclear generation [GW(e) a]	80	1000	10000	10000
Annual collective effective dose equivalent (man Sv)	500	10000	200000	250000
World population	$4\ 10^9$	10^{10}	10^{10}	10^{10}
Annual per caput effective dose equivalent (μSv)	0.1	1	20	25
Percentage of average exposure to natural sources of radiation (%)	0.005	0.05	1	1

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ANNEX G

Medical exposures

CONTENTS

Introduction

1. Medical irradiation of the human body is done in the course of diagnostic x-ray procedures, in diagnostic nuclear medicine by internally administered radionuclides, and in radiation therapy. In many countries medical exposure gives the largest man-made contribution to the population dose. In developed countries such exposure may approach the contribution from natural sources, and much effort is devoted to minimize it. This Annex follows the trends in medical procedures giving rise to exposure and in relevant doses to patients and to the population; it also presents data on the distribution of doses among irradiated persons.

2. The Committee has reviewed information on the medical irradiation of patients in a number of reports since 1958 [U3, U4, U5, U6, U7]. Doses to patients from various medical procedures have been assessed, both in order to follow trends and to make it possible to see which procedures are most significant with regard to possible radiation risks. For any one procedure the dosimetric information is complex, with considerable variation of the absorbed doses in different organs. It is therefore not easy to find a simple basis for comparisons.

3. In its 1958 report, the Committee was mainly interested in exposures relevant to the risk of hereditary effects. The genetic significance of a gonadal dose depends on the child expectancy of the exposed individual. Therefore, the age distribution of patients subject to various radiological examinations must be considered in the assessments. This led the Committee

to the introduction of the genetically significant dose (GSD) (see Annex A), which was the quantity of primary interest in 1958. It was evident that the major part of the genetically significant dose was contributed by rather few types of examinations. At that time there was little biological ground for quantitative assessment of any somatic risk of a stochastic nature. The correlation between leukaemia and radiation exposure of the active bone marrow was being studied and the Committee included some assessments of mean marrow doses.

4. In its 1977 report [U7], the Committee made an effort to estimate mean doses to other tissues, e.g., thyroid, lung and breast. In the evaluation of the significance of such exposures, assumptions need to be made on the dose-response relationship for cancer induction in these organs. Because of the long latent periods involved, this would also strictly call for consideration of the age at exposure.

5. Some discussion of the possible development of a somatically significant dose equivalent is included in Annex A. However, refinement of this concept is felt to imply a precision of knowledge that is at present lacking. Development of the concept of a somatically significant dose equivalent is, however, considered to be useful to supplement the conventional information on the genetically significant dose because the emphasis that has been given to the latter might distort the relative importance of the various examinations from the point of view of total risk.

6. In 1977, the International Commission on Radiological Protection (ICRP) [I6] introduced a method for calculating a quantity later called effective dose equivalent, for the purpose of application of dose limits in radiation protection of workers (see Annex A). This method involved a weighting of the mean organ dose equivalents with factors derived to reflect the relative risk of cancer and severe hereditary effects from exposures of the corresponding organs. The effective dose equivalent, as defined by ICRP, is the sum of all the weighted organ dose equivalents.

7. The effective dose equivalent as calculated is independent of age and sex, because the organ weighting factors are average values for both sexes and all ages. It is obvious, therefore, that they are not based on the best estimate of risk for any given individual and that they are not intended to apply to population groups with sex- or age-distributions which substantially differ from the normal. It was not the original intention of ICRP that the effective dose equivalent should be calculated for patients.

8. In its effort to find a quantity that would indicate the significance, from the point of view of total risk, of the heterogeneous exposure of patients, the Committee found that the organ weighting factors that would be appropriate could only be estimated with great uncertainty and could not be shown to deviate substantially from the weighting factors used by ICRP, although for a different purpose. The Committee therefore decided to estimate the effective dose equivalent for patients and presents that quantity in this report, enabling dose comparisons which are believed to be more relevant than in previous reports, where only organ doses and the genetically significant dose were given. The reader is advised to interpret the results with caution because of the shortcomings of the concept when applied to medical exposures.

9. In particular, the effective dose equivalent would not satisfactorily reflect the true risk when applied to groups of patients with substantially reduced life expectancy (as in radiotherapy of some malignant disease) or with age- and sex-distribution grossly differing from those in a normal population (for example, in mammography or pelvimetry).

10. When effective dose equivalents are compared, it must therefore be recognized that they may over- or under-estimate the risk, depending upon the way in which the group of patients differs from a normal population. There is not yet sufficient information on the dose-response relationships for somatic stochastic effects to permit a reliable quantitative correction in such cases. For the total collective dose equivalent contribution from medical practice, specific calculations must ideally be made for the population of interest.

11. There is a very great potentiality for variation of individual organ doses, depending upon the value of a number of physical parameters that influence the dose per examination. It is also found that doses are in fact very different from hospital to hospital, depending upon the radiological technique and equipment. In order to assess average dose values representative for large population groups, it is therefore necessary to make extensive surveys. Data reported from single clinics, or calculated on the basis of some assumed practice, cannot usually be taken to be representative. These uncertainties influence the reliability of any dose estimates per caput for large regions of the world, such as the genetically significant dose and the per caput mean marrow dose as earlier assessed by the Committee, and of the effective dose equivalent.

12. Trends in frequencies of the various radiological procedures are reviewed in this Annex. Individual absorbed doses in the various organs per unit procedure, and the effective dose equivalent per type of procedure, are also compiled and discussed. Recent reports on exposure of patients have considered organ doses and the accuracy and precision of their measurements, and are reviewed here. Efforts have also been devoted to the compilation of biological data on the distribution of radionuclides administered to patients. Much of this information has been used to derive absorbed doses in organs, and effective dose equivalents, from the medical use of radionuclides [K2, K3].

13. Dosimetry of the tissues outside the treatment area during radiotherapy cannot be quantified in the same manner and to the same extent as in diagnostic exposure. This is mainly due to the lack of published information on absorbed doses in tissues outside the treatment area. For these reasons the chapter on the therapeutic use of radiation is rather more descriptive than quantitative.

I. DIAGNOSTIC X-RAY EXAMINATIONS

A. TRENDS IN FREQUENCY

1. General survey

14. In the 1977 report [U7] there was a brief review of the frequency of diagnostic x-ray examinations in various countries. Surveys made in Japan up to 1974, in Sweden up to 1974 and in the United States in 1964 and 1970, were analysed in terms of frequency of diagnostic

x-ray examinations by type. Since then new surveys have become available from Australia [S20], Finland [L7], Federal Republic of Germany [T8], Japan [H26], Poland [J5], Romania [F3], Sweden [N1, N11], the USSR [K11] and the United Kingdom [K12]. The data available have been expressed in terms of the annual per caput examination rate in order to allow comparisons between countries to be made. Various examinations have been grouped according to the organ or system examined.

15. The classification scheme for diagnostic radiological examinations, recommended by a joint ICRP/ICRU report [I14], is adopted in this report as a means of presenting statistics of x-ray diagnostic examinations. To that recommended classification scheme it was necessary to add three additional categories: x-ray examination of the breast (mammography), computed tomographic scanning (CT-scan) and other examinations not included elsewhere.

16. In industrialized countries, the frequency of various examinations per 1000 inhabitants is given in Table 1 which includes only the most recent data available [F3, H13, H14, H26, J5, K12, L7, M19, N11, S20, T8]. Earlier compilations are found in previous reports [U3, U7]. It is difficult to draw overall conclusions applying to countries whose reporting systems may not be comparable. However, existing data point to examination frequencies, per 1000 inhabitants, of between 300 and 900 in these countries, excluding dental examinations and mass miniature radiography, for which reporting is not consistent (however, see also paragraphs 28 and 29). The frequency of examinations of different anatomical sites estimated for various world areas, is given in Table 2. It is interesting to note that by far the most common types of examinations are those of the thorax and of the skeleton.

2. Survey of developing countries

17. Data on the availability of diagnostic radiological equipment, and on the frequency of diagnostic x-ray examinations in developing countries, are particularly difficult to obtain. The WHO has recently made major efforts to increase this knowledge by analysing the available sources [W11, W12] and by sending out a questionnaire which was worked out in co-operation with UNSCEAR [W13].

18. The current situation of radiodiagnostic services in each of five WHO regions, including most of the developing countries, is summarized in Table 3 [W12], which provides information about the distribution of the numbers of diagnostic x-ray equipment. The above data are not truly representative of the availability of the equipment in various regions because most of it is concentrated in urban areas, particularly in the larger cities, while the rural population has very limited access to such facilities.

19. The annual frequency of diagnostic x-ray procedures, as reported by WHO regional offices, is shown in Table 4, subdivided for various types of examination [W3, S8]. The total frequency of diagnostic x-ray examinations in developing countries is often between 100 and 200 per 1000 inhabitants, or lower, which is much less than in industrialized countries.

B. TRENDS IN TECHNIQUE AND EXPOSURE

1. Trends in reduction of exposure

20. In recent years, efforts, including testing and evaluation of various types of films and fluorescent screens, have been made in many countries to reduce unnecessary exposure of the patient. The results of these efforts are particularly good in regard to dental examinations [J1]. The data of Neuweg [N4], Johnson [J1], and Bunge [B19, B20], who reported average annual exposure during the 1970s, show little or no reduction in medical exposures for selected examinations.

21. Various technical improvements in diagnostic radiology, such as rapid films, more sensitive screens and image-intensifying television systems, may be presumed to reduce the dose to the patient, if applied correctly. However, a study of diagnostic procedures in Sweden from 1960 to 1975 revealed little decrease of the dose, despite technical improvements. On the other hand, the study showed a significant reduction of the dose for selected examinations, due to the introduction of high sensitivity screens and to a reduction of the number of films [G4].

22. Many data show that there is still a great variability in entrance doses for standard patients, brought about by the difference in sensitivity of the various detector systems used. According to several studies in the Federal Republic of Germany, the United Kingdom and the United States, the ratio between the lowest and highest entrance dose is about 1:100 [B19, J1, K30, U8, U9, W20, W21].

23. In 1971 a programme for a nationwide evaluation of the trends in the use of x rays, the NEXT project, was set up in the United States. The survey procedure allows estimation of radiation exposure to the patient and its variation in the course of time [J1, U9, U12, U13]. In addition, other parameters may be studied. For example, the ratio of beam-area to film-area (S_{beam}/S_{film}) used in the various projections was found to vary from 1.1 to 2 for various examinations. Few significant differences were found in the above ratio and in the exposure levels for different facilities or for different operators. The mean ratio for chest radiography decreased from 1.6 to 1.2 during the period 1973–1978. Hospitals and radiology facilities had significantly lower S_{beam}/S_{film} ratios than other groups (internal medicine, general practitioners, health agencies). Among operators, trained radiology technologists delivered lower values of the S_{beam}/S_{film} ratio and lower values of the exposure-area product than did non-trained personnel [W10].

24. In another case, improvements in the protection of patients during the period 1970–1975 resulted in a 15% decrease in the annual dose per individual averaged over the whole body, in spite of an increased frequency of examinations during the same time [Z2]. In other reports the mean gonad dose and the genetically significant dose did not change appreciably because the frequency of examinations giving the highest contribution to the gonadal dose was rather stable [K27, K28, T3, T4, T5, T6, T7].

25. Other studies indicate that many diagnostic facilities produce poor quality images, and give unnecessary radiation exposure, because of poor equipment performance [S4]. The introduction of quality assurance

programmes in diagnostic radiology and nuclear medicine, recommended by ICRP [I20] and WHO [W22], can be of great value in improving the diagnostic information content, thus leading to a reduction of radiation exposure.

26. A noteworthy reduction in the use of fluoroscopy has been reported from France [S34]. In that country, in 1976, there were some 13 000 fluoroscopic installations used for general medical purposes; by 1982 the number was 5000, of which 2000 were operated by specialists in cardiology and chest diseases. It is expected that the remaining 3000 fluoroscopic installations will have been eliminated by 1985 [P12].

2. Mass chest x-ray examinations

27. In most countries about 50% of all medical x-ray examinations are of the chest. There is a trend to abandon fluorography in favour of radiographic techniques. There is also a decline in mass chest x-ray examinations in some industrialized countries because the incidence of tuberculosis is declining; furthermore, there is now good evidence that early detection of lung cancer by radiological techniques is not associated with any significant improvement in the prognosis of the condition [B28, L9, S33].

28. Information from various countries and areas on gonad exposure from mass survey examinations of the chest was given in the 1962 report [U4], the frequency of examination per 1000 total population ranging from about 100–300 in most industrialized countries. At the time most surveys were performed by miniature radiography although in some countries examinations were still performed by fluoroscopy. Declining trends are now seen in the data reported from Sweden, the United Kingdom and the United States, where current frequencies are below 50 examinations per 1000 inhabitants. Other countries, however, still report frequencies above 300 examinations per 1000 inhabitants [F3, H14, K11, S20].

3. Dental examinations

29. Dental radiography is the most frequent type of diagnostic x-ray examination in many industrialized countries. There are however great difficulties in obtaining accurate statistical data on the frequency of dental x-ray examinations. In some countries the numbers are included in medical x-ray examinations and in others they are reported separately. Japan reports, for 1980, an annual frequency of 851 dental films per 1000 inhabitants; the corresponding value for the United Kingdom in 1977 is 212 dental films [K12, M19].

30. The radiation exposure caused by dental x-ray examinations may be reduced by increased filtration and collimation of the beam, adequate shielding of the head and by the use of faster films. In 1957 Baily [B1] was able to reduce the average facial exposure, in routine full-mouth set of 14 apical film examinations of adults, with 60-kVp x rays, from 5.9 mC kg^{-1} with no filtration to 4.1 mC kg^{-1} with 1 mm Al additional filter. Corresponding exposure values for the examination of children were 1.6 mC kg^{-1} with no filtration and 1.3 mC kg^{-1} with 1 mm additional Al filter. Because no collimation was used, the exposure to the thyroid was increased with additional filtration from 0.22 mC kg^{-1} to 0.28 mC kg^{-1} for adults and from 0.09 mC kg^{-1} to 0.13 mC kg^{-1} for children. In the same investigation the exposure to the bony structure per full-mouth set of 14 films ranged from 2 mC kg^{-1} to 6 mC kg^{-1} for adults, and from 0.8 mC kg^{-1} to 2.3 mC kg^{-1} for children, depending on operating voltage and added filtration [B1].

31. Bjärngard et al. [B9] studied the absorbed doses from full-mouth radiographic examinations. They reported absorbed doses in the lens of 15 mGy, in the thyroid of 5 mGy, and a maximum skin dose of 260 mGy. Further studies by the same group [B10] reported doses to the lens from 4 to 110 mGy, to the thyroid from 2 to 9 mGy, and maximum skin doses from 70 to 500 mGy. A study of the doses delivered in various anatomical sites of the head and neck from 14-film periapical examinations was carried out by Richards et al. [R3]. Values in this series that were comparable with the previous one were about 6 times lower, due to the use of faster films [R3, B10].

32. O'Shaughnessy and Mitchell [O1] performed a systematic study of the relative amounts of primary and secondary beam received by tissues, in relation to various changes made to the x-ray equipment and techniques (cone length, filtration, collimation). Collimation of the beam was the most important single factor in reducing unnecessary radiation.

33. A laboratory investigation was performed by Winkler [W9] to determine the reduction in exposure to be gained by the use of small rectangular x-ray beams restricted to the approximate size of the film, combined with a shield to absorb most of the radiation behind it. The absorbed dose during a 22-film intra-oral examination was reduced significantly with the use of a rectangular film holder. In the skin the absorbed dose was 11 $\pm$ 4 mGy without, and 4 $\pm$ 2 mGy with, film holder. Corresponding values for salivary glands were 5.3 mGy and 0.9 mGy, respectively, and for mandibular bone at the area of the third molar 21 mGy to 7.8 mGy. In the cornea of the eye the absorbed dose was reduced from 3.4 mGy without, to 0.2 mGy with, film holder.

34. Weissman and Sobkowski [W7] reported on a comparative clinical dosimetric evaluation of four intra-oral periapical radiographic survey methods, including the device proposed by Winkler [W9]. Their results showed that the absorbed dose to the cornea of the eye could be reduced from 8.6 mGy to 0.2 mGy by cone shielding and rectangular collimation of the primary beam. The absorbed dose in the thyroid was reduced from 0.6 mGy to 0.06 mGy. They concluded that radiographic methods using unshielded cones result in unnecessary irradiation without improvement of the image and should no longer be accepted.

35. The effect of adding accessories to a conventional x-ray machine to reduce patient exposure during full-mouth dental radiography was investigated by Yülek et al. [Y1, Y2]. Maximum reductions were observed at the eyes (80%) when the x-ray machine was protected by a cylinder of 1 mm Al and 0.1 mm Pb and the patient was made to wear 0.1 mm Pb-shielded glasses. With, in addition, a shield around the neck to protect the sites below the neck, reductions of absorbed doses amounted to 70.6% in the thyroid, 59.9% under the collar bone and 44.5% at the gonads [Y1, Y2].

36. Bushong et al. [B21] carried out measurements on patients undergoing full-mouth (18 films) examinations

at three different facilities. Skin exposure in the primary beam area was 1 mC kg^{-1} at the facility employing slow films and 65-kVp x rays. Ultra-speed films and 90-kVp x rays resulted instead in an average exposure of 0.2 mC kg^{-1}. Panographic examinations delivered average exposures of about 8 μC kg^{-1}. The study of Ice et al. [I1] compared radiation exposures from various types of position-indicating devices. Both at 65-kVp and at 90-kVp it showed that lead-lined cones are most effective in reducing patient skin exposure outside the useful beam in clinical dental radiography.

37. A study was also conducted by Alcox and Jameson [A2] of exposures at selected areas of the head and neck from conventional dental radiographic procedures. Their results indicated that the exposure at any specific area of the patient's face was much less than the exposure at the tip of the cone. Thyroid exposure, in particular, was around 0.3 μC kg^{-1} per film, which was about 1% of the exposure at the tip of the cone.

38. Absorbed doses in the marrow of the skull, mandible and cervical spine were measured by White and Rose [W8] during dental examinations of phantoms using intra-oral, panoramic and cephalometric radiography. Table 5 shows the mean dose equivalent to the marrow at different sites and for various types of examination. Mean absorbed doses to various organs and tissues from intra-oral and orthopantomographic examinations have been evaluated in detail by using phantoms [I18, J4, M4, S23].

39. Pantomographic radiology, which provides an image of all teeth from root to crown on a single film, has become increasingly used in the last few years. Its introduction, however, has led to a considerable increase in the number of patients examined [W17]. Pantomographic equipment from seven manufacturers has been investigated along with other procedures for obtaining similar information using conventional dental x-ray sets (Table 5). Absorbed doses in the head and neck region ranged from 0.1 to 0.8 mGy for the pantomographic technique and from 0.01 to 6.4 mGy for the conventional one. The mean values for the absorbed doses in the marrow were 0.05 and 0.08 mGy, respectively [B6]. Thus, the patient exposure for both techniques is of the same order of magnitude.

40. A study of the absorbed dose in panoramic view or full-mouth examination (11 intra-oral films) was performed on 22 patients [N12]. The average absorbed dose values from the panoramic view was 0.05 mGy and from a full-mouth examination 0.1 mGy. Corresponding absorbed dose values in the cheek were 0.09 mGy and 3.3 mGy, respectively, and in the skin 0.13 mGy and 3.5 mGy [N12]. In organs outside the beam the difference decreased and no significant difference was found in the gonads where the absorbed dose was about 0.01 mGy for both techniques.

4. Mammography

41. The number of mammography examinations is steadily increasing. Data have been reported from Sweden [N17] where the total number of examinations increased from 17 (1977) to 40 (1979) per 1000 women. In the same study the number of mammography examinations for screening purposes increased from 11 to 22 per 1000 women in the same period of time. Similarly, in the United States, the number of examinations in women of 35 years or older went from 30 to 72 and in women of 40–46 years of age rose from 56 to 136 per 1000 women over the same time. Screening of female breast for malignancy in the United States is treated extensively in a special report [N18].

42. The imaging media used in mammography may be medical x-ray films or various combinations of films and screens. Xerography is also a special method of imaging used for mammography, whereby the image is produced by the use of a photoconductive surface, electrostatic charges and xerographic-type processing. Owing to the "edge enhancement" effect of xerography, this technique is advantageous for the detection of certain types of breast diseases, such as dense fibrocystic conditions [U11].

43. A programme was established in the United States to reduce unnecessary examinations, to improve the image quality and to collect data on radiation exposure [J1]. This programme, known as BENT (Breast Exposure: Nation-wide Trends) made its first evaluation in 1976. The mean exposures for xerography, film-screen and non-screen medical and industrial film techniques have been reported by a number of investigators [A3, H2, J2, P1, U10, U11] and are shown in Table 6.

44. If current risk estimates for radiation carcinogenesis are to be applied to mammography, then the relationships between surface exposure and absorbed dose in tissues at risk should be considered. Information specifically related to mammography is available and several authors have adopted mid-breast dose as the critical parameter on which risk analyses should be based [E4, K1, P1, U10, Z1].

45. The most relevant indicator of the risk of mammography would be the energy imparted in the gland tissue of the breast, but before this quantity can properly be applied to the problem of risk assessment more information would be needed on the amount and distribution of the tissue at risk in individual cases. One could, however, assume very roughly that the linear density of the gland tissue might be 35 g/cm and its total mass 175 g, on the average. On these assumptions, the average absorbed dose per unit exposure to the glands of an average breast has been calculated for different radiographic techniques and found to vary between 1 and 4 mGy [H2].

46. The evolution of the mammographic technique is also summarized in Table 6. The average absorbed dose and the mid-breast dose are given for various systems [A3, K16, M16, P11, S24, U10]. There is a steady decrease in all dose values during the period of study. Some further reduction of absorbed dose might be achievable without compromising the mammographic image quality [S24]. These improvements would include photon energy control, scatter removal and improvement in detector response [M16].

47. The probability of an increase in five-year survival as a result of early detection and treatment of breast cancer has been used as a specific estimate of the benefit of mass application of mammography [K29]. Mammography increases the probability of diagnostic detection of stage I breast cancer by 3 times; the detection of stages II and III is however less efficient by comparison with other methods of examination [F5, G5, K29]. The five-year survival after treatment may be improved by 11%, following mammography. If this

benefit is then compared with the risk of developing fatal malignancies, it may be calculated to exceed the risk by a factor of 2 to 30 (according to the different techniques used) [K29].

5. Computed tomography

48. Diagnostic radiology has generally used methods for two-dimensional imaging of the body. Since 1971 a new tomographic method has been introduced in which a finely collimated x-ray beam is used for scanning across the plane of interest at various discrete angles. The attenuation of the transmitted beam is recorded by a detector and the relevant data are processed by computer with a mathematical algorithm to generate a cross-sectional image of the body in terms of relative attenuation coefficients in the layer examined. Because of the paramount role of the computer in the imaging procedure the method is called "computed tomography" (CT) [B14].

49. Computed tomography is considered to be the greatest improvement in the diagnostic use of ionizing radiation since the discovery of x rays, and it overshadows other major technical achievements, such as tomography, image intensification, cine- and video-roentgenology. The value of CT-scanners was quickly recognized and technical developments have proceeded very rapidly.

50. The number of CT-examinations in Sweden from 1973 to 1979 is given in Table 7. In 1979, 8 head scanners and 7 whole-body scanners were in operation. The average number of examinations per head scanner was about 2050, and per whole-body scanner about 1300. In the same year about 2 head examinations and about 1 whole-body examination per 1000 population were performed in that country [N17]. In Japan, the frequency of CT-scanning examinations in 1979 was reported to be 0.44 for head examinations and 0.24 for whole-body scans, per 1000 population [N14].

51. If one images a uniform material, for example, a water bath, in a CT-scanner, one finds that the values of the attenuation coefficient μ are not all the same but are distributed approximately at random around an average value. The standard deviation of μ, designated as σ_μ, is called the noise of the apparatus; it is a very important measure of its performance, because the naturally-occurring variation of the attenuation coefficient between various normal tissues, and between normal and pathological tissues, is quite low. The noise depends on various parameters, such as the size of the patient or its body diameter, the mean energy of the photons and their energy spread, the width of the picture elements, the thickness of the scan and the skin dose [C4, C8, M6].

52. The x-ray beam of CT-units is highly collimated, particularly in a plane perpendicular to the axes of the trunk or the head. For single scans the x-ray beam is generally collimated to a length ranging from 3 to 15 mm perpendicular to the scan plane [M6]. For dual-scan CT-units the length is essentially double.

53. The eye may receive as much as 50 mGy for a complete CT-examination of the head [H30, I12]. The distribution of the skin doses varies with the angle of rotation. In the first-generation scanners having a 180° angle the highest absorbed doses for organs in the scan were around 35 mGy and the lowest about 0.5 mGy per scan. With other systems (360° rotation) a different distribution of the absorbed doses is obtained, and maximum doses in the skin can be as high as 560 mGy, although for normal clinical use they are around 60 mGy [B24, H21, H23, I13, K8, N3, N15, M6, P5, R2, S10, V1, W3]. Absorbed doses in the skin, the centre of the body and the gonads from CT-examinations are found in the following references: [B3, B13, H21, K8, K9, L8, M6, N5, P3, P4, W3, W18]. Organ doses and risk-weighted absorbed doses have been calculated by the Monte Carlo technique for head and whole-body scans. The data are given per slice and are normalized to exposure-free-in-air at the axis of rotation [K32]. Absorbed doses in various organs, and the average number of slices in different CT-scanning procedures, as derived by Stieve et al. [S15], are given in Table 8. A comparative study of doses from kidney CT-examinations, contrasted with conventional radiography, has been performed [K10, S18] and the results are given in Table 9.

C. ABSORBED DOSE IN THE PATIENT

54. The geometry in external irradiation is described by the projection and view — anterior/posterior (A/P), posterior/anterior (P/A), lateral (LAT) — x-ray field size at image receptor plane, x-ray field location relative to anatomical landmarks, and source-to-image-receptor distance. The conversion of exposure to absorbed dose in the body organs is obtained by using the tissue/air ratio. This is defined as the ratio of the absorbed dose at a given point in a tissue-equivalent phantom to the absorbed dose which would be measured at the same spatial point in free air within a volume of the phantom material just large enough to provide the maximum electron build-up at the point of reference [I5].

55. Estimation of organ doses from x-ray diagnostic procedures can be made either by direct measurements or by calculations. In vivo measurements are difficult and, with internal organs, phantom studies must be performed [J5, H15]. For calculations, the Monte Carlo method has been used extensively and the results of such estimates can be of considerable help in estimating the absorbed dose in various organs [K15, R6, R7].

56. Estimation of the effective dose equivalent depends on the availability of data about absorbed doses in the gonads, the breast, the red bone marrow, the lungs, the thyroid, the bone surfaces, the skin and up to five other most exposed organs or tissues [I6]. The distribution of organ doses measured or estimated for the same type of examination usually spans several orders of magnitude, with coefficients of variation ranging from 100 to 300%. This is in spite of considerable advances in the techniques of diagnostic radiology, many of which were actually expected to reduce the variability mentioned above [U9, U12, U13, W21].

57. Values of absorbed doses in diagnostic x-ray examinations are presented in various ways by different authors. Some authors report the absorbed dose in organs relative to the exposure or absorbed dose at the entrance surface [K15]. By measuring one of these values during a whole examination, the absorbed dose to various organs may thus be estimated individually. Most authors, however, report average absorbed doses in various organs, either per exposure or per full examination. Unless stated otherwise, all values in this report

refer to a full examination. The number of films used per full examination varies considerably and this makes it very difficult to estimate a good average [H1].

58. The absorbed doses in various tissues exposed in the course of diagnostic procedures, as reported from a large number of surveys conducted in different countries, are found in the following references: gonads [B5, F3, H27, J5, K30, L2, S20, U15, W15]; breast [B5, H15, J5, L2]; red bone marrow [B5, B18, C5, F3, H3, H11, H15, H27, J5, K30, L2, S9, S20, W5]; lungs [B5, H15, H27, J5, L2]; thyroid [B5, H15, H27, J5, L2]; bone surfaces [H15, J5]; skin [H15, J5, K30, S20]; remainder [H15, H27, J5, K30]; uterus and other organs [B2, H12, H30, I12, L2]. Great differences between various reports are due to different techniques. The reported organ doses for all types of diagnostic examinations range from less than 0.01 to about 50 mGy per examination.

59. Tabulation of all these data would have made the text unnecessarily complex. The Committee therefore decided to show, as an example, representative data from Japan and Poland, as supplied to the Committee by the delegations of those two countries. These are the only two series where reasonably complete values of the organ doses are available for calculating the effective dose equivalent (see section E). The relevant data are shown in Tables 10, 11 and 12.

60. These data show that there are inhomogeneities in the presentation, and, for those entries which are common, the differences in the values are very large. These differences must be attributed, to a great extent, to the variations in the techniques of exposure, and, in part, to the dosimetric techniques used. The extreme variability of the data base made it impossible for the Committee to carry out an independent assessment of effective dose equivalent which might have a more general applicability. It should be emphasized that the data from Japan and Poland cannot be considered representative of the situation applying in other countries.

D. GENETICALLY SIGNIFICANT DOSE EQUIVALENT

61. The genetically significant dose equivalent for a population is a widely used measure of the genetic detriment from medical irradiation. Its definition is found in Annex A, section II.B. Details of many GSD surveys have been given in the previous reports of the Committee and are summarized in the 1977 report [U7]. Since that time a few further data in various countries and areas have become available and are reviewed in this Annex [D5, H26, K21, S20, W21].

62. The variation with age in the frequency of all radiological examinations per 1000 population has been studied in the United Kingdom [D5]. The results indicate a general increase with age, with a superimposed increased frequency for very young children, teenagers and people in their early twenties. The increase in frequency for each age group and for both sexes relative to that found in 1957 is most marked for examinations of children and of old people (particularly women). A relatively larger increase in examinations of children and older people was also seen in the United States between 1960 and 1970 [U10].

63. The GSD from diagnostic radiology in National Health Service hospitals of the United Kingdom in 1977 was estimated to be 113 μSv, with a standard error of about 12 μSv, arising mostly from uncertainties in the frequency data. A summary of diagnostic radiology performed in 1977 in other hospitals and the contributions to GSD is given in Table 13 together with comparable data for 1957 [A6]. The GSD from all types of diagnostic radiology was estimated to be 118 μSv in 1977. Although this is somewhat lower than the figure of 141 μSv from the 1957 survey, the difference is less than twice the standard error of the mean GSD and therefore does not provide strong evidence of a decrease. The main contributions to the GSD in the United Kingdom in 1977 were examinations of the pelvis and lumbo-sacral area, upper femur and hip, urography, cystography and barium enemas. The contributions are broadly similar to those found in 1957, except that there has been a fall in the contribution from obstetric examinations from 45 to 6 μSv. On the other hand, there has been an increase by a factor of twenty in the contribution from cystography, largely due to an increase in the frequency of this examination [D5].

64. The variation with age in the frequency of all radiological examinations in Australia shows a pattern similar to that in the United Kingdom. The numbers of all x-ray diagnostic examinations per 1000 population were 209 under 2 years, 163 in the age group 2–14 years and 450 over 15 years, with a mean of 370. The examination rate of the foetus was 15.4 per 1000 population. The GSD from all x-ray diagnostic examinations in Australia during 1970 was estimated to be 149 μSv. The highest contributions were from urography, lumbo-sacral spine and obstetrical examinations [S20].

65. The most recent estimates of the GSD from medical examinations in Japan were based on a 1974 nation-wide survey of randomly sampled hospitals and clinics. The resultant annual GSD for 1979 was 150 μSv, which was approximately the same as that of 1974, although the annual number of examinations had increased in the meantime by about 30%. Table 14 shows a comparison between the 1979, 1974 and 1969 data. The GSD in the USSR due to diagnostic x-ray procedures was found to be 230 μSv per year, about two-thirds of which were attributed to radiography and the rest to fluoroscopy [K11].

66. On the basis of the data in Table 8 the annual GSD from CT-scanning in the Federal Republic of Germany was reported in 1977 at about 0.8 μSv. It was foreseen that this value might increase by a factor of 5 to 6 when optimal use of CT-tomography is reached [S15].

67. The most complete series on the GSD equivalent from diagnostic radiology has been reported from Japan. Table 15 summarizes the values for the various years and types of examination [H4, H5, H6, H7, H9, H10, H13, H14, H16, H17, H18, H19, H26, H27, H28, H35, M3, M4, M5, M19].

E. EFFECTIVE DOSE EQUIVALENT

68. The calculation of the effective dose equivalent from diagnostic procedures must take account of the technical parameters involved, i.e., beam quality, typical entrance exposure and the number of films for

each view. The expression of dose equivalent in an organ per examination is given by the formula

$$H_T = \sum_k n_k D_{T,k} Q \qquad (1)$$

where k is the type of view involved in the examination (i.e., A/P, P/A or LAT); n_k is the number of films for view k in the examination in question; $D_{T,k}$ is the average absorbed dose in an organ for view k; and Q is the quality factor. This factor is taken to be unity for x rays used in diagnostic radiology.

69. The effective dose equivalent, $H_{eff,l}$ for an examination of type l is thus obtained from the following equation

$$H_{eff,l} = \sum_T w_T H_{T,l} \qquad (2)$$

where the weighting factors w_T are those given by ICRP [16] and reproduced in Annex A, Table 3. In the case of the weighting factor for skin, ICRP [17] recommended a value of 0.01 to be applied to the mean dose over the entire body surface. The average field size used in x-ray examinations covers about 5% of the body surface. Therefore the mean dose used in the calculation of the effective dose equivalent is only a small fraction of the absorbed dose in the skin at the entrance field.

70. The weighting factors w_T given by ICRP for various organs are average values for both sexes and all ages in a population with normal age distribution. The assumed variation of the individual risk of late stochastic effects with age has been shown in ICRP publication 27 [I19]. For patients undergoing diagnostic examinations, the age- and sex-distributions often deviate from those in a normal population. Considering all other uncertainties in dose and risk assessments, such deviations are not believed to invalidate the use of the ICRP weighting factors except in a few cases. The breast is an organ for which the risk assessment is particularly sensitive to the composition of the exposed group. The main risk relates to young women, but the ICRP weighting factor, being an average for men and women of all ages, would underestimate the risk for this category, e.g. for mammography patients. Older patients would run no risk of hereditary harm and little risk of radiation-induced cancer, because of the long latent periods. For patient groups with a high proportion of old individuals, the effective dose equivalent will therefore overestimate the risk.

71. The weighting factors w_T are given for the organs which are assumed to contribute most to the total risk at a given dose. In addition to the weighting factors specified for these organs, a weighting factor of 0.06 is allotted to each of the five other organs which are estimated to receive the highest doses. This is equivalent to applying a weighting factor of 0.30 to the average dose for these five organs (the "remaining" organs). In some cases, e.g., if these organs include the eyes and the brain, for which a weighting factor of 0.06 probably overestimates the risk, the contribution of the "remainder" to the effective dose equivalent may be too high.

72. The ICRP weighting factors are derived from assumptions of the risk of lethal cancer. The effective dose equivalent therefore reflects the risk of dying from cancer. If also non-lethal cancers were to be considered, they would have to be given a detriment weight in relation to lethal cancers. This involves a value judgement. The risk of additional non-lethal cancer is particularly high in the case of exposure of the thyroid and the breast. In case of examinations where these organs receive proportionally high doses, the effective dose equivalent will underestimate the total detriment.

73. The weighting factor for the gonads is derived from assumptions of the risk of severe hereditary effects in the first two generations of offspring. It will thus underestimate (by a factor of two) the total risk of hereditary harm in all generations.

74. Modified weighting factors could be derived to compensate for the over- and under-estimation of risk which will occur by the use of the ICRP weighting factors. However, if other factors are used, the derived quantity is no longer the effective dose equivalent, since this is linked, by definition, to the weighting factors given by ICRP. Since, in most cases, the errors are expected to be less than a factor of two, the Committee does not feel that such (apparent) precision would be justified. It would tend to give the false impression that it is possible to derive a quantity which would accurately indicate the true risk. It must be emphasized that any organ-weighted dose is only a very crude indicator of the real risk.

75. Calculations of the effective dose equivalent for different types of diagnostic x-ray examinations have been reported from Poland, 1976, and Japan, 1979. Recalculations of these data were submitted to the Committee in 1982 by the delegations of these two countries and are given in Table 16. They show large variations for individual examinations.

76. The total collective effective dose equivalent from diagnostic x-ray examinations in Poland in 1976 was reported to be 20 000 man Sv, which corresponds to about 600 man Sv per million people. Examinations of GI-tract, lumbar spine and urography give the highest contribution, with about 25% each [J5]. Very recent unpublished information submitted to the Committee by the delegation of Poland indicates that the value of 600 man Sv may be an underestimate.

77. The collective effective dose equivalent from diagnostic x-ray examinations in Japan, in 1974, was estimated to be 200 000 man Sv which corresponds to about 1800 man Sv per million population. Examinations of the stomach, which is a frequent examination in Japan [H15], gave by far the highest contribution.

78. The Committee had no other quantitative information from which to obtain a reasonable estimate of collective effective dose equivalent applying generally to the population of the world. The data from Poland and Japan differ by a factor of about 3. On the assumption that these data might be applicable to other areas, then the annual collective effective dose equivalent attributable to medical irradiation for diagnostic purposes might be of the order of 1000 man Sv per million population in industrialized countries. This is an annual per caput effective dose equivalent of 1 mSv. In developing countries, having a lower frequency of radiological examinations, the value would be correspondingly less.

F. SUMMARY

79. Data on the frequency of x-ray examinations have now been reported from many countries. Per 1000 total population, the number is found to vary between 300 and 900, excluding mass surveys and dental examinations.

80. Mass chest surveys show a decreasing trend, being below 50 per 1000 people in some industrialized countries, but in other countries still as high as 300 or more per 1000 people. Reports of dental x-ray examinations are not common, but the relevant value is probably in the region of 0.2–1 film per person per year in developed regions. There is an increase in the number of patients examined by pantomographic dental x ray; the exposure of these patients is comparable with that from conventional techniques.

81. Mammography techniques currently in operation result in a considerable reduction of the dose absorbed in breast tissue. This has stimulated interest in the examination, and the number of patients undergoing it is steadily increasing.

82. Computed x-ray tomography has introduced a new dimension in diagnostic radiology. Technical developments have taken place rapidly during the last decade. Recent figures point to an examination frequency of 1 to 3 per 1000 total population per year, two thirds of which are performed on the head. This technique has also resulted in a decrease of complex angiographic examinations and radioisotope tests. The net effect of such changes may be a lower exposure of the population.

83. Absorbed doses in various organs and tissues resulting from diagnostic x-ray examinations were found to be in the range of less than 0.01 to about 50 mGy per examination. The few available assessments indicate that the effective dose equivalent for the most common types of x-ray examinations ranges from about 0.05 mSv to about 10 mSv per full examination. In the absence of any other data, the Committee has tentatively, for the purpose of this report, used the round number of 1000 man Sv per million population as the annual collective effective dose equivalent for industrialized countries. In developing countries, where the frequency of radiological examinations is lower, the value would be correspondingly less.

84. Because of the differences in the classification of diagnostic x-ray examinations in various countries it is not easy to compare data from one country to another. There is therefore a need for an internationally accepted classification scheme for diagnostic x-ray examinations to be used in reporting frequencies and dosimetric data.

II. DIAGNOSTIC USE OF RADIOPHARMACEUTICALS

A. TRENDS IN FREQUENCY AND TECHNIQUES

85. The use of radionuclides in the field of diagnostic nuclear medicine has been rapidly increasing all over the world. Since this medical specialty began its development about 30 years ago, the frequency of examinations has steadily increased. Studies have indicated a continuing rate of growth, in the number of examinations performed, by about 25% per year during 1965–1975 in the United States, which has decreased to about 10–15% per year since that time [B16]. For some European countries the annual growth rate is now of the order of a few per cent [H36, H37, N2, R11, R12, S26, S27], while figures from Australia indicate an average growth rate of about 7% per year during 1970–1980.

86. Reasonably complete statistics are only available from a few countries (Australia, Austria, Denmark, Sweden, United States) [F6, K13, M8, N2, S13, S25, S26, S27, U16]. For Berlin (West) there are statistics for the period 1953–1975; per 1000 inhabitants the most recent figures on the number of examinations are: 1968, 10.3; 1970, 15.0; 1975, 32.1; 1978, 33.9 [H36]. There is also a value for Munich for 1978, 47.8 [R12]. In Austria the frequency in 1977 was reported to be 17.5 per 1000 inhabitants [F4, F6].

87. The examination frequency of various organs by radiopharmaceuticals (examinations per 1000 inhabitants) increased from 8.4 in 1971 to 13.6 in 1976 in Sweden [N2]. In the United States the examination rate increased from 3.7 in 1966 to 37 in 1975 [M8, U7, U16]. In Denmark it increased from 3.8 during 1973–1974 to a plateau of about 14 in 1978 and 1979 [S13, S25]. For some countries, the relative frequency of various nuclear medicine procedures is shown in Table 17 [K13, N2, M8, S13, S25, S27, U7, U16]. The data indicate that, in general, the relative frequency of examinations of liver, lungs and kidneys is approximately constant, the frequency of the thyroid examinations is decreasing, while that of bone examinations is increasing. The frequency of brain scintigraphy has decreased during recent years and has been replaced by computed tomography.

88. The annual frequencies of in vivo diagnostic nuclear medicine procedures per 1000 inhabitants in two countries, as reported by WHO, are shown in Table 18, while Table 19 gives the frequencies for a number of other countries, subdivided into the various types of procedure [W13].

89. The recent introduction of nuclides such as ^{99m}Tc has had a great impact on the development of nuclear medicine. In Annex F of the last report of UNSCEAR [U7] the trends for liver scanning, for which ^{198}Au colloid was being replaced by ^{99m}Tc colloid, were clearly demonstrated. The increased use of ^{99m}Tc is also evident in Table 20, together with the main trends for the most widely used radionuclides [N2]. The relative frequency of use of pharmaceuticals for various nuclear medicine procedures in the United States is also given in Table 20 [H16, M8]. Exhaustive data on the application of various radiopharmaceuticals in nuclear medicine are also available from Denmark and Sweden for the 1970s [M20, N2, S13, S25, S26, S27].

90. The scintillation gamma camera is the standard imaging instrument in nuclear medicine. The major reason for this is the excellent spatial resolution possible with the thin sodium iodide crystal when ^{99m}Tc is used. The increase in the number of gamma cameras installed in Europe is shown in Table 21 [P9]. These data should not be taken to infer that there has been an equal increase in the total number of procedures performed, since, in many instances, gamma cameras have simply been replacing rectilinear scanners. Newer techniques of single-photon and positron-emission

tomography have been developed, but, at present, these are predominantly used for research purposes.

B. DOSE ESTIMATES FOR RADIOPHARMACEUTICALS

1. Absorbed dose

91. Many biological parameters influence the mean absorbed dose to organs after administration of radionuclides. For the purpose of dose assessment, and for most radiopharmaceuticals in use, the relevant biological data are taken from animal experiments and are assumed to be applicable to man, when results from human studies are not available. However, these data are often incomplete and not suitable for the calculation of the effective dose equivalent. As in the case of external irradiation, this latter value should thus be taken as the best approximation to be obtained under the circumstances [R12, R13, R14, R18].

92. Physical methods for the calculation of the dose from internally-administered radionuclides are now well established. They are based on the concept of mean absorbed dose per unit cumulated activity (time integral of activity), as developed by MIRD [M10] and adopted by the ICRU [I16]. Experimental evaluation of organ doses from various radionuclides confirms the validity of the calculations [G1].

93. Table 22 gives, for various radiopharmaceuticals, the mean absorbed dose per unit administered activity in the most heavily exposed organs, in the gonads, and in the whole body and the effective dose equivalent per unit of activity of administered radiopharmaceuticals. The values have been estimated from data published by MIRD [M10], Kaul et al. [K2, K3, K20, K21, K23], Kereiakes et al. [K22], Roedler et al. [R4, R5, R11, R12, R13, R14] and from the recent Swedish compilation of doses from radiopharmaceuticals in medical use [N13]. Calculation of the effective dose equivalent has been made possible by a development of the MIRD concept to estimate the contribution from the activity in the "remainder" organs and tissues [C10, R15, R16, R17]. The values of effective dose equivalent are not applicable to therapeutic uses of radiopharmaceuticals.

94. With administered activity in the range of 100 to 800 MBq of various ^{99m}Tc-labelled radiopharmaceuticals the effective dose equivalent for the most common examinations is estimated to be in the range of 1 to 10 mSv per examination. For thyroid uptake measurements, with an average activity of 0.4 MBq of ^{131}I the effective dose equivalent is about 6.4 mSv per examination, assuming 35% uptake. For thyroid scintigraphy (activity 1.5 to 3 MBq of ^{131}I) the effective dose equivalent is about 85 mSv per examination. In Sweden, where thyroid examinations are still done with ^{131}I, this nuclide gives the most significant contribution (about 60%) to the collective effective dose equivalent.

2. Collective dose

95. A nation-wide survey was carried out in Japan in 1977 to collect data on the irradiation of the population from diagnostic uses of radiopharmaceuticals. The resulting genetically significant dose equivalent was about 3.6 μSv per year. The annual effective dose equivalent was estimated to be in the order of 20 μSv per person. With a population of about 10^8 people, this would result in an annual collective effective dose equivalent of about 2000 man Sv [H17].

96. In an attempt to estimate the collective effective dose equivalent from various radiopharmaceuticals in Sweden it was found that the most significant contribution comes from ^{131}I [P10]. By using reported values of the average administered activity per procedure and of the frequency of procedures, the Committee derived the following values of the collective effective dose equivalent, expressed in man Sv per million total population: Australia, 20; Denmark, 60; Sweden, 80; United States, 150 [F6, N2, M8]. These numbers are of the order of 2–15% of the collective effective dose equivalent from diagnostic x-ray examinations that the Committee has adopted in this Annex for industrialized countries.

III. THERAPEUTIC USE OF RADIATION

A. TRENDS IN FREQUENCY AND TECHNIQUES

1. External beam therapy

97. The IAEA, with assistance from the WHO, has published information on the use of high energy radiotherapy units and trained personnel in radiotherapy centres throughout the world [I2]. Owing to unavoidable delays in the flow of information and in data processing, the published information is often outdated by several years; moreover, it is often difficult to obtain complete data from all countries [W14].

98. For the year 1976 the total number of high-energy radiotherapy units installed in the world was reported as being 3117 in 2174 institutions. Some 4000 radiotherapists and 1600 physicists were estimated to be involved in this work. Of all the high energy units, 75.6% utilized ^{60}Co and 5.6 % ^{137}Cs, 6.9% were betatrons and 10.7% were linear accelerators. For the years 1970–1976 the percentage increase in a number of countries was between 20% and 50%, the higher rate applying to countries where few units were previously installed [I2].

99. Only limited data are available for the frequency of radiotherapy procedures. Table 23, from data published by the WHO [W13], gives the frequency of such procedures in three countries; this table also includes some data on the therapeutic use of radiopharmaceuticals.

100. Neutrons have been used in radiotherapy, from time to time, since their discovery. Summaries of the type and output of equipment used in a number of centres, and the numbers of patients treated, have been published [M22, S19, T2]. Research is currently being undertaken in some countries on the clinical use of π-mesons and heavy ions.

2. Brachytherapy

101. Brachytherapy designates the therapeutic use of encapsulated radionuclide sources applied in close vicinity of the tumour to be irradiated. In interstitial brachytherapy the source is implanted into the tumour mass. Intra-cavitary brachytherapy is performed by introducing the radiation sources into one of the body cavities. Data available from Japan on the frequency of use of brachytherapy, of the various nuclides and about the major categories of tumours treated, are reported in Table 24.

3. Therapeutic use of radiopharmaceuticals

102. Radioiodine has been used since 1946 in the treatment of hyperthyroidism and of thyroid carcinoma. Phosphorus-32 was introduced at about the same time for the therapy of polycythaemia vera and still remains the best therapeutic agent for this disease. On the other hand, the use of the same nuclide for the treatment of leukaemia has become less common with the discovery of other chemotherapeutic antileukaemic drugs.

103. Table 25 shows the annual number of treatments per million population in Sweden during the last several years using radiopharmaceuticals [N2]. There is a trend to a slight increase of thyroid treatments and a constant rate of treatments for polycythaemia vera. The use of ^{198}Au colloid for treatment of metastases in the pleural or peritoneal cavities has almost ceased and so has the treatment of rheumatic arthritis with other nuclides. The use of radiocolloids for therapy of diseases of the knee or other joints seems to have increased slightly. In Japan, treatments for thyroid diseases with ^{131}I were only about 56 per million in 1977 [H17]. In Berlin (West) the number of ^{131}I treatments per million inhabitants was reported as follows: 1968, 257; 1970, 188; 1975, 129; 1978, 305. For the same number of people ^{198}Au treatments were about 35 and ^{32}P treatments about 23, constantly over the years [K24, R19].

B. DOSE SPECIFICATIONS IN RADIOTHERAPY

1. General

104. The total absorbed dose of ionizing radiation at any point in a patient can be separated into a component from the primary beam and one from scattered radiation. The absorbed dose component from the primary beam is a function of attenuation and geometry. The absorbed dose component from scattered radiation depends upon the field size, beam quality and distance from the central axis. Several methods have been described to determine this component [B15, B25, N10].

105. For ^{60}Co radiation the total dose outside the primary beam is dominated by scattered radiation, while at 4 MVp the leakage contributes at least half the dose outside the beam at 30 cm from the beam axis [K17]. At energies above 10 MeV there is production of photoneutrons which contribute to the dose outside the primary electron beam [H41, M18, S29, S30].

2. Dose to the gonads

106. Table 26 shows the fraction of absorbed dose to the gonads at two different treatment field locations. The x-ray field size was 10 x 10 cm^2 at 100 cm source-to-skin distance (SSD) and the electron field was defined by a cone of 12 cm diameter at 120 cm SSD [N9]. Table 27 shows the average gonadal doses from ^{60}Co gamma radiation from various treatment conditions, as measured by thermoluminescent dosimetry. Extensive measurements of the absorbed dose to the gonads from ^{60}Co irradiation were also carried out by Novotny et al. in the Alderson phantom and in vivo [N8].

107. Most of the above measurements were carried out with treatment fields without filters and field-shaping devices. However, modern radiotherapy commonly makes use of field-shaping because of the considerable improvement in therapeutic gain that it allows. Measurements by Jetne [J3] showed that as much as 50% of the absorbed dose in the gonads during treatment of Hodgkin's disease may originate from scattering in field-shaping devices; similar effects have also been seen in other types of treatment [N6]. Thus, precautions should be taken to reduce this portion of the gonadal dose.

108. Extensive measurements of gonad doses in phantoms irradiated with a given surface dose have been reported for cobalt units, conventional x-ray units and 10-MV linear accelerators [H19]. These data have been summarized in Table 28.

3. Dose to other organs

109. The 1977 report of the Committee (Annex F) reviewed the available information on mean marrow dose. Since then bone marrow doses were evaluated in Japan, using dose distributions measured in phantoms and the technical factors of radiation therapy as used in that country [H19]. The per caput mean marrow dose was reported to be 540 μGy per year for males and 980 μGy per year for females [H19]. Table 29 gives the absorbed doses in various organs outside the treatment area, expressed per unit absorbed dose in the beam entrance surface. Per unit skin surface, these doses vary from less than 0.001 to 0.3 mGy per Gy of the entrance dose.

110. The absorbed doses outside the pelvic compartment in radium treatment of patients with cancer of the cervix have been studied [S28]. A series of measurements was performed in water phantoms simulating a standard adult, an adolescent (12-year-old) and a child (3-year-old). Encapsulated radium sources were positioned in the pelvis compartment and in an arrangement normally used in the treatment of carcinoma of the cervix. The results indicate that when a patient is treated with a standard radium technique the absorbed dose in the bone marrow is 10 Gy or higher for the pelvis, and between 1 and 5 Gy for the thighs and abdomen. Absorbed doses in the bone are about 0.1 Gy for thorax and legs and 0.01–0.1 Gy for head and feet. These doses are delivered in approximately 30 days. Several epidemiological surveys of leukaemia in patients with cancer of the cervix treated with radiation were reported [B26, H31, H33, K18], but the studies did not involve actual dose measurements.

4. Dose from therapeutic use of radiopharmaceuticals

111. The absorbed dose to the ovaries and to the uterus in the course of ^{131}I treatment of thyroid cancer or hyperthyroidism was estimated in one instance by in vivo measurements and by calculations. The calculated value per unit of administered activity amounted to 46 ± 19 and to 37 ± 18 μGy MBq^{-1} to the uterus and to the ovaries, respectively. The value measured inside the uterus cavity was 49 ± 29 μGy MBq^{-1} [B23]. Further data on the absorbed dose to various organs outside the treatment area per unit administered activity are summarized in Table 30 [K24].

5. Genetically significant dose equivalent

112. Recent data on genetically significant dose equivalent estimates in radiotherapy are summarized in Table 31. An average value applying at present in Europe might be in the order of 7 μSv a^{-1} [S2, S3, S4], while Australia and the United States report values around 23 μSv a^{-1} [S20, T1].The genetically significant dose equivalent may also be classified according to various parameters: Table 32 shows some values of GSD by type of disease in clinical departments or in private practice in Berlin (West) (1973) and in Munich (1971) [S2, S3, S4]. About 16% of the patients that had malignant disease were treated in private practice, and 84% in clinical departments; the child expectancy of this group was assumed to be zero. In a Japanese study performed in 1971 [H5] the genetically significant dose equivalent was classified by age and sex, for malignant and for benign conditions and the relevant findings are given in Table 33. Comparable figures for 1978 are given in the same table.

113. The genetically significant dose equivalent from brachytherapy has been estimated in Japan for 1971 on the basis of a nation-wide survey. In that year the number of brachytherapy treatments in the country was around 5 10^4, 60% of which were due to treatments of cancer of the cervix by ^{226}Ra and ^{60}Co gamma sources. The relevant genetically significant dose was estimated to be 0.12 μSv. For comparison, the GSD from x-ray diagnostic radiology amounted to 265 μSv and that from teletherapy to 9.8 μSv [H8, H35].

114. The effective dose equivalent has not been evaluated for patients receiving radiotherapy, for the following reasons: (i) the concept of effective dose equivalent is based on the assumption of "linearity", i.e., proportionality between dose and response. If organ doses exceed a few gray, the risk of non-stochastic effects becomes significant and the effective dose equivalent is no longer a reasonable indicator of risk. Such doses are given in the treatment field in radiotherapy; (ii) patients treated for malignant disease often have a short life expectancy, either because of age or as a result of the disease. This will invalidate the assumptions behind the choice of the organ weighting factors for the derivation of effective dose equivalent; (iii) few data are available on the actual dose distribution outside the target volume; (iv) in the therapeutic use of radionuclides, the metabolic data assumed in normal dose assessments may not be valid.

IV. CONCLUSIONS

115. The frequency of x-ray examinations (including mass surveys and dental examinations) is in the range of 300 to 900 per 1000 inhabitants per year in a number of industrialized countries, excluding mass surveys and dental examinations. In the same countries, examinations of the skeleton and the thorax prevail among the various organs examined. In developing countries, the frequency of examinations is often between 100 and 200 per 1000 inhabitants per year, skeleton and thorax being also most frequently examined. Mass chest surveys show a decreasing trend in most industrialized countries, while other types of examinations (dental pantomography, mammography and computed tomography) are becoming more frequent. New diagnostic techniques, such as ultrasound and nuclear magnetic resonance imaging, are being developed as alternatives to x-ray examinations. However, it is difficult to predict now whether these new technologies might result in a dose reduction from x-ray examinations in the future.

116. Improvements in radiological techniques may entail increases or decreases in radiation dose. In some instances, considerable gains in clinically important diagnostic information or therapeutic efficiency have been associated with moderate increases in dose. In other instances, the dose has been substantially reduced without loss of diagnostic or therapeutic value. In both cases, the objective has been to minimize the clinically necessary exposure.

117. The absorbed dose in the patient depends on many factors, such as geometry and beam quality. Estimation of organ doses may be done using the Monte Carlo method or by actual dosimetry measurements. The absorbed organ doses reported for diagnostic examinations have been reviewed, and they vary widely, often by as much as three orders of magnitude for the same examination in the same country. The reported organ doses for all types of diagnostic examinations range from less than 0.01 to about 50 mGy per examination. In developed countries the genetically significant dose equivalent from diagnostic radiology is of the order of 0.15 mSv per year.

118. The use of the effective dose equivalent has been expanded to include medical exposures, although the concept is unusable in some important diagnostic and radiation protection situations (e.g., mammography). The validity of applying the concept of effective dose equivalent to the other types of diagnostic examinations depends upon the actual age and sex distribution of patients for each particular type of examination. Such data are currently lacking for most countries. For this and other reasons (e.g., questionable applicability of ICRP weighting factors to the case of medical irradiation) the Committee cautions the reader about the interpretation and application of the results, but feels that the concept is more meaningful than the GSD for making comparisons with other sources.

119. Estimates of the effective dose equivalent have been made in two countries for different types of x-ray examinations. They range from less than 0.05 to about 10 mSv per full examination. These values are useful in comparisons of the detriment from different types of examination but were not used by the Committee to assess collective dose equivalents. For the purposes of this report, the Committee has used the round figure 1000 man Sv per million population as a tentative value for the annual collective effective dose equivalent from diagnostic x-ray examinations in industrialized countries. In developing countries, where the frequency of radiological examinations is lower, the value would be correspondingly less.

120. The above tentative value is subject to a number of uncertainties due mainly to the variability of the absorbed doses in various organs in the course of different radiological examinations, and to the wide variations that have been reported for the same type of examination. Future work may usefully be directed towards obtaining accurate additional data on the frequencies of examinations and on the doses absorbed in various organs and tissues so that firmer and more precise estimates of collective effective dose equivalents may be obtained.

121. The frequency of diagnostic nuclear medicine examinations in most industrialized countries is at present of the order of 10 to 40 per 1000 inhabitants per year. The rapid growth of these values that has taken place during the last decade appears now to be levelling off. In developing countries, frequencies in the range of 0.2 to 2 examinations per 1000 inhabitants per year are currently found.

122. In developed countries the use of ^{99m}Tc-labelled radiopharmaceuticals has replaced the use of longer-lived compounds for most imaging procedures. However, ^{131}I continues to be used for thyroid therapy and in some labelled compounds. Data on types of isotopes used in developing countries are not available.

123. The effective dose equivalent received by patients in the course of nuclear medicine diagnostic examinations with the most frequently used radionuclide, ^{99m}Tc, was found to be in the range of 1 to 10 mSv per examination.

124. The annual collective effective dose equivalent from the diagnostic use of radiopharmaceuticals may be estimated to be in the range of 20–150 man Sv per million of total population in industrialized countries, which is a small fraction of the collective effective dose equivalent from diagnostic medical x-ray examinations.

125. The number of high-energy radiotherapy machines installed in the whole world may at present be estimated at about 4000. About 4000 radiotherapists and 2000 physicists are estimated to work at present in radiotherapy centres in the world. While most developing countries are reported to use ^{60}Co-teletherapy and low-energy x-ray therapy units, developed countries are adopting increasing numbers of high-energy electron accelerators.

126. Absorbed doses in the target region during radiotherapy treatments are quite high, commonly 20–60 Gy given in fractionated courses. Absorbed doses in organs and tissues outside the target area depend on scattered and leakage radiation. They may vary from less than 0.001 to 0.3 mGy per Gy of radiation in the entrance surface.

127. The genetically significant dose equivalent due to radiotherapeutic treatments has been recently estimated in 4 countries to be between 0.7 and 23 μSv per year.

128. Since the contribution from diagnostic x-ray examinations dominates over all other components, the individual average effective dose equivalent from all medical exposure may be taken to be of the order of 1 mSv per person and year in developed countries (see paragraph 119). Differences in the radiological techniques, and in the spectrum of diseases over the whole population, may bring about considerable variations. On the assumption that the individual average may be proportional to the annual frequency of radiological procedures, the variation of the individual average dose equivalent could also be by a factor of three between various developed countries. If the frequency of diagnostic examinations in developing countries is taken to be one-tenth of that in developed countries (and that of radiotherapy still lower) it may be estimated on the same assumption that the individual average dose equivalent might be correspondingly lower. The value that might apply globally could, therefore, be 0.4 mSv per person and year.

129. A precise estimate of the collective effective dose equivalent from medical exposure is not possible at present owing to the lack of appropriate information from most countries and the lack of applicability to certain categories of exposure such as radiation therapy. The Committee would like to express the wish that in the future, medical irradiation statistics be reported in such a way that some evaluation of the genetically significant dose equivalent and of the effective dose equivalent may be possible.

Table 1

Annual frequency of diagnostic x-ray examinations
in various countries expressed in number of examinations per 1000 inhabitants

	Type of examination	Australia (1970) [S20]	Finland (1975) [L7]	Germany, Fed. Rep. (1978) [T8] M	F	Total	Japan (1979) [H13,H14,H26,M19] M	F	Total	Poland (1976) [J5] M	F	Total	Romania (1977) [F3] M	F	Total	Sweden (1977) [N11]	United Kingdom (1977) [K12] M a/	F a/	Total
01	Hip and upper femur	8.7	403.3 b/	4.1	7.7	11.8	6.3	9.0	15.3	23.3 c/	29.3 c/	52.6 c/	3.1	2.0	5.1	19.2	8.2	10.7	9.9
02	Femur	13.5		-	-	-	3.2	1.7	4.9				15.5	9.2	24.7	4.0	5.7	7.3	6.5
03	Pelvis	7.6	-	15.7	22.0	37.3	1.9	2.8	4.7	-	-	-	3.3	1.8	4.1	13.2	12.9	18.3	15.6
04	Pelvimetry	0.7	-	-	-	-	-	1.0	1.0	-	-	-	-	-	-	1.6	-	-	-
05	Lumbo-sacral	15.2		-	-	-	-	-	-				18.2	18.8	36.9	2.6	6.5	6.6	6.5
06	Lumbar spine	8.8		9.3	12.6	21.9	27.8	23.8	51.6				-	-	-	17.8	10.8	12.8	11.8
07	Urography	12.0	21.7	21.7	20.3	42.0	9.6	5.2	14.8	5.6	5.3	10.9	3.6	3.5	7.0	18.5	10.2	7.7	8.9
08	Retrograde pyelography	0.8	-	-	-	-	-	-	-	-	-	-	-	-	-	1.1	-	-	-
09	Urethrocystography	0.6	-	-	-	-	5.8	2.6	8.4	-	-	-	-	-	-	3.2	1.0	1.0	1.0
10	Stomach and upper G.I.T.																		
	(a) Radiography	1.6	127.4	29.7	38.1	67.8	66.8	52.7	118.7	-	-	-	5.3	2.9	8.2	17.5	10.1	10.1	10.1
	(b) Fluroscopy	17.1	-	-	-	-	71.4	58.4	129.8	19.8	16.9	36.7	64.4	43.5	107.9	-	-	-	-
	(c) Mass survey	-	-	-	-	-	21.3	15.6	36.9	-	-	-	-	-	-	-	-	-	-
11	Small intestine	6.8	-	-	-	-	3.6	4.4	8.0	1.0	1.1	2.1	10.8	8.9	19.7	15.1	5.0	6.7	5.8
12	Abdomen	14.3	-	1.2	2.9	4.1	17.6	17.4	35.0	8.3	8.9	17.2	-	-	-	11.7	15.2	18.4	16.8
13	Abdomen (obstetrical)	2.6	-	-	-	-	-	1.5	1.5	-	-	-	-	-	-	2.2	-	1.2	0.6
14	Hysterosalpingography	1.0	-	-	-	-	-	1.1	1.1	-	0.5	0.5	-	0.4	0.4	0.6	-	0.8	0.4
15	Cholecystography	9.4	-	-	-	-	16.7	17.9	34.6	3.7	8.9	12.6	2.6	5.8	8.4	11.8	4.6	10.1	7.3
16	Chest (lungs, heart)																		
	(a) Radiography	118.8	382.2	168.7	165.2	333.9	194.3	140.6	334.9	88.6	81.7	170.3	29.0	15.4	44.4	159.6	140.4	120.3	130.4
	(b) Fluoroscopy	1.4	-	-	-	-	2.4	1.8	4.2	4.0	2.4	6.4	229.3	142.5	371.8	-	-	-	-
	(c) Chest mass miniature	146.7	-	-	-	-	165.5	135.5	301.0	174.0	154.9	328.9	214.1	219.7	433.8	-	-	-	26
17	Head	40.9		51.4	56.8	108.2	33.5	25.6	59.1	39.8	39.0	78.8	16.8	20.2	37.0	43.3	45.2	39.4	42.3
18	Dorsal spine	7.3		16.5	19.2	35.7	3.2	3.5	6.7	-	-	-	12.6	11.2	23.8	9.6	4.0	5.8	4.9
19	Thorax	13.4	63.7	-	-	-	12.1	7.6	19.7	-	-	-	6.1	4.0	10.1	17.2	8.3	9.8	9.0
20	Arm and hand	37.4		36.7	41.9	78.6	18.9	9.4	28.3	32.6	21.2	53.8	9.3	5.9	15.2	46.0	50.1	39.1	44.6
21	Lower leg and foot	28.5		46.2	48.1	94.3	31.8	29.0	60.8	29.9	23.3	53.2	27.5	18.3	45.8	66.0	55.2	47.4	51.3
22	Dental	80.9	170.0	32.4	89.5	71.9	248.0	311.0	559.0	18.5	25.4	43.9	16.5	18.3	34.9	2.1	6.1	6.9	6.5
23	Breast	0.3		0.6	27.3	27.9	-	1.2	1.2	-	-	-	-	-	-	6.4	-	1.7	0.8
24	CT-scan	-	-	-	-	-	7.6	4.9	12.5	-	-	-	-	-	-	-	1.3	1.3	1.3
25	Other	-	21.2	-	-	-	16.3	15.6	31.9	0.6	0.6	1.2	6.1	5.8	11.9	6.0			23.0

a/ National Health Service, per 1000 males and females, respectively.
b/ Including all skeleton and bones.
c/ Including whole femur, lumbo-sacral and lumbar spine examinations.

Table 2

Relative frequency of diagnostic x-ray examinations in various areas

Type of examination	Africa [SB] Type of hospital: General and university	Africa [SB] Type of hospital: Regional and district	Africa [SB] Type of hospital: Small rural	Japan 1979 [H26]	Australia 1970 [S20]	Europe a/ 1977 [F3, J5 N11, K12]	United States 1970 [U8]
Head and neck	7.6	4.3	3.6	7.0	6.0	7.9	7.7
Thorax	37.9	53.8	58.5	43.2	58.9	50.2	52.0
Digestion organs	7.5	1.2	0.1	18.4	5.2	7.7	10.4
Urogenital organs	11.6	2.9	3.3	7.7	4.7	7.0	11.0
Skeleton, extremities	35.4	37.8	34.5	24.7	25.2	27.2	18.9

a/ Poland, Romania, Sweden and United Kingdom.

Table 3

Percentage of the population with availability of diagnostic x-ray machines in WHO regions [W11]

(Number of countries is given in parentheses)

Number of x-ray machines per 10^6 persons	Thousands of persons per x-ray machine	Region (WHO classification): Africa	America	Eastern Mediterranean	South-east Asia	Western Pacific
> 100	> 10		24.4 (9)	1.9 (2)	0.2 (1)	0.2 (1)
99-50	11-20		55.0(11)			71.0 (3)
49-33	21-30	1.0 (1)	6.8 (3)	6.2 (4)		3.7 (1)
32-20	31-50	0.7 (2)	7.3 (5)	6.4 (4)		20.4 (3)
19-13	51-75	19.6 (3)	0.5 (2)	15.2 (5)	92.6 (1)	4.7 (1)
12-10	76-100		0.7 (2)	18.1 (2)		
9.9-6.7	101-150	22.8 (2)		41.1 (4)		
6.6-5	151-200	6.6 (1)	2.4 (1)		5.3 (2)	
< 5	> 200	49.3 (8)	3.0 (2)	11.1 (2)	1.9 (1)	

Table 4

Annual frequency of diagnostic x-ray procedures as reported by WHO Regional Offices [W13] expressed in number of examinations per 1000 population

	Type of examination	Barbados 1978	Brazil 1978	Chile 1978	Colombia 1978	Cuba 1978	Fiji 1978	Guatemala 1978	Sri Lanka 1979
01	Hip and upper femur	] 11.3	-	2.5	0.15	1.4	-	2.4	1.43
02	Femur		-	15	-	-	-	-	1.07
03	Pelvis	-	-	7.9	-	-	-	-	-
04	Pelvimetry	-	-	-	-	-	-	-	0.07
05	Lumbo-sacral	14.9	-	-	30.0	9.2	-	0.26	-
06	Lumbar spine	-	-	6.9	-	9.4	-	-	-
07	Urography	6.2	38.0	5.1	30.0	27.2	1.77	-	0.14
08	Retrograde pyelography	0.42	-	0.35	-	-	0.17	-	0.07
09	Urethrocystography	4.1	-	0.19	-	20.1	11.1	-	0.40
10	Stomach and upper G.I.T.	6.9	15	17	-	21.9	65	0.16	0.11
11	Small intestine, colon, etc.	2.2	-	6.4	1.59	10.5	1.36	0.02	0.30
12	Abdomen	0.15	0.68	7.9	-	6.1	0.02	1.11	0.28
13	Abdomen (obstetrical)	6.1	] 7.0	0.23	-	17.4	4.6	0.25	0.32
14	Hysterosalpingography	1.04		0.7	-	3.0	0.25	-	-
15	Cholecystography	2.1	-	17.2	0.11	13.8	1.48	0.06	0.07
16	Chest (lungs, heart)	91.0	42.0	45.9	78.9	-	0.03	0.56	12.9
17	Head	24.0	0.4	14.7	7.3	-	6.7	0.97	0.33
18	Dorsal spine	0.51	-	4.2	63.0	-	-	-	0.43
19	Thorax	12.0	-	-	0.46	-	0.62	2.7	0.48
20	Arm and hand	-	-	6.4	-	-	-	-	-
21	Lower leg and foot	-	-	0.4	-	-	-	-	-
22	Dental	-	-	3.9	-	-	39.0	-	0.8
23	Breast	-	-	-	-	-	-	-	-
24	CT-scan	-	-	-	-	-	-	-	-
25	Other	0.13	77.0	3.6	0.35	0.54	-	0.07	1.78

Table 5

Mean bone marrow dose equivalent (μSv) at different sites for various radiographic dental examinations [W8]

Site	Panorex	Pan-elipse	Ortho-pantomo-graph	Intra-oral	Collimated intra-oral	Lateral cephalo-metric
	4 films 75-kVp 14 mA	80-kVp 15 mA	80-kVp 15 mA	21 films 80-kVp 15 mA	21 films 80-kVp 15 mA	20 exp. 70-kVp 200 mA
Mandible	141	318	239	8500	2820	188
Calvaria	59.6	122	93.1	91.2	101.8	129
Cervical spine	131	237	532	1160	24.1	151

Table 6

Data on the evolution of mammography technique [A3, H2, J2, K16, M16, S24, U10]

Year x-ray unit introduced	Target	Focal spot (mm)	Filtration	Film/focus distance	Detector system	Absorbed dose in the breast	
						Average	Mid-plane
Before 1969	W	3.2	Inherent	70	Industrial film	16	8.5
1971	Mo	1.0	0.7 Al	44	Electrostatic	8.2	5.5
1972	Mo	1.0	0.003 Mo	44	Screen-film	2.8	1.7
			or 0.5 Al		Direct film	16.9	-
1975	Mo/W	1.8	1.1 Al	60	Electrostatic	4.1	3.3
1976	Mo/W	1.8	1.5 Al	60	Screen-film	1.2	0.65
1977	W	0.15	0.03 Mo	30	Screen-film	1.5	0.7
	W	0.15	0.2	94	Electrostatic	0.75	0.6

Table 7

Number of CT-examinations per 1000 population in Sweden [N17]

Type of examination	1973	1974	1975	1976	1977	1978	1979
Head	0.03	0.20	0.33	0.51	1.22	1.94	2.00
Whole-body	-	-	-	0.01	0.21	0.54	1.00
Total	0.03	0.20	0.33	0.52	1.41	2.48	3.00

Table 8

Effective dose equivalent and absorbed dose in gonads, eyes, and thyroid from various CT scanning procedures [S15]

Dose in organ or tissue	Head (8-14 slices)	Thorax (10-18 slices)	Abdomen (18-20 slices)
Effective dose equivalent (μSv)	40-100	60-110	80-120
Absorbed dose (μGy)			
Gonads (M/F)	1/5	1/1	10-50/10-150
Eyes	4000-6000	-	10
Thyroid	40-200	140	3-10

Table 9

Comparison of absorbed dose in skin and gonads from CT-scanning examinations of the kidney or from conventional urography [S18]

	CT-scanning (average of 10 patients)	Urography
Absorbed dose in skin (mGy)	31	166
Gonad dose (M/F) (mGy)	0.02/0.46	0.95[a]/12.7

a/ With gonad shielding 0.06 mGy.

Table 10

Doses in organs and tissues from various diagnostic x-ray examinations in Japan

The data were supplied to UNSCEAR by the delegation of Japan, 1982[a], as derived from [H27]

Type of examination		Average dose equivalent H_T (mSv) in the various tissues per full x-ray examination (radiography)						
		Gonads	Breast	Red bone marrow	Lung	Thyroid	Bone surface	Mean of other five organs or tissues
01	Hip and upper femur	2.7	0.0004	0.018	0.0014	0.002	0.054	0.52
03	Pelvis	0.5	0.0006	0.3	0.003	0.003	0.9	0.9
06	Lumbar spine	0.09	0.006	0.4	0.9	0.009	1.0	1.9
07	Urography	0.11	0.007	0.6	0.12	0.009	1.8	2.7
09	Urethrocystography	2.6	0.0011	0.34	0.0011	0.002	1.0	0.9
10	Stomach and upper G.I.T.							
	(a) Radiography	0.05	0.11	2.8	1.8	0.03	8.4	2.8
	(b) Photofluorography	0.06	0.6	2.5	4.0	0.17	7.5	5.5
11	Small intestine	2.9	0.0014	3.4	0.06	0.004	10.3	5.1
12	Abdomen	0.18	0.0018	0.8	0.004	0.002	2.3	0.9
15	Cholecystography	0.01	0.007	0.7	0.04	0.006	2.5	0.9
16	Chest (lungs, heart)							
	(a) Radiography	0.0001	0.3	0.07	0.3	0.10	0.2	0.12
	(b) Tomography	0.2	35	0.7	16.3	0.014	2.0	3.9
	(c) Photofluorography	0.0006	0.5	0.3	0.9	0.05	1.0	0.13
17	Head	0.001	0.03	0.3	0.09	0.13	0.8	0.17
24	CT-scan (head)	0.006	0.3	2.5	0.4	2.7	7.4	1.3

a/ These values should be used for males, as those for females are slightly different, mostly for the gonads.

Table 11

Doses in organs and tissues from various diagnostic x-ray examinations in Japan

The data were supplied to UNSCEAR by the delegation of Japan, 1982[a], as derived from [H27]

Type of examination		Average dose equivalent H_T (mSv) in the various tissues per full x-ray examination (fluoroscopy)						
		Gonads	Breast	Red bone marrow	Lung	Thyroid	Bone surface	Mean of other five organs or tissues
01	Hip and upper femur	0.4	0.0001	0.11	0.0004	0.0006	0.015	0.15
03	Pelvis	0.04	0.0001	0.06	0.0005	0.0005	0.17	0.17
06	Lumbar spine	0.004	0.0004	0.04	0.06	0.006	0.07	0.14
07	Urography	0.07	0.002	0.3	0.04	0.003	0.6	1.0
09	Urethrocystography	0.10	0.0004	0.12	0.0004	0.0008	0.4	0.3
10	Stomach and upper G.I.T	0.05	0.3	5.3	4.8	0.08	22	7.4
11	Small intestine	4.7	0.004	12.2	0.17	0.01	28.6	14.3
12	Abdomen	0.06	0.0008	0.11	0.0018	0.001	0.3	0.4
15	Cholecystography	0.015	0.014	0.4	0.07	0.01	1.2	1.7
16	Chest (lungs, heart)	0.0001	0.08	0.02	0.08	0.03	0.05	0.03
17	Head	0.0000	0.0002	0.002	0.0008	0.0011	0.007	0.0015

a/ These values should be used for males, as those for females are slightly different, mostly for the gonads.

Table 12

Doses in organs and tissues from various diagnostic x-ray examinations in Poland

The data were supplied to UNSCEAR by the delegation of Poland, 1982, as derived from [J5]

Type of examination	View	Dose equivalent (mSv)						
		Gonads	Breast	Red bone marrow	Lungs	Thyroid	Bone surface	Liver a/
Mass miniature radiography (70-kVp; HVL 2.9 mm Al)	P/A	<0.01	0.11	0.46	0.75	0.20	0.83	0.07
Chest radiography (70-kVp; HVL 2.9 mm Al)	P/A	<0.01	0.03	0.11	0.18	0.05	0.20	0.02
Chest tomography (70-kVp; HVL 2.9 mm Al)	A/P	0.02	46.0	2.0	15.0	25.0	3.6	4.15
Stomach and upper G.I.T. (fluoroscopy) (90-kVp; HVL 4.2 mm Al)	P/A	3.75	1.3	6.2	6.4	0.6	11.1	4.0
Urography (80-kVp; HVL 3.6 mm Al)	A/P	8.95	2.3	3.3	9.85	0.22	5.95	45.0
Cervical spine (fluorography) (70-kVp; HVL 2.9 mm Al)	A/P	<0.01	5.2	0.68	1.9	13.5	1.2	0.03
Dental (fluorography) (60-kVp; HVL 2.0 mm Al)	A/P	0.02	0.01	0.08	0.01	0.01	0.14	0.01
Humeral joint (fluorography) (60-kVp; HVL 2 mm Al)	A/P	<0.01	0.71	0.02	0.09	0.30	0.04	<0.01
Hip joint (fluorography) (80-kVp; HVL 3.6 mm Al)	A/P	5.0	0.09	0.47	0.38	<0.01	0.85	4.4
Cholecystography (70-kVp; HVL 2.9 mm Al)	P/A	0.97	0.20	2.75	1.55	0.02	4.95	1.4
Cholangiography (70-kVp; HVL 2.9 mm Al)	P/A	0.92	0.34	3.60	1.85	0.02	6.50	2.05
Sinuses (fluorography) (70-kVp; HVL 2.9 mm Al)	P/A	<0.01	0.02	1.7	0.08	0.33	3.05	<0.01
Lumbo-sacral spine (fluorography) (80-kVp; HVL 3.6 mm Al)	A/P	2.35	0.85	0.8	2.20	0.03	1.50	12.5

a/ As representative of the remainder.

NOTE:

1. The data refer only to adult patients (above 14 years of age).
2. Examinations in adults account for 91.7 % of all x-ray examinations in Poland.
3. The examinations included in the table account for 78.5 % of the total number of x-ray examinations of adults in Poland in 1976.
4. For the application of the ICRP weighting factors and procedure for calculation of the effective dose equivalent the data are averaged for both sexes.
5. As a first approximation the absorbed dose in the liver was assumed to represent the dose for the "remainder" of tissues.
6. In the case when absorbed dose in a given organ was lower than 0.01 mSv, the value 0.01 mSv was taken for calculation of the effective dose equivalent.

Table 13

Summary of diagnostic radiology performed in the United Kingdom showing contributions to the genetically significant dose equivalent (comparison of the 1957 and 1977 national surveys)
[D5]

Type of examination and/or type of institution	1957		1977	
	Thousands of examinations	GSD (μSv)	Thousands of examinations	GSD (μSv)
The Armed Services	412	4.1	418	2.2
Hospitals not in the National Health Service	286	2.4	323	1.7
Private medical radiology	100	0.8	250 a/	1.3
Mass miniature radiology	4770	0.1	1400	-
Other	288	1.0	135	-
Total	5856	8.4	2526	5.2
Hospitals in the National Health Service	13000	132.4	21338	112.6
Total (excluding dental)	18856	140.8	23864	117.8
Dental	2000	0.1	5750	0.3
Total (including dental)	20856	140.9	29614	118.1

a/ Including chiropractors.

Table 14

Summary of diagnostic radiology in Japan and genetically significant dose equivalent (comparison between the years 1969, 1974 and 1979)
[H26]

	1969	1974	1979
Total number of examinations	$6.4\ 10^7$	$7.3\ 10^7$	$9.6\ 10^7$
Number of examinations per 1000 population	621	664	830
Genetically significant dose (μSv)	257	165	150

Table 15

Genetically significant dose equivalent from diagnostic x-ray examinations in Japan

[H4,H5,H6,H7,H9,H10,H13,H14,H16,H17,H18,H19,H26,H27,H28,H35,M3,M4,M5,M19]

Type of medical irradiation	GSD (μSv)					
	1960	1969	1974	1975	1979	1980
x-ray radiography	174	152	111	-	100	-
x-ray photofluorography						
Chest	5.7	7.9	-	0.32	-	-
G.I.T.	-	0.4	-	1.5	-	-
x-ray fluoroscopy	50	105	-	-	49.9	-
Dental intra-oral radiography	-	-	0.13	-	-	0.08
Dental orthopantomography	-	-	0.00088	-	-	0.01

Table 16

Estimates of the effective dose equivalent (mSv) from various diagnostic x-ray examinations in Japan and Poland

The data were supplied to UNSCEAR by the delegations of those two countries, as derived from [H27] *and* [J5]

Type of examination		Japan [H27] 1979		Poland [J5] 1976
		Radiography	Fluoroscopy	
01	Hip and upper femur	0.84	0.16	2.71
03	Pelvis	0.46	0.07	-
06	Lumbar spine	0.78	0.06	4.87
07	Urography	0.98	0.38	17.85
09	Urethrocystography	0.99	0.14	-
10	Stomach and upper G.I.T.			
	(a) Radiography	1.67	-	-
	(b) Fluoroscopy	-	4.15	4.2
	(c) Photofluoroscopy	2.77	-	-
11	Small intestine	2.98	7.81	-
12	Abdomen	0.48	0.16	-
15	Cholecystography	0.44	0.61	1.36
	Cholangiography	-	-	1.75
16	Chest (lungs, heart)			
	(a) Radiography	0.13	-	0.06
	(b) Fluoroscopy	-	0.04	-
	(c) Photofluoroscopy	0.29	-	0.22
	(d) Tomography	8.57	-	11.05
17	Head			
	(a) Conventional	0.13	0.001	0.32
	(b) CT-scan	1.09	-	-
	Cervical spine	-	-	1.54
22	Dental	-	-	0.023
	Humeral joint	-	-	0.14

a/ The data refer only to adult patients (above 14 years of age) and are averages for the two sexes.

Table 17

Relative frequency (per cent) of diagnostic nuclear medicine procedures in various countries

Type of examination	Australia		Denmark					United States		
	1970 [K13]	1980 [L10]	1973 [S13]	1975/76 [S25]	1977 [S26]	1978 [S27]	1979 [S27]	1966 [U7]	1977 [M8]	1978 [U16]
NERVOUS SYSTEM										
Brain scintigraphy	24.2	18.4	17.6	19.25	20.26	16.50	14.29	8.6	47.3	23.2
Regional brain perfusion imaging	-	-	-	1.51	1.90	1.31	1.80	-	-	-
Cisternography	0.5	-	-	0.14	0.11	0.11	0.14	-	-	-
Craniopharyngeoma imaging	-	-	-	-	-	-	-	-	-	-
NECK ORGANS										
Salivary glands	-	-	-	-	0.14	-	0.04	-	-	-
Thyroid-uptake	27.2	1.5	10.4	8.60	6.00	5.21	4.90	41.6	5.3	1.0
Thyroid-scintigraphy	9.2	9.0	7.8	6.39	8.16.	8.31	9.1	21.0	6.6	8.5
Parathyroid scintigraphy	-	-	-	0.01	-	-	-	-	-	-
THORAX										
Lung scintigraphy (per fusion)	13.1	11.3	2.16	4.0	3.7	3.88	3.58	3.2	7.2	12.8
Lung ventilation study	-	3.4	-	0.89	0.3	0.6	0.54	-	3.1	4.1
Cardiovascular imaging	-	-	-	0.12	0.08	0.45	0.23	-	-	2.9
Myocardial scintigraphy	-	1.7	-	0.15	0.49	-	-	-	0.7	-
AV shunt	-	-	-	-	-	-	-	-	-	-
DIGESTIVE TRACT ORGANS										
Liver-spleen	12.9	21.5	5.06	8.35	8.54	8.44	8.57	8.4	14.6	21.1
Liver-gallbladder	-	1.7	0.25	0.52	0.84	0.81	0.89	-	0.6	0.8
Liver-pancreas	0.9	-	0.09	0.1	0.07	0.03	0.03	-	0.7	-
Spleen	0.4	-	-	0.31	0.35	0.36	0.51	-	-	0.2
Stomach and GI-blood or protein loss	0.6	0.1	-	0.97	1.73	1.18	1.08	-	-	-
Vitamin B12 absorption	1.0	0.3	4.18	3.16	2.27	2.07	1.86	23.0	-	-
UROGENITAL ORGANS										
Renography	1.6	0.5	5.4	19.66	17.22	17.6	17.6	-	0.9	0.4
Kidney GFR test	-	-	2.1	3.32	3.5	4.02	4.04	-	0.6	-
Kidney scintigraphy (dynamic and static)	1.6	1.4	15.5	5.66	4.79	5.94	5.71	-	1.8	3.5
Kidney, ureter, bladder	-	-	-	0.52	0.55	0.97	0.81	-	-	-
Adrenal glands imaging	-	-	-	0.09	0.05	0.07	0.06	-	-	-
Placenta imaging	1.8	-	-	0.86	0.48	0.30	0.21	-	-	-
SKELETON AND MARROW										
Skeleton scintigraphy	1.2	24.4	2.9	7.08	11.3	14.43	17.65	0.9	5.8	17.2
Scintimetry of joints	-	-	-	0.04	0.05	0.06	0.2	-	-	-
Bone marrow imaging	0.1	-	-	0.01	0.05	0.01	<0.01	-	-	-
Ca-metabolism	-	-	-	-	-	-	-	-	-	-
OTHER										
Deep vein thrombosis	1.0	-	-	0.07	0.31	0.48	0.33	-	-	-
Iron kinetics	0.4	-	0.29	-	0.04	0.04	0.03	-	-	-
Lymph scintigraphy	0.1	0.1	-	0.04	0.18	0.36	0.2	-	-	-
Blood cell survival time and plasma volume	1.0	0.8	-	1.99	1.59	1.48	1.72	14.0	-	-
Peripheral circulation	-	-	-	4.29	3.06	2.71	3.12	-	-	-
Whole-body profile	-	2.0	-	-	0.03	0.02	0.02	-	-	-
Other	1.4	0.1	6.2	0.83	1.27	1.72	0.87	-	1.5	3.1
Number of all types of examinations										
Total in thousands	52.0	117.3		57.8	68.3	72.7	71.7			8000
per 1000 population	4.1	8.0	3.8	11.4	13.4	14.3	14.1	3.71		36.7

Table 17, continued

Type of examination	Sweden [N2]							
	1971	1972	1973	1974	1975	1976	1977	1978
NERVOUS SYSTEM								
Brain scintigraphy	9.06	9.4	11.19	12.9	13.19	14.04	13.3	13.3
Regional brain perfusion imaging	-	-	-	-	-	-	0.29	0.38
Cisternography	-	-	-	-	-	-	0.25	0.19
Craniopharyngeoma imaging	-	-	-	-	-	-	0.01	-
NECK ORGANS								
Salivary glands	-	-	-	-	-	-	0.01	0.02
Thyroid-uptake	17.24	17.7	15.81	12.7	10.73	9.2	8.22	4.86
Thyroid-scintigraphy	19.83	14.9	14.95	14.6	12.6	11.8	11.11	11.99
Parathyroid scintigraphy	-	-	-	-	-	-	0.03	0.02
THORAX								
Lung scintigraphy (per fusion)	1.97	2.5	2.55	2.9	3.05	3.87	4.21	4.44
Lung ventilation study	2.64	2.5	3.15	2.8	1.28	2.40	2.00	0.77
Cardiovascular imaging	-	-	-	-	-	-	0.34	0.4
Myocardial scintigraphy	-	0.03	0.045	0.08	0.23	1.16	1.01	1.02
AV shunt	-	-	-	-	-	-	0.16	0.18
DIGESTIVE TRACT ORGANS								
Liver-spleen	10.94	11.34	11.35	12.0	12.91	11.9	13.0	14.0
Liver-gallbladder	-	-	0.005	0.07	-	-	0.15	1.1
Liver-pancreas	0.27	0.13	0.51	0.59	0.84	0.72	0.47	0.59
Spleen	-	-	-	-	-	-	1.18	0.09
Stomach and GI-blood or protein loss	-	-	-	-	-	-	0.096	0.25
Vitamin B12 absorption	3.93	4.3	3.4	2.5	2.61	2.21	1.86	2.0
UROGENITAL ORGANS								
Renography	20.39	22.0	24.03	23.3	26.34	22.95	17.68	16.7
Kidney GFR test	-	-	-	-	-	-	4.46	5.15
Kidney scintigraphy (dynamic and static)	1.35	1.7	1.26	1.8	0.99	1.09	1.76	1.02
Kidney, ureter, bladder	-	-	-	-	-	-	0.20	0.20
Adrenal glands imaging	-	-	-	-	-	-	0.11	0.12
Placenta imaging	-	-	-	-	-	-	0.4	0.25
SKELETON AND MARROW								
Skeleton scintigraphy	1.21	1.5	3.7	5.3	7.06	10.01	11.8	14.82
Scintimetry of joints	-	-	-	-	-	-	1.15	0.91
Bone marrow imaging	-	-	-	-	-	0.08	0.08	0.1
Ca-metabolism	-	-	-	-	-	-	0.07	-
OTHER								
Deep vein thrombosis	0.27	0.89	0.08	0.46	0.84	1.68	1.25	1.53
Iron kinetics	0.65	0.57	0.64	0.74	0.6	0.24	0.52	0.55
Lymph scintigraphy	0.19	-	0.18	0.17	0.06	0.012	0.054	0.06
Blood cell survival time and plasma volume	3.15	2.4	2.34	2.5	2.28	2.05	1.89	2.67
Tumour and abscess imaging	-	-	-	0.22	0.39	-	0.20	0.01
Peripheral circulation	0.58	0.2	0.5	0.36	0.07	0.01	0.29	1.16
Whole-body profile	-	-	-	-	-	0.33	0.82	0.81
Other	6.9	5.13	3.53	4.0	3.93	4.1	0.9	1.03
Number of all types of examinations								
Total in thousands	66.9	71.2	88.4	95.7	98.9	112	114	120
per 1000 population	8.29	8.79	10.9	11.7	12.1	13.6	13.8	14.5

Table 18

Frequency of in vivo diagnostic nuclear medicine procedures per 1000 population in two countries according to a WHO survey, 1979 [W13]

Country	Year	Frequency per 1000 population
Burma	1972	0.16
	1973	0.17
	1974	0.18
	1975	0.20
	1976	0.20
	1977	0.24
	1978	0.22
Cuba	1976	0.79
	1977	0.85
	1978	0.81

Table 19

Annual frequency of diagnostic nuclear medicine procedures for 1978 as reported by WHO Regional Offices [W13]

(Annual number of examinations per million population in parentheses)

Type of examination	Burma	Colombia	Cuba	Guatemala	Peru	Sri Lanka
	Number of population (in millions)					
	33	25.7	9.6	6.6	17	14.2
NERVOUS SYSTEM						
Brain scintigraphy	268 (8.1)	220 (8.56)	567 (59)	147 (22)		40 (2.8)
Regional brain per fusion imaging					2000 (118)	
Cisternography		1 (0.03)				
Craniopharyngeoma imaging					31 (1.8)	
NECK ORGANS						
Thyroid-uptake	2776 (84)	1700 (66)	3230 (336)	466 (71)	19500 (1147)	4051 (285)
Thyroid-scintigraphy	1468 (44.5)	1200 (47)	2004 (209)		5330 (313)	1222 (86)
THORAX						
Lung scintigraphy (perfusion)	3 (0.1)	80 (3)	48 (5)	4 (1)	393 (23)	
Cardiovascular imaging		115 (4.5)				
Myocardial scintigraphy	15 (0.5)					
DIGESTIVE TRACT ORGANS						
Liver-spleen	1774 (53.8)	680 (26)		115 (17)	2205 (130)	34 (2.4)
Liver-gallbladder			270 (28)			50 (13.5)
Liver-pancreas			43 (4.5)			
Spleen			72 (7.5)			
Vitamin B12 absorption	8 (0.24)		67 (7.0)		10 (0.6)	
UROGENITAL ORGANS						
Renography	993 (30)	150 (5.8)	980 (102)		340 (20)	500 (35)
Kidney GFR test		315 (12)				
Kidney scintigraphy (dynamic,static)	47 (1.4)	195 (7.6)		2 (0.3)	446 (26)	1 (0.07)
Placenta imaging	143 (4.3)	30 (1.2)			74 (4.4)	
SKELETON						
Skeleton scintigraphy	9 (0.27)	120 (4.7)	64 (6.7)		550 (32)	
OTHER						
Iron kinetics			57 (5.9)		10 (0.6)	
Lymph scintigraphy					5 (0.3)	
Red cell survival time or volume	65 (2.0)		140 (14.6)		43 (2.5)	10 (0.7)
Tumour scintigraphy	4 (0.1)		17 (1.8)			
Other			234 (24.4)		20 (1.2)	

Table 20

Relative frequency (per cent) of radiopharmaceuticals administered in diagnostic nuclear medicine procedures

Radio-nuclide	Chemical form	Australia		Denmark				Sweden			United States	
		1970 [K13]	1980 [L10]	1976 [S25]	1977 [S26]	1978 [S27]	1979 [S27]	1976 [N2]	1977 [N2]	1978 [N2]	1976 [M8]	1978 [U16]
^{3}H	water, labelled compounds	0.08	-	0.97	0.17	1.14	0.37	0.4	0.32	0.31	-	-
^{14}C	labelled compounds	-	0.05	0.46	0.4	0.38	0.32	0.54	0.51	0.55	-	0.05
^{18}F	fluoride	0.7	-	0.03	0.1	-	-	-	-	-	-	-
$^{22,24}Na$	chloride	0.08	-	0.19	0.17	0.08	0.04	0.09	0.04	0.04	-	-
^{32}P	phosphate	0.3	0.04	<0.01	<0.01	0.01	<0.01	0.04	0.03	0.01	-	0.03
^{42}K	chloride	-	-	0.23	0.08	0.01	0.04	-	<0.01	-	-	-
$^{45,47}Ca$	chloride	-	-	0.46	0.77	0.47	0.76	0.04,0.09	0.04,0.03	0.03	-	-
^{51}Cr	chromate, RBC	2.0	1.0	3.5	4.0	4.35	4.27	4.32	4.9	5.6	-	0.04
^{55}Fe	citrate	-	-	-	-	-	-	0.04	0.2	0.24	-	-
^{57}Co	cyanocobolamin, bleomycin	0.6	0.8	1.46	1.42	1.28	1.16	1.35	0.98	1.29	-	0.19
^{58}Co	cyanocobolamin (vit. B-12)	0.4	0.5	1.84	0.94	0.86	0.79	0.88	0.88	0.81	-	0.01
^{59}Fe	citrate	0.45	0.03	0.13	0.04	0.04	0.03	0.2	0.33	0.31	-	-
^{64}Cu	ion	-	-	0.29	-	-	-	-	-	-	-	-
^{65}Zn	ion	-	-	-	-	-	-	0.08	0.06	0.06	-	-
^{67}Ga	citrate	-	2.0	0.54	0.64	0.77	0.32	0.01	0.13	0.06	2.8	2.8
^{68}Ga	citrate	-	-	-	-	-	-	-	-	0.04	-	0.4
^{75}Se	selenomethionine	0.85	0.03	0.1	0.07	0.03	0.03	0.73	0.46	0.34	-	-
$^{81}Rb/^{81m}Kr$	gas	-	-	-	-	0.16	0.1	-	0.05	<0.01	0.14	-
^{82}Br	bromide	-	-	0.12	0.13	0.01	-	-	-	-	-	-
^{85}Kr	gas dissolved in saline	-	-	0.02	-	-	-	-	<0.01	<0.01	-	-
^{85}Sr	chloride	-	-	49.8	-	-	-	0.83	0.78	0.64	-	-
^{87m}Sr	chloride	0.5	-	-	-	-	-	-	-	-	-	-
^{99m}Tc	pertechnetate, labelled compounds, colloid and particles	53.3	89.0	-	56.2	56.7	57.8	45.8	49.8	54.5	80.5	81.7
^{111}In	DTPA	-	0.02	-	0.06	0.09	0.14	0.03	0.6	0.19	-	0.09
^{113m}In	DTPA, colloid and particles	2.8	0.1	0.93	0.52	0.31	0.25	0.54	0.01	0.29	4.1	-
^{123}I	iodide, labelled compounds	-	-	0.12	-	0.11	0.06	0.05	0.08	0.1	0.01	0.8
^{125}I	iodide, labelled compounds	1.35	0.3	6.5	7.73	7.92	7.61	10.5	8.42	8.56	-	0.19
^{127}Xe	dissolved in saline	-	0.02	0.01	0.01	0.1	0.17	-	-	-	-	-
^{131}I	iodide, labelled compounds	31.1	0.9	26.5	22.1	21.4	21.0	29.7	27.9	23.04	8.0	8.38
^{132}I	iodide	-	-	1.31	0.56	0.55	0.41	-	-	-	-	-
^{131}Cs	iodide	0.35	0.3	-	-	-	-	-	-	-	-	-
^{133}Xe	gas and dissolved in saline	0.02	3.4	4.15	3.88	3.49	4.29	2.91	2.62	2.2	3.1	3.8
^{169}Yb	DTPA	0.3	-	0.06	0.03	0.01	0.01	0.1	0.04	-	-	0.05
^{197}Hg	chlormeodrin, BMHP	1.55	-	0.35	0.01	-	-	0.03	-	-	0.03	-
^{198}Au	colloid	0.85	-	-	-	-	-	0.19	0.16	0.06	-	-
^{201}Tl	chloride	-	1.6	-	-	0.04	0.01	0.47	0.66	0.75	-	-
^{203}Hg	chlormeodrin	0.02	-	-	-	-	-	-	-	-	0.07	-

Table 21

Estimated installations of scintillation cameras and population per scintillation camera in Europe 1978 with annual growth rate from 1977 to 1978 [P9]

Country	Population in millions	Installed scintillation cameras 1978	Growth of installations as compared to 1977 (%)	Population per scintillation camera (1000)
Austria	7.51	34	26	220
Belgium	9.84	63	5	160
Bulgaria	8.81	3	50	2940
Czechoslovakia	15.15	28	4	540
Denmark	5.1	37	6	140
Finland	4.75	28	17	170
France	53.28	134	7	400
German Dem. Rep.	16.76	8	14	2100
Germany, Fed.Rep.of	61.32	498	44	120
Greece	9.36	13	44	720
Netherlands	13.94	104	22	130
Hungary	10.69	3	50	3560
Italy	56.7	86	32	660
Norway	4.06	22	10	180
Poland	35.01	11	10	3180
Portugal	9.8	4	0	2450
Romania	21.85	7	0	3120
Spain	37.11	35	25	1060
Sweden	8.28	69	8	120
Switzerland	6.34	45	10	140
United Kingdom	59.06	206	26	290
Yugoslavia	21.91	23	64	950

Table 22

Mean absorbed dose in the most heavily exposed organs, in the gonads and in the whole body and effective dose equivalent per unit of administered activity [K2, K3, M10, N13, R5]

Radionuclide and compound	Type of administration	Mean absorbed dose per unit administered activity (μGy/MBq)				Effective dose equivalent (μSv/MBq)
		Tissues most heavily exposed	Testes	Ovaries	Whole body	
^{3}H water	i.v.	whole body, 15	15	15	15	15
	oral	colon, 33; G.I.T., 30			15-22	15
^{3}H inulin	i.v.	kidneys: normal, 1 no outflow, 1300	0.1	0.1	0.1	1
^{11}C monoxide	inhalation or i.v.	heart, 23; lungs, 9-12	2.5	2.5	3	5
^{14}C inulin	i.v.	kidneys: normal, 8 no outflow, 11000	1	1	1	11
^{13}N ammonium	i.v.	lung, 49; kidneys, 5	3	3	2.5	10
fluoride	i.v.	skeleton 30-60; bone marrow, 50	5-12	5-12	5-20	21
^{22}Na chloride	i.v. or oral	skeleton,6200; bone marrow,4400	3200	3200	3100	3100
^{24}Na chloride	i.v. or oral	bone marrow, 450; skeleton, 410	340	350	400	340
^{32}P phosphate	soluble i.v.	skeleton,7600; bone marrow,8000	1300	1300	2200	1700
	oral	colon, 5400; G.I.T., 2000			1900	2400
	insoluble oral	colon, 21000; G.I.T., 1500			1300	2700
^{42}K chloride	i.v.		220	220	250	220
^{45}Ca chloride	i.v.	skeleton, 19000; bone marrow, 5900	300	300	2600	1400
	oral	colon, 6300; G.I.T., 130			520	670
^{51}Cr chromate	oral	colon, 160; G.I.T., 30	3.5	41	6.3	35
chrom III ion	i.v.	skeleton, 90; bone marrow, 70	70	70	65	45
erythrocytes	i.v.	spleen, 1500; kidneys, 240	80	100	140	210
denatured erythrocytes	i.v.	spleen, 3400-24000; kidneys,140	17	25	50	400
ethylene diamine triacetate		kidneys: normal, 0.007 no outflow, 1500	0.2	0.8	0.5	2
^{55}Fe ion	i.v.	bone marrow; 4000; liver, 1000	91	230	250	550
^{57}Co vitamin B12	oral	liver, 25000; kidneys, 4300	30	1100	3500	2900
bleomycin	i.v.	kidneys, 100; liver, 50	20	28	15	29
^{58}Co vitamin B12	oral	liver, 85000; kidneys, 10000	500	2600	5000	5900
^{59}Fe ion complex	i.v.	spleen, liver, 17000 bone marrow, 13000	12000	6300	6400	12000

Table 22, continued

Radionuclide and compound	Type of administration	Mean absorbed dose per unit administered activity (μGy/MBq)				Effective dose equivalent (μSv/MBq)
		Tissues most heavily exposed	Testes	Ovaries	Whole body	
^{67}Ga citrate	i.v.	colon, 190; bone marrow, 160	65	76	70	110
^{68}Ga citrate	i.v.	intestine, 57; colon, 46	11	13	14	23
DTPA a/	i.v.	bladder, 500; kidney, 54	13	23	10	41
^{75}Se L-seleno methionine	i.v.	liver, kidney, 6800; pancreas, 3200	3000	1400	2200	2900
^{82}Br bromide	i.v.		440	410	370	430
^{85}Sr chloride	i.v.	skeleton, 5500; bone marrow 4500	850	1100	1500	1000
^{87m}Sr	i.v.	skeleton, 20; bone marrow, 10	4	4	4	7
^{99m}Tc pertechnetate	i.v.	ventricle, 68; thyroid 35	2	6	4	11
	oral	colon, 110; G.I.T., 55	1	25	5	25
albumin	i.v.	liver, 35; heart, 21	7	8	3	6
denatured red blood cells	i.v.	spleen, 150; pancreas, 43	< 1	1	5	53
dimercaptosuccinate	i.v.	kidney cortex, 280; kidney av.185	3	5	4	16
DTPA a/		kidneys:normal, 10; no outflow 420	3	6	5	7
red blood cells		spleen, 30; lungs, 25			9	7
phosphate complex	i.v.	skeleton, 14; kidneys, 9	5	6	3	7
iminodiacetate complex,	i.v.	gallbladder, 45; liver, 25	1	9	4	20
colloides	i.v.	liver, 92; spleen, 56	< 1	2	5	13
macroaggregates	i.v.	lungs, 50; thyroid, 23	2	2	3	16
plasmin	i.v.	spleen, 51; liver, 40	4	6	7	13
^{111}In ion	i.v.	liver, 880; bone marrow, 850			73	210
leucocytes	i.v.	spleen, 2800; liver, 610			140	330
bleomycin	i.v.	liver, 210	31	45	45	47
DTPA a/	i.v.	kidneys: normal, 15; no outflow, 7600			94	490
thrombocytes	i.v.	spleen, 6700; liver, 170				
^{113m}In ion	i.v.		4	4	4	4
aerosol	inhalation	lungs, 200	< 1	< 1	2	30
denatured red blood cells	i.v.	spleen, 1100; pancreas 21	1	2	5	72
DTPA a/	i.v.	kidneys: normal,50; no outflow 710	4	5	2	15
colloid	i.v.	liver, 140; spleen, 42	1	2	3	14
^{123}I iodide	i.v.	thyroid (35%), 5200; ventricle, 53	3	8	9	170
albumin	i.v.	spleen, 42; lungs, 29	16	18	17	21
o-hippurate	i.v.	kidneys: normal,10; no outflow 1500	3	4	2	15
^{125}I iodide	i.v.	thyroid (35%),330000; liver, 140	8	12	190	10000
albumin	i.v.	spleen, 550; lungs, 400	170	210	220	290
fibrinogen	i.v.	spleen, 260; lungs, 170	44	53	60	95
o-hippurate	i.v.	kidneys: normal,10; no outflow 7500	1	2	2	11
^{131}I iodide	i.v.	thyroid (35%), 530000; ventr., 340	26	38	260	16000
albumin	i.v.	spleen, 800; lungs, 670	460	480	480	680
macroaggregates	i.v.	lungs, 1900; liver, 410	120	120	50	360
o-hippurate	i.v.	kidneys: normal,10; no outflow 4500	3	4	3	16
^{127}Xe gas	inhalation	broncus epith., 14; lungs, 1			0.2	0.3
in saline	i.v.	lungs, 6; fat tissue, 1	0.3	0.4	0.4	0.5
^{133}Xe gas	inhalation	broncus epith., 30; lungs, 3	0.3	0.4	0.4	0.3
in saline	i.v.	lungs, broncus, 25; fat tissue 3	0.3	0.4	0.4	0.7
^{169}Yb DTPA a/	i.v.	kidneys: normal, 28; no outfl.32000	13	17	7	43
^{198}Au colloid	i.v.	liver, 11000; bone marrow, 730	10	38	380	1000
^{201}Tl ion	i.v.	colon, 220; kidneys, 200	750	100	35	94

a/ DTPA = diethylenetriaminepentaacetate.

Table 23

Frequency of radiotherapy procedures in 1978 as reported from some WHO regional offices [W13]

(Annual frequency per million population in parentheses)

Radiotherapy procedure	Burma	Indonesia	Sri Lanka
	Millions of population in 1978		
	33	146.9	14.2
External beam			
Cobalt-60 teletherapy		955 (6.5)	4454 (314)
x-ray therapy 100-150 kV			171 (12)
Brachytherapy			
Interstitial			
Gold-198 seeds			6 (0.4)
Radium-226 needles			118 (8.3)
Intracavity			
Radium-226 tubes		148 (1.0)	221 (15.6)
Applicators			
Radium-226 moulds			31 (2.2)
Strontium-90 eye applicators			11 (0.77)
Radiopharmaceuticals			
Thyroid cancer: iodine-131	4 (0.1)		
Thyreotoxicosis: iodine-131	165 (5)		22 (1.6)
Polycythaemia vera: phosphorus-32			2 (0.1)

Table 24

Data on the annual frequency of brachytherapy in Japan [H9]

		1971	1979
Treatments (number per million)	Female	400	217
	Male	54.5	16.2
	Total	454.5	233.2
Radiation source (relative frequency, %)	^{226}Ra	50.3	38.5
	^{222}Rn	2.3	a/
	^{137}Cs	7.2	16.0
	^{60}Co	28.5	38.5
	^{90}Sr	11.7	6.0
	^{90}Y	-	1.0
Source position (relative frequency, %)	Mouth	12.0	4.1
	Maxilla	1.6	3.2
	Neck	0.6	
	Breast	0.7	
	Cervix	60.0	85.5
	Femur	0.2	-
	Other	24.9	7.2

a/ Radon-222 has not been used for brachytherapy in Japan since 1976 because production has been stopped due to radiation protection problems.

Table 25

Annual number of treatments and relative frequency of various treatments with radiopharmaceuticals in Sweden during the years 1971-1978
[N2]

Radio-pharmaceutical	Disease or site treated	Annual number of treatments per million population (relative frequency in per cent of all treatments in brackets)							
		1971	1972	1973	1974	1975	1976	1977	1978
^{131}I	Thyroid diseases	249.8 (82.5)	271.0 (84.1)	297.3 (85.3)	300.1 (88.0)	298.4 (87.8)	387.1 (90.1)	357.6 (88.58)	350.3 (89.6)
^{32}P	Polycythemia vera	40.6 (13.4)	36.0 (11.2)	38.8 (11.1)	31.5 (9.22)	31.5 (9.3)	31.0 (7.2)	33.8 (9.38)	32.3 (8.3)
^{198}Au	Pleura and abdomen	2.4 (0.8)	1.9 (0.57)				0.4 (0.09)	1.44 (0.36)	0.96 (0.24)
^{32}P, ^{90}Y	Rheumatic arthritis	3.1 (1.0)	4.0 (1.23)	0.3 (0.07)	0.1 (0.04)	0.3 (0.07)			
^{198}Au, ^{90}Y	Knees and joints	1.8 (0.6)	3.5 (1.07)	4.4, (91.2)	3.3 (0.97)	5.0 (1.47)	6.9 (1.56)	9.1 (2.08)	5.9 (1.50)
^{90}Y	Pleural and perime-diastinal carcinoma	3.9 (1.3)	4.9 (1.53)	0.5 (0.14)	4.6 (1.36)	3.8 (1.11)		1.08 (0.27)	0.36 (0.09)
^{90}Y	Cystic craniopharyngeoma	1.3 (0.4)	0.4 (0.11)		1.5 (0.43)	0.6 (0.18)	1.0 (0.23)	1.08 (0.27)	1.2 (0.31)
^{32}P	Mycosis fungoides		0.5 (0.15)						
^{32}P	Metastasis, generalized carcinoma		0.13 (0.04)					0.24 (0.06)	
^{198}Au	Spinal cord cyst		0.1 (0.03)						

Table 26

Percentage of absorbed dose in ovaries and testes of the total treatment dose at maximum build-up at two different field locations
[N9]

(The last two columns give the gonad doses resulting from 45 Gy maximum absorbed dose in the treatment region)

Treatment region	Type of radiation	Percentage dose		Absorbed dose (mGy) with 45 Gy at maximum in treatment region	
		Ovaries	Testes	Ovaries	Testes
Mediastinum $10 \times 10\ cm^2$	45 MV x ray	0.15	0.2	68	90
	10 MV x ray	0.2	0.24	90	110
	45 MeV electron	0.3	0.2	135	90
	18 MeV electron	0.05	0.09	23	41
Paraaortal lymph nodes $10 \times 10\ cm^2$	45 MV x ray	0.4	0.1	180	45
	10 MV x ray	0.6	0.4	270	180
	45 MeV electron	0.15	0.07	68	32
	18 MeV electron	0.03	0.02	14	9

Table 27

Average percentage gonadal doses for various treatments using cobalt-60
[N8]

Type of treatment	Site or condition	Average CGD a/ (cm) field size (cm^2)	M	F	Percentage dose calculated M	F	Measured M	F
Head fields	Nose, middle ear, sinuses, paratoid, brain, CNS, pituitary, antrum	50	70	60	0.085	0.115	0.096	0.128
Neck fields	Pharynx, larynx, thyroid, upper oesophagus, upper postcricoid	100	60	50	0.130	0.200	0.195	0.254
Thorax fields	Bronchus, lung	150	40	30	0.445	0.900	0.468	0.850
	Lower oesophagus	130	50	40	0.252	0.395	0.220	0.382
	Breast	120	-	40	-	0.345	-	0.377
	Shoulder	200	60	50	0.150	0.225	0.170	0.210
Mante fields	Hodgkin's disease	850	40	30	1.200	3.250	1.150	3.300
		850	50	40	0.450	1.200	0.550	1.010
Abdominal fields	Stomach, bowel	120	30	20	0.850	2.200	0.915	2.410
	Lymphoma	220	30	20	1.150	3.400	1.250	3.280

a/ CGD = centre-of-the-field to gonad distance.

Table 28

Absorbed dose in the gonads of males and females per 1 Gy at the surface due to primary beams plus scatter radiation and from generalized leakage radiation
[H19]

Irradiation position	Male ^{60}Co gamma rays		200 kV x rays		10 MV x rays		10 MeV electrons		50 kV x rays	
	a/	b/	a/	b/	a/	b/	a/	b/	a/	b/
Head	0.21	-	0.043	-	0.487	-	0.25	-	0.005	-
Neck	0.35	-	0.075	-	0.54	-	0.385	-	0.015	-
Chest	0.475	0.0025	0.068	0.01	0.44	0.0015	0.5	-	0.016	-
Abdomen	0.382	0.006	0.06	0.018	0.29	0.0026	0.414	-	0.015	-
Ovaries	-	-	-	-	-	-	-	-	-	-
Pelvis	0.638	0.129	0.062	0.104	0.16	0.0043	0.657	0.002	0.015	0.028
Thigh	0.483	0.135	0.06	0.06	0.067	0.0274	0.507	0.0017	1.68	0.041
Testes	845	0.37	808	0.1	796	0.265	785	-	495	0.18
Lower leg	0.2	-	0.05	0.01	0.22	-	0.23	-	0.015	-
Foot	0.15	-	0.05	-	0.23	-	0.18	-	0.01	-

Irradiation position	Female ^{60}Co gamma rays		200 kV x rays		10 MV x rays		10 MeV electrons		50 kV x rays	
	a/	b/	a/	b/	a/	b/	a/	b/	a/	b/
Head	0.18	-	0.027	-	0.302	-	0.218	-	-	-
Neck	0.34	0.003	0.03	0.01	0.34	0.001	0.38	-	-	-
Chest	0.42	0.009	0.33	0.027	0.228	0.006	0.44	-	-	-
Abdomen	0.32	0.032	0.02	0.067	0.08	0.023	0.32	0.002	0.001	
Ovaries	460	0.64	165	1.11	607	0.48	1.8	-	30.6	-
Pelvis	0.38	0.075	0.03	0.2	0.05	0.05	0.37	0.005	0.01	-
Thigh	0.384	0.0072	0.026	0.022	0.096	0.005	0.4	0.001	0.01	-
Testes	-	-	-	-	-	-	-	-	-	-
Lower leg	0.16	-	0.02	-	0.175	-	0.065	-	-	-
Foot	0.075	-	0.02	-	0.11	-	0.045	-	-	-

a/ Gonad dose due to primary plus scatter radiation, in mGy per Gy at the surface of beam entrance.
b/ Gonad dose due to generalized leakage radiation, in mGy per Gy and cm^2 of the beam entrance surface.

Table 29

Absorbed dose in various organs outside the treatment area per unit absorbed dose in the surface of the beam entrance for 10 MV x ray radiotherapy

Irradiation position	Absorbed dose from scatter radiation in (mGy Gy^{-1} cm^{-2})						
	Thyroid	Breast	Stomach	Lungs	Bladder	Testes	Ovaries
Head	0.05	0.004	0.0004	0.015	-	-	-
Neck	-	0.009	0.0035	0.1	0.0002	0.1	0.001
Thorax	0.04	0.02	0.03	0.09	0.0008	0.002	0.006
Abdomen	0.004	0.03	0.17	0.11	0.007	0.004	0.023
Pelvis	0.001	0.003	0.07	0.005	0.16	0.03	0.31
Thigh	-	0.001	0.01	0.001	0.25	0.12	0.005

Table 30

Absorbed dose in various organs outside the treatment area per unit administered activity in radiopharmaceutical therapy [K24]

Administered radiopharmaceutical	Type of disease	Organ	Absorbed dose per unit administered activity (mGy/MBq)
^{131}I-iodide	Hyperthyroidism	Gonads	0.08
		Bone marrow	0.19
^{32}P-phosphate	Polycythemia vera	Gonads	0.14
^{198}Au-colloids	Malignant intraperitoneal and intrapleural infusions	Gonads	0.08
		Bone marrow	1.62
^{32}P-lipiodol F (with I-131 for scintigraphic localization of lymph nodes)	Malignant lymphoma	Lung	22.9
^{198}Au	Joint diseases	Regional lymph nodes	176
		Lymphocytes	2.7
		Liver	0.14
		Total body	0.35
^{90}Y	Joint diseases	Regional lymph nodes	246
		Liver	0.14
		Total body	0.35

Table 31

Genetically significant dose equivalent values (μSv) for radiation therapy reported at different times from various countries

Country	Year				Ref.
	1970	1971	1973	1978	
Australia	23	-	-	-	[S21]
Germany, Fed.Rep.of	-	-	6±2	8±3	[S2,S3,S4]
Japan	-	7	-	0.7	[H5, H19]
United States	-	23±1	-	-	[T1]

Table 32

Genetically significant dose equivalent value (μSv a^{-1}) and its percentage distribution, in Berlin (West) and in Munich [S2, S3, S4]

Type of disease	Berlin (West) (1973			Munich (1971)		
	Private GSD=1.7	Clinic GSD=6.5	Total GSD=8.2	Private GSD=1.9	Clinic GSD=4.1	Total GSD=6.0
Haemangioma	1.6	41.5	10.0	2.9	83.7	57.5
Arthrosis and arthritis	9.0	8.0	8.6	72.1 17.7	2.3	30.1
Keloid	71.0	7.0	57.7		6.0	4.5
Spleen or kidney transplants		10.5				
Anal region	13.0	31.0	23.7		0.1	
Other benign conditions	4.0	2.0		7.3	7.7	7.9
Malignant diseases	0	0	0	0	0	0

Table 33

Annual genetically significant dose equivalent from external beam therapy in Japan, by age and sex of the patients and by the nature of the conditions requiring radiotherapy

Age class	Annual genetically significant dose equivalent (μSv)				Ref.
	Male		Female		
	Benign	Malign	Benign	Malign	
0-14	0.41	0.39	3.10	0.61	
15-29	0.06	0.97	3.40	0.22	
30-44	0.01	0.29	0.02	0.11	
> 45	0	0	0	0	
Total 1971	0.48	1.65	6.52	0.94	[H5]
Total 1978	0.03	0.36	0.08	0.58	[H19]

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ANNEX H

Occupational exposures

CONTENTS

Introduction

1. The Committee discussed the doses received from occupational exposure to radiation in its 1962 [U1] and 1972 [U2] reports. A detailed review of the subject was presented in Annex E of the most recent comprehensive report in 1977 [U3]. In this Annex the main intent is to focus on significant changes in the pattern of exposure which have since appeared and to present information on trends or particular causes of high exposures. It has been found useful to update the data presented in some areas, and in many cases this is done by reference to the original publications. A further object is to clarify the reasons for which the Committee requires data on occupational exposure and to suggest areas in which better data collection or analysis may be performed. The Committee has also collected and reviewed data on accidents involving the exposure of workers to substantial radiation doses. Some conclusions are drawn as to the frequency and severity of such accidents for different types of work involving radiation.

I. OBJECTIVES OF DATA COLLECTION AND ANALYSIS

2. The primary purpose of monitoring occupational radiation exposure is to provide information to be used to control the dose accumulation pattern of individuals. The information is also used to demonstrate compliance with occupational exposure limits. Neither of these require the reporting of collated data on particular work groups or sections of an industry. However, such collating and reporting is of use for radiological protection purposes such as assessing the degree to which doses within a particular industry have been reduced to levels as low as reasonably achievable [I1]. None of these purposes are those for which the Committee uses the information which has been collected and data are not therefore always presented in the form which is most useful for the Committee.

3. For particular practices the Committee wishes to assess the annual collective dose and the collective dose associated with some normalized measure so that the data from different countries and practices can be collated. This can be used to give an indication of the radiation-induced detriment to the population from each practice. The data can also be used for comparisons; for example, of the contribution of different sectors of an industry to the total radiation-induced detriment. For each type of work and for subgroups of workers within practices, the Committee wishes to assess the average level of dose and hence risk, together with the distribution of doses among the workforce. These data can be used to compare risks from radiation with non-radiation risks in the same or other occupations.

4. Data over several years can be used to assess trends in average doses, dose distributions and collective doses from complete industries or practices or from subgroups. These can be used to review whether the trends are with time, with the age of installations, with changes in technological aspects of plants or in the management of workers, with increasing size of the practice, or for some unknown reason.

5. Data on occupational exposure can also be used in principle as an input to epidemiological studies. Such data are not, however, used for this purpose by the Committee, although the Committee welcomes the opportunity to review the results of epidemiological studies carried out by others. Considerable care is needed in using the reported results of occupational dosimetry for this purpose, for the reasons pointed out in chapter II.

II. ANALYSIS OF OCCUPATIONAL DOSE DISTRIBUTIONS

A. LIMITATIONS OF THE DATA

1. The quantities measured

6. It is necessary to establish the relationship between measurements made in the radiation field by film, thermoluminescent or other personal dosimeters and the absorbed doses in the tissues and organs of the body. For relatively unshielded high energy gamma or x-radiation which does not give rise to variable absorbed dose rates throughout the body, reasonably constant relationships can be adopted. For spatially variable radiation fields, partial shielding of the body, extreme variations in distances of parts of the body from the source and similar situations, the relationships are more complex [K8, K9]. In some circumstances the complex relationships may be clarified by extra measurements and careful interpretation of measurements; these appear to be sometimes carried out, but not consistently. There are also problems peculiar to some exposures such as the orientation of the body with respect to the source.

7. As has been discussed in Annex A, for the control of dose to individuals the effective dose equivalent should be obtained by assessing doses to individual organs and tissues. In practice this is normally not done because of insufficient information on the radiation field characteristics. Monitoring badges are not generally designed to provide basic information such as the energy and type of radiation from which depth dose calculations could be carried out. In the case of non-uniform exposure of the body it is rare that sufficient information is available from monitoring devices to indicate the spatial extent and variability of the radiation field well enough to assess organ and tissue doses. These aspects have been studied in detail by Maruyama et al. [M14], who calculated organ doses and the effective dose equivalent in a phantom exposed at various orientations to radiation of different energies.

8. Dosimeters normally indicate an approximation to the absorbed dose at the surface of the body, that is to say averaged over a relatively shallow depth in tissue under a thin surface layer, together with the absorbed dose at a greater depth in tissue [M17]. Sometimes dosimeters are used for particular purposes such as to measure doses to finger tips, arms and feet. These results are often noted on individual dose records and may be used for comparison with limits on exposure of extremities. Neutron doses are recorded by special badges of a wide variety of types, intended in each case to be appropriate for the neutron energy spectrum to be encountered. Many simple neutron badges are not appropriate for measurement of intermediate energy neutrons; they should only be used if it has been demonstrated that the neutron spectrum is mainly fast or thermal.

9. The level of internal contamination is easy to determine by biological monitoring for some radionuclides (e.g., ^{3}H), but very difficult for others (e.g., ^{239}Pu), especially at long times after intake or in cases of multiple intake. Biological monitoring is taken to include excreta monitoring and external counting. Previously, in most organizations, attempts were made to estimate body content as a fraction of the Maximum Permissible Body Burden and the results of monitoring were expressed in these terms. With the change by ICRP to Annual Limits of Intake there is likely to be a corresponding change in attempting to estimate and report annual intakes and committed doses. One difficulty in compiling statistics is that reporting levels for internal contamination vary widely.

10. The Committee has previously adopted the convention that all numerical results reported by monitoring services represent the average absorbed dose in the whole body and recognized that it is almost always the reading from the dosimeter which is reported, without consideration of its relationship to the absorbed dose in the body. This is still regarded as a reasonable convention as most data are on external exposure of the whole body to ionizing photon radiation of moderately high energy for which the quality factor is one. The same convention has again been adopted in this Annex. In situations where exposure of the body may be non-uniform, especially in medical practice, it may be misleading to average across different types of work as the relationship between reported dosimeter reading and average absorbed dose in the whole body will not be constant. Such variations will be noted when information is available.

2. Monitoring and dose recording practice

11. The number of workers subjected to different levels of monitoring is a function of management and enforcement agency decisions on the likelihood of exposure at or above different levels. It is not therefore consistent within an industry or in a given country, and certainly not between industries or between countries. The ICRP [I1, I2] recommends that in cases where it is most unlikely that annual doses will exceed three-tenths of the dose limit, individual monitoring is not necessary, although it may sometimes be carried out as a method of confirming that conditions are satisfactory. However, the relative ease, low cost and sensitivity of monitoring devices for external radiation means that these are much more widely issued than would be expected from such a criterion. Having been issued, even trivial doses from the devices are often reported, despite the ICRP recommendation of a recording level of one-tenth of the annual limit. There is some discrepancy in the treatment of external and internal radiation, which may be because monitoring for internal irradiation is only undertaken in those few circumstances where there is a clear need. Internal doses can be assessed indirectly by monitoring activity concentrations in air, but there is considerable uncertainty over the relationship between the measured concentrations and the retained body content. The result of such monitoring is not always transferred to individual dose records.

12. Difficulties such as these contribute to the problem of defining the number of exposed workers and may lead to differences in reported average doses. The Committee feels that whether the reported data are for all of those monitored and the basis on which they were selected for monitoring should be clarified. How dose estimates are obtained for those individuals who are not monitored, e.g., air crew, underground miners, should also be made clearer. It is assumed throughout that natural background radiation has been subtracted from the reported results and that medical doses are not included. Even medical exposures required as a condition of employment or given as a result of employment are not included.

13. There is also some variation in the procedures used for reporting dosimeter readings which are less than the minimum detectable level for the particular dosimeter. These may be entered into the records as either zero or the minimum level. Due to difficulties of this type the Committee has developed certain analytical procedures, described later, to extract information from dose distributions. More information on precise procedures used in reported results would be useful.

3. Notional doses

14. When dosimeters are lost, or the readings are otherwise not available, it is a common procedure for compliance with legal or statutory requirements to assume that the individual exposed has received the appropriate proportion of the annual authorized limit for the period for which results were lost. However, this procedure can distort records, particularly if large numbers of dosimeters are lost within a particular occupational group. The Committee therefore would find it most useful if doses could be reported with an indication of the number of notional doses, the procedure adopted and, if possible, a revised dose estimate with the notional doses substituted by a dose calculated from the average dose over the remainder of the year for each individual. This procedure is only appropriate in routine situations; when high exposures are suspected, such as after an accident, then biological monitoring may be more appropriate.

B. CHARACTERISTICS OF DOSE DISTRIBUTIONS

15. Dose distributions are the results of many constraints imposed by the nature of the work itself, by the management, by the workers and by legislation. In some job categories it may be unnecessary for workers ever to receive more than very low doses, whereas in other jobs workers may have to be exposed to high doses fairly routinely. Management controls in particular act as a feedback mechanism which applies especially as individual doses approach the annual dose limit, or some proportion of it, in a shorter period of time. Individual doses may be reduced to lower levels in some circumstances by management decisions but, unless changes are made to the job or the working conditions, more workers will be needed to carry out the job and the collective dose will generally increase [G1, H1].

1. Example of a dose distribution

16. In order to clarify the discussion on the characteristics of dose distributions the Committee has found it useful to take an example of a dose distribution which exhibits many of the characteristics of interest. This

example, which is given in Table 1, is not an actual distribution, although it is similar to those distributions found for workers on light water reactors (LWRs), in fuel reprocessing, in research and development, in industrial radiography and in luminizing. It must be emphasized that this is not a typical or an optimum distribution; it is no more than an illustrative example.

17. In Annex E of the 1977 report, it was noted that many dose distributions exhibit a log-normal character, especially at doses well below the annual dose limit. This property can be readily identified by plotting the cumulative frequency on a probability axis against the logarithm of dose. This procedure was referred to in Annex E of the 1977 report as a "log-probability plot" and will be used again in this Annex. The log-probability plot of the data from Table 1 is shown in Figure I. The straight line in the Figure is the result of a least squares fit to the points up to and including the point at 15 mGy. The results calculated from this fit are

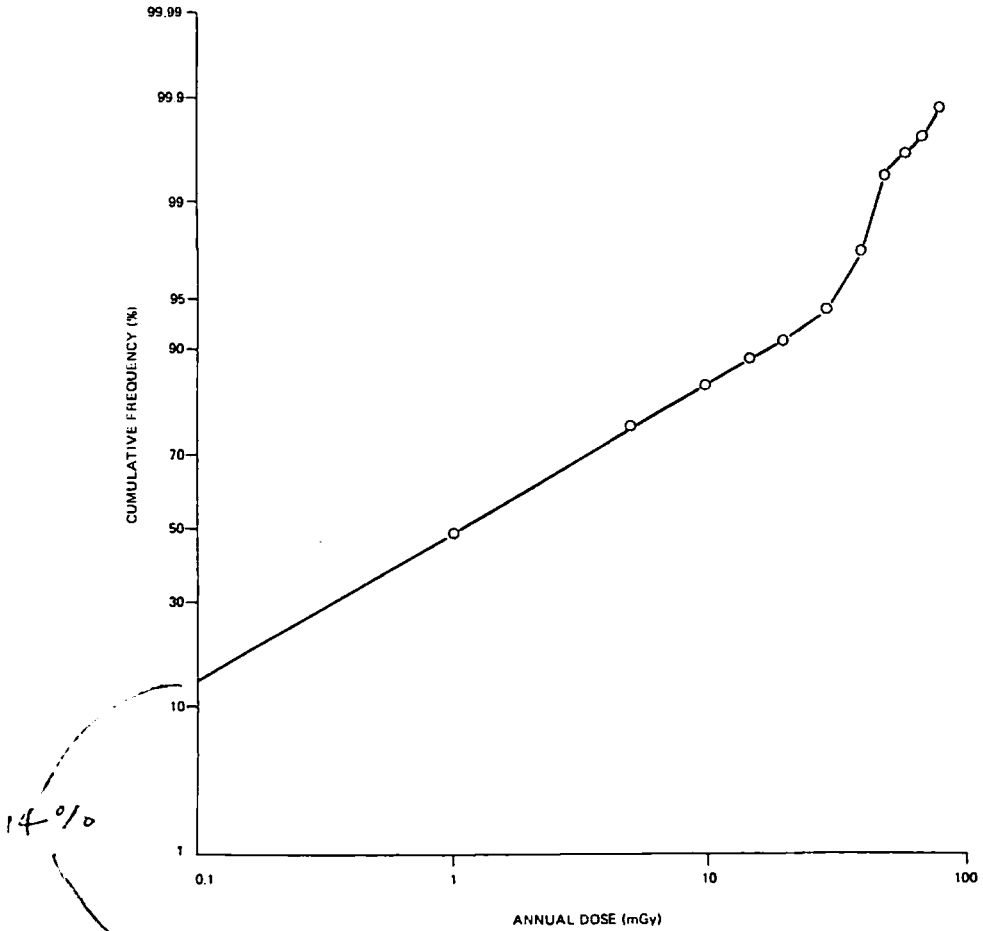

Figure I. Example log-probability plot of data from Table 1

compared in Table 1 with those obtained from simple arithmetic mean doses in each range.

18. Table 1 and Figure I show some of the characteristics of interest and that there is some lack of clarity of the number of workers taken to be unexposed. From the log-probability plot it is possible to obtain the collective dose as described later. The average dose is of course related to the number of workers so that if the collective dose is extracted from the distribution using a fit to the log-normal if appropriate, then the average dose is determined by the number of workers. The main point of the log-normal fitting is to make a better allowance for the skewness of the distribution towards zero doses than using the mid point dose in the lowest dose band. This is illustrated in Table 1.

19. In principle, if the dosimetry data are reported with doses below the threshold of detection as zero, then addition of any arbitrary number of unexposed workers will not affect the collective dose, nor the average dose to those workers actually exposed. However, it will clearly increase the total number of workers considered and decrease the average dose based on that total. There is no precise method to determine the number of unexposed workers, but it is possible to calculate the number of workers in the sample below any arbitrarily selected annual dose level from the log-normal fit. For example, using the distribution in Table 1, if this level is taken as 0.1 mGy, the number found from the log-normal fit to receive less than 0.1 mGy is 140 people. Procedures of this type have not been used in this Annex but the determination of the numbers of exposed and unexposed workers merits further consideration, as has been done in recent reports by the United States Nuclear Regulatory Commission [B17, B18]. Drexler et al. [D9] have assessed the average doses to all those monitored and to those with measurable doses for a number of occupations; the ratio of the two averages ranges from about 1.5 to 20 for different occupations.

20. Another characteristic which may be seen in Figure I is the deviation from log-normal as the doses approach 50 mGy per year, the currently recommended dose limit for occupationally exposed workers [I1],

which has become progressively observed as an annual limit during recent years. This means that the log-normal is not a complete description of the dose-frequency characteristics. Since there are likely to be only a few people in the higher dose ranges it is reasonable to request that those reporting data give collective doses based on summation of individual results at higher individual doses. It would also be helpful to give the number of workers in individual dose bands which are rather narrower than has been the practice. These data would clarify the effects on the distribution of dose limits; and if such reporting were routine then all the required data on the upper end of the distribution could be derived directly without introducing any further assumptions or approximations. It has been suggested by Kumazawa and Numakunai [K12] that the control of doses approaching the dose limits leads to a normal distribution in the higher dose range; this presumption can be used to carry out analysis as a hybrid normal/log-normal distribution.

21. A characteristic of the dose distribution identified by the Committee in 1977 [U3] as being of interest was the fraction of the collective dose delivered above a given annual dose level taken in that report as 15 mGy. This fraction is plotted in Figure II as a function of the annual dose level for the example distribution of Table 1. It clearly shows the effect of efforts to keep doses within the dose limit.

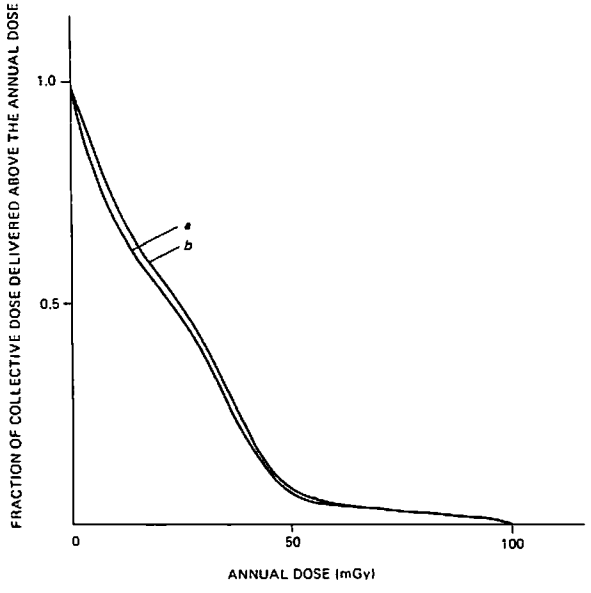

Figure II. Example of the fraction of collective dose above a given annual dose level (data from Table 1)

[a] Calculated as the number of workers in each range multiplied by the mid-point dose.
[b] Calculated from the log-normal fit below 15 mGy.

22. The three characteristics of the dose distribution previously identified by the Committee as of interest still seem to describe the distribution in a useful fashion. These characteristics are:

(a) The annual average dose, $\overline{D}$, which is related to the average level of individual risk. For consistency, in this Annex the average is generally calculated for all individuals monitored in a given occupational group.
(b) The annual collective dose, M, which is related to the impact of the practice.
(c) The ratio of the annual collective dose delivered at individual doses exceeding 15 mGy per year to the total collective dose, MR, which is related to the proportion of workers exposed to higher levels of individual risk.

23. These characteristics may be obtained for any form of the dose distribution, whether or not it exhibits a log-normal response over some part of the dose range. They should be obtained from the detailed basic data on the dosimetry results and reported with any collated reports of the data where possible. The definitions of the annual collective dose, M, are as follows:

$$M = \sum_{n=1}^{N} D_n \qquad (1)$$

where N is the total number of workers, D_n is the annual absorbed dose received by the nth worker. In practice M is often calculated from collated dosimetry results using the alternative definition

$$M = \sum_{0}^{\infty} N_i \overline{D}_i \qquad (2)$$

where N_i is the number of individuals in the ith absorbed dose range for which $\overline{D}_i$ is the mean annual absorbed dose. In some circumstances, because in general the dose distribution is skewed towards low doses, use of the mid-point dose in a range as an approximation to $\overline{D}_i$ will lead to an overestimate of the collective dose. For typical dose ranges the overestimate is thought to be less than 10% [B22]. The annual average absorbed dose, $\overline{D}$, is given by

$$\overline{D} = \frac{M}{N} \qquad (3)$$

where N is the total number of workers monitored. The annual collective dose distribution ratio, MR, is defined as

$$MR = \frac{M(>15)}{M} \qquad (4)$$

where $M(>15)$ is the annual collective absorbed dose delivered at annual individual doses exceeding 15 mGy. This should, where possible, be calculated from the summation of individual doses.

24. Normal ranges for similar characteristics were given in Annex E of the 1977 report [U3]. These were intended to highlight those distributions with values either above or below the normal range, which could be used for decisions on dosimetry practices or causes of exposure. The normal ranges for the characteristics used in this report which replace those in the 1977 report, are:

$\overline{D}$ from 1 to 10 mGy
MR from 0.05 to 0.5

2. The reference distribution

25. The Committee in Annex E of the 1977 report [U3] defined a reference distribution such that:

(a) The distribution of annual doses is log-normal;
(b) The mean of the annual dose distribution is 5 mGy;
(c) The proportion of workers exceeding an annual dose of 50 mGy is 0.1%.

26. It was not the intent of the Committee that this reference distribution be considered an ideal or optimal distribution of doses and it should not be so interpreted. The distribution was only intended to give some basis for intercomparison and in so far as the parameters were defined ab initio it was artificial. It also did not show the common characteristic noted in Section B.1 of deviation from the log normal. This reference distribution, together with the observed range of parameters in the 1977 report, was used to obtain a normal range for the parameters of interest for dose distributions. One of the parameters, the proportion of the collective dose delivered at annual individual doses exceeding 15 mGy, was normalized with respect to the reference distribution. As has been pointed out [B17, B19, K10, K11], there were some errors in the normalization procedure used to obtain the parameter Ω, (the ratio of the fraction of the collective dose due to annual doses above 15 mGy for the observed distribution to the fraction for the reference distribution) the main result of which is that the fraction of the collective dose due to annual doses above 15 mGy for the reference distribution should have been 0.202 rather than 0.310. The normal ranges for the parameters given in the 1977 report were: $\overline{D}$ from 1–10 mGy; Ω from 0.1–2.0 (if Ω is recalculated correctly the range would be from 0.15 to 3.0).

27. In view of the difficulty over calculational inaccuracies and because the attention which has been paid to the reference distribution was more than anticipated, it was decided, as noted in the previous section, to revert to a basic characteristic concerned with each distribution. This characteristic is the fraction of the collective dose delivered at individual doses exceeding 15 mGy. The range for this characteristic, MR, which would correspond to the range used in the previous report for Ω, is from 0.03–0.6; however, it has been decided to adopt the normal range given earlier of 0.05–0.5 for MR.

3. Techniques for analysis of dose distributions

28. If the complete data on annual individual doses within a distribution were available, together with the treatment used for reporting dosimeter readings below the detection threshold and the treatment used for reporting notional doses, then it would be straightforward to extract the characteristics required by the Committee. However, data are normally reported grouped into dose ranges of different widths, often without such additional indications. The 1977 report used the observation that the distribution is often log-normal, especially for doses which do not approach the dose limit [B20, S18]. Where the required information cannot be extracted directly from the reported results, a log-normal fit to the appropriate part of the distribution is therefore used to extract the collective dose, and the fraction of the collective dose delivered in different individual dose ranges. This procedure is used, where possible, to assess collective doses to the large numbers of people in the lowest dose band who may receive very low or zero dose but are given dosimeters for administrative reasons.

29. A variable D is said to be distributed log-normally if the values of $y = \ln D$ are distributed normally. The mean, median and mode of the distribution of y is μ ; the variance of the distribution is σ^2. The probability that a value of D will lie between D and D + dD is [F5]

$$P(D)dD = \frac{1}{\sigma\sqrt{2\pi}}\frac{1}{D}e^{-\frac{(\ln D-\mu)^2}{2\sigma^2}}dD \qquad (5)$$

Since the data rarely fit a log-normal over the whole range, the quantity of use is the collective dose, M_D, up to a certain annual dose, D. This is given by

$$M_D = \frac{N_D}{\sqrt{2\pi}}e^{\left(\mu+\frac{\sigma^2}{2}\right)}\int_{-\infty}^{t}e^{-t^2/2}\,dt \qquad (6)$$

where the substitution variable $t = \frac{(\ln D-\mu-\sigma^2)}{\sigma}$, and N_D is the number of people receiving annual doses up to D; this is usually determined directly from the original data. The substitution using t is made to render M_D in the form shown since tabulations of the cumulative normal distribution function are readily available. The choice of the appropriate value of D for each distribution is made by inspection of the data plotted on log probability graph paper; very often 10 or 15 mGy is a convenient value.

30. Graphical techniques are of sufficient accuracy for analyses of dose distributions and are described both in standard texts [F5] and in the context of occupational dose distribution analysis [B20]. If a straight line is fitted by eye or by the method of least squares to the plot of the cumulative frequency versus ln D, then the value of D is $(\mu-\sigma)$ at a cumulative frequency of 15.87% and $(\mu+\sigma)$ at a cumulative frequency of 84.13%. M_D can then be obtained from standard tabulations.

31. An alternative procedure used for the analyses in this Annex for which sufficient data were available is to apply the method of least squares to obtain the equation for the best fit line up to the annual dose, D, chosen from inspection of the plot, and then a numerical integration to obtain the collective dose up to the value D, and up to 15 mGy if this was equal to D. The collective dose in the ranges above D is obtained from the original data using either the number in each range and the mid-point dose or the actual doses in higher ranges if provided. If D is less than 15 mGy, then M_{15} is calculated from

$$M_{15} = M_D + M_{(15-D)} \qquad (7)$$

where M_D is obtained from the least squares fit and $M_{(15\text{-}D)}$ from the original data.

32. Recently some analyses of distributions as a combination of log-normal and normal distributions have been made [K12]. The hybrid log-normal is derived from the log-normal by including a feedback mechanism which relates control of future doses to the previous cumulative dose. As this includes constraint functions which appear to apply rather generally it is probably a better way to represent observed distributions. However, it has not yet been developed and utilized sufficiently for use in this report.

33. It must be emphasized that use of the log-normal fitting procedure to extract data is necessary largely because of the inadequacies of the reporting. If data were reported in narrower ranges and with explanations of the treatment of notional doses and of measurements less than the limit of detection, then the use of the log-normal technique to extract information would

be unnecessary. It would be preferable if the original data were analysed more completely to give the collective dose and average dose, based on either the number of workers issued with dosimeters or the number of workers receiving measurable doses. It would also be desirable to report the distribution of doses, especially high individual doses, and the fractions of the collective dose delivered at individual doses above and below an annual dose level such as 15 mGy.

C. LIFETIME DOSE PREDICTIONS

34. In Annex E of the 1977 report [U3] the Committee used a simple linear extrapolation to predict lifetime doses for a few categories of workers for whom data on the average dose and years of employment were available for individuals. Very few new data have become available on which even this simple treatment could be used [B22, I4], and it is clear that the treatment does not take adequate account of the complexities of the prediction.

35. It was hoped that the simple treatment would have stimulated more investigation of the relationship between the rate of accumulation of dose over the years of a person's employment and the total dose received in that employment. This investigation would need to consider whether higher doses are received randomly throughout a group of workers or consistently by the same individuals each year, whether workers tend to stay in the high dose occupations for long periods or move into lower dose occupations with age, or even whether the reverse happens. It would also be useful to investigate the correlation between predictions based on historical records using various assumptions and actual total doses.

36. Clearly such investigations, which by their very nature deal with actual doses to individuals, can only be performed by those authorities having access to individual dose records. The Committee would like to encourage those authorities to carry out such investigations and analyses and report the results in a suitably anonymous fashion so that the privacy of the records of the individual workers is safeguarded.

III. THE NUCLEAR FUEL CYCLE

37. The nuclear fuel cycle is a major identified practice giving rise to occupational exposure. It was discussed in some detail in the 1972 [U2] and 1977 [U3] reports of the Committee and is generally well documented. There are considerable quantities of data on occupational dose distributions available. All aspects of the complete fuel cycle, whether or not carried out globally, are considered, except for the final treatment and disposal of the major wastes including high level wastes.

38. The output from the nuclear power industry is the quantity of electric energy supplied. Whether the reported energy is that generated by the station or that supplied for use, i.e., less that consumed by the station, is sometimes uncertain. The uncertainty is small compared with other uncertainties in the data but in general the energy supplied for use has been used in this Annex. Of more importance is whether the installed generating capacity may be a more appropriate measure in some circumstances for normalizing than energy generated. This is particularly the case with the reactor component of the fuel cycle, as a reactor may be shut down for most of a given year so that the collective dose per unit energy generated becomes very large and may even be infinite if the shut-down is for a complete year. For this reason the collective dose per unit energy generated is not a very meaningful quantity to calculate for individual reactors on an annual basis, and figures should be averaged over several years if possible. The appropriate averages can give indications of performance over a complete power programme or over several years. For the other stages in the fuel cycle, averaging over a complete power programme is necessary in any case so this difficulty does not arise.

A. URANIUM MINING AND MILLING

39. The main source of irradiation of uranium miners is exposure to radon and daughters. This subject is discussed in detail in Annex D in which data for several countries are reported; a summary of recent data is given in Table 2 for the late 1970s. For the United States the average exposure of about 5000 miners is reported by Richardson [R1] as approximately 4 WLM per year. This is considerably higher than the average reported in Annex E of the 1977 report [U3] of 1.4–1.9 WLM per year and that reported by Cook and Nelson [C9] of 1.1 WLM per year. The exposures reported by other countries are in agreement with the lower values reported for the United States, with Canada having about 4000 underground workers exposed to approximately 0.75 WLM per year on average and workers in France exposed to approximately 1.5 WLM per year on average. Taking all these values into account, an appropriate annual average exposure to radon daughters can be taken as about 1.5 WLM which can be converted using the appropriate coefficient from Annex D (8.4 mSv/WLM) to an annual effective dose equivalent of about 13 mSv. Underground miners are also exposed to some gamma radiation. This was estimated in the 1977 report as 10 mGy per year as a world-wide average. More recent Canadian data show a value closer to 1–2 mGy, but these are based on very few measurements and are believed to be low [A1].

40. Surface uranium miners have a very much lower exposure to radon daughters (see Annex D) and their dose from external radiation is also lower at about 1–2 mGy per year [A1, M1, L13]. It seems reasonable therefore to take the estimate of annual effective dose equivalent from external and internal irradiation of surface uranium miners as about 5 mSv.

41. Overall the collective dose per unit energy generated can be obtained but it is a somewhat complex calculation depending on the production of ore, taken as 3 t a^{-1} of natural uranium per miner, and the efficiency of conversion. The best available estimate of the latter is likely to be that made during the International Nuclear Fuel Cycle Evaluation [I11] which is that for current reactors the natural uranium requirement is about 200 t [GW(e) a]$^{-1}$. The estimate in Annex E of the 1977 report was 0.05 man rad [MW(e) a]$^{-1}$ (0.5 man Gy [GW(e) a]$^{-1}$) from gamma radiation plus 0.1 man rad [MW(e) a]$^{-1}$ (1.0 man Gy [GW(e) a]$^{-1}$) of alpha irradiation of the lungs. A similar calculation carried out for mines in Argentina gave a higher value for 1977–1979

of about 20 man Sv [GW(e) a]$^{-1}$ but this dropped to 4 man Sv [GW(e) a]$^{-1}$ in 1980 [P20] associated with a shift from underground to surface mining. Taking the INFCE value of 200 t [GW(e) a]$^{-1}$ of natural uranium, the mining rate of 3 t a^{-1} and the average effective dose equivalent of 13 mSv a^{-1}, then the collective dose equivalent per unit energy generated is 0.9 man Sv [GW(e) a]$^{-1}$. An appropriate rounded estimate of the collective effective dose equivalent per unit energy generated is 1 man Sv [GW(e) a]$^{-1}$.

42. The most detailed surveys of doses received by workers at uranium mills are for the United States in 1975 [C1, C9] and 1978 [B17]. An extrapolated total of about 1000 workers was estimated to be involved at an average measurable annual dose equivalent of 4 mSv in 1975, but only 2 mSv in 1978. The MR was estimated for the 1975 data as 0.2. A similar survey for millers in Australia [S19] gave average weekly doses of 0.06 mSv to 73 workers for a six-month working period in 1979–1980. The collective dose equivalent of 2 man Sv, taking the more recent estimate, and based on an energy production of 32 GW(e) a in the United States in 1978, makes a minimal contribution to the collective dose equivalent per unit energy generated of less than 0.1 man Sv [GW(e) a]$^{-1}$ and is not included as a separate item in the summary.

B. FUEL MANUFACTURE

43. New information on doses received at fuel manufacturing plants is available from Canada and India. In addition, there are data from the United Kingdom and the United States to update those given in Annex E of the 1977 report. Some new information on the doses to workers concerned with fuel manufacture under licence to the United States Nuclear Regulatory Commission have been published. These data are summarized in Table 3 [C1, U4, B1, B17]. Log-probability plots of the data from 1974 to 1978 are given by Brooks et al. [B17] and show a steady reduction in both $\bar{D}$ and MR. Only workers with measurable doses have been included. The results for 1975 are taken from a special survey [C1]. In 1977 [B1] and 1978 [B17] more detail was given of the activities within the category of fuel processing and fabrication which includes uranium and plutonium fuel fabrication and scrap recovery, reprocessing plants, and the manufacture of plutonium sources. The collective dose for plants engaged in uranium fuel fabrication in 1977 and 1978 were 10 and 9 man Gy, respectively, which in each case is about 60% of the total. Even this value will overestimate the dose from fuel fabrication because other activities are also carried out at some of these plants. The energy generated in the United States during the four-year period 1975–1978 was 100 GW(e) a [B22, H4]. Assuming that about 60% of the dose received in fuel processing and fabrication results from the fabrication of fuel for power reactors, the collective dose per unit energy generated from fuel manufacture was 0.5 man Gy [GW(e) a]$^{-1}$. This estimate is considerably below that given in Annex E of the 1977 report [U3] because of the decreased doses and increased energy generated; this may reflect an approach to equilibrium since in the early 1970s fuel was being fabricated for the large number of reactors which were shortly to become operational.

44. The doses to fuel fabrication and fuel enrichment workers in the United Kingdom from 1976 to 1978 [U5,

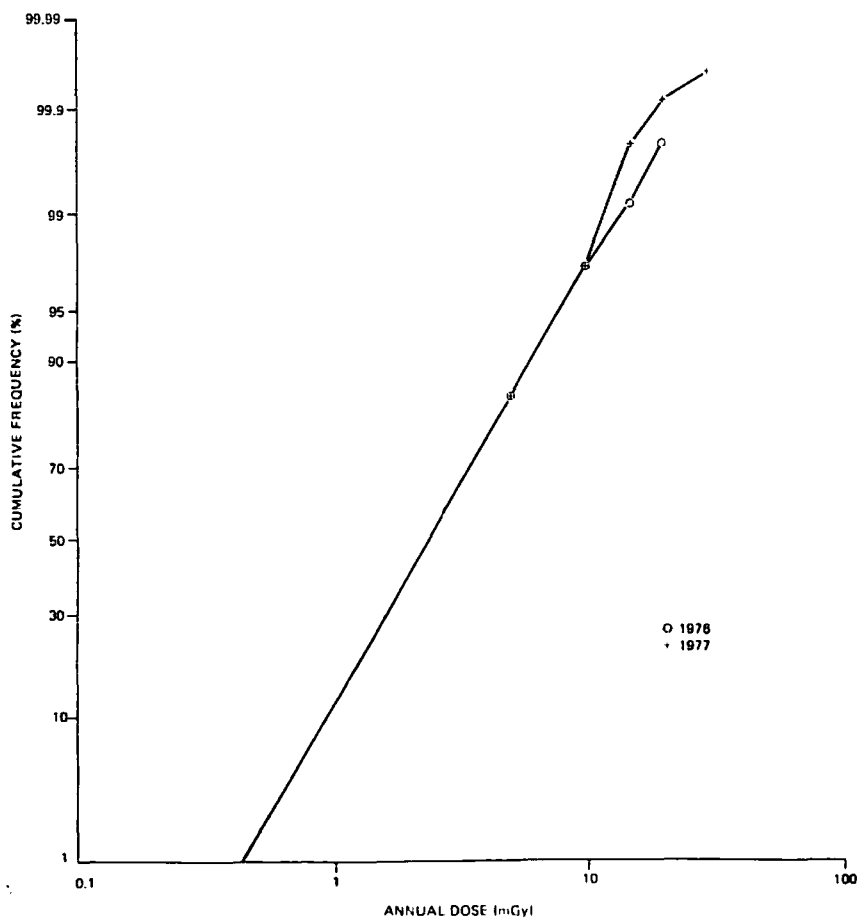

Figure III. Log-probability plots of annual doses to fuel fabrication workers in the United Kingdom in 1976 and 1977 [U5, R2]

R2, U16] are summarized in Table 4. Log-probability plots for fuel fabrication workers are shown in Figure III. The electrical energy generated in the United Kingdom during each of these years was about 3.3 GW(e) a [G2, N1] so the collective dose per unit energy generated has dropped from about 2.0 to 1.5 man Gy [GW(e) a]$^{-1}$. This may still be an overestimate since some fuel would have been manufactured over this period for the new advanced gas-cooled reactors (AGRs).

45. Data have been published on the doses received by workers at the six fuel manufacturing plants in Canada [A1]. The annual collective dose and annual average doses from 1970–1978 are shown in Table 5. One company refines uranium and produces UO_2 and UF_6 while the other five fabricate fuel. The doses have decreased since 1974 although production has increased. The collective dose per unit energy generated has dropped from about 1 man Gy [GW(e) a]$^{-1}$ in the mid-1970s to about 0.25 man Gy [GW(e) a]$^{-1}$ in 1978 since several large stations started to produce power in 1977 and 1978.

46. The doses received by workers in fuel fabrication facilities in India from 1966 to 1978 have been published [I4]. Of about 800 workers at the factory, 300 to 400 received measurable doses in recent years, with an annual average dose in 1978 of 1 mGy and a collective dose of 0.4 man Gy. The electrical energy generated in India up to the year 1978 was 2.4 GW(e) a which, combined with the total collective dose over the period of 6.6 man Gy, leads to a collective dose per unit energy generated of about 3 man Gy [GW(e) a]$^{-1}$.

47. Annual average doses from fuel fabrication are generally low, being about 0.3 mGy in Argentina [P20], 1 mGy in Canada and 2–3 mGy in the United Kingdom and the United States from 1977–1978. The fraction of the collective dose delivered above 15 mGy is in general small, often approaching zero.

48. The more recent estimates of dose per unit energy generated from fuel manufacture are considerably reduced from the previous estimates, possibly because the fuel manufacturing industry is reaching equilibrium with the number of reactors in use. There is some difficulty in estimating the collective dose per unit energy generated since fuel manufacture may take place some time before the fuel is used to generate energy. Results from the United Kingdom show that the collective dose equivalent per unit energy generated has remained fairly constant from 1972 to 1977 at 1.5 man Sv [GW(e) a]$^{-1}$, whereas in the United States the figure has dropped from 2.5 in 1973–1974 to 0.5 in 1975–1978. The best estimate at present for Canada is 0.25 man Sv [GW(e) a]$^{-1}$; an estimate over many years for India yields 3 and for Argentina 0.2 man Sv [GW(e) a]$^{-1}$ [P20]. Overall probably the best estimate of the collective dose equivalent per unit energy generated from fuel manufacture is 1 man Sv [GW(e) a]$^{-1}$.

C. REACTORS

49. More data on occupational exposure to radiation are reported for reactor operation than for any other area. The major focus in this Annex is to assess trends in the collective dose, individual average doses, the number of workers per unit energy generated for different reactor types, and to see whether these correlate with the age of the plant, experience in operation, reactor type, etc. Another objective is to revise the overall estimate of collective dose equivalent per unit energy generated. The difficulties, referred to earlier, of normalizing to the energy generated are clearest in this section. Especially for water reactors, most doses result from routine or special maintenance, so in the year during which such maintenance occurs, when there is less energy generated because of shut down, collective doses are high. Thus the only figures of use are those derived over several years for many reactors. Normalized results are not useful indicators for a particular plant in any one year. It is assumed throughout that all the dose accumulated by workers on reactors is related to the energy produced so that doses due to training or other jobs are included. In many countries, transient workers are brought in for short periods during the year to carry out special maintenance; it is not always clear whether these have been included but where possible this is specified.

1. Light water reactors

50. Most light water reactors are installed in the United States, where considerable operating experience has now been accumulated. Summaries of occupational radiation exposure at light water reactors in the United States up to 1979 have been published by the United States Nuclear Regulatory Commission [J1, P1, B18, B22]. Some of the data presented in Annex E of the 1977 report [U3] have been revised to make them consistent with those which are now required to be reported to the United States Nuclear Regulatory Commission.

51. The data reported on boiling water reactors (BWRs) and pressurized water reactors (PWRs) for the years 1973–1979 are summarized in Tables 6 and 7. Over this period the number of reactors included increased from 12 to 25 BWRs and from 12 to 42 PWRs. The most striking trend is the increase in the number of workers per reactor with measurable doses, especially over recent years, and the corresponding decrease in the average individual dose; by contrast, the annual average collective dose has remained reasonably steady. Figure IV shows the trend in the annual average values of the number of workers and collective dose per reactor, together with the average dose per worker for all LWRs in the United States from 1971 to 1979 [B22]. The average value for the collective dose per unit energy generated over the 5 years 1975–1979 is 12 man Gy [GW(e) a]$^{-1}$. The figures for individual reactors in any one year are very much more variable, ranging from less than 1 to over 100 man Gy [GW(e) a]$^{-1}$ for PWRs in 1979; this shows again that only broad average values of this parameter are useful. A detailed analysis was carried out [B22] of the data from each reactor over the 5-year period 1975–1979. This showed that in general the newer plants had lower collective doses per reactor, annual average doses to workers and collective doses per unit energy generated than older plants. It was noted that some of the increases in collective doses in 1979 resulted directly from safety-related actions required by the United States Nuclear Regulatory Commission following the Three Mile Island accident.

52. Figure V is a log-probability plot of the annual doses to workers at all LWRs in the United States in 1978 [B18]. This distribution, which is typical of recent years, shows clearly the effect of efforts to reduce the number of individuals exposed to high annual doses.

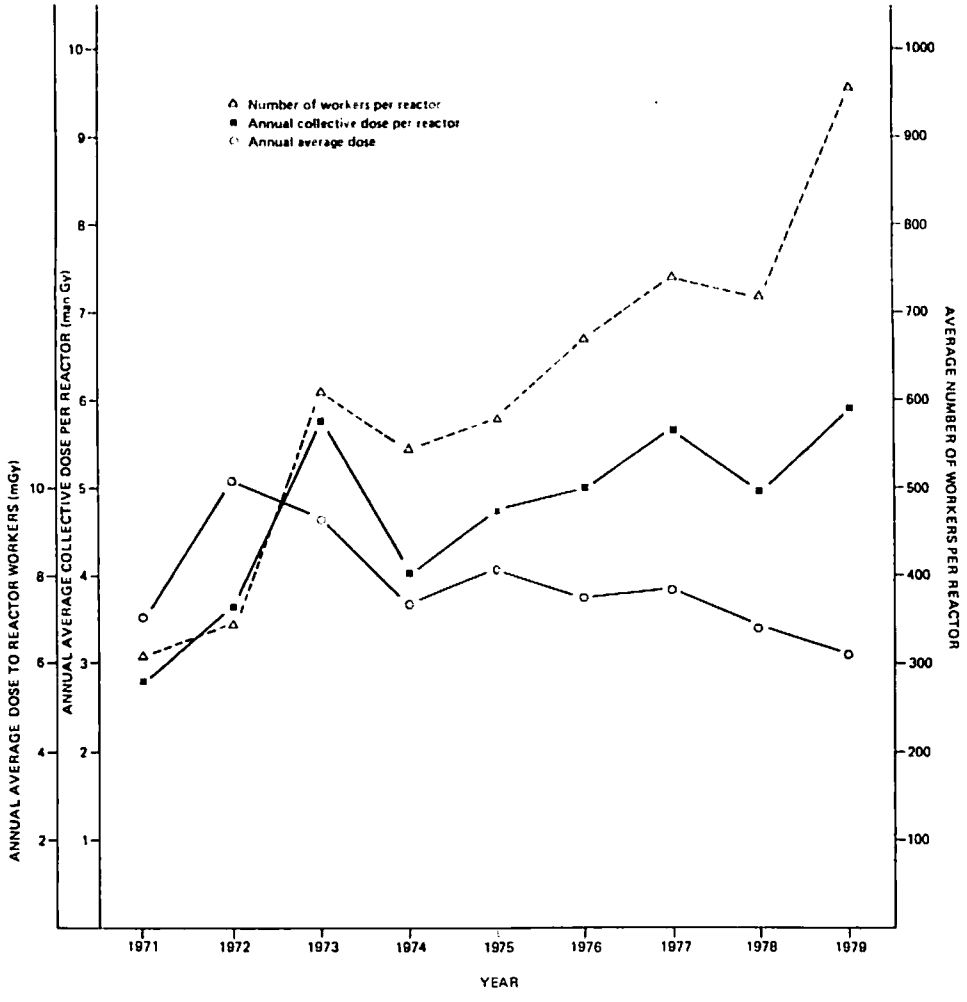

Figure IV. The number of workers and annual collective dose per reactor, and the annual average dose for all LWRs in the United States 1971–1979 [B22]

The value of MR for the distribution is 0.55, representing a steady decrease from a figure of 0.73 in 1973 [B22].

53. There are also a considerable number of light water reactors in Europe, (excluding the United Kingdom), in Japan and in some other countries. Data from these are not in all cases reported systematically but some collated information is published by the IAEA [I5, I6, I7] and a survey has been carried out by the Nuclear Energy Agency of OECD [I8]. Additional and more detailed reports have been published for the Federal Republic of Germany [M3, P4] the German Democratic Republic [S1], Japan [M15], Spain [F1, G4], Sweden [P2] and Switzerland [K2, G3, P3]. Table 8 gives details for some of the BWR reactors by country and installed capacity; it also gives, for some recent years, the average value of the collective dose per unit energy generated. Table 9 gives the same data for PWRs. It is noticeable that the values of average collective doses per unit energy generated are quite variable, due to the relatively small numbers of reactors in some cases. In most cases high values occur when reactors were shut down for a significant part of the year. For some countries only the collective dose from all LWRs is available; in the Federal Republic of Germany in 1978 this was 41 man Gy giving a collective dose per unit energy generated in that year of 4 man Gy [GW(e) a]$^{-1}$ and a cumulative average up to 1978 of 17 man Gy [GW(e) a]$^{-1}$ [M3]. The trend in collective dose per unit energy generated has been examined by the Nuclear Energy Agency [I8] as a function of the age and type of reactor. There is some evidence for an increase with time in service for BWRs commissioned prior to 1973 but this is less marked for those commissioned later; there is a slight but similar trend for PWRs. This increase is attributed to build-up in the reactor circuits of gamma-emitting activation products such as ^{60}Co, leading to increased doses during maintenance.

54. A clearer trend which emerges from the Nuclear Energy Agency survey [I8], and from special studies in the United States [B22] and the Federal Republic of Germany [M3], is towards lower collective doses per unit energy generated. In general, taking into account all those countries reporting data but giving due weight to the United States experience, the best estimate of the average collective dose equivalent per unit energy generated from LWRs is 10 man Sv [GW(e) a]$^{-1}$. This is the same as the estimate in Annex E of the 1977 report [U3].

55. The average dose to reactor workers is reported in the references cited for many of the countries referred to earlier and does not appear to have changed very greatly from the estimate made in Annex E of the 1977 report. In general, annual average doses to reactor workers range from 3 to 8 mGy. However, there has been a significant increase in the number of workers per reactor, particularly in the United States, for which data are available, in the period from 1970 to 1980. In the United States the number of workers per reactor has

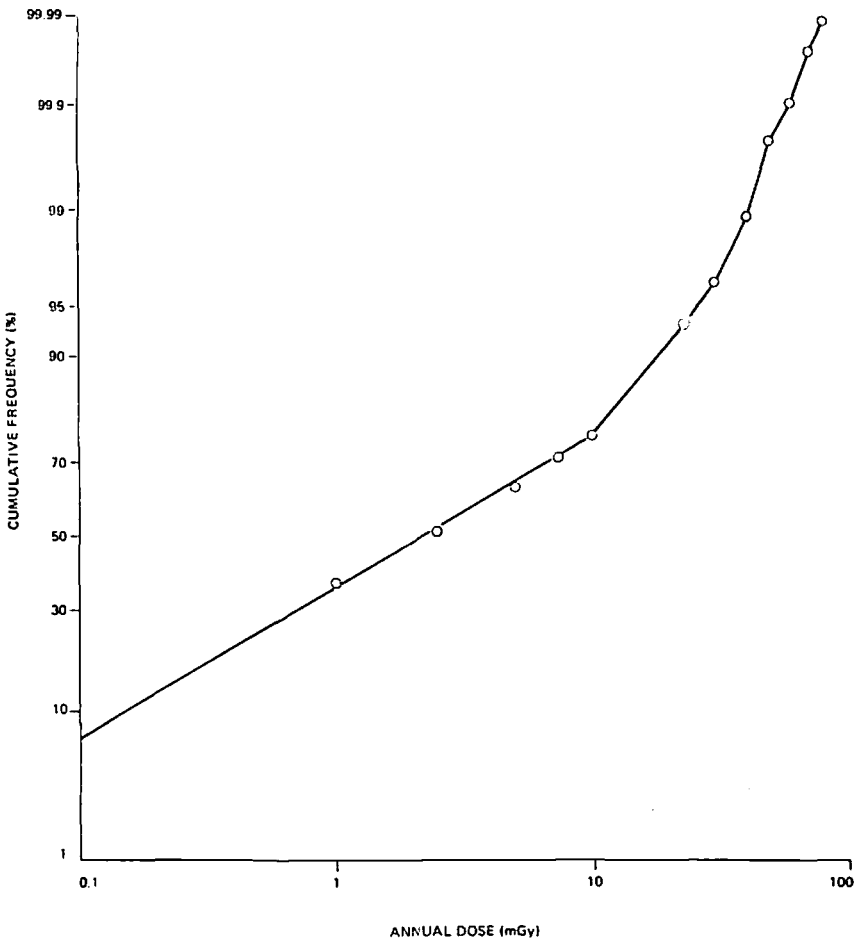

Figure V. Log-probability plot of annual doses to workers receiving measurable doses at LWRs in the United States, 1978 [B18]

increased by a factor of between 3 and 4 over this period.

56. Only in a few of the special studies are sufficient data available on the dose distribution to enable the value of the collective dose distribution ratio MR to be assessed. The values for both direct employees and contractors at Swedish LWRs are all less than 0.3 over the years 1976–1978 [P2]; that for Swiss LWRs fell from 0.6 in 1976 [P3] and 1977 [K2, G3] to 0.4 in 1978 [G3] and was accompanied by a drop in the annual average dose; for the small and rather old BWR at Gundremmingen in the Federal Republic of Germany the collective dose distribution ratio has remained close to 0.7 from 1970 to 1977 [P4]. As already mentioned, the collective dose distribution ratio for United States LWRs has fallen from about 0.7 to a value approaching 0.5 [B18].

2. Heavy water reactors

57. New information has been published concerning the Canadian CANDU reactors [A1]. The stations were not named in the paper but they can be identified from the information given by using reference [N1]. The average doses for the stations operating in 1977 were given and these are shown with the characteristic of the stations in Table 10. The collective dose equivalent per unit energy generated by all stations between 1972 and 1978 is given in Table 11. In 1975 and 1976 the collective doses at Pickering were higher than in other years because the pressure tubes in two of the four units were changed [L1]. In most years about 30% of the dose at Pickering results from the intake of tritium [E3]. The collective dose per unit energy generated from 1972 to 1978 inclusive is 7 man Gy [GW(e) a]$^{-1}$, slightly lower than the value in Annex E of the 1977 report [U3].

58. The annual average doses shown in Table 10 vary considerably between the five stations. Until 1977 the situation was characterized by the practice at Pickering, then the largest station, and an annual average dose approaching 10 mGy was reasonably representative [A1]. The dose distribution at this station in 1976 is shown in Figure VI. In 1977 Bruce A became operational and initial experience is that both external and internal annual average doses are very much lower, being less than 1 mGy combined. It is not yet clear if this early experience has been maintained. As can be seen from Figure VI, the value of the collective dose distribution ratio MR for Pickering in 1976 was difficult to estimate due to the extreme deviation at higher doses; it is probably about 0.3. No value has yet been established for Bruce but it will clearly be very low for 1977.

59. Some information has been published for the 335 MW(e) net installed capacity pressurized heavy water reactor at Atucha, Argentina [P20]. The annual collective and average doses are summarized for the period 1977–1979 in Table 12. The values of collective dose and average dose include a contribution of about 20% from internal exposure due to tritium. The collective dose per unit energy generated is also shown in Table 12: as is to be expected for a single reactor, it is quite variable.

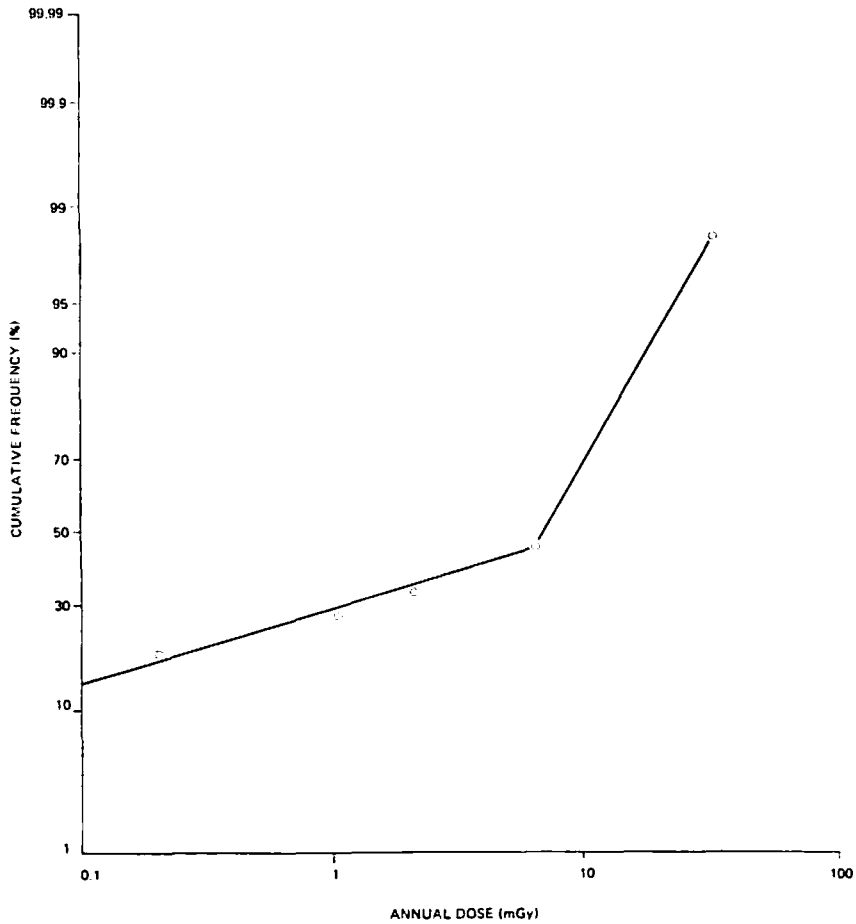

Figure VI. Log-probability plot of annual doses to workers at Pickering heavy water power station in Canada, 1976 [A1, N1]

60. Giving due weight to the Canadian experience with CANDU, for which the collective dose per unit energy generated is about 7 man Gy [GW(e) a]$^{-1}$, and taking note of Atucha in Argentina which is also a heavy water reactor, the collective dose equivalent per unit energy generated from heavy water reactors does not seem very different from that at light water reactors at about 10 man Sv [GW(e) a]$^{-1}$.

3. Gas cooled reactors

61. Most experience with gas cooled reactors is in the United Kingdom where they have been installed and operating for many years. There have been no significant changes in the pattern of dose distribution, the number of workers or the average dose since the 1977 report [U3]. The doses received by workers at all the United Kingdom GCRs in 1975, 1976 and 1977, and the Central Electricity Generating Board stations only in 1978 and 1979, are summarized in Table 13 [G5, H18, G7, G6, U5, P5]. The value of MR is less than 0.15 for all the years reported. In 1977 the South of Scotland Electricity Board station at Hunterston employed over 1000 more contractor employees than usual; many of these may only have been employed for short periods. Most of the reactors are of the Magnox type; two advanced GCRs started operation in 1976. The collective dose per unit energy generated is also given in Table 13 [U3, G2, H2, H4]; this has decreased slightly during the 1970s; the figure for the years 1972–1979 inclusive is 6 man Gy [GW(e) a]$^{-1}$. Those data which are available on GCRs installed in France, Italy, Japan and Spain [I5, I6, I7] are in broad agreement with the United Kingdom experience.

4. Fast reactors

62. There are no commercial fast reactors yet operating but some indications of doses can be obtained from data on the prototype fast breeder reactors (FBRs) in the United Kingdom and France. At the French LMFBR, Phenix, in 1975–1976 a total of nearly 300 workers were exposed with a mean dose of about 0.1 mGy [M4]. Since the maximum individual dose was 2.7 mGy, the collective dose distribution ratio MR was zero. The energy generated was only 0.1 GW(e) a [I6] but this gave a value of 0.3 man Gy [GW(e) a]$^{-1}$ for the collective dose per unit energy generated. Further data on the collective doses over recent years is given in Table 14 [P9]. Data for the prototype FBR at Dounreay, United Kingdom, are given in Table 15 [A2]. The maximum individual dose received in 1977 was below 4 mGy and therefore in that year the collective dose distribution ratio MR was zero; data on dose distributions for the previous years were not given.

63. It appears from these preliminary data that prototype FBRs, at least, can be operated with low annual average doses and give low values for the collective dose per unit energy generated. Very few workers are exposed to annual doses above 15 mGy, but it is not clear whether these dose distributions include routine or special maintenance.

5. Nuclear powered ships

64. The radiation exposure of personnel on the Nuclear Ship "Otto Hahn" over the period 1969 to 1977

has been reported [R4]. The annual average dose rose after the first two years but then remained fairly constant between 3 and 6 mGy. The distribution of doses to the 50 crew members in 1974, which was a year of normal operation, was given in detail; the collective dose distribution ratio was zero and the collective dose was 0.2 man Gy. Higher doses are received by some individuals during maintenance periods; the collective dose to personnel during a maintenance period of unspecified duration was calculated as 0.2 man Gy with a collective dose distribution ratio of 0.2. The doses received by the crew of the Nuclear Ship "Mutsu" are also very low; no crew member exceeded a dose of 0.1 mGy during the test cruise in 1974 [I10].

65. In addition to these demonstration nuclear powered merchant ships, several navies operate nuclear powered ships of various types. Information on doses to workers at United States naval nuclear propulsion plants and their support facilities [M10] over the years 1970 to 1978 is summarized in Tables 16 and 17. As would be expected, the doses, collective doses and MR values are very much higher at the shipyards where maintenance is carried out than on ships, tenders or at submarine bases.

6. Doses to particular occupational subgroups

66. There is a general problem in comparing doses received by different occupational subgroups in that breakdowns of workers into occupational categories or job descriptions in different countries do not exactly match; however, workers can be divided into a few broad groups. Workers have been assigned to one of four broad areas: operations, maintenance, health physics and supervision/ administration. Where the job description did not match exactly the most appropriate category was selected. Sometimes workers are brought in for specific maintenance jobs; it is not always clear whether their doses are included in the reported data, but where possible this is indicated.

67. The collective doses received at BWRs and PWRs in the United States from 1977 to 1979 are shown in Table 18 for the four broad areas given above [P1, B18, B22]. The category given in the references as "engineering" was assumed to be principally a supervisory function. Just over half of the total collective dose in each year is received by contract workers. Special and routine maintenance account for about 70% of the collective dose received at United States LWRs.

68. Similar information for LWRs in a number of other countries, generally for 1978, is shown in Table 19. The distribution is expressed as the percentage of the total collective dose quoted in each category. Where the average annual doses were given or could be calculated, the highest values were about 10 mGy. Average doses of this general level were received by some health physics workers [P2] and by particular groups of maintenance workers such as insulation installers or mechanics [P2, S2]. Another category of work giving rise to a high proportion of the collective dose is inspection. This has been recently identified at United States reactors [B22] and has been cited as important at reactors in the Federal Republic of Germany [U6]. Inspection requirements can be part of routine operating procedures or quality assurance programmes, or they can be specially devised by regulatory bodies in response to fault analysis; the situation will differ from country to country.

69. With regard to LWRs, data from the United States and other areas summarized above clearly show that the majority of the collective dose is received during maintenance operations. These are separated in water reactors from the normal operation of the reactor since they are generally performed during identified shutdown periods. However, it must be recognized that planned maintenance is essential to the operation of a reactor, and therefore both categories of work should really be considered part of normal operations. A more difficult category is "special maintenance" which is not very clearly defined but presumably means maintenance jobs either not foreseen, though proving to be routine, or jobs of an infrequent nature. In recent years about half the collective dose received by workers in the United States reactors was due to special maintenance.

70. The annual average dose to different groups of workers at Canadian nuclear power stations in 1979 is given in Table 20 [A10]. In general the most exposed groups, as they have been for some years [A1, J2], are mechanical maintenance workers, control technicians and operators. About 30% of the collective dose is received by operators and a similar proportion by mechanical maintenance workers. A similar study for workers on the Atucha reactor [P20] showed about 60% of the collective dose being received by maintenance workers, 25% by operators and 15% by health physics workers.

71. Information on the doses received by different occupational groups has been published for two United Kingdom Magnox reactors; a summary of this is given in Table 21 [K3, K4]. No one group stands out as receiving much higher annual average doses than others, although maintenance workers tend to be among the most highly exposed, as do health physicists at Dungeness. However, the highest annual average dose was 3.4 mGy to instrument maintenance workers [K3].

72. Many detailed studies have been carried out on particular operations at individual reactors. These studies can often reveal areas of work giving rise to high individual doses or high collective doses [G9, P4, S3, H4, V1, P2, U6, H4, R3, M5, M6, M7, A3, I8]. These are then clear areas for study to see whether doses can be further reduced to levels which are as low as reasonably achievable. This is however a matter for local study and is not appropriate for consideration in detail by the Committee.

73. The general conclusion is that there are two major sources of collective dose at all reactors. These are the routine operations and maintenance which are essential to the operation of the reactor, have presumably been planned for in the design, and which cannot be much affected in broad terms once the reactor has been designed and built. The other source is unforeseen, special maintenance, which has often to be carried out in areas without designed routine access, under high dose rates and in cramped or otherwise poor working conditions. It is a feature of concern that this source of exposure appears to be dominating the collective dose per unit energy generated from water reactors; however much of this work is unscheduled repairs to essential components, which clearly has to be carried out.

D. FUEL REPROCESSING

74. Although fuel reprocessing is not universally practised at present, some form of extraction of unburnt fissile material from the used fuel elements and some form of processing for eventual disposal of the elements is very likely to form part of the complete fuel cycle. It is accordingly useful to examine the experience in fuel reprocessing, while recognizing that this is limited to a small number of countries and that the plant design and historical operating conditions may well not represent the best current potential for new plants. Reprocessing, incorporating waste treatment, is identified in Annex E of the 1977 report as one of the largest contributors to the collective dose per unit energy generated. That estimate was based only on the Windscale plant in the United Kingdom. Data are now also available on the plant at Cap de la Hague in France.

75. The distribution of doses in 1977 at the Magnox fuel reprocessing plant, the plutonium fuel fabrication plant and other plants operated by British Nuclear Fuels Ltd. (BNFL) at Windscale, United Kingdom, is plotted in Figure VII. This clearly shows the effect of efforts to restrain annual doses within a limit of 50 mGy.

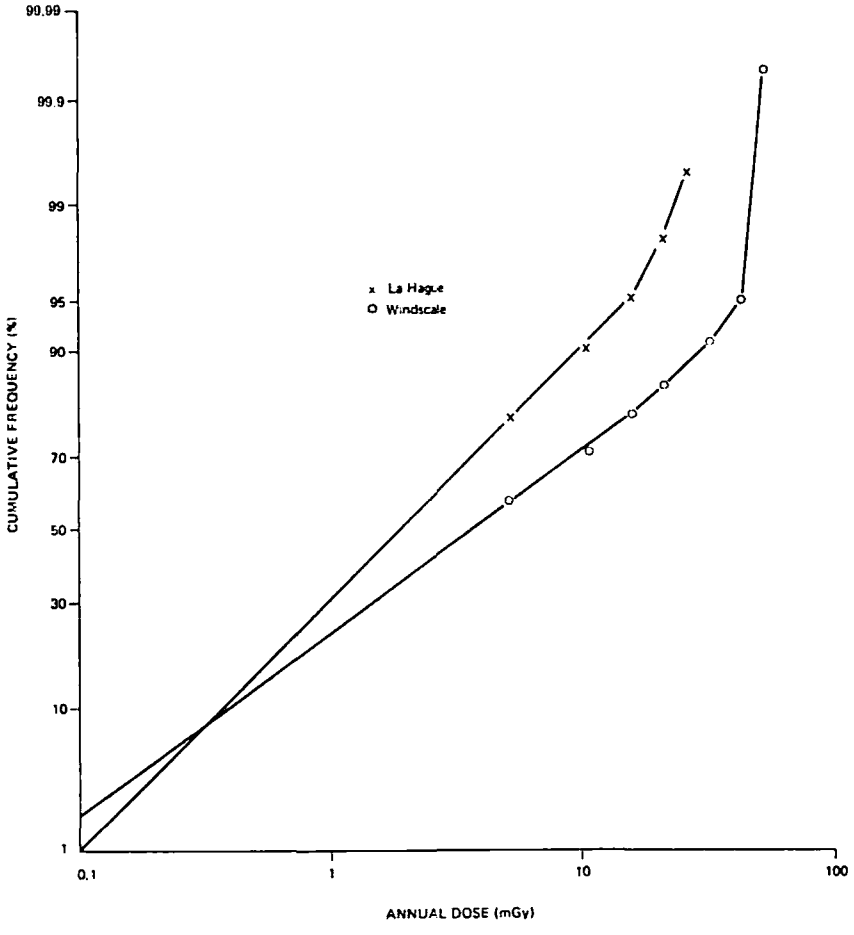

Figure VII. Log-probability plot of annual doses to fuel reprocessing workers at Windscale, United Kingdom, in 1977 and at Cap de La Hague, France, in 1978 [J3, U16]

The parameters for 1976 to 1978 are summarized in Table 22 [U5, U16, R2]. The throughput of the plant in terms of energy generated has been estimated from the ^{85}Kr discharges [C2, H5, H6, H7, A4] using the normalized value of 14 PBq [GW(e) a]$^{-1}$ from Annex F. The collective dose per unit energy generated is given in Table 23. The average value over the 8-year period is 18 man Gy [GW(e) a]$^{-1}$. These values are overestimates for reprocessing alone because of the other activities on the site. It is very likely that any new plant built to reprocess fuel will have a significantly lower collective dose per unit energy generated [P6].

76. Information on the doses received by workers at the COGEMA reprocessing plant at Cap de La Hague, France, for the period 1970–1979 has been made available [B4, J3]. Until 1976 only fuel from gas cooled reactors was reprocessed at La Hague; the first reprocessing of LWR fuel took place during 1976 [C2]. The occupational doses are summarized in Table 24 from 1970 to 1979 [J3, J9]. The log-probability plot of doses for 1978 is shown in Figure VII. The throughput of the plant in terms of energy generated has been estimated from the ^{85}Kr discharges between 1972 and 1976 [C2]. The collective dose per unit energy generated for this period is given in Table 25; the average value over the 5 years of 6 man Gy [GW(e) a]$^{-1}$ is less than half that estimated for Windscale.

77. The dose distribution at both plants indicates substantial work forces exposed to significant doses. The annual average dose at Windscale has been constant or has dropped slightly over recent years; however, this decrease in average dose has been accompanied by an increase in the number of workers and a roughly constant collective dose. This may be correlated with efforts to reduce all individual doses to less than 50 mGy per year. Data for Cap de la Hague over the 1970s show the annual average dose at about half that received by Windscale workers but decreasing

slightly in recent years, also accompanied by an increase in the number of workers and a relatively constant annual collective dose.

78. There are some data for different work groups at Cap de la Hague given in Table 26 [B4] and there are also data taken at the Karlsruhe plant [S5], but the differences in average dose are not great and it is hard to separate out different groups within the overall operation of what is essentially a chemical plant. A similar comment applies to the doses reported by the Idaho Chemical Processing Plant [C5] and the Savannah River Reprocessing Plant [H9].

79. Some information is available on the demonstration fuel reprocessing plant at Mol, Belgium, and is shown in Table 27 [O1]; the plant however stopped reprocessing in 1964. The average doses were comparable with those at Windscale in the United Kingdom, as was the MR value, both being higher during the years for which reprocessing took place. Some data, which are given in Table 28 [S5], are also available on the pilot fuel reprocessing plant at Karlsruhe; workers at this plant had average doses similar to those at Cap de la Hague.

80. Normalizing to the fuel throughput is difficult since other work takes place at Windscale and it is not at all clear that doses from the operation of the plant bear any close relationship to the throughput. Nonetheless, assuming that all the doses at Windscale are related to fuel reprocessing gives a collective dose per unit energy generated of about 18 man Gy [GW(e) a]$^{-1}$ and for Cap de La Hague a similar assumption gives about 6 man Gy [GW(e) a]$^{-1}$. It is worth noting that the projected collective dose per unit energy generated from new fuel reprocessing plant is much lower. It may well be that a realistic estimate of the likely global collective dose equivalent per unit energy generated from fuel reprocessing and waste processing for disposal is about 10 man Sv [GW(e) a]$^{-1}$. This would imply that the overall impact of this part of the fuel cycle will eventually be comparable with that from reactor operations.

E. RESEARCH AND DEVELOPMENT

81. In Annex E of the 1977 report the Committee estimated that the largest single contributor to the collective dose per unit energy generated was research and development. It was noted that this was reasonable in the early stages of a nuclear power programme but that the proportion should decrease as the number of operating power reactors increased. It is also relevant that countries such as the United States, on which the estimate was largely based, carry out major research backup both for domestic and overseas reactors. A further important factor is that many of the research organizations carry out research and development not connected with the nuclear fuel cycle but the doses are often reported in a collected fashion.

82. Research associated with the nuclear industry in the United States has been carried out mainly by the Energy Research and Development Administration (ERDA), which was taken over by the Department of Energy (DOE) in 1977. ERDA also covers accelerators, irradiation facilities and work for defence purposes, such as nuclear weapons manufacture and naval reactors. The information for 1975–1979 is taken from ERDA and DOE annual reports [U8, U9, U17, U18, U19]. The summary includes reactor work, fuel fabrication and processing, uranium enrichment, general and other research; a considerable proportion of work under these categories may include defence work. The doses to workers with measurable exposure are summarized in Table 29. The total collective doses at the ERDA and DOE sites allocated by the Committee to nuclear research and development is about 75%. The electrical energy generated during the period 1975–1979 was 128 GW(e) a [B22] which would lead to a collective dose per unit energy generated of about 3 man Gy [GW(e) a]$^{-1}$.

83. Information has been received on the doses to workers at the Atomic Energy of Canada Limited sites [M8] where nuclear research is carried out for the Canadian power programme and for production of isotopes for medical use. The average and collective doses from external exposure and tritium intake are given in Table 30 for 1970–1978. Over 4000 workers were monitored each year. The distribution of doses from external radiation and tritium combined for workers receiving measurable exposure in 1978 is plotted in Figure VIII; the MR value was estimated as about 0.4 in 1978. The electrical energy generated in Canada during the period 1972–1978 was 13.6 GW(e) a [A1]. The collective dose per unit energy generated for this period was about 6 man Gy [GW(e) a]$^{-1}$.

84. In the United Kingdom most nuclear research is undertaken by the United Kingdom Atomic Energy Authority (UKAEA). In addition the Central Electricity Generating Board (CEGB) runs a research laboratory at Berkeley. The doses for the period 1975–1979 are summarized in Table 31 [T1, G7, H18, G6]; the collective dose distribution ratio MR is in general less than 0.3. Figure VIII gives a log-probability plot of the doses at UKAEA establishments for 1977. The electricity supplied during the period 1975–1977 was 9.3 GW(e) a [G2] which leads to a value for the collective dose per unit energy generated of 13 man Gy [GW(e) a]$^{-1}$. The UKAEA also undertakes research work which is not associated with the nuclear power programme, so that this value is likely to be an overestimate.

85. One of the major nuclear research centres in the Federal Republic of Germany is at Karlsruhe. The annual collective and average doses to all workers and the average doses received by certain groups of workers are given in Tables 32 and 33 [K5]. Since there is in the Federal Republic of Germany another nuclear research centre at Jülich, for which no estimates of dose are available, a value for the normalized collective dose equivalent cannot be calculated.

86. Some information is shown in Table 34 on doses to nuclear research and development workers at the Institute for Reactor Research in Switzerland [K2, G3, P3], the Atomic Energy Industry, excluding nuclear power production, in Japan [M15], at Mol in Belgium [D1] and in Argentina [G8, P20]. Using the values for the energy generated in each country over the period shown [I6, I7, H2, S4], and assuming all the research was in support of the power programme (except where specified) the collective doses per unit energy generated were calculated and are shown in Table 34. These may be overestimates in some cases other than for Argentina where, for example, over half of the dose at the sites covered is received in connection with non-nuclear power research.

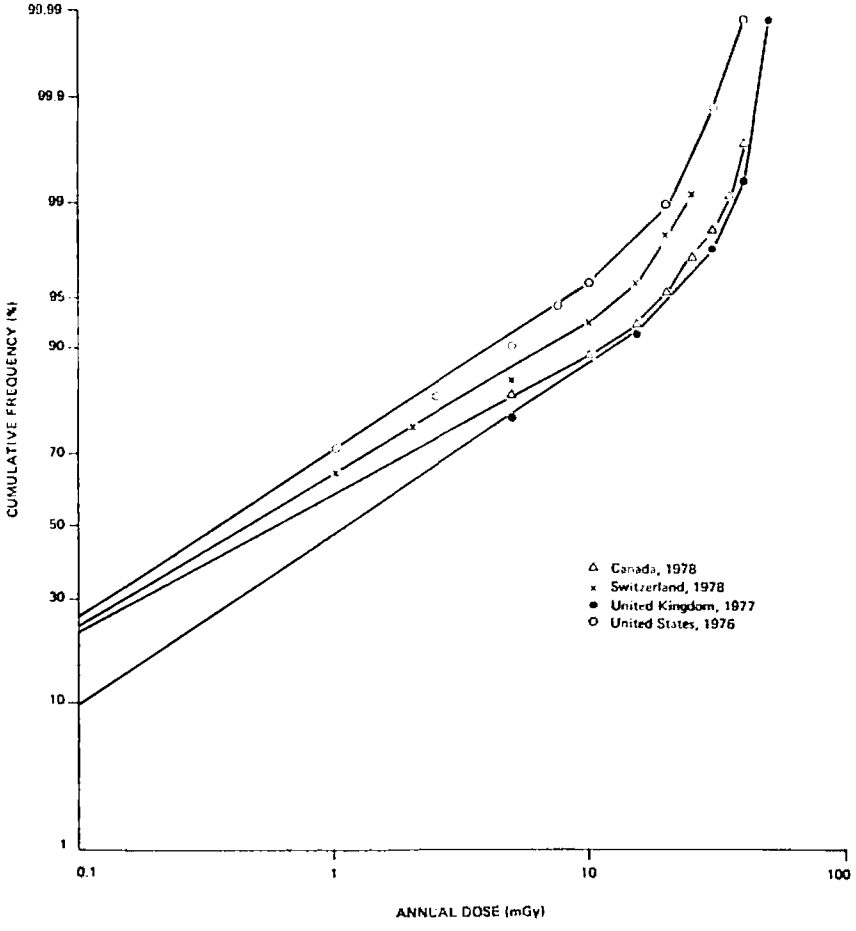

Figure VIII. Log-probability plot of annual doses to workers in nuclear power research and development in various countries [G3, M8, U9, U16]

87. In conclusion, data have been presented on doses and dose distributions in research and development for several countries; there are considerable differences if these are normalized to the energy produced by the country. A further complication is the existence of other non-nuclear power related research which may be carried out within establishments. For example, if this had been included in the data for the United States in Table 28, then the overall figure for the collective dose per unit energy generated would have been 4 man Gy [GW(e) a]$^{-1}$. Nonetheless, if the figures are taken at face value and the collective doses from the major nuclear oriented research establishments are related to the energy generated in each country, as has been done in this section, the values of collective dose per unit energy generated range from 1 man Gy [GW(e) a]$^{-1}$ in Japan and Switzerland to 13 man Gy [GW(e) a]$^{-1}$ in the United Kingdom. The high values obtained for the United Kingdom and some other countries should not be allowed to dominate this picture, since much of this research is thought to be related to development of future reactor types or to non-nuclear power research. Giving due weight to the value for the United States, which clearly also supports reactors in many other countries, a global estimate of about 5 man Sv [GW(e) a]$^{-1}$ seems more reasonable than the value of 14 man Gy [GW(e) a]$^{-1}$ given in Annex E of the 1977 report.

F. SUMMARY

88. The summary of the contributions to the collective dose equivalent per unit power generated is given in Table 35. The largest contributors are reactors and fuel reprocessing plants; the value for nuclear research is much lower than that estimated in Annex E of the 1977 report [U3]. The estimates in that report were based largely on experience in the United States and the United Kingdom, but data from a number of other countries are now available. It should be noted that this collective dose is received at essentially the same time as the energy is produced and may not be directly comparable with collective dose commitments calculated in other Annexes. There is reasonable consistency, between values from various countries, of the collective dose per unit energy generated for reactors, but there is wider variation in other parts of the fuel cycle. The values given above are regarded as representative of world experience, although they are biased towards the United States because of its comparatively large nuclear power programme. Based on an estimate of 70 GW(e) a as the total energy generated in the world in 1979 [112], the annual occupational collective dose equivalent due to the nuclear generation of electric energy in that year can be assessed as about 2000 man Sv. This may also be expressed for comparison purposes as about 0.5 man Sv per 10^6 population.

IV. MEDICAL USES OF RADIATION

89. Medical uses of radiation may be separated into two broad categories, diagnostic and therapeutic. These differ in that for diagnostic radiology or nuclear medicine the objective is to use the minimum exposure to radiation of both subject and medical workers to obtain the desired information; for therapy, however,

the intent is to deliver a well defined but generally very high dose to the appropriate tissues of the patient and at the same time the minimum dose to the medical workers. It is not always easy or even possible to separate these categories in the reported data. The Committee wishes to encourage the identification and reporting of the type of work leading to doses to medical workers. By the nature of medical work, exposures are frequently non-uniform over the body so the effective dose equivalent may not be easily obtainable from the dose indicated by a dosimeter, due to the energy or spatial inhomogeneity of the radiation field [M14]. More data on these aspects would be of use.

A. DIAGNOSIS

1. Diagnostic radiology using external beams of radiation

90. This is the most widespread and common use of radiation in medicine. It has been surveyed in many countries from the point of view of doses to patients but there are not such well identified data on occupational doses. The situation is further complicated because workers within this general field may have different jobs; doses are often reported separated between medically qualified or other professional workers and technicians [M9] or between all workers in general practice and in hospitals [C1, P9]. However, by appropriate grouping it is possible to obtain an indication of the annual average doses to all workers in this area, which range from fractions of a mGy to a few mGy. Collective doses are also obtainable, as are estimates of the numbers of workers. For certain procedures the doses to radiologists may be highly non-uniform. Under these circumstances information on doses to particular body organs or tissues will be of use. The data available have not been reviewed but, for example, information on the doses to hands, chest and head of surgeons carrying out angiography has been reported by several authors [B23, K13, L12].

91. Doses to medical workers under license from the United States Nuclear Regulatory Commission have been reported in 1975 in a special survey [C1]. The distributions of doses for different categories are plotted in Figure IX. Only a small proportion of the

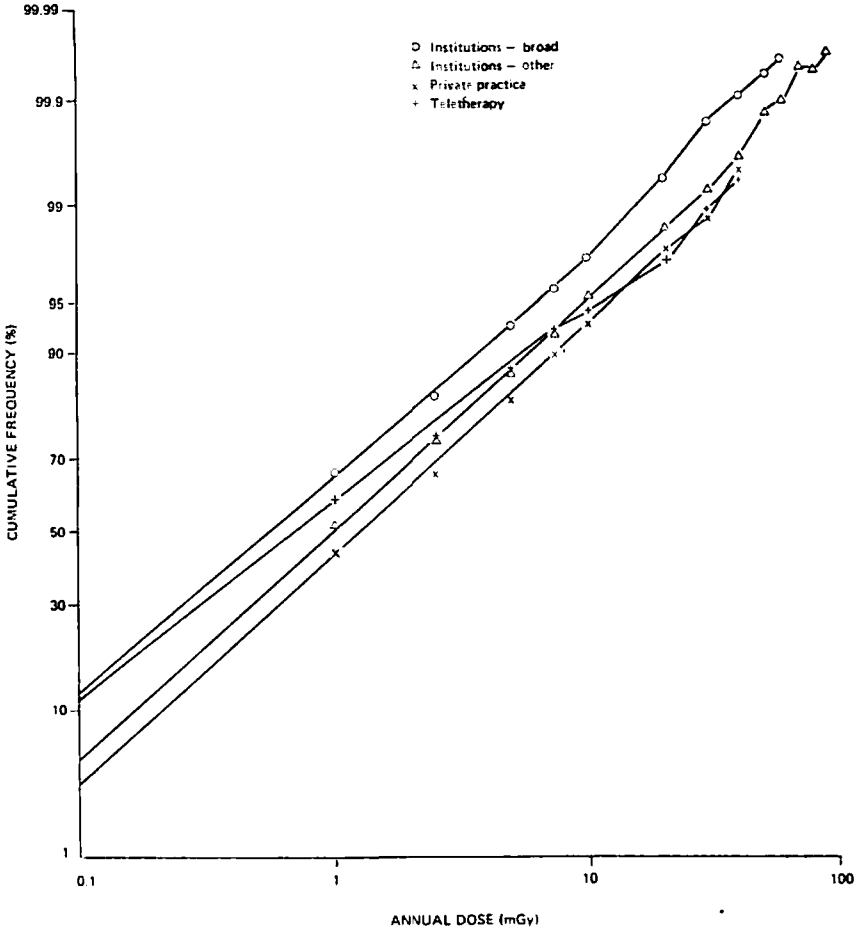

Figure IX. Log-probability plot of doses to medical workers with measurable exposure in the United States in 1975 [C1]

licensees took part in the survey. A more comprehensive review is available for 1978 [B17] and a summary of the data from this is given in Table 36. Data are also available for the workers who are monitored by the Bureau of Radiological Health [M9] and are summarized in Table 37 for 1972–1978. The values of MR are all less than 0.1. The average doses to different groups connected with radiology are given in Table 38; they are generally low but radiologists are consistently the most highly exposed group.

92. The doses received by Swiss medical workers for 1976–1978 are summarized in Table 39 [P3,' P7, P8]. Information on the doses received by medical workers

using diagnostic x rays in France, monitored by the Service Central de Protection Contre les Rayonnements Ionisants, is given in Table 40 [P9, S17].

93. For many countries it is not possible to tell from the reported results which medical workers are connected with diagnostic radiology, other forms of diagnosis or with therapy; frequently all medical workers are considered as a single category. On the basis that for any given country most medical workers will be connected with diagnostic radiology rather than any other specialty, these results are reported in this section and may be found in Table 41 together with more detailed results from some other countries. The results for Australia [S19] and Canada [A10] are based on recent detailed surveys; the results for Australia have been extrapolated from a survey estimated to cover 50% of workers, as have those for Japan [M15]. The Japanese data are for all workers with x rays and will therefore include dental workers. The figures given for the Federal Republic of Germany are extrapolated from those reported by eight states [F2]; they are expected to be supplemented in due course through an extensive statistical exercise being carried out by Färber et al. [F6, F7]. No further data are available from the United Kingdom on the doses received by medical workers; however, the number of medical workers has been re-estimated as 33 000 [T1]. On this basis the collective dose to medical workers, most of whom are connected with diagnostic radiology, would be 70 man Gy, assuming the same annual average dose equivalent of 2.1 mGy as in Annex E of the 1977 report.

94. Estimates of throughput in terms of numbers of films used for x-ray examinations are available and therefore some comparison of the collective dose per unit throughput can be made and are given in Table 42. Data given in Annex E of the 1977 report [U3], those given earlier in this section and some other sources [T1, E1] have been used to compile Table 42. The data do not necessarily correspond to the same year but only data relating to years after 1970 have been used. Information on the number of x-ray diagnostic examinations alone are used, since most examinations are of this type and they are probably adequate as an indicator of total practice. It is not clear how useful such comparisons are in this field, since the number of films used may not directly relate to benefit to patients if there are other reasons for taking x rays. However, the average values are fairly constant at about 1–2 man Sv per 10^6 films. This figure varies from about 0.5 to 4 man Sv per 10^6 films.

95. Dentists form a large sub-category of practitioners who use x rays for diagnosis. Exposures of this group are characterized by large numbers of workers being exposed to low individual doses, as shown in Table 43 for several countries. The annual average doses range from almost zero to 0.5 mGy.

96. A smaller group also using x rays for particular purposes are chiropractors and osteopaths. These groups use x rays to aid in subsequent non-radiation treatments and the use is closer to diagnosis than therapy. Doses to this group are not in general separately identified, although information from Australia indicates about 100 workers exposed to annual average doses of 0.2–0.3 mGy [S19] and from Canada several hundred workers at annual average doses less than 0.1 mGy [A10]; more data would be of interest.

2. Diagnosis with incorporated radionuclides

97. Diagnosis with incorporated radionuclides, normally referred to as nuclear medicine, is characterized by the use of particular radionuclides which may be chosen because they concentrate in specific organs. The problems of dose control are in most cases more related to protection against ingestion or inhalation, especially during preparation, analysis and administration of radiopharmaceuticals. However, there is also an external radiation field from some nuclides such as ^{99m}Tc, which can give very high dose equivalent rates to the hands, approaching some hundreds of mSv without syringe protection [G12]. The use of nuclear medicine has increased rapidly in many countries over the last decade, and it would be helpful to have more detailed data on exposures of organs or tissues from particular radionuclides, together with estimates of quantities used, numbers of workers exposed, etc. Data are given in Table 44, showing annual average whole-body doses which are fairly low, of the order of 1–2 mGy, although extremity doses could be much greater. The collective dose distribution ratio is close to zero in all cases. Data on doses to nursing staff from the residual activity in patients on return to wards would also be useful in assessing the overall impact of nuclear medicine on occupational exposure.

B. RADIOTHERAPY

1. Radiotherapy with external beams

98. Radiotherapy with external beams is carried out inside well shielded rooms and, since there is no residual radioactivity in the patient, there is no resulting dose to nursing staff when the patient is returned to the ward. Doses to medically qualified staff are therefore very low, as the operation of these facilities is generally the responsibility of other technically or professionally qualified staff. These staff are not always easily identifiable in dose records but assuming that they are within the category reported in the United States as working with teletherapy, or in France as workers with cobalt or conventional radiotherapy as given in Table 45, then annual average doses would appear to be about 2–3 mGy. The collective dose distribution ratio MR, where this can be obtained from the data given, is in the range 0.2 to 0.4.

99. There are some special categories of treatment under this general heading of radiotherapy. One such is identified in data from France as high energy treatment, with other than conventional x-ray or cobalt-60 therapy machines. There is no reason why such treatment should give rise to higher doses to the operators than conventional machines and indeed the data for France shown in Table 45 confirm this. Another special category is the use of neutron beams, for which some data have been reported [S6]. As would be expected from a correctly designed and shielded facility, no staff exposures to neutrons were recorded. However, activation of the target led to annual average doses from external radiation of the order of a few mGy to medical, nursing and other professional staff.

2. Radiotherapy using interstitial and intracavitary sources

100. To obtain highly localized doses to malignant tissues in certain positions in the body it is necessary to

apply or implant sealed sources of various types. This has traditionally been carried out manually by skilled medical workers, including surgeons and gynaecologists, who could receive substantial doses especially to their hands and faces, which could not be effectively shielded. Subsequent to implant, the nursing staff could also receive substantial doses while ministering to the patients on the wards.

101. The trend in these treatments has been towards finding ways to reduce both sources of occupational exposure. This has been carried out primarily by trying to develop techniques such as afterloading, which enables the surgical or other preparatory procedures to be carried out without the source, which is introduced mechanically afterwards. This also makes possible the use of more active sources than could be directly handled, reducing irradiation time, and usually enables the source to be removed before the patient is returned to the ward. More information on these procedures, and the changes in occupational doses resulting from their introduction, would be useful. For example, a survey of four hospitals in Boston, United States [C3] over the period 1973–1976 showed annual average doses to nursing staff between 0.2 to 1.5 mGy; afterloading procedures were used in most cases. In Australia annual average doses to nurses of patients with sealed sources were 4.4 mGy to over 200 nurses in 1974 and 1978 [S19].

102. Because of the highly non-uniform irradiation possible, it is difficult to be clear about the relevance of reported annual average whole-body doses such as the few mGy reported for French workers in interstitial and intracavitary therapy [P9].

3. Radiotherapy with unsealed sources

103. Treatment of malignancies in some organs can be carried out using radiopharmaceuticals which preferentially seek the organ in question. The most common examples are treatment of hypothyroidism and cancer of the thyroid with radioiodine. This form of treatment raises special problems of nursing and aftercare, as the activity is gradually lost from the patient by the normal bodily elimination processes, including exhalation and perspiration as well as excretion in urine and faeces. There may also be a substantial external dose rate, depending on the radionuclide used.

C. SUMMARY

104. A number of recommendations have been made of areas where more data could be gathered and reported to clarify the situation regarding occupational doses in medical practice. One general recommendation is that there should be a clearer indication of the type of work leading to the dose and of the uniformity or otherwise of the exposure of body organs or tissues. More information on the exposure of certain groups of workers is required; these are nuclear medicine workers including nurses, radiotherapy workers especially those changing to afterloading techniques, chiropractors and osteopaths.

105. Doses to workers involved in the use of radiation for medical purposes are highly variable, and in some instances are characterized by an extremely non-uniform distribution over the body. It is also not possible to identify and quantify the beneficial output of all medical work, although an attempt has been made in paragraph 94 to relate the doses from diagnostic radiology to the number of films processed. To obtain an indication of the total occupational exposure it is probably best to express this as the annual collective dose equivalent per million population of the country, on the grounds that total medical care should be roughly proportional to population. Even from the few available data, however, it is clear that this measure varies greatly from one country to another. Some estimates are given in Table 46. A representative value to adopt for the annual collective dose equivalent per million population in countries with a high standard of medical care seems to be 1 man Sv per 10^6 population, although a considerably lower figure would be more appropriate for countries with a lower usage of radiation in medicine.

V. USES OF RADIATION IN INDUSTRY AND RESEARCH

106. Radiation is now used for very many purposes in general industry. Most of these uses involve sealed radioactive sources giving rise to such trivial doses that the users are not normally regarded as radiation workers. Examples include such ubiquitous products as smoke and fire detectors and thickness gauges. Of more interest to the Committee are those occupations in which the users are exposed to radiation doses comparable with those received from other uses of radiation. Those research and development uses of radiation which it is possible to identify separately from the research in support of the nuclear power programme are also covered in this section.

A. INDUSTRIAL RADIOGRAPHY

107. Industrial radiography may be divided into two categories of use, those in which the radiography installation is reasonably permanent and samples are tested under moderately controlled conditions, and those in which sources are used under fairly primitive conditions on construction or other sites. The standards of control, supervision and protection are markedly different in the two cases. This is illustrated later by the preponderance of over-exposures of workers in the latter category, site radiographers.

108. When dose information is reported, these categories of use are frequently not separated. Data from the United States for NRC licensees shown in Table 47 [B2] identify radiographers as receiving annual average doses of 2–3 mGy, but this is the result of averaging over more than 10 000 workers and may well obscure some imbalance in the dose distribution for certain smaller subgroups. This was investigated by Brooks et al. [B17] who examined the differences between radiography at single or multiple locations. The annual average doses to those working at multiple locations were higher than to those at single locations but still only 5 mGy for those with measurable exposures. The collective dose distribution ratio MR was 0.4, similar to the values in Table 47. The annual average doses received by non-NRC licensed workers engaged in radiography were lower, generally less than 2 mGy. Similarly annual average doses to industrial radiographers as a group were reported in France [P9], Canada [A10] and Japan [M15] as about 1–2 mGy. There is some apparent discrepancy between the annual average doses and dose distributions as reported and

the widely held view that industrial radiographers are among the most highly exposed groups of workers. This view is supported to some extent by the fact that workers in this group are more liable to receive accidental over-exposures than those in any other occupation. This is an area which was identified by the Committee in its previous report as being unclear and further information specifically on the exposure of site radiographers would be extremely useful.

B. LUMINIZING

109. Radioactive materials have been used in luminizing for decades but there has recently been a trend away from the use of radium to tritium and, to a lesser extent, to ^{147}Pm. The practice of luminizing is still fairly widespread. Tritium is used both mixed with a phosphor in a paint and as a gas enclosed in a phosphor-lined glass walled tube. Data on the internal doses to luminizers are available for several countries and are shown in Table 48, although this group cannot be separated in the United States data.

110. Annual average doses are fairly high, ranging up to 15 mGy, and are due almost entirely to internal doses from tritium, with a dose distribution showing a substantial proportion of workers receiving annual doses above 15 mGy, although only a few are exposed above 50 mGy. This is illustrated, for several groups of workers, by the log-probability plots in Figure X.

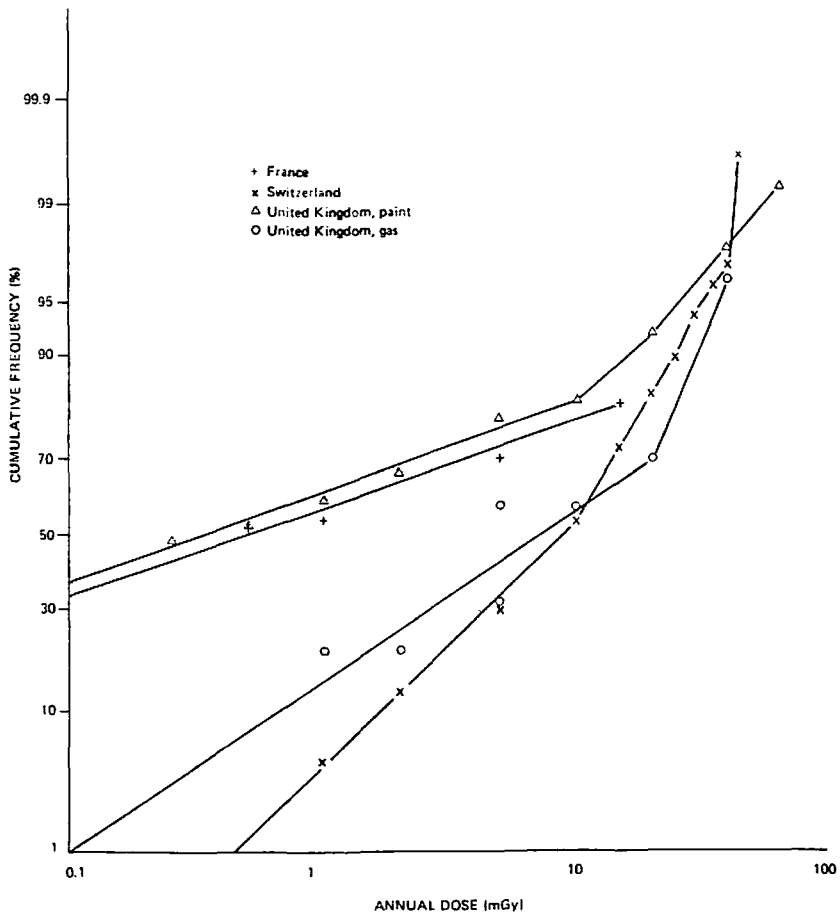

Figure X. Log-probability plot of annual doses to luminizers in the United Kingdom in 1976, in Switzerland in 1978, and in France in 1978 [P8, P9, T1]

C. RADIOISOTOPE PRODUCTION

111. Reporting conventions for this type of work vary from country to country. Most of the industrial preparation of sealed and unsealed sources in the United States is described under the category of by-product material, although this also appears to include some production of radiopharmaceuticals. A similar situation applies in the United Kingdom where The Radiochemical Centre Ltd. (now known as Amersham International Ltd.) produces both medical and industrial sources using the same workforce. This is one area in which workers are potentially exposed to intakes of radionuclides into the body. It is somewhat surprising that there is not more reporting of internal doses; even if checks were to show that intakes and doses were very low this would still be useful information. The annual average doses reported in the United States were a few mGy for a workforce of 2000–3000 people, including primary distributors [B17]. The radiochemical industry in the United Kingdom operates at annual average doses of 7–8 mGy for a workforce of nearly 1000 [T1]. Production workers are not separately identified in other countries.

112. Some workers at airports and other places are irradiated during the transport of these packages of sources. A major study in the United States has estimated the annual average dose to cargo handlers, who might be expected to have the highest doses of these groups, as less than 1 mGy, with a maximum dose to any individual of less than 5 mGy [S7]. Annual average doses to pilots and other aircrew from radioactive packages, most of which would be expected

to contain radiopharmaceuticals, have been assessed as less than 0.01 mGy [B6]. The maximum individual dose to any individual flight attendant from radioactive packages has been estimated as 1 mGy [T2].

D. OTHER INDUSTRIAL USES

113. There are many other uses of both sealed and unsealed sources ranging from tracer experiments to well logging and other measurement systems. Information on exposure from these is not separately identified in many countries; that which is available is shown in Table 49. It appears that there may be many thousands of workers associated with such uses, and some occupations such as well logging, in which the annual average dose equivalent is estimated to be as high as 5 mSv, could merit further investigations, such as those carried out by Romanova [R6] and summarized in Table 49.

114. All these industrial uses of radiation give rise to radioactive wastes, often of large volumes and not suitable for homogeneous treatment or packaging. Disposal of such wastes is handled in most countries somewhat separately to disposal of wastes from the nuclear power industry. However, the doses to this group of workers are difficult to identify from the reported data. In the United States the annual average dose to a group of less than 100 workers in this category was estimated in 1975 as 13 mGy [C1]. This small group showed one of the highest average doses of any identified occupational group. A lower annual average dose of 6 mGy was however reported for waste disposal workers in 1978 [B17]. More data and evaluation of the situation in other countries would be useful.

E. RESEARCH

115. Many workers in a vast range of disciplines use radiation as a research tool. As has been pointed out in Section III E, many large research establishments serve the nuclear power industry but also carry out other research on the application of radionuclides or radiation. This is frequently difficult to separate and may have been included in that section. In the majority of these research disciplines the annual average doses are very low, of the order of 1 mGy, as is shown by the comprehensive United States survey summarized in Table 50 [B17, U17, U18]. Some research categories, however, give higher average doses: these are workers with accelerators who receive annual average doses of 4–5 mGy and investigators using unsealed sources who, although there are only 20 of them, receive annual average doses of 10 mGy.

116. Doses to research workers in other countries for which data are available are given in Table 51. Annual average doses are very low, generally less than 1 mGy, with very few doses above 15 mGy.

F. SUMMARY

117. There are many industrial uses of radiation under the control of many different employers and often under different regulations in different countries. The reporting of data is not therefore consistent, and the Committee has identified many special occupational groups on which more reported information would be highly desirable. These groups are site radiographers, radioisotope producers (especially those receiving internal doses), general dental workers, workers in radioactive waste disposal, research workers with accelerators and those handling unsealed sources. It may be that some of these groups are receiving the highest annual average doses of any occupationally exposed workers.

118. Data are reported in several countries on all industrially exposed workers, with only a limited breakdown into different work categories, or none at all. The numbers of workers are quite large in some cases. There is no clearly identified common measure of output from industry or research so, as for medical workers, the collective dose equivalent per million population is used as a measure of the total occupational exposure. Some estimates are given in Table 52. A reasonable average estimate of the annual collective dose equivalent per million population for industrialized countries is 0.5 man Sv per 10^6 population; a considerably lower figure would be more appropriate for countries that are not heavily industrialized.

VI. OTHER EXPOSURES TO RADIATION

119. Most of the occupations referred to in this chapter are those in which, by virtue of the materials or surroundings, some increased exposure to radiation is incurred by workers. This radiation is generally of natural origin. Workers in these occupations are generally not subjected to individual monitoring although the doses may be estimated from area monitoring or special checks.

A. CIVIL AVIATION

120. The major source of exposure of air crew is the increase of cosmic radiation with altitude; the small additional doses due to transport of radioactive packages have been discussed in paragraph 112. The dose to any individual thus results from a combination of flying time and altitude, modified to some extent by the latitude, etc. The average additional annual dose from cosmic radiation has been assessed as 1–2 mGy [B6, T1, B7]. Approximately 70 000 air crew are exposed at about this level in the United States and a further 20 000 in the United Kingdom. The doses received by security personnel working near baggage inspection systems have also been surveyed [S8]; annual average doses were less than 1 mGy.

B. NON-URANIUM MINING

121. Data were given in Annex E of the 1977 report of exposure of non-uranium miners to radon and radon daughters; the subject is reviewed in detail in Annex D. New data from a number of countries show that average exposures are variable but can exceed 4 WLM per year depending markedly on the local conditions. Average exposures in mines for metals such as iron, zinc, lead and copper appear to be about 1 WLM for work forces of typically a few thousand workers. There are some indications that exposures in large coal mines are somewhat lower.

C. OTHER WORK UNDERGROUND

122. Other occupations which entail exposures to radon and radon daughters include work in under-

ground spaces such as telephone communication tunnels and water conduits. Some hydroelectric power stations also have considerable underground workings. A small amount of information is available and is presented in Annex D, which shows that although only a few workers are involved, annual average doses can be similar to those in non-uranium mines.

123. Radon spas have for many years been places to which people resort for supposedly beneficial treatments. These treatments include exposures to radon-rich atmospheres and waters. In this report, workers in such spas have not been classified as medical workers exposed to radiation, since there is no known medical benefit of the treatment. The small amount of data summarized in Annex D shows that radon daughter exposures of some of these workers, though admittedly only of small numbers, approach or even exceed those of uranium miners, and may reach 40 WLM per year.

D. USE OF PHOSPHATE FERTILIZERS

124. Although the levels of activity concentration of natural radionuclides in phosphate fertilizers are not great, the quantities of material involved and the processes used indicate a potential for irradiation of the workers. This has been intensively studied in the Federal Republic of Germany [P10]; the survey showed that annual average doses were generally less than 0.2 mGy and the maximum annual dose to any individual was less than 0.5 mGy. The annual collective dose was estimated to be about 2 man Gy.

E. SUMMARY

125. Very large numbers of people are exposed to higher than average levels of natural radiation in the course of their work, but generally to quite low levels of occupational dose. Only in a few cases need this exposure be the subject of control or even of interest. The most important practical case is that of radon daughter exposure to underground workers, especially non-uranium miners and radon spa workers. The largest collective dose is from civil aviation. On the basis of the small amount of data reported, the annual collective dose equivalent per million population appears to be of the order of 1 man Sv per 10^6 population.

VII. ACCIDENTAL EXPOSURE TO RADIATION

126. In this chapter the Committee reviews information on accidental exposures to radiation. This subject was not discussed in Annex E of the 1977 report [U3] and was covered only briefly in the 1972 report [U2]. The objective of this review is to identify those types of accident that occur most frequently and which give rise to clinical consequences. Minor accidents and simple over-exposures are not included but are referenced in some instances. There is no obvious dividing line between an inadvertent over-exposure to radiation as a result of bad practice and an accident leading to over-exposure. This is particularly clear where industrial radiography sources have been involved and over-exposures have occurred as a result of insufficient training or poorly maintained equipment. The information on accidents is categorized by the sectors of the industry in which the work leading to the accident was carried out.

127. Information on major accidents is usually given in the published literature. Minor accidents are reported regularly to some national regulatory bodies and often these reports are freely available. Only the data made available to the Committee or found in the published literature could be included and therefore the coverage may be incomplete. The Nuclear Regulatory Commission in the United States publishes regular reports on occupational exposure, including over-exposures, and also reports to Congress on abnormal occurrences for its licensees. The Bureau of Radiological Health in the United States keeps records of accidents where clinical effects have occurred. The Health and Safety Executive in the United Kingdom makes similar reports to Ministers on accidents covering nuclear installations. Details of accidents are included in the Annual Reports of the Ministry of the Interior in the Federal Republic of Germany. Other sources of useful data are the reports of the cytogenetic dosimetry services in France and the United Kingdom. Many of their investigations are initiated because an abnormally high dose has been recorded on a dosimeter; this may or may not be a genuine high dose to a person. The more recent data presented in this chapter have been taken mainly from the sources described above. The emerging picture is by no means complete but may probably be taken as fairly representative of accidents occurring throughout the world.

128. Data available to the Committee on accidents that have occurred in the nuclear industry since 1945 and which had clinical consequences are given in Table 53. The majority of these occurred in the early development of nuclear power and were criticality excursions, several at experimental reactors. Some of those early accidents resulted in deaths after whole-body doses estimated to exceed a few Gy, although in certain cases heroic measures such as bone marrow transplants may have helped to avert death. No similarly serious accidents have been reported since the mid 1960s; indeed only one accident since then resulted in clinical symptoms. A number of accidents in the 1970s have involved minor wounds, usually when the worker was using a glove box [S12, O2, U10, O3, L3, H13]; in many of these the radioactive material was removed by excision. Another type of accident involved inhalation of various radionuclides, usually inside process buildings as a result of faults in the air flow pattern [F4, S13, H11, U10, B10, L2, E2]; in some cases a chelating agent was administered in an attempt to accelerate elimination of the radionuclide [S13]. Other accidents generally involved unsuspected high dose rates [U10, P14, U4, U11] or contamination [P13, B11, L4, H14] but no remedial actions were needed.

129. Accidents in general industry (excluding industrial radiography) since 1960 which had clinical consequences are given in Table 54. Only one death was reported after a whole-body dose of 10 Gy but in several instances isolation was required and in others amputations had to be carried out. Most of those accidents occurred either during servicing or use of large irradiators or generators capable of delivering high dose rates; many of them were clearly the result of inadequate carrying out of safety precautions by the workers involved, although some were due to equipment failures. Other reported accidents which did not result in clinical consequences were generally of the same type [H15, P15, P17, C8, G11, P18, B13, Y1, L4,

P7, L9, J4, D3]. Apart from the systematic reporting in the Federal Republic of Germany of minor accidents involving internal contamination [B25, B26], two other minor accidents have been reported involving exposure to tritium gas as a result of leaks or cracks in vessels or connecting lines [L6, L9].

130. Accidents involving industrial radiographers since 1960 which had clinical consequences are shown separately in Table 55. Some other serious accidents but not involving workers, some of which resulted in deaths, occurred when high activity sources were kept in homes for long periods by people who did not know what they were [K6, M12, Y2, S17]. Some of the other serious clinical consequences resulted from what appears to have been intentional exposure on the part of those involved.

131. A further 53 minor accidents involving over-exposures to radiation have been reported in the period 1969–1979, mainly from the United Kingdom and the United States, which have systematized reporting of such incidents [P13, D5, P15, P17, U10, B15, J5, P18, L4, U13, U4, U14, L9, B1, D6, H17, U15].

132. Almost all the accidents occurring in the normal course of work are attributable either to deliberate flouting of safety precautions or to equipment failures resulting in sources being left exposed. It appears that the first type, and many of the second type, have as their root cause lack of appreciation for the hazard, possibly through over-familiarity or insufficient training and explanation. Use of simple dose rate monitors would have shown the hazard in the majority of cases.

133. The relatively small number of accidents in research and development outside the nuclear power industry since 1960 which had clinical consequences are shown in Table 56. Several of these resulted from deliberate circumventing of safety measures by scientists who clearly should have been aware of the hazards; others were due to equipment failure. A few additional similar accidents have been reported [U10, P18, P7, L9, L1, L10, W3].

134. No accidents involving medical workers, and which led to clinical consequences, have been reported in the last decade. Of the accidents reported, the majority were a result of faults with switches or interlocks controlling x-ray generators [P15, J6, P14, P19, L4, L9]. One accident of internal contamination with ^{131}I was also reported [B11].

SUMMARY

135. Considering the number of workers involved with radiation and radioactivity over the last several decades, the number of deaths and serious injuries is not large. Many of these occurred in the early development phase of nuclear reactors when safety precautions were very much less stringent. Nonetheless there is one area of work, industrial radiography, in which the mishandling of sources and equipment failures has lead to a large number of reported accidents with potentially serious consequences.

VIII. CONCLUSIONS

136. The Committee reviewed occupational exposure in detail in Annex E of the 1977 report and suggested methods for the analysis of dose distributions and criteria against which to assess the parameters extracted from the dose distributions. These methods of analysis have been used by several organizations since the report was published; in this Annex they have been refined slightly. It still appears that the observation that data often fit a log-normal distribution, especially at lower doses, enables an improved estimate of the parameters of a distribution to be made. The techniques for extracting the relevant parameters are described in this Annex.

137. The three characteristics of the dose distribution previously identified by the Committee as of interest may still be used to describe distributions in a useful fashion. These characteristics are:

(a) The annual average dose, which is related to the average level of individual risk;
(b) The annual collective dose, which is related to the total impact of the practice;
(c) The ratio of the annual collective dose delivered at individual doses exceeding 15 mGy per year to the total annual collective dose, which is related to the proportion of workers exposed to higher levels of individual risk.

138. The reference distribution introduced in the 1977 report has not proved as useful as was hoped and the Committee has therefore decided to revert to the basic parameters given above which may be extracted from any dose distribution, rather than normalizing them to the reference distribution.

139. In previous reports the Committee has adopted the convention that all numerical results reported by monitoring services represent the average absorbed dose in the whole body while recognizing that it is almost always the reading from the dosimeter which is reported, without consideration of the relationship between this and the absorbed dose in the body. This is, however, still regarded as a reasonable convention in that most data are on external exposure of the whole body to ionizing radiation. The same convention has again been adopted in this Annex. In situations where exposure of the body may be non-uniform, especially in medical practice, it may be misleading to average across different types of work as the relationship between reported dosimeter reading and average absorbed dose in the whole body will not be constant.

140. In Annex E of the 1977 report the Committee used a very simple linear extrapolation to predict lifetime doses for a few categories of workers for whom data were available. The Committee had hoped that this simple treatment would have stimulated more investigation of the relationship between the pattern of accumulation of dose over the years of a person's employment and the total dose received in that employment. Clearly such investigations can only be carried out by those authorities having access to individual dose records. The Committee would like to encourage such investigations and analyses, the results of which should be reported in a suitably anonymous fashion.

141. A major re-evaluation of the doses occurring in the nuclear fuel cycle has been carried out. Revised estimates of the collective dose equivalent per unit energy generated have been obtained for each part of the cycle and are shown in Table 35. The most notable features are that the estimated doses from reactor operations are unchanged from the previous report but

that the estimated doses from reprocessing and research, which were much less soundly based, have now been considerably reduced. Based on an estimate of 70 GW(e) a as the total nuclear energy generated in the world in 1979, the annual occupational collective dose equivalent associated with it can be assessed as about 2000 man Sv. This may also be expressed as about 0.5 man Sv per 10^6 population for comparison purposes.

142. Reported exposures of uranium miners to radon and daughters are reviewed in Annex D. Although some data from the United States show an average exposure of about 4 WLM per year, other reports from the United States and those from other countries are closer to 1 WLM per year. Taking all these into account, an appropriate annual average exposure to radon and daughters appears to be about 1.5 WLM, which can be converted to an annual effective dose equivalent of about 13 mSv.

143. Annual average doses to workers on power reactors have been maintained at about 5 mGy; however this has been attained by a significant increase in the number of workers per reactor, particularly in the United States for which most data are available, in the period from 1970–1979. In general the number of exposed workers per reactor in the United States has increased by a factor of between 3 and 4 over this period for light water reactors. Annual average doses at heavy water reactors are in general similar to those at light water reactors and those at gas cooled reactors have remained low at about 2–3 mGy.

144. The general conclusion is that there are two major sources of collective dose at all reactors. One of these is the routine operations and maintenance which are essential to the operation of the reactor, have presumably been planned for in the design, and cannot be much affected in broad terms once the reactor has been designed and built. The other source is unforeseen special maintenance, which must often be carried out in areas without designed routine access, in high dose rates and in poor working conditions. Much of this work consists of unscheduled repairs to essential components, which clearly has to be carried out. This source of exposure currently appears to be dominating the collective dose per unit energy generated from water reactors.

145. More data are now available on doses to commercial reprocessing plant workers in France as well as the United Kingdom, together with some information on research or pilot plants. The results indicate substantial workforces exposed to dose distributions with an annual average dose of about 10 mGy. It is emphasized, however, that many of these are historical data, often based on old plants, and may well not be typical of the more recent plants or of doses to be expected in the future.

146. Data have been presented on doses and dose distribution in research and development work connected with the nuclear power industry in several countries. Annual average doses generally range from 1–5 mGy, but large numbers of workers are involved.

147. Exposures during medical uses of radiation have been briefly reviewed but there is not much recent information. Medical uses have been divided into two major categories, diagnosis and therapy. By the nature of medical work, exposures are expected to be non-uniform and the effective dose equivalent may not be easily obtainable from the dose indicated by a simple dosimeter, due to the energy or spatial inhomogeneity of the radiation field. The general situation, especially for diagnostic radiology, appears to be characterized by low annual average doses, often less than 1 mGy, to large numbers of workers. The only exception appears to be the use of sealed sources in radiotherapy where these are implanted or applied to the patient. There is evidence that doses are very greatly reduced by changing to techniques which do not require direct handling of the radiation sources, for example, after-loading techniques. It is not possible to identify and quantify the beneficial output of all medical work, although an attempt has been made to relate the doses from diagnostic radiology to the number of films processed. An indication of the total occupational exposure is expressed as the annual collective dose equivalent per million population of the country, on the grounds that total medical care should be roughly proportional to population. Even from the available data, it is clear that this measure varies considerably from one country to another, but a reasonable value to adopt for countries with a high standard of medical care seems to be about 1 man Sv per 10^6 population. A lower figure would be more appropriate for countries with a lower usage of radiation in medicine.

148. Other exposures to radiation in general industry have also been reviewed. Some anomalies are shown in exposure of industrial radiographers where a reasonably low average dose is reported, accompanied by a relatively high proportion of over-exposures. This situation needs closer investigation in detail by those with access to the individual dose results. Average doses to luminizers remain high, but the number of people involved is relatively small. The Committee has identified several special occupational groups on which more reported information in the appropriate detail would be highly desirable.

149. There are some other occupations in which, by virtue of the materials or surroundings, some increased exposure to radiation is incurred by workers. This radiation is generally of natural origin. The two major occupations falling into this category are air crew and non-uranium miners. There is a very large number of air crew exposed to enhanced cosmic ray dose rates and the average additional annual dose is now estimated as 1–2 mGy. Non-uranium miners are exposed in moderately large numbers to radon daughter levels which can be as high as those in uranium mines.

150. There is no clearly identified common output from industry and research and therefore the collective dose has been normalized to population. A reasonable estimate of the annual collective dose equivalent per million population from industrial and research uses of radiation is 0.5 man Sv per 10^6 population in industrialized countries; a considerably lower figure would be appropriate for developing countries. On the basis of the small amount of data available, the annual collective dose equivalent per million population from enhanced exposure to natural radiation, especially cosmic radiation while flying, is of the order of 1 man Sv per 10^6 population.

151. The Committee has reviewed the available data on accidental exposures to radiation. The objective was to identify those types of accident which occur most frequently and which give rise to clinical consequences. It is clear that most accidents are concerned with industrial uses of radiation rather than with the nuclear fuel

cycle. The overall number of accidents is very small when considering the large number of people using radiation or radioactivity in their work but the distribution of accidents between different types of work is highly non-uniform. Nonetheless there is one area of work, industrial radiography, in which the mishandling of sources and equipment, coupled with a high incidence of equipment failures, has led to a relatively large number of reported accidents with potentially serious consequences.

152. The Committee has made a number of suggestions concerning areas where more analysis of data is required to extract pertinent information. This could usefully be performed by those gathering the data. The Committee has also made suggestions regarding the level of detail which would be useful in reported data and the content of such reports. If these suggestions are acted upon there should be a very much clearer indication of the occupational exposure situation in some areas of work within a few years.

Table 1

An example of a distribution of annual individual doses within dose ranges for a nominal group of 1000 workers

Dose range (mGy)	Number of workers in the range	Cumulative frequency (%)	Collective dose in the range (man Gy) a/	b/	Fraction of collective dose above the range a/	b/
0 - 1	500	50.0	0.25	0.16	0.95	0.97
1 - 5	280	78.0	0.84	0.70	0.80	0.84
5 - 10	80	86.0	0.60	0.59	0.68	0.72
10 - 15	40	90.0	0.50	0.50	0.59	0.62
15 - 20	20	92.0	0.35		0.53	0.56
20 - 30	30	95.0	0.75		0.39	0.41
30 - 40	30	98.0	1.05		0.19	0.20
40 - 50	15	99.5	0.67		0.06	0.07
50 - 60	2	99.7	0.11		0.04	0.05
60 - 70	1	99.8	0.07		0.03	0.03
70 - 80	1	99.9	0.07		0.02	0.02
80 - 90	0	99.9	0		0.02	0.02
90 - 100	1	100	0.10		0	0
Total	1000		5.36	5.12		

a/ Calculated as the number of workers multiplied by the mid point dose.
b/ Calculated from the log-normal fit below 15 mGy in Figure I.

Table 2

Approximate exposures to radon daughters and calculated conversions to effective dose equivalent and collective effective dose equivalent for underground uranium miners in Canada, France and the United States in the late 1970s

Country	Approximate number of workers	Approximate annual average radon daughter exposures (WLM)	Approximate annual average effective dose equivalent (mSv)	Approximate annual collective effective dose equivalent (man Sv)
Canada [A1]	4000	0.75	6	25
France [B24]	1500	1.5	13	20
United States				
[C9]	3300	1.1	9	30
[R1]	5000	4.0	34	170

Table 3

Doses at fuel manufacturing plants in the United States (NRC Licensees) 1975-1978 [B1, B17, C1, U4]

Year	Number of workers monitored	Number of workers with measurable doses	Annual collective dose (man Gy)	Annual average dose (mGy) All those monitored	Those with measurable doses	MR
1975	11614	5602	32	2.7	5.7	0.5
1976	11227	5285	18	1.6	3.5	0.4
1977	11496	7004	17	1.5	2.5	0.4
1978	11305	5896	14	1.2	2.4	0.3

Table 4

Doses in fuel fabrication and enrichment plants in the United Kingdom 1976-1978
[R2, U5, U16]

Process	Year	Number of workers	Annual collective dose (man Gy)	Annual average dose (mGy)	MR
Fuel enrichment	1976	570	0.40	0.7	0
	1977	598	0.35	0.6	0
	1978	706	0.36	0.5	0
Fuel fabrication	1976	2234	5.9	2.6	0.05
	1977	2484	6.3	2.5	0.03
	1978	2652	4.4	1.7	0.04

Table 5

Doses received by fuel manufacturing workers in Canada 1970-1978
[A1]

Year	Annual collective dose (man Gy)		Annual average dose (mGy)	
	Refining	Fabrication	Refining	Fabrication
1970	0.42	0.18	1.7	1.0
1971	1.68	0.31	6.6	1.6
1972	1.37	0.53	4.7	2.1
1973	2.12	0.84	6.2	2.9
1974	2.44	1.24	6.7	3.6 a/
1975	2.10	0.97	5.7	3.1 a/
1976	1.58	0.42	3.8	1.2
1977	0.68	0.69	1.4	1.8
1978	0.48	0.61	0.9	1.2

a/ Includes some estimated doses.

Table 6

Annual information reported on occupational exposure at BWRs in the United States 1973-1979
[B22]

Year	Number of workers with measurable doses	Energy generated in the year [GW(e) a]	Annual collective dose (man Sv)	Annual average dose to those with measurable doses (mGy)	Average number of workers with measurable doses per reactor	Collective dose per unit energy generated [man Gy (GW[e] a)$^{-1}$]
1973	5340	3.39	46	8.5	445	13
1974	8769	4.06	71	8.1	626	17
1975	14607	5.79	126	8.6	812	22
1976	17859	8.59	126	7.1	776	15
1977	21388	9.10	190	8.9	930	21
1978	20278	11.77	151	7.4	811	13
1979	25245	11.67	183	7.3	1010	16

Table 7

Annual information reported on occupational exposure at PWRs in the United States 1973-1979
[B22]

Year	Number of workers with measurable doses	Energy generated in the year [GW(e) a]	Annual collective dose (man Sv)	Annual average dose to those with measurable doses (mGy)	Average number of workers with measurable doses per reactor	Collective dose per unit energy generated [man Gy (GW[e] a)$^{-1}$]
1973	9440	3.77	94	10.0	787	25
1974	9697	6.82	66	6.8	485	10
1975	10884	11.98	83	7.6	419	7
1976	17588	13.33	138	7.9	586	10
1977	20878	17.35	135	6.5	614	8
1978	25720	19.84	167	6.5	659	8
1979	38828	18.25	214	5.5	924	12

Table 8

Annual collective dose and collective dose per unit energy generated at BWRs in various countries
[F1, G3, I5, I6, I7, K2, M15, N1, P2]

Country	Year	Energy generated in the year [GW(e) a]	Annual collective dose (man Gy)	Collective dose per unit energy [man Gy (GW[e] a)$^{-1}$]
Japan a/	1975	0.80	41	51
	1976	1.19	50	42
	1977	0.74	61	83
	1978	1.62	115	71
Spain	1977	0.22	7	32
	1978	0.38	4	10
	1972-1978	0.33 b/	4 b/	12 b/
Sweden	1977	1.70	8	5
	1978	2.13	6	3
Switzerland	1977	0.19 c/	3	16
	1978	0.19 c/	3	16

a/ Including a GCR in Japan.
b/ Average over the 7-year period.
c/ Based on a 60 % load factor.

Table 9

Annual collective dose and collective dose per unit energy generated at PWRs in various countries
[G3, G4, I5, I6, I7, I10, K2, M15, N1, P2, S1]

Country	Year	Energy generated in the year [GW(e) a]	Annual collective dose (man Gy)	Collective dose per unit energy [man Gy (GW[e] a)$^{-1}$]
German Dem.Rep.	1966-1978	3.9 a/		13 b/
Japan	1975	1.25	10	8
	1976	1.61	10	6
	1977	1.57	15	10
	1978	2.21	15	7
Spain	1977	0.14	1.5	11
	1978	0.12	3.9	32
	1970-1978	0.12 c/	1.7 c/	14 c/
Sweden	1977	0.47	2	4
	1978	0.47	2	4
Switzerland	1977	0.45 d/	5	11
	1978	0.45 d/	3	7

a/ Cumulative total over the 13-year period.
b/ Average over the 13-year period.
c/ Average over the 9-year period.
d/ Based on a 65 % load factor.

Table 10

Doses at nuclear power stations of the CANDU-PHW reactor type in Canada in 1977
[A1, N1]

Station	Installed capacity in 1977 [GW(e) a]	Annual average dose (mGy)	
		External	Internal (tritium)
Rolphton NPD 2	0.025	2.1	1.7
Douglas Point	0.22	3.3	3.5
Pickering A	2.17	4.7	4.4
Bruce A	2.34	0.6	0.2

Table 11

Annual collective dose per unit energy generated at nuclear power stations in Canada, 1972-1978
[A1, N1]

Year	Energy generated in the year [GW(e) a]	Annual collective dose per unit energy generated [man Gy (GW[e] a)$^{-1}$]
1972	0.8	15
1973	1.7	8
1974	1.7	5
1975	1.4	11
1976	2.0	7
1977	2.5	6
1978	3.5	5

Table 12

Doses at Atucha nuclear power station, Argentina, 1977-1979
[P20]

Year	Annual average dose (mGy)	Annual collective dose (man Gy)	MR	Collective dose per unit energy generated [man Gy (GW[e] a)$^{-1}$]
1977	16	10.0	0.8	56
1978	14	6.7	0.8	22
1979	17	9.0	0.8	32

Table 13

Doses at GCRs in the United Kingdom, 1975-1979
[G5, G6, G7, H2, H4, H18, P5, U3, U5]

Year	Number of workers	Annual average dose (mGy)	Annual collective dose (man Gy)	Collective dose per unit energy generated [man Gy (GW[e] a)$^{-1}$]
1975	6264	2.7	17	6
1976	6837	2.6	18	6
1977	9432	2.2	21	6
1978 a/	7025	2.3	16	5
1979 a/	6732	2.5	17	5

Table 14

Doses at the FBR Phenix, France, 1975-1979
[P9]

Year	Annual collective dose (man Gy)
1975	0.05
1976	0.08
1977	0.16
1978	0.08
1979	0.04

Table 15

Doses at FBR Dounreay, United Kingdom, 1974-1977
[A2]

Year	Annual average dose (πGy)	Annual collective dose (man Gy)
1974	1.2	0.3
1975	1.6	0.5
1976	1.8	0.6
1977	1.7	0.6

Table 16

Doses in United States naval nuclear power ships, supporting tenders and submarine bases, 1970-1978 [M10]

Year	Number of workers	Annual average dose (mGy)	Annual collective dose (man Gy)	MR
1970	26980	1.1	31	0.1
1971	26813	1.2	33	0.3
1972	34108	1.0	33	0.3
1973	31570	1.0	32	0.3
1974	18749	1.1	21	0.2
1975	17997	1.2	22	0.2
1976	18229	1.4	26	0.2
1977	20716	1.4	28	0.3
1978	22403	1.0	22	0.2

Table 17

Doses to naval shipyard workers in the United States associated with nuclear propulsion plants, 1970-1978 [M10]

Year	Number of workers	Annual average dose (mGy)	Annual collective dose (man Gy)	MR
1970	25923	5.0	131	0.8
1971	23925	4.4	106	0.7
1972	20199	3.5	70	0.6
1973	15252	4.0	61	0.6
1974	15157	4.8	72	0.6
1975	14663	3.6	53	0.6
1976	14973	3.5	53	0.5
1977	15723	3.3	52	0.5
1978	14984	2.5	37	0.4

Table 18

Annual collective doses (man Gy) by work function at BWRs and PWRs in the United States, 1977-1979 a/ [B18, B22, P1]

Work function	1977	1978	1979
B W R s			
Operations	17	15	17
Maintenance	124	98	127
Supervision/Administration	19	13	13
Health physics	11	9	10
P W R s			
Operations	9	11	13
Maintenance	71	78	96
Supervision/Administration	12	16	20
Health physics	7	10	16

a/ The totals from this table are not the same as those in Tables 6 and 7, as some parts of the annual collective dose were not characterized by work function.

Table 19

Percentage of the annual collective dose by work function for LWRs in several countries

Work function	German Dem. Republic [S1]	Fed.Rep.of Germany [U6]	Spain [F1]	Sweden [P2]	Switzerland [S2]
	1978	mid 1970s	1978	1978	1978
Operations	13	20	24	14	34
Maintenance	65 a/	80	65	72	57 a/
Supervision/ Administration	18 c/	b/	b/	6 c/	2 c/
Health physics	4	b/	11	8	7

a/ Including contractors.
b/ No values given.
c/ Including work categorized as "other".

Table 20

Annual average and collective doses received by reactor workers in Canada, 1979 [A10]

Work function	Collective dose (man Gy)	Per cent of total collective dose	Annual average dose (mGy)
Operations		45	
Reactor operations	6.0		6.5
Fuel handling	0 a/		0.02
Control technician	3.2		5.1
Maintenance		47	
Electrical	0		0
Mechanical	7.7		11.5
General	1.1		1.4
General workers	0.7		1.1
Health physics		2	
Health physics	0.02		0.9
Chemical and radiation control	0.3		3.1
Administration/Supervision		6	
Administration, security,janitorial	1.2		0.9

a/ Less than 0.001 man Gy.

Table 21

Collective doses received by workers at two GCRs in the United Kingdom [K3, K4]

Work function	Dungeness A (1977)		Wylfa (1978)	
	Collective dose (man Gy)	Per cent of total collective dose	Collective dose (man Gy)	Per cent of total collective dose
Operations	0.35	27	0.19	32
Maintenance	0.56	42	0.25	42
Administration/ Supervision	0.27	21	0.05	8
Health physics	0.13	10	0.11	18

Table 22

Doses at BNFL Windscale, 1976-1978
[U5, U16, R2]

Year	Number of workers	Annual average dose (mGy)	Annual collective dose (man Gy)	MR
1976	4406	11	49	0.7
1977	5055	10	48	0.7
1978	5722	8	48	0.7

Table 23

Annual collective dose per unit energy generated at BNFL Windscale, 1971-1978
[A4, C2, H5, H6, H7, R2, U5, U6]

Year	Annual collective dose per unit energy generated [man Gy $(GW^{r}e)^{-1}$ a^{-1}]
1971	12
1972	20
1973	13
1974	13
1975	15
1976	19
1977	28
1978	25

Table 24

Doses at Cap de La Hague, France, 1970-1979
[J3, P9]

Year	Number of workers	Annual average dose (mGy)	Annual collective dose (man Gy)	MR
1970	1140	2.3	2.6	0.3
1971	1187	2.9	3.5	0.4
1972	957	3.5	3.3	0.3
1973	1068	4.6	4.9	0.3
1974	1143	4.7	5.4	0.4
1975	1361	5.2	7.1	0.4
1976	1451	4.8	7.0	0.4
1977	1715	3.9	6.7	0.3
1978	1897	3.3	6.3	0.3
1979	1914	3.0	5.7	0.2

Table 25

Annual collective dose per unit energy generated at Cap de La Hague, France, 1972-1976
[C2, J3]

Year	Annual collective dose per unit energy generated [man Gy $(GW^{r}e)^{-1}$ a^{-1}]
1972	6
1973	9
1974	3
1975	5
1976	8

Table 26

Doses received by various groups of workers at reprocessing plants in France, 1974-1978 [84]

Group	1974		1975		1976		1977		1978	
	Number of workers	Annual average dose (mGy)	Number of workers	Annual average dose (mGy)	Number of workers	Annual average dose (mGy)	Number of workers	Annual average dose (mGy)	Number of workers	Annual average dose (mGy)
Reprocessing	318	5.4	353	5.4	377	4.7	420	4.4	503	3.8
Decontamination	218	7.1	241	7.9	195	9.7	311	6.2	296	6.2
Maintenance	328	3.3	433	4.8	456	4.7	558	4.0	543	3.1
Chemical and electrical technicians, health physics	173	1.7	177	1.7	188	1.8	226	1.6	283	1.5

Table 27

Doses at the Eurochemic Fuel Reprocessing Plant at Mol, Belgium, 1970-1978 [01]

Year	Number of workers	Annual average cose (mGy)	Annual collective dose (man Gy)	MR
1970	268	13	3.4	0.8
1971	285	11	3.2	0.8
1972	235	18	4.3	0.8
1973	225	16	3.7	0.8
1974	187	14	2.7	0.8
1975	169	9	1.6	0.7
1976	175	8	1.5	0.7
1977	180	10	1.7	0.6
1978	212	11	2.2	0.3

Table 28

Doses at the Fuel Reprocessing Plant at Karlsruhe, Federal Republic of Germany, 1972-1978 [55]

Year	Number of workers	Annual average dose (mGy)	Annual collective dose (man Gy)
1972	216	13	2.9
1973	241	11	2.7
1974	284	5	1.4
1975	325	2	0.6
1976	311	3	1.0
1977	318	4	1.4
1978	373	5	1.7

Table 29

Doses to workers in nuclear research and development in the United States, 1975-1979
[U8, U9, U17, U18, U19]

Year	Number of workers with measurable dose	Annual average dose (mGy)	Annual collective dose (man Gy)	MR
1975	34428	3	96	0.4
1976	40802	2	88	0.3
1977	40660	2	87	0.3
1978	43647	2	77	0.3
1979	41881	2	73	0.3

Table 30

Doses at Atomic Energy of Canada Ltd. sites, 1970-1978
[M8]

Year	Number of workers with measurable exposure		Annual average dose (mGy)		Annual collective dose (man Gy)	
	External	Tritium	External	Tritium	External	Tritium
1970	1334	412	11	1.7	15	0.7
1971	1439	480	8.2	1.9	12	0.9
1972	1527	483	8.5	1.8	13	0.8
1973	3677	187	2.8	1.5	10	0.3
1974	3758	347	3.0	1.3	11	0.5
1975	3615	320	3.0	1.2	11	0.4
1976	3554	315	3.3	1.9	12	0.6
1977	3565	341	3.5	1.8	13	0.6
1978	3902	389	3.4	2.5	13	1.0

Table 31

Doses at United Kingdom research and development establishments connected with the nuclear power industry, 1975-1979
[G6, G7, H18, T1, U16]

Organization	Year	Annual average dose (mGy)	Annual collective dose (man Gy)	MR
United Kingdom Atomic Energy Authority	1975	5.5	41	0.2
	1976	5.8	44	0.3
	1977	4.3	34	0.2
Central Electricity Generating Board, Berkeley Nuclear Laboratories	1975	1.1	0.7	0.2
	1976	1.2	0.7	0.1
	1977	1.3	0.9	0
	1978	0.9	0.6	0.1
	1979	1.1	0.8	0

Table 32

Doses at Karlsruhe Nuclear Research Centre, Federal Republic of Germany, 1970-1978
[K5]

Year	Number of workers	Annual average dose a/ (mGy)	Annual collective dose a/ (man Gy)
1970	2785	0.6	1,8
1971	2992	0.7	2.1
1972	2894	1.3	3.8
1973	3096	1.3	4.1
1974	2841	1.2	3.4
1975	2782	0.7	2.0
1976	3000	0.8	2.3
1977	3157	0.8	2.4
1978	3194	0.8	2.5

a/ With natural background assumed to be 0.82 mGy a^{-1} subtracted.

Table 33

Doses received by different groups of workers at Karlsruhe Nuclear Research Centre, Federal Republic of Germany, 1975-1978
[K5]

Group	Annual average dose (mGy) a/			
	1975	1976	1977	1978
Waste handling	7.2	5.3	4.5	4.2
Health physics	3.0	2.7	2.7	2.9
Cyclotron	1.8	1.9	2.7	3.9
Reactor	1.8	1.9	1.4	1.5
Chemistry	0.9	1.9	1.6	1.6
Supply service	0.5	0.4	0.3	0.4
Physics	0.1	0	0.1	0.2
Biology	0	0	0.1	0.3
Others	0	0	0.1	0

a/ With natural background assumed to be 0.82 mGy a^{-1} subtracted.

Table 34

Doses to nuclear research and development workers in various countries
[D1, G3, G8, K2, M15, P3, P20]

Country	Year	Number of workers	Annual average dose (mGy)	Annual collective dose (man Gy)	Collective dose per unit energy generated [man Gy (GW[e] a)$^{-1}$]
Argentina	1977	476	1.3	0.6	
	1978	525	1.2	0.6	3 a/
	1979	700	0.9	0.6	
	1980	516	1.2	0.6	
Belgium (Mol)	1976	1427	3.8	5.4	
	1977	1444	1.9	2.8	3
	1978	1469	1.9	2.8	
Japan (Atomic Energy Industry) b/	1978	17800	0.2	4.2	1
Switzerland (Reactor Research Institute)	1976	294	2.6	0.8	
	1977	360	2.8	1.0	1
	1978	351	2.4	0.8	

a/ This figure would be 7 man Gy [GW(e) a]$^{-1}$ if doses due to non-nuclear power research and development at the same sites had been included [P20].
b/ Numbers extrapolated from a survey estimated to cover 50 % of workers.

Table 35

Contribution to the collective dose equivalent per unit energy generated in the nuclear fuel cycle

Part of the cycle	Collective dose equivalent per unit energy generated [man Sv (GW[e] a)$^{-1}$]
Mining and milling	1
Fuel manufacture	1
Reactors	10
Reprocessing	10
Research and development	5
Total	27

Table 36

Doses to workers in medicine using radionuclide sources under NRC Licenses in the United States, 1978 [B17]

Category of licensee	Number of workers with measurable dose	Annual average dose (mGy)	Annual collective dose (man Gy)	MR
Institutions				
- broad	10570	1.5	16	0.2
- others	24660	2.5	63	0.2
Private practice	1620	3	5	0.1
Teletherapy	1570	2	3	0.3
Other	410	1	0.4	0.1

Table 37

Doses to medical workers in the United States monitored by the Bureau of Radiological Health, 1972-1978 [M9]

Year	Number of workers	Annual average dose (mGy)	Annual collective dose (man Gy)
1972	3874	0.5	2.1
1973	3843	0.5	2.0
1974	3829	0.5	2.1
1975	4017	0.8	3.2
1976	4549	0.9	4.3
1977	5048	0.4	1.8
1978	5483	0.3	1.7

Table 38

Doses received by some groups of medical workers in the United States monitored by the Bureau of Radiological Health, 1972-1978 [M9]

	Annual average dose (mGy)						
Group	1972	1973	1974	1975	1976	1977	1978
Radiologists	1.2	0.7	1.1	3.6	3.2	1.3	1.7
Other physicians	0.4	0.3	0.5	0.8	0.9	0.3	0.3
x-ray technicians	0.8	0.7	0.9	1.6	1.4	0.7	0.5
Other technicians	0.4	0.3	0.4	0.6	1.6	0.3	0.3

Table 39

Doses to medical workers in Switzerland, 1976-1978
[P3, P7, P8]

Group	Year	Number of workers	Annual average dose (mGy)	Annual collective dose (man Gy)	MR
Hospitals	1976	6259	0.5	2.9	0.3
	1977	7164	0.5	3.9	0.2
	1978	7641	0.6	4.2	0.1
General practice	1976	6059	0.1	0.8	0.1
	1977	6901	0.1	1.0	0.02
	1978	8185	0.2	1.3	0.1
Radiologists	1976	182	0.8	0.1	0.1
	1977	193	0.9	0.2	0
	1978	439	0.6	0.3	0.2

Table 40

Doses to medical workers using x rays for diagnosis in France, 1976-1979
[P9, S17]

Group	Year	Number of workers	Annual average dose (mGy)	Annual collective dose (man Gy)	MR
Private general medicine	1976	759	2.5	1.9	0.1
	1977	804	1.1	0.9	0.2
	1978	841	2.5	2.1	0.1
	1979	901	1.0	0.9	0.1
Private special clinics	1976	2259	2.0	4.5	0.2
	1977	2421	1.5	3.6	0.2
	1978	2532	1.7	4.3	0.2
	1979	2731	1.6	4.4	0.1
Private radiology	1976	1446	2.2	3.2	0.2
	1977	1534	2.6	4.0	0.2
	1978	1568	2.3	3.6	0.1
	1979	1845	1.7	3.1	0.1
Industrial medicine	1976	4731	1.1	5.2	0.1
	1977	4699	1.0	4.7	0.1
	1978	4444	0.3	1.3	0.2
	1979	4403	0.4	1.8	0.1
Hospitals	1976	10309	1.7	18	0
	1977	11600	1.3	15	0.2
	1978	13106	1.2	16	0.1
	1979	14973	0.8	12	0.1

Table 41

Doses to medical workers assumed to be mainly involved with diagnostic radiology in various countries
[A10, F2, I9, M15, S19, W2]

Country	Description of work	Year	Number of workers	Annual average dose (mGy)	Annual collective dose (man Gy)
Australia a/	Hospital radiology	1978	520	1.2	0.6
	Private radiology		100	2.3	0.2
	General practice		170	0.2	0.03
	Radiography		2700	0.8	2.1
	Assistants, nurses, etc.		1000	0.5	0.5
Canada	Radiologists	1979	1354	0.4	0.6
	Radiological technicians		7380	0.2	1.8
	Physicians		1478	0.4	0.5
	Nurses		2993	0.4	1.0
Germany, Fed.Rep.of	Medical workers	1976	101500	0.4	45
		1977	118449	0.4	53
Israel	Medical workers	1975	1860	1.0	2
Japan a/ b/	Doctors	1978	40800	0.6	23
	Technicians		28600	0.8	23
	Nurses		21700	0.3	7.4
	Other		9600	0.3	2.6
Other Asia	Medical workers	1975	1300	1.7	2.3

a/ Numbers extrapolated from a survey estimated to cover 50 % of workers.
b/ Workers with x rays and gamma rays.

Table 42

Comparison of medical occupational doses with medical practice
[E1, M15, T1, U3]

Country	Estimated annual collective dose equivalent to all medical workers (man Sv)	Number of films used for x-ray examinations per year (10^6)	Annual collective dose equivalent per film to medical workers (10^{-6} man Sv per film)
German Dem. Rep.	11	11	1.0
Germany,Fed.Rep.of	50	100	0.5
India	9	19	0.5
Japan	78	120	0.7
Sweden	22	5.3	4.2
Switzerland	7	8.5	0.8
United Kingdom	70	40	1.8
United States	270	130	2.1
Other Asia	2.5	0.7	3.6

Table 43

Doses to dental workers in various countries
[A10, C1, P3, P7, P8, P9, S19]

Country	Description of work	Year	Number of workers	Annual average dose (mGy)	Annual collective dose (man Gy)
Australia a/	Dentists, nurses and assistants	1974	2000	0.1	0.2
		1978	1600	0.1	0.2
Canada	Dentists	1979	4028	0.05	0.2
France	Dental stomatology	1976	3952	0.5	2.0
		1977	4751	0.4	1.9
		1978	5399	0.3	1.6
		1979	6382	0.5	3.2
Switzerland	Dental practice	1976	6634	0.2	1.4
		1977	7026	0.2	1.0
		1978	7683	0.2	1.2
United States	Dental practice	1975	265000	0.2	53

a/ Numbers extrapolated from a survey estimated to cover 50 % of workers.

Table 44

Doses to workers in nuclear medicine in Australia and France
[P9, S19]

Country	Description of work	Year	Number of workers	Annual average dose (mGy)	Annual collective dose (man Gy)
Australia a/	Nuclear radiographers and assistants	1974	960	0.8	0.8
		1978	930	0.4	0.4
France	Nuclear medicine	1976	2105	1.7	3.6
		1977	2275	0.9	2.0
		1978	2215	1.5	3.3
		1979	2453	0.5	1.2

a/ Numbers extrapolated from a survey estimated to cover 50 % of workers.

Table 45

Doses to workers in radiotherapy in various countries
[C1, P9, S19]

Country	Description of work	Year	Number of workers	Annual average dose (mGy)	Annual collective dose (man Gy)
Australia	Dermatologists	1978	60	1	0.06
	Radiologists and gynaecologists		40	2	0.08
	Radiographers and hospital physicists		350	1	0.4
France	Conventional radiotherapy	1976	947	1.7	1.6
		1977	1005	1.3	1.3
		1978	937	1.4	1.3
		1979	880	1.5	1.3
	Cobalt therapy	1976	1255	2.4	3.0
		1977	1310	2.6	3.4
		1978	1442	2.6	3.7
		1979	1564	1.3	2.0
	High energy therapy	1976	656	1.0	0.7
		1977	727	2.3	1.7
		1978	791	1.4	1.1
		1979	864	0.8	0.7
United States	All therapy a/	1975	20000	3	60

a/ Numbers extrapolated from returns from NRC Licensees [C1].

Table 46

Annual collective dose equivalents in the mid to late 1970s from occupational exposures connected with medical practice, normalized to population
[A10, C1, E1, F2, I9, M15, P3, P7, P8, P9, T1, U3, W2]

Country or area	Estimated collective dose equivalent (man Sv)	Number of workers	Population (10^6)	Annual collective dose equivalent per 10^6 population (10^6 (man Sv per 10^6 population)
Canada	8	32000	24	0.3
France	45	38000	53	0.8
German Dem.Rep.	10	a/	17	0.6
Germany,Fed.Rep.of	50	110000	61	0.8
India	9	a/	600	0.02
Israel	2	1900	4	0.5
Japan	78	110000	116	0.7
Sweden	22	a/	8	2.8
United Kingdom	70	33000	55	1.3
United States	270	100000	210	1.3
Other Asia	3	1300	17	0.2

a/ Not reported.

Table 47

Doses to industrial radiographers in various countries
[A10, B17, C1, C4, M15, P9, S17, S19]

Country	Description	Year	Number of workers	Annual average dose (mGy)	Annual collective dose (man Gy)	MR
Australia a/	Users of open installations, including industrial radiographers	1974	850	2.4	2.0	-
		1978	750	1.3	1.0	-
	Users of enclosed installations, or quality control sources	1974	870	0.1	0.1	-
		1978	780	0.1	0.1	-
Canada	Industrial radiography	1979	1061	3.3	3.5	
France	Industrial radiography	1976	1091	1.5	1.6	0
		1977	1203	1.3	1.6	0
		1978	1351	0.9	1.2	0.1
		1979	1436	1.1		
Japan a/	Non-destructive inspection	1978	3670	1.2	4.3	-
United States (NRC licensed)	Industrial radiography	1974	8792	3 b/	29	0.5
		1975	9178	3 b/	28	0.5
		1976	11245	3 b/	36	0.5
		1977	10569	3 b/	32	0.4
		1978	13093	2 b/	30	0.4
(non-NRC licensed)	Radiography	1970-1975	4300	2	7	0.5
	Analysis		600	0.1	0.1	
	Mixed and other		1700	2	3	0.4

a/ Numbers extrapolated from a survey estimated to cover 50 % of all workers.
b/ Annual average dose to all those monitored; the average to those with measurable doses is in the range 4-6 mGy.

Table 48

Doses to luminizers in various countries
[A10, P3, P7, P8, P9, T1]

Country	Description	Year	Number of workers	Annual average dose (mGy)	Annual collective dose (man Gy)	MR
Canada	Dial painters	1979	3	0.1	< 0.001	0
France	Tritium luminizers	1976	80	3.5	0.3	0.6
		1977	71	4.7	0.3	0.6
		1978	63	6.6	0.4	0.7
		1979	69	6.8	0.5	0.7
Switzerland	Luminizers	1976	208	11	2.2	0.4
		1977	221	11	2.5	0.5
		1978	232	12	2.8	0.6
United Kingdom	Gas luminizers	1975	49	15	0.7	0.7
		1976	41	16	0.7	0.8
	Paint luminizers	1975	97	4	0.4	0.5
		1976	88	5	0.4	0.2

Table 49

Doses to some identified industrial users of radiation in various countries
[A10, B17, R6, S19]

Country	Use description	Number of workers	Annual average dose (mGy)	Annual collective dose (man Gy)	MR
Australia (1978) a/	X-ray analysis, electron microscopy etc.	660	0.1	0.1	-
	Radioactive tracers	720	0.5	0.4	-
	Installation and maintenance engineers	200	0.2	0.05	-
Canada (1979)	Well loggers	685	1.4 b/	1.0 b/	0.1
	Instrument technicians	675	0.4	0.3	0.2
	Laboratory technicians	1790	0.3	0.5	0
	Field scientists/engineers	484	0.7	0.4	0.1
United States (1978)	Well logging	6380	2.7 b/	17 b/	0.3
	Other measuring systems	24720	0.3	6.5	0.1
	Leak test	150	0.7	0.1	0.2
UkSSR	Borehole loggers (neutron sources)	95	5.0 b/	4.9 b/	0.3

a/ Numbers extrapolated from a survey estimated to cover 50 % of workers.
b/ Annual average dose equivalent (mSv) and collective dose equivalent (man Sv) including a contribution from neutrons.

Table 50

Doses to research workers in the United States, 1974-1978
[B17, U7, U8, U9, U17, U18]

Category	Number of workers with measurable dose	Annual average dose (mGy)	Annual collective dose (man Gy)	MR
DOE and DOE Contractors, 1978				
Academic				
Broad	4110	1.3	5.6	0.1
Other	2930	1.2	3.6	0.1
Research and development				
Broad	2361	1.1	2.7	0.2
Other	2120	0.7	1.6	0
Irradiators < 370 TBq	310	1.1	0.4	0.1
Irradiators > 370 TBq	630	1.6	1.0	0.1
Uses of special nuclear material				
Uranium sources	30	2.2	0.1	0.6
Unencapsulated sources	20	9.9	0.2	0.6
Neutron source	530	1.1 a/	0.6 a/	0.2
Other uranium uses	350	2.0	0.7	0.3
DOE Contractors				
Accelerators, 1976	1384	4.8	6.7	0.5
1977	1692	4.7	7.9	0.5
1978	1579	3.6	5.7	0.4
ERDA Contractors				
Accelerators, 1974	2357	4.8	11.3	0.6
1975	2382	4.5	10.7	0.6

a/ Annual average dose equivalent (mSv) and collective dose equivalent (man Sv) including a contribution from neutrons.

Table 51

Doses to research workers in various countries
[F2, I9, M15, P3, P7, P8, P9, T1, W2]

Country or area	Work description	Year	Number of workers	Annual average dose (mGy)	Annual collective dose (man Gy)	MR
Canada	Laboratory scientists	1979	1575	0.3	0.4	0
	Other		2310	0.5	1.0	0
France	Research workers	1976	1729	0.8	1.4	0
		1977	2000	0.9	1.8	0
		1978	2398	0.5	1.2	0
		1979	2856	0.2	0.6	0
Germany, Fed.Rep.of	Research workers	1976	10169	0.4	4.6	-
		1977	12689	0.6	8.0	-
Israel	Research workers	1975	1393	0.3	0.4	-
Japan	Research and education	1978	20000	0.04	0.8	-
Switzerland	Research workers	1976	5046	1.1	5.7	0.2
		1977	6429	0.9	5.6	0.3
		1978	8838	0.7	6.2	0.3
United Kingdom	Research, mainly university	1977	11000	2.5	27	0
Other Asia	Research workers	1975	187	0.4	0.1	0

Table 52

Annual collective dose equivalents in the mid and late 1970s from occupational exposure connected with industry and general research normalized to population

[A10, B17, F2, I9, P3, P7, P8, P9, T1, W2]

Country or area	Estimated collective dose equivalent (man Sv)	Number of workers	Population (10^6)	Annual collective dose equivalent per 10^6 population (10^6 (man Sv per 10^6 population))
Canada	7	8500	24	0.3
France	7	9000	53	0.1
Germany, Fed.Rep.of	50	25000	61	0.8
Israel	1	2000	4	0.3
Switzerland	10	10000	15	0.7
United Kingdom	35	12000	55	0.6
United States	100	110000	210	0.5
Other Asia	1	1100	17	0.06

Table 53

Accidents to workers in the nuclear industry 1945-1979

Year	Description of accident	Dose	Clinical effects
1945	USA. Worker at Los Alamos stacking tungsten carbide bricks around plutonium core accidentally made the system critical. He remained to unstack the assembly. Army guard also exposed [S10, T3]	Total body doses (1) 3 Gy n and γ (2) 1.18 Gy n, 0.02 Gy γ	(1) Vomiting and nausea within 2 h, fever, hair loss, death after 25 days. (2) Some weakness after 60 days.
1946	USA. Worker at Los Alamos was demonstrating the creation of a critical assembly when beryllium shell fell into assembly; six others were exposed [S10, T3]	Total body doses (1) 12 Gy n, 1.2 Gy γ (2) 2.2 Gy n, 0.2 Gy γ (3) 1.2 Gy n, 0.12 Gy γ (4) 0.5 Gy n, 0.05 Gy γ (5) 0.3 Gy n, 0.03 Gy γ (6) 0.25 Gy n (7) 0.25 Gy n, 0.02 Gy γ	(1) Vomiting within 1 h, GI syndrome, fever, death after 9 days. (2) Nausea and vomiting within 6 h, fever, epilation.
1953 or 1954	USSR. Criticality accident at a reactor [G10, T3]	Total body doses (1) 3 Gy; (2) 4.5 Gy	(1) and (2) Nausea and vomiting within 1 h, fever, infection, weakness.
1958	USA. Criticality accident at Oak Ridge in an area where soluble enriched uranium was recovered, as a result of the inadvertent accummulation of aqueous enriched uranium solution in a vessel [C6, H10, A6]	Total body doses (1) 3.7 Gy; (2) 2.7 Gy (3) 3.4 Gy; (4) 3.3 Gy (5) 2.4 Gy; (6) 0.7 Gy (7) 0.7 Gy; (8) 0.2 Gy)	(1)-(5) Nausea after 2-48 h, vomiting (4 only) lymphocytes fell within 48 h and serious depression of white cells and platelets 25-30 days after the accident.
1958	Yugoslavia. Experimental reactor of Vinca became uncontrolled when the amount of heavy water moderator was abnormally increased [A7]	Total body doses (1) 4.36 Gy; (2) 4.14 Gy (3) 4.26 Gy; (4) 4.19 Gy (5) 3.23 Gy; (6) 2.07 Gy	Nausea, depression of white cells and platelets, haemorrhages. (1) died after 4 weeks (1)-(5) bone marrow transplants.
1958	USA. Criticality excursion at the plutonium recovery plant at Los Alamos occurred when excess plutonium was washed into a large vessel. The excursion occurred when the operator started a stirrer. Two other operators exposed to help their colleague [S11]	Total body doses (1) 45 Gy; (2) 1.3 Gy (3) 0.35 Gy	(1) Neurological syndrome, coma within 10 min, erythema, virtual disappearance of lymphocytes with 6 h, death from cardiac failure after 35 h. (2) and (3) Lymphocyte depression
1961	USA. Nuclear excursion at SL-1 reactor at Idaho probably due to an excessive withdrawal of the central control rod. Hot water expelled violently from core [C7, P11]	Total body doses (1) 0.3-78 Gy (2) 19-100 Gy (3) 350 Gy	All died as a result of the explosion.
1962	USA. Criticality excursion at Hanford plant when excess plutonium bearing waste was added to a small tank [F3]	Total body doses (1) 0.63 Gy γ; 0.2-0.3 Gy n (2) 0.23 Gy γ;0.09-0.12Gy (3) 0.13 Gy γ; 0.03 Gy n	(1) Fever, depression of lymphocytes.
1964	USA. Criticality excursion at Wood River Junction uranium recovery plant. Technician poured concentrated liquor into a tank, mistaking it for slightly contaminated trichloroethane. Second excursion occurred when tank stirrer was turned off exposing two supervisors [A8, P12]	Total body dose (1) 12-46 Gy n (2) 0.06-0.2 Gy n (3) 0.28 Gy n	(1) GI prodrome within minutes, death after 46 h.

Table 53, continued

Year	Description of accident	Dose	Clinical effects
1965	Belgium. Nuclear excursion in experimental reactor during manual displacement of control rods [B9, N2]	Dose to left foot 39 Gy γ, 4.2 Gy n Dose to abdomen 0.5-8 Gy Dose to head > 3 Gy	GI prodrome, haematological depression, reverse barrier nursing bone marrow transplant, fever, necrosis and amputation of left foot.
1968	UK. Scientist handled highly active fuel element section [P13]	Total body dose 0.15 Gy	Burns on thumb and two fingers on right hand.
1976	USA. Worker injured by the chemical explosion of an ion exchange column used for americium recovery at Hanford [H12]	Dose up to 1978 bone 8.6 Gy; lung 2.0 Gy; liver 1.6 Gy; Dose to bone expected to continue at 10 mGy d^{-1}	Ulcer near right eyebrow. Some depression of lymphocytes. Patient decontaminated and treated with DTPA.

Table 54

Accidents to workers in non-nuclear industry (excluding industrial radiography) 1960-1979

Year	Description of accident	Dose	Clinical effects
1960	USA. Worker exposed to an electron beam [U12]	Dose to face 7.6 Gy	Multiple burns to middle section of face, abdomen and hands
1965	USA. Worker entered room where linear accelerator was scanning products on conveyor belts with an electron beam by going under the barrier. He placed a mould on the conveyor belt near the output port of the accelerator [L5]	Dose estimates Interior of body 0.002-0.05 Gy Anterior and right surface 2.4-3.3 Gy Eyes 0.43 Gy Right toes 110 Gy Right instep 290 Gy Right 5th digit 420 Gy Right thumb 2400 Gy	Erythema on right hand and foot within 4 h. Right arm amputated above elbow. Right leg amputated above knee
1965	USA. Two operators exposed to radiation from a fluoroscope with a broken interlock [V2]	Not quoted	Burns on hands
1967	India. Cobalt-60 teletherapy source jammed during transfer. Operator, wearing lead gloves, inserted source manually [B12]	Dose to skin approximately 80 Gy	Burning and blisters on one hand
1967	USA. Operator bypassed interlocks and energized a fluoroscope during cleansing [V2]	Not quoted	Several burns to exposed parts of body
1969	USA. Two service engineers bypassed safety circuits and energized a spectrometer	Not quoted	Burns on hands
1970	USA. Factory worker exposed hands when he failed to observe that warning light on unit (unspecified) was on [V2]	Not quoted	Burns on hands
1971	USA. Two factory workers exposed to radiation from a fluoroscope [V2]	Not quoted	(1) Blistering on right index fin (2) Burns and blisters covering both hands and open lesions on three fingers on each hand
1971	USA. Operator exposed to 300 TBq cobalt-60 source at an irradiation facility when he entered the room while the source was exposed [V3, P16]	Total body dose 1.27 Gy Dose to right hand 2-12 Gy	Vomiting, haematological depression, pain in fingers and palm of right hand
1971	USA. Factory worker's hands were exposed to the beam from fluoroscope which still emitted x rays with the top open because of faulty wiring [V2]	Not quoted	Erythema on hands
1971-1972	UK. Engineer servicing x-ray equipment received high dose to fingers on three occasions [P17]	Dose to fingers several hundred Gy	Small burn on fingers
1972	UK. Engineer servicing x-ray crystallography equipment at a Technical College exposed to a narrow beam of x rays because the shutter had been removed [L7, P15]	Dose to two fingers 15-20 Gy	Burn, which subsequently healed, on two fingers
1974	USA. Operator entered cobalt-60 irradiation cell believing that the 4 PBq source was in its storage pool [S14]	Total body dose 1.65-4 Gy	Vomiting, depression of haemopoietic system. In reverse isolation for 6 weeks

Table 54, continued

Year	Description of accident	Dose	Clinical effects
1974	USA. Three workers exposed to x rays from a quantometer when the beam inadvertently remained on during maintenance [V2]	Not quoted	(1) and (2) Burns on hands (3) required hospitalization
1974	USA. Serviceman exposed to x rays from a research spectrometer when his partner accidently energized the tube [V2]	Not quoted	Erythema on right hand
1975	Italy. Worker exposed to cobalt-60 radiation at an agricultural installation [N2, L8]	Total body dose 10 Gy	Death
1976	USA. Worker exposed to radiation from an x-ray analyser while making a repair when the unit was on [V2]	Not quoted	Burns on fingers
1976	USA. Operator exposed while cleaning the vacuum x-ray quantometer because the microsafety switch failed as a result of faulty wiring [V2]	Not quoted	Burns on right hand and finger
1977	USA; Operator entered cobalt-60 irradiation cell while the 20 PBq source was exposed. The interlock system had been deactivated [S15]	Total body dose 2 Gy	Nausea, hair loss, light erythema, depression of haemopoietic sustem, kept in reverse isolation
1977	USA. Operator exposed fingers while attempting to adjust lead aperature diaphragm on a diffractometer [V2]	Not quoted	Burns on 2 fingers
1977	USA. Repairman exposed during check of vacuum leak on a spectrometer as a result of failure of automatic cut-off switch [V2]	Not quoted	First degree burns to face and finger tips
1978	USA: Operator of a fluoroscope at a soup company exposed when relay on the door interlock fused [V2]	Not quoted	Pigmentation on back of hand

Table 55

Accidents to workers in industrial radiography 1960-1979

Year	Description of accident	Dose	Clinical effects
1960	USSR. A demented person placed a caesium-137 source in his trouser pocket [D4]	Total body dose 14.8 Gy Maximum dose to skin 1650 Gy	GI prodrome after 7 h, necrotic skinlesions, death after 18 d.
1967	USA. Two radiographers exposed when 2.6 TBq source became disconnected from its control cable [M13]	(1) Total body dose 0.2 Gy Dose to right hand 40-60 Gy (2) Total body dose 0.15 Gy	(1) Hand oedema, formation of vesicles, slight atrophy of finger
1968	Argentina. Worker carried 0.5 TBq caesium-137 source in his trouser pockets for 18 h [B14]	Total body dose 0.5 Gy Maximum skin dose to thighs 17000 Gy Dose to gonads 20 Gy	Necrotic lesions on thighs, desquamated surface of scrotum and base of penis. Ulcers on right hand. Both legs amputated
1968	FRG. Worker carried iridium-192 source in jacket pocket [S16]	Total body dose 1 Gy Maximum dose to pelvis and thigh 40-60 Gy	Aspermia Inflammatory skin alterations
1968	India. Worker picked up a 52 GBq iridium-192 source which had fallen from a radiography camera and kept it in his pocket for 2 h [A9]	Dose skin near source 130 Gy Dose to testes 1.3 Gy	Ulcer wound took a year to heal completely. Sterility 2 years
1969	UK. Radiographer exposed to gamma-radiation from a 0.9 TBq iridium-192 source while travelling in a car with the source housing open. Also believed to have placed a source in his breast pocket for a short while. Both occurrences denied by individual [H16]	Total body dose 0.6 Gy Dose to small area of chest 20-200 Gy Dose to wrist, finger tips 15 Gy	Chest inflammation, blistering necrotic tissue, involving ribs and heart. Skin graft required, left wrist and finger tips lesions and blistering
1970	UK. Worker exposed while carrying a 0.8 TBq iridium-192 source up a ships ladder with the container open [P13]	Dose to irradiated area not quoted Dose at chest level 300 μGy	Erythema on thighs, septic spot and reddish mottling

Table 55, continued

Year	Description of accident	Dose	Clinical effects
1971	Japan. Construction worker found an iridium-192 source in a shipyard and took it back to his lodging. Five other people were exposed during the 8 d before it was recognized. Some handled the source [K7]	Total body dose (1) 1.3-1.5 Gy; (2) 0.5 Gy (3) 0.1-0.4 Gy; (4) 0.2-0.25 Gy; (5) 0.13-0.17 Gy (6) 0.15-0.16 Gy; (2) Maximum dose to skin of hip 30-60 Gy (1, 2, 3) Dose to skin of hands 26-90 Gy	(1) GI prodrome (1, 2, 3) skin lesions, lesions on hip of (2) removed surgically (1, 2, 3, 4) depression of blood cells
1971	UK. Worker handled 0.2 TBq iridium-192 source [P15]	Dose to finger 30 Gy	Burns on finger tips
1972	FRG. Worker at Bremen exposed to a 1.1 TBq iridium-192 source [S20, S21].	Total body dose 0.3 Gy Dose to hand 50 Gy	Erythema and moist desquamation. Necrosis followed by amputation of finger
1974	Middle East. Radiographer exposed when iridium-192 source became detached and lodged in the delivery tube for 2-3 d [P18]	Total body dose 0.3 Gy	Pain and swelling in leg and loss of hair
1975	Iraq. Radiographer exposed to 2.3 TBq iridium-192 source [L10]	Total body dose 0.27 Gy	Burns on several fingers
1976	USA. Radiographer approached and unscrewed source tube while the 3.5 TBq iridium-192 was not fully retracted into its shield [U13, U4]	Total body dose 0.05 Gy Dose to hand 4.48-37.21 Gy	Erythema and thickening of skin on palm of right hand
1976	USA. Radiographer touched a guide tube containing an unshielded 6.1 TBq cobalt-60 source. He had overridden the radiation alarm system [U13, U4]	Dose to hand 15 Gy Dose to lens 0.09 Gy	Erythema and dry desquamation of left hand
1977	UK. Radiographer working in a confined space held a 0.8 TBq iridium-192 source with his finger tips for 90 s whilst radiographing a weld [L9]	Total body dose 0.1 Gy	Burns on three fingers
1977	South Africa. Maintenance engineer picked up a 0.25 TBq iridium-192 source from a factory floor without recognizing it. He showed it to several colleagues and took it home. Doses to three most exposed individuals given [L9, B16]	Total body dose (1) 1.16 Gy; (2) 0.17 Gy (3) 0.1 Gy Maximum skin dose (1) 50-100 Gy	(1) Burns on chest and hands, skin graft on chest

Table 56

Accidents to workers in research and development (excluding nuclear industry) 1960-1979

Year	Description of accident	Dose/activity	Clinical effects
1960	USA. Graduate student exposed to a 7 TBq cobalt-60 source when it became detached during irradiation of samples [R5]	Total body dose 2.5-3 Gy Maximum dose to skin 30 Gy	GI prodrome, depression of white cell count, necrotic lesion on stomach, sterility
1965	USA. Researcher assumed diffractometer was off, removed shielding and reached inside to change samples [V2]	Not quoted	Burns to three fingers
1965	USA. Chemist exposed to primary beam of spectrometer when interlocks failed [V2]	Not quoted	Burns to fingers
1967	USA. Technician exposed for 20 min to the beam of a Van de Graff generator [V2]	Not quoted	Nausea, amputation of legs and arms
1970	Australia. Three workers exposed to low energy radiation from a wrongly assembled x-ray analysis unit [L11]	Dose to skin (1) Abdomen 15-45 Gy Hands 20 Gy (2) Arm 4-15 Gy Hands 15 Gy (3) 0.14-0.5 Gy	(1, 2) Erythema and dry desquamation (3) No clinical symptoms
1970	USA. Scientist removed valuable specimen from spectrometer bypassing interlocks because he feared he would lose it [V2]	Not quoted	Moderate conjunctive infection, blisters and erythema on fingers
1971	USA. Chemist exposed two fingers because he did not realize his hand was in an unfiltered beam of x rays from a diffraction apparatus [V2]	Not quoted	Swelling and stiffness of knuckles

Table 56, continued

Year	Description of accident	Dose/activity	Clinical effects
1973	USA. Chemist looked directly into primary beam from a diffractometer while aligning the beam [V2]	Not quoted	Burns to eyes
1974	USA. Technician in a geological survey laboratory held an energized fluoroscopic tube near to his chest while testing for a vacuum leak [V2]	Not quoted	Severe erythema of chest
1974	USA. Radiochemist placed hands near the beam port of a spectrometer not realizing it was on [V2, U12]	Dose to hand 24-48 Gy	Some loss of tissue and function to left index finger and injuries to several other fingers and right thumb
1975	USA. Chemist exposed to x rays when the shutter on a diffractomer failed [V2]	Not quoted	Burns on index and middle finger
1976	USA. Research worker inadvertently moved lead shielding plate while aligning the beam of a diffractomer [V2]	Not quoted	Burns on palm of hand
1977	USA. Research worker exposed hands while changing samples in a diffractometer because safety cut-off system had defective wiring [V2]	Not quoted	Burns and swollen hands
1978	Switzerland. Physicist handled a silver source which had been irradiated in a research reactor [P8]	Dose to fingers 20-100 Gy Total body dose 0.007 Gy	Second degree burns on fingers
1978	USA. Worker exposed near view port of a linear accelerator while attempting to cure a problem with insulation [V2]	Not quoted	Blistering on lips, back of hands and reddening of thighs and stomach

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ANNEX I

Genetic effects of radiation

CONTENTS

Introduction

1. The 1977 UNSCEAR report [U1] presented a detailed review of the genetic effects of ionizing radiation. This Annex is aimed at an updating of the 1977 report, especially those parts that require significant revisions in the light of new data. Particular emphasis is given to those data that are relevant to the evaluation of genetic radiation hazards in man.

I. HUMAN DATA

A. NATURALLY-OCCURRING HEREDITARY DISEASES AND DEFECTS

2. In the 1977 report, the results of the British Columbia Survey [T1] on the frequency of liveborn individuals affected by hereditary or partially hereditary defects and diseases were presented. These results and considerations based on the degree of completeness of reporting in the Registries used as data-source and possible biases due to delay in disease onset, migration etc., allowed an estimate of 9.44% for the total frequency of diseases believed to be of genetic origin (0.12% autosomal dominant and sex-linked diseases, 0.11% recessive and 0.20% chromosomal ones, 4.28% congenital malformations and 4.73% other multifactorial ones).

3. The Committee reappraised the above figures, taking into account Stevenson's data from the Northern Ireland Survey [S1], the results from several ad hoc surveys for specific dominant conditions (reviewed in reference [V1]), data from newborn surveys for chromosomal anomalies and the uncertainties involved in the aetiology of diseases classified as congenital malformations, multifactorial diseases and irregularly inherited diseases. It was concluded that for the purpose of estimating genetic radiation hazards in man, it is appropriate to use the following revised figures (adding up to a total of 10.5%): (a) 1.0% dominant and X-linked diseases; (b) 0.1% recessive diseases (excluding those maintained through heterozygous advantage); (c) 0.4% chromosomal diseases; and (d) 4.3% congenital malformations, and 4.7% other multifactorial and irregularly inherited diseases, together, 9%.

4. Some new information has become available since the 1977 report. Czeizel [C1] has published the results of a nation-wide survey on congenital malformations in 1970 in Hungary. The classification of these malformations into the various categories and sub-categories has been based on the International Classification of Diseases [W1], with some modifications. The data cover a 7-year period (1970–1976) and involve a total of 1 188 509 births of which 10 658 were stillbirths, the rest being livebirths. The frequency of malformed babies varied from 2.2% in 1970 to 3.7% in 1976 with an average of 3.1%. These figures are very similar to that given as a minimal estimate (3.6%) for the British Columbia data by Trimble and Doughty [T1]; the latter estimate however relates to livebirths only. Czeizel et al. [C2] noted that, for the period 1972–1975, the incidence of multiply-malformed babies ranged from 7.5 to 8.5% of all notified congenitally malformed ones suggesting that from 2.6 to 2.9 per 1000 total births showed multiple malformations; the majority of these were found to be severe: 6.9% of such babies were stillborn and 45% of those that were liveborn died during infancy.

5. The Hungarian Congenital Malformation Monitor, operational since the beginning of 1973, makes use of the so-called indicator congenital malformations[1] to monitor the temporal and spatial trends in the incidence of these malformations. During the period 1973–1976, trends for a continuous increase were found for three of the indicator traits: congenital dislocation of the hip, congenital limb reduction and hypospadias [C3]. Czeizel [C3] suggests that these trends may be related to the more complete notifications although the increase in limb reduction deformities is only partly explained by this factor. Other trends noted were of a transitional type, i.e., increases for short periods (e.g., anencephaly in the fourth quarter of 1974; spina bifida in the second quarter of 1974, in the third quarter of 1975 and in the fourth quarter of 1976; cleft lip ± palate in the third quarter of 1973). While statistical analysis revealed that these trends are not due to chance, Czeizel has stressed the point that the contribution of three possible technical biases (changes in diagnosis, notification and evaluation of the given congenital malformation) must first be excluded before the trends become amenable to meaningful interpretations or to the search for causal factors.

6. In their extensive paper, Myrianthopoulos and Chung [M52] have reported the results of a comprehensive prospective study of congenital malformations in children born in the Collaborative Perinatal Project (CPP: a cooperative endeavour of twelve institutions throughout the United States and the National Institute of Neurological Diseases and Stroke of the National Institutes of Health, set up in 1959). Pregnant women have been followed from the first months of their pregnancy through labour and delivery and the children born to "project mothers" were followed up to one year of age. The project population was classified by the researchers in the United States as about 45% "white" and 55% "non-white".[2] The collection of information, medical examinations and laboratory tests have been done in uniform fashion and according to pre-established protocols.

7. The total data pertain to 53 394 single deliveries including 52 390 live births and 1004 foetal deaths; in 137 of the total, the sex of the children was not known either because they were macerated foetuses or because, for one reason or another, they were lost to the study. All analyses were based on 53 257 deliveries with known sex; 15.6% of the children (8288 out of 53 257) were born with known malformations, 13.0% or 6906 with single and 2.6% or 1382 with multiple malformations.

8. The authors point out that the high rate of malformations found in this study (relative to others published in the literature) can be explained on the basis of the period of time through which the malformations were observed and the conditions which made almost complete ascertainment possible: only about one-third of malformations observed during the first year of life were diagnosed at birth.

9. Other interesting findings that emerged from this study include the following: (i) major malformations (e.g., anencephaly, microcephaly, congenital dislocation of the hip, cataract, cleft palate, cleft lip, pyloric stenosis, hypospadias, cystic kidney etc.,) were present in about 7% of the children, minor malformations (e.g., polydactyly, syndactyly, low set ears, supernumerary nipples etc.,) in about 7% of the children and a combination of major and minor in about 1% of the cases; of the major malformations, about 42% were multiple and

[1] Those that can be diagnosed easily and unequivocally within the first six days of life: anencephaly, spina bifida, hydrocephaly, cleft palate, cleft lip ± palate, oesophageal atresia, rectal atresia,hypospadias, reduction deformities of the limbs, congenital hip dislocation and Down's syndrome.

[2] The mention of racial or ethnic groups reported here or elsewhere in this report does not imply that the United Nations accepts or recognizes such categories.

of the minor malformations, about 25% were multiple; the cardio-vascular system had the highest frequency of multiple malformations (about 80%); (ii) the highest incidence of malformations was found among neonatal deaths and deaths which occurred during the first year of life; (iii) males had significantly more malformations than females and this was entirely due to an increase in the frequency of major malformations; and (iv) there were no significant differences in the overall frequencies of major malformations between "non-whites" and "whites", but the "non-whites" had significantly more minor malformations than "whites", largely due to an increase in "non-whites" of polydactyly, branchial cleft anomalies and supernumerary nipples; the frequency of multiple malformations was significantly higher in "whites" than in "non-whites".

10. Leck [L2] summarized the estimates on prevalence rates at birth for several potentially lethal or handicapping malformations in the United Kingdom (excluding Down's syndrome; data derived from different sources; see Leck [L2] for details). For this purpose, data on cardiac malformations, pyloric stenosis, non-postural talipes equinovarus, hydrocephaly, penial and perineal hypospadias and many others were included. Conditions of minor importance (i.e., those that cause no appreciable handicap or threat to life) such as accessory auricle, glandular hypospadias, most postural foot deformities, polydactyly, syndactyly, etc., were excluded. The overall estimate is 24.4 cases per 1000 total births. In terms of severity (expressed as percentage alive five years after birth), about four-sevenths of the children with cardiac malformations (prevalence at birth: 6.5 per 1000) and two-thirds of all the malformed survive up to that age.

11. Leck also examined the transmissibility of the common malformations mainly using figures on frequency in sibs and offspring of index patients published by Carter [C6]. These data, summarized in Table 1, show that the percentages of first-degree relatives affected (in each case by the same malformation as the index patients) all lie between 2 and 5%, except for pyloric stenosis and hip dislocation (which are very much commoner in one sex than in the other); the recurrence risk seems to be higher when the index patient is of the less frequently affected sex. These findings are consistent with the hypothesis that the aetiology of each of the common defects involves a multiplicity of causes, some genetic and some environmental. The rates are all much lower than expected if single genes with complete penetrance for major effects were involved.

12. Altukhov [A1] compared the rates of occurrence of rare electrophoretic variants (i.e., those with an altered electrophoretic mobility or activity) in normal healthy newborns (group a), in premature infants and in babies with multiple congenital malformations (group b). The sample sizes for groups (a) and (b) were, respectively, 504 and 227, although the number of individuals screened for any given enzyme varied from 156 to 504 (a) and from 82 to 227 (b). Over twenty genetic loci coding for the synthesis of enzyme proteins and erythrocyte antigens were studied. Five variants were found in group (a) and 15 in group (b). As it was possible to exclude familial variants, it would appear that a much higher rate of incidence of these variants in premature infants and in those with multiple congenital malformations is of significance.

13. Recently, there has been considerable discussion by Neel [N1, N2, N3] on the contribution of mutation to ill-health in man. He has argued that current and anticipated developments in research[3] are likely to lead to a significant upward revision of the UNSCEAR [U1] estimates of the frequencies of dominant, sex-linked and chromosomal diseases; and, more importantly, that the "UNSCEAR report probably grossly underestimates the contribution to disease of mutations which technically must be classified as 'recessives'". The latter argument rests on the following considerations.

14. The existence of a wide range of diseases known to be due to the absence of activity of an enzyme or of a transport or receptor protein is now amply documented. For instance, many of the classical "inborn errors of metabolism" (reviewed in [H1, K1]) are associated with the absence or near-absence of enzymatic activity as are some of the inherited bleeding disorders, thyroid disorders (reviewed by [S2]) and a class of non-spherocytic haemolytic anaemias due to the absence or near-absence of enzymes such as pyruvate kinase, hexose kinase, glucose-phosphate isomerase, etc. (reviewed by [M1]). The defects in DNA repair mechanisms now known in the various forms of xeroderma pigmentosum, ataxia telangiectasia and Fanconi's anaemia are the result of enzyme deficiencies. Familial hypophosphatemic rickets, Hartnup disease and a dozen other rare entities are probably due to the absence or malfunction of a transport protein (reviewed in [S3]), and testicular feminization and the severe form of familial hypercholesterolaemia are due to absence or malfunction of a receptor protein [A2, G1, M2]. These defects are all due to what in the past have been termed "null" mutations, usually with, in classical terminology, a recessive form of inheritance although heterozygotes when properly studied show impaired activity as well. Since it is difficult to envisage heterozygote advantage for these null mutants, it seems likely that most, if not all, are maintained by mutation pressure.

15. A rough idea of the magnitude of the total impact of this type of mutations can be arrived at through the following lines of reasoning. Based on a study of five enzymes in Drosophila, Mukai and Cockerham [M3] estimated that null mutations (characterized by the loss of enzyme activity) arise at a rate of 1.0 10^{-5}/locus/generation whereas electrophoretic variants arise at a much lower rate (0.2 10^{-5}/locus/generation) giving a ratio of 5 nulls: 1 electrophoretic variants. In Amerindians, Neel et al. [N4] estimated that mutations resulting in electrophoretic variants of a series of proteins of the blood serum and erythrocytes occur at a rate of 1.6 10^{-5}/locus/generation. If it is assumed that the rate in man is only 1.0 10^{-5}/locus/generation for electrophoretic variants, and if the ratio of nulls to electrophoretic variants is only 2, then null mutations for a given polypeptide should be expected with a frequency of 2 10^{-5}/locus/generation.

16. In man, there must be at least 5000 proteins whose absence or failure of function can lead to diseases such as those mentioned in the preceding paragraphs. Assuming no allelism, equilibrium between input and

[3] For instance, McKusick's 1978 catalogue [M16] lists 736 proved autosomal dominant (+753 probable ones), 521 proved autosomal recessive (+596 probable ones) and 107 proved X-linked (+98 probable ones) diseases in man. In the 1975 catalogue [M17] the respective numbers were: autosomal dominants: 583 (+635); autosomal recessives: 466 (+481) and X-linked ones: 93 (+78).

loss of mutants in the population, no heterozygous advantage or disadvantage and neglecting linkage, the probability that a zygote would be homozygous for at least one of these is ($1-0.99998^{5000}$) or 0.095. While there is no doubt that this estimate needs to be viewed with many reservations, it does serve to illustrate the point that the impact on health in toto of this class of mutations may exceed the commonly visualized gross phenotypic abnormalities.

17. To what extent null mutations contribute to foetal loss in humans is not known. In Drosophila, null homozygotes or null/deficiency heterozygotes at 12 out of 13 autosomal loci studied are viable and fertile [O1, O2]. Neel points out that this is certainly not the case with all null mutants in humans and that the apparent difference between Drosophila and man may be an artifact, i.e., flies with the degree of impairment experienced by many of the human null homozygotes are probably so inviable as to preclude scoring. He speculates that the null homozygotes may make a significant contribution to the relatively high foetal loss in humans, but the demonstration that as much as 50% of recognized foetal losses are due to one or another kind of chromosome anomaly [C4] "preempts a large part of that selection arena" [N1, N2, N3]. While the proportion of null homozygotes that survive to term is not known, it is probably a sizeable fraction. Furthermore, since the accumulation in the gene pool of null mutations should facilitate the expression of classical recessive genes, one cannot, by invoking intrauterine selection against most of them, dismiss the nulls as scarcely contributing to the social burden of mutation [N1, N2, N3].

18. Carter [C51] who recently examined the above arguments and their implications, points out that the thesis that almost 10% of foetuses are homozygous for a null mutation and that a substantial proportion of null homozygotes may survive to term is difficult to reconcile with the current stillbirth, infant and childhood mortality figures which in some areas are each well below 1% and the majority of which are caused by prematurity and congenital malformations, which are not recessive conditions; spontaneous abortions which occur at about 150 per 1000 recognized pregnancies offer more scope, but, as Neel notes, as many as half of these are due to chromosomal abnormalities, and others will have purely obstetrical causes. Neel's estimates imply that, on the average, every individual is heterozygous for about 50 null mutants; this is also difficult to reconcile with the health of most children born to first-cousin marriages, since zygotes conceived in such marriages, would be homozygous for one to two null mutants on the average; furthermore, first-degree incestuous unions (where zygotes would be, on the average, homozygous for six null mutants) would be almost incapable of producing viable children and this is not the case. As Carter stated, if "recessive" null mutations do occur with the frequency Neel suggests, then "... one must assume that their gene frequency is kept low in the population by selection against them in heterozygotes and ... are best classed with the dominants" [C51].

B. EFFECTS OF RADIATION: HIROSHIMA AND NAGASAKI STUDIES

19. Neel et al. [N20], Satoh et al. [S132], Schull, Otaka and Neel [S130] and Schull et al. [S131] have presented some preliminary results of their continuing studies on mutations affecting protein structure in the children of atomic bomb survivors of Hiroshima and Nagasaki. The papers of Satoh et al. [S132] and of Schull et al. [S131] are the most recent ones. The study populations consisted of children born to "proximally exposed" parents whose average conjoint gonadal dose was approximately 0.59 Sv and those of "distally exposed" parents estimated to have received less than 0.01 Gy. The total number of children identified in each of the groups is well over 27 000. The mutation data pertain to variants of 28 different (erythrocyte and plasma) proteins analysed using one-dimensional electrophoresis and involved the equivalent of 419 666 and 282 842 locus tests, respectively in the first and second groups. Once a rare variant was encountered, its occurrence was verified in a second sample and studies of both parents and available siblings were carried out. In the event that neither parent exhibited the variant, appropriate serological studies were performed to resolve possible discrepancies between the stated and biological parentage.

20. Thus far two probable mutations have been observed in children of proximally exposed parents. One is a slowly migrating variant of glutamic pyruvate transaminase and the other, a slow migrating variant of phospho-glucomutase-2. No probable mutations have been found in the children of distally exposed parents. Schull et al. [S131] point out that the number of mutations observed is still too small to provide a meaningful estimate of mutation rates. (Data on chromosomal aberrations in the children of survivors of Hiroshima and Nagasaki are discussed in Section C.)

C. NUMERICAL AND STRUCTURAL CHROMOSOME ABNORMALITIES

1. Surveys of newborn children

21. In its 1977 report, the Committee discussed the results of surveys carried out in different parts of the world on the cytogenetic analysis of chromosomes in peripheral blood lymphocytes of liveborn infants. The data available at that time showed that out of 55 679 babies examined, 336 (0.60%) had abnormal chromosome constitutions (pooled data). The break-down of the above frequency was: 0.22% sex chromosomal anomalies; 0.14% autosomal trisomies; 0.19% autosomal structural euploid abnormalities (Robertsonian and reciprocal translocations) and 0.5% autosomal structural aneuploid anomalies. The karyotypes were examined with conventional staining techniques except in the Hamilton Survey [L1] in which banding methods were used.

22. The compilation of Hook and Hamerton [H3] focuses attention on consecutive newborns only, and includes additional data from the Boston survey [W2] but excludes the data of Lin et al. [L1] and those of Bochkov et al. [B1] (these were included in the 1977 report). The basis for exclusion of the data mentioned above was the use of banding techniques in the work of Lin et al. (and conventional techniques in the case of others) and the possibility of some selection in the study of Bochkov et al. However, the frequencies of chromosomally abnormal infants recorded in these two surveys (0.48% in the work of Lin et al. and 0.76% in that of Bochkov et al.) fall within the range of frequencies recorded in the other surveys (0.48% in London, Canada; 0.47% in Winnipeg, Canada; 0.83% in Arhus, Denmark; 0.67% in Edinburgh, United Kingdom;

0.61% in Boston, United States and 0.50% in New Haven, United States).

23. Buckton et al. [B20] and Maeda et al. [M53] have now published the results of other newborn cytogenetic surveys carried out in Scotland and Japan, respectively (referred to as Edinburgh-UK-II and Kanagawa, Japan in Table 2). The Edinburgh survey includes: all babies born alive in one of the Edinburgh hospitals sampled previously [J2]; and all babies born alive in 1976 and most of 1977 in a maternity hospital in the Fife region. A total of 3993 babies were karyotyped of which 3835 could be analysed using G-banding. The Japanese data pertain to 2626 consecutive newborns screened in one hospital. Banding techniques were used. The data from these studies are summarized in Table 2. Not included in this table are the data of Turner and Wald [T3] and those of Higurashi et al. [H36, H48]; the reasons for this will be discussed later.

24. It can be seen that of the 424 (0.63%) chromosomally abnormal infants, 158 (about one-third) carry sex-chromosomal anomalies. There are 95 (about one-quarter), numerical autosomal anomalies; there are 134 (about one-third), balanced structural anomalies[4] and 37 (about one-tenth), unbalanced structural anomalies. The incidence of sex-chromosomal anomalies alone is 3 per 1000 male births and 1.5 per 1000 female births. Of the autosomal numerical anomalies (1.4 per 1000 births), the +G anomalies (Down's syndrome) constitute the predominant group. Among the balanced autosomal structural anomalies (2 per 1000), reciprocal translocations and Robertsonian translocations are about equally frequent; among the latter, those involving two D group chromosomes are more common (48 out of 60) than those involving D and G group chromosomes. Finally, aneuploid structural abnormalities occur at a frequency of about 0.6 per 1000 births.

25. Turning now to results not included in Table 2, the work of Turner and Wald [T3] on newborns at Magee Women's Hospital in Pittsburg was carried out between 1962 and 1964 and was published only in 1970. In this study which involved 1000 infants (517 males and 483 females), very strict attention was paid to randomization: neonates born were selected for study by the use of a random sampling frame in which one of the six four-hour time periods of each of the first four days of the week was chosen by random numbers; the first four deliveries of the selected periods were studied. Details of other aspects of the randomization procedures are given in the paper of Turner and Wald [T3].

26. The number of chromosomally abnormal babies in the above study was 33 (i.e., 3.3%; 2% with sex-chromosomal anomalies and the remainder with autosomal anomalies). This frequency is about five times higher than that reported by others and different from that of any other single study (see Table 2). The increase was in all types of abnormalities with the exception of 47, +21. Hook and Hamerton [H3] have suggested several possible reasons for this discrepancy, but none appear to be satisfactory and no further information from this study appears to be available.

[4] At least in two of the three studies in which banding procedures were used (Hamilton and Edinburgh-II), the frequencies of balanced reciprocal translocations and inversions tend to be slightly higher than in those in which such procedures were not used. This may suggest that without the use of banding procedures the frequencies of chromosomal abnormalities of these kinds may be underestimated.

27. The design of the study of Higurashi et al. [H36] on the incidence of chromosome anomalies in newborns in a Tokyo maternity hospital differed in several respects from those of others. Firstly, cytogenetic analysis of the karyotypes was not carried out for all the babies. The babies were first screened for clinical manifestations during the first day of life; a buccal smear was obtained for an examination of both X and Y chromatin (primary screening method). A secondary screening included repeated buccal smears and lymphocyte analysis for Y chromatin after two or three months and this was done to ensure that there were no false positives or negatives. All suspected cases were examined by detailed chromosome analysis. Secondly, babies thought to have congenital malformations were re-examined and this included a study of their dermatoglyphic patterns (in the experience of the authors, malformations associated with mental retardation and abnormal dermatoglyphic patterns were strongly suggestive of autosomal aberrations [H37]). Those judged abnormal by the criteria of malformations, dermatoglyphic patterns, low birth weight (and history of abortions in the mothers) were then examined through analysis of karyotypes.

28. Of the 3311 phenotypically normal male babies studied through analysis of sex chromatin, 31 were suspected of possibly carrying sex-chromosomal anomalies; chromosome analyses of these showed two cases of 47,XXY, two of 47,XYY and one of 46,XY,-D,5 t(Dp;Yq). In 2054 phenotypically normal female babies likewise examined, sex-chromosome anomalies were suspected in 21 and out of the latter, one had a 45,X karyotype.

29. For autosomal anomalies, the total number of babies initially screened was larger. Of the 12 319 babies (total sample), 694 were suspected of having autosomal anomalies (353 males and 341 females). Of the 694, two were +13, three were +18 (with one case of mosaicism), eleven were +21 (with one case of mosaicism), one with B5p partial trisomy and one which was 5p– (cri-du-chat syndrome). The total frequency of chromosomally abnormal individuals in this study (25 in 12 319) cannot be readily compared with those obtained in other studies because the design is different; this is true also of some individual classes (sex-chromosomal aneuploidies, autosomal trisomies).

30. The other study of Higurashi et al. [H48] was focused on ascertaining the birth frequency of multiple congenital anomalies in new-born infants (14 430 newborns out of which 7455 were males and 6975 were females). It was found that 33 of the babies had multiple congenital anomalies. The birth frequencies of the three major trisomies (13, 18 and 21) were, respectively, 0.14, 0.21 and 1.11 per 1000 births, in good agreement with those recorded in the other surveys listed in Table 2. The authors point out that most cases of sex-chromosomal anomalies remained undetected as these showed no obvious manifestations at birth.

2. Clinical significance of chromosome abnormalities

31. Hook and Hamerton [H3] used the data pertaining to the 56 952 babies reviewed in their paper to estimate the frequency of "clinically significant" abnormalities. The authors included in this category all the non-mosaic XXY and 45,X instances, XYY and XX (male) genotypes, all autosomal trisomies and all unbalanced structural rearrangements reported to have been

associated with congenital malformations at birth. The balanced structural abnormalities and sex-chromosomal mosaics were excluded. The reasons for the exclusion of the latter were: (a) the variation in ascertainment between the studies; (b) the lack of information on the extent of abnormalities in the tissue concerned; and (c) the inability at present to decide about the clinical significance of mosaicism detected in peripheral blood lymphocytes in phenotypically normal babies.

32. The estimate arrived at is 2.91 per 1000, i.e., about one-half of the total of all chromosomal anomalies detected in newborns. If the XYY and XX (male) karyotypes are excluded, the rate is 2.27 per 1000. An analysis by sex of those affected indicated that the rate in male newborns is about twice as high as in females primarily because of the unequal contribution of the sex-chromosomal abnormalities judged by these authors as "significant". If one excludes the XYYs and XX males, the rate is still 60% higher in males.

33. An extension of the criteria used by Hook and Hamerton to the total data given in Table 2 gives a rate of about 3.3 per 1000 for the abnormalities that may be deemed to be "clinically significant", again about one-half of all the abnormalities detected in newborns. If the XYY and XX (male) genotypes are excluded, the rate is 2.6 per 1000. These figures are in good agreement with those reported by Hook and Hamerton.[5]

34. There are several reasons why the estimates arrived at in paragraphs 32–33 may be underestimates. Firstly, only long-term follow-up studies will provide definitive answers to the question of what proportion of the anomalies may have clinical significance. While it is true that the clinical significance of certain chromosomal conditions such as trisomies for chromosomes 21, 13 or 18 can be relatively easily diagnosed at birth, this is by no means true for all abnormalities. Secondly, the frequency of sex-chromosome mosaics detected in many newborn surveys may be lower since the number of cells analysed may not be adequate and, to determine the extent of mosaicism, more cells need to be analysed. Furthermore, as Hook and Hamerton have pointed out, it is difficult to assess the clinical significance of mosaicism from chromosomal analysis of peripheral blood lymphocytes of phenotypically normal individuals. Probably, at least some individuals with 45,X/46,XY 45,X/46,XX or related karyotypes may eventually prove to be of clinical significance, but this depends on the magnitude of mosaicism and the tissues involved. Only long-term follow-up of individuals detected in such surveys may provide clear-cut answers.

35. Thirdly, data showing that apparently balanced or euploid structural rearrangements (translocations and inversions) in man can have deleterious phenotypic effects (and thus assume clinical significance) are slowly accumulating. Jacobs [J1] examined the data from the Edinburgh survey of the general population, of newborns and of mentally subnormal groups and found a significantly higher proportion of "mutant" balanced rearrangements in the mentally retarded group (excluding Down's syndrome) than in the others (5 out of 7 rearrangements in the mentally retarded group were of de novo origin, whereas in the other two groups combined the respective figures were 7 out of 39; see also [E1] for a recent discussion of these data). Breg's updated results [B2] on chromosome analysis of the mentally retarded at the Southbury Training School in Connecticut [B3] show a similar situation: a total of 9 balanced structural rearrangements (1 Robertsonian translocation, 6 reciprocal translocations and 2 inversions) were detected in 1087 individuals. In this study, however, the relative proportions of familial versus de novo rearrangements were not ascertained.

36. Other clinical data come from the work of Tharapel et al. [T4], Funderburk et al. [F1], Aurias et al. [A3] and Fryns and van den Berghe [F2]. Tharapel et al. [T4] found 6 cases of de novo apparently balanced reciprocal translocations which were associated with mental retardation and multiple congenital abnormalities (5 cases) or with ambiguous genitalia and multiple congenital anomalies (1 case). Funderburk et al. [F1] reported that the incidence of balanced chromosome rearrangements was higher among mentally retarded children (7 in 455) than among patients with psychiatric disorders (4 in 1679). In the latter group, all the four were pericentric inversions. The more recent results of Aurias et al. [A3] show that among 2341 children with malformations and/or mental retardation, 13 had balanced reciprocal translocations (of which 7 were familial), 5 had Robertsonian translocations and 2 had pericentric inversions. In addition, in 762 children with trisomy 21, three familial balanced reciprocal translocations were observed and none of these affected chromosome 21.

37. The studies of Fryns and van den Berghe [F2] on lymphocytes of 12 160 patients (using currently available banding techniques) showed that 32 of these patients were carriers of apparently balanced, reciprocal autosomal translocations. Eleven out of the 32 were detected in patients with mental retardation and/or some malformation. In 7 of these, the translocation was familial; in one newborn with multiple congenital anomalies, one of the parents could not be karyotyped and in the remaining 3, the translocations were of de novo origin. The authors point out that while the occurrence of mental handicap with or without congenital anomalies in patients with a de novo translocation may be explained as due to the possible occurrence of a deletion (during the formation of the translocation) which may be undetectable by present techniques, it is hard to envisage such a situation in the case of familial translocations.

38. Data bearing on the clinical significance of chromosomal anomalies are also being collected in the Collaborative Perinatal Project (CPP) mentioned earlier. The paper of Patil et al. [P1] summarizes some of the main findings from cytogenetic studies carried out on the children when they were 7 or 8 years old in five of the twelve centres involved in the study (these children have extensive neurological, developmental, psychological and other clinical and family data systematically recorded from birth onwards without knowledge of their chromosome constitution and therefore the cytogenetic study of the 7 or 8 year old children is an unbiased one).

39. A total of 4342 children (2156 females and 2186 males) were examined and 21 (0.48%) showed major chromosomal anomalies. There were 8 translocations, 3 pericentric inversions (1 autosomal and 1 each in an X and Y chromosome), 2 trisomy 21's, 3 X chromosome mosaics, 2 other X chromosome aberrations and 3 XYYs. Of the 8 translocations, 3 were balanced Robert-

[5] If the XXX condition is included among "clinically significant" abnormalities, the figures would be slightly higher.

sonian and the rest balanced reciprocal ones. The frequency of sex-chromosomal anomalies in females was 0.23% (5/2156: 2 mosaics and 3 structural anomalies) and in males, 0.23% (5/2186: 1 pericentric inversion of the Y, 1 mosaic (47,XXY/46,XY) and 3 XXYs). No partial autosomal monosomies or trisomies were detected. Table 3 in which the overall frequencies observed in the CPP are compared with those in newborn surveys shows that these are in good agreement except in the case of autosomal trisomies. The lower frequency of these in the CPP results is presumably due to the fact that infants with trisomies 13 and 18 and some of the children with trisomy 21 died (or in the latter case were institutionalized) and consequently were not included in the sample.

40. Six of the children carrying translocations (although of normal weight and length at birth) had minor clinical problems including clubfoot, reading disability, abnormal hearing and an abnormal skull shape. Three of the children who had de novo translocations had at least one of the above-mentioned abnormalities. All the five chromosomally-abnormal female children (including mosaicism) had one or another kind of problems such as mental deficiency, neurological abnormalities, abnormal speech and motor development, small height and weight throughout development, and so on.

3. Chromosome anomalies in perinatal deaths

41. Only a few studies [A4, B4, K2, M4, S5, S86] have so far been carried out to examine the prevalence of chromosomal anomalies in perinatal deaths (i.e., those babies who die before or during delivery or during the first week). The frequency of anomalies have been estimated to be of the order of 5–6%, this being higher among macerated stillbirths than in fresh stillbirths and in early neonatal deaths [A4]. The recent compilation of results from four different centres [S86] shows that the frequency of chromosomal abnormalities in macerated stillbirths is 11.6% (13/112) dropping to 3.8% (13/340) in non-macerated stillbirths and to 5.0% (41/824) in early neonatal deaths. Among the anomalies recorded, trisomies predominate, particularly those involving chromosomes of group E, followed by structural anomalies, triploidy and others.

4. Chromosome anomalies in spontaneous abortions

42. The incidence of chromosomal anomalies in spontaneous abortions in humans was extensively reviewed in the 1977 report. The recent summary of results presented by Carr and Gedeon [C4] and other papers published in the literature [H4, H49, K29] support and extend the conclusions of the Committee given in the 1977 report, which follow:

(a) The overall frequency of chromosomal anomalies among spontaneous abortions may be as high as 50% when corrections are made for non-hospitalized patients and for undetected induced abortions;

(b) Trisomies as a group constitute the most common accounting for about 50% of all chromosomal anomalies among abortuses, followed by monosomy-X (18%); triploidy (17%), tetraploidy (6%) and others (7%; includes double trisomies, mosaics and structural rearrangements);

(c) Trisomies for all members of the chromosome complement have been found among abortuses except those for chromosome 1 and 5, although the relative involvement of the different chromosomes is different; thus, for instance, trisomy 16 is clearly the most common amounting to 30% of all trisomies; trisomies for chromosomes 6, 11, 12, 17, 19 and X are rare; trisomy 21 and 22 have approximately equal frequencies (10% each);

(d) Unbalanced translocations account for about 2 to 4% of all abnormalities observed in foetuses and this frequency is much higher than among liveborns.

43. Evidence for the maternal age-dependence for trisomies involving acrocentric chromosomes (D and G groups) was discussed in the 1977 report. The more recent results of Hassold et al. [H50] document and extend the earlier findings. In this study in which data from 362 trisomic and 790 chromosomally normal spontaneous abortions were compared with respect to the age of the mothers, it was found that trisomies as a group were associated with a substantial increase in maternal age, although there were considerable differences in the magnitude of the effect between different trisomies. The effect of maternal age was most pronounced for trisomies involving the small chromosomes, both acrocentric and non-acrocentric. Trisomy 16 was conspicuously different from trisomies for all other small chromosomes, both in the reduced importance of increased maternal age and in the high frequency with which it occurred. The effect of increasing maternal age on trisomies for chromosomes in groups A, B and C was less clear than for the small chromosomes.

44. Hassold et al. [H50] speculate that the maternal age-dependent trisomies may result from precocious disjunction of the bivalents and random segregation of the resulting univalents, a process which would affect chromosomes with the fewest chiasmata and which might be more prevalent in oocytes of older women. They further suggest that true non-disjunction (i.e., the failure of bivalents to separate at anaphase) may also result in the production of trisomies and that this process may be independent of, or only slightly influenced by, increasing maternal age, but be affected by the presence of large blocks of heterochromatin.

45. With the advent of banding techniques to study human chromosomes, it became clear that several chromosomes contain heteromorphic regions which are inherited like Mendelian genes and that these heteromorphisms are frequent in the acrocentric chromosomes. Applied to trisomic cases, these markers provide a powerful tool to ascertain, in favourable situations, in which sex and at which meiotic division non-disjunction has occurred. This has been done for trisomies for certain chromosomes in abortus material and in the case of Down's syndrome.

46. The data summarized by Jacobs and Hassold [J15] given in Table 4 permit the following inferences: for trisomy 16, non-disjunction can occur at any one of the meiotic divisions in either sex with meiotic I error in the female predominating; for others (trisomy 13, 14, 15, 21 and 22), non-disjunction seems to occur almost exclusively at division I in the female. The predominance of meiotic I errors in the female for both age-related (D and G group chromosomes) and in apparently age-unrelated (trisomy 16) is of importance in considering the mechanism of non-disjunction (see also [F21]).

5. Mutation rates

47. The 1977 report presented estimates of mutation rates for the different kinds of chromosome anomalies that result in liveborn children. For numerical errors of autosomes, the estimated rates were 7.5 10^{-4}/gamete/generation for sex-chromosomal errors and 6.7 10^{-4}/gamete/generation for autosomal errors (giving a total rate of 14.2 10^{-4}/gamete/generation). The estimates based on the results summarized in Table 2 are nearly the same, being 8.3 10^{-4}/gamete/ generation for sex-chromosomal errors and 6.9 10^{-4}/gamete/generation for autosomal errors (giving a total of 15.1 10^{-4}/gamete/generation).

48. The earlier estimates [U1] for balanced structural rearrangements of autosomes and for unbalanced rearrangements were, respectively, 1.9 10^{-4}/gamete/generation and 0.45 10^{-4}/gamete/generation. In two recent papers, Jacobs [J3, J16] has given revised estimates based on the data for 48 650 and 59 452 babies, respectively. Much of the information on which these estimates are based overlaps with that given in Table 2 and, consequently, these rates may be considered to reflect our current state of knowledge in this area. Jacobs [J16] has also presented some estimates based on the incidence of structural (balanced and unbalanced) chromosomal anomalies in spontaneous abortions. All these, taken from her more recent paper, are summarized in Tables 5, 6 and 7.

6. An overview of the importance of aneuploidy and structural aberrations

49. Three recent papers have extensively dealt with different aspects of spontaneously arising aneuploidy and structural aberrations including their contribution to foetal wastage and genetic ill-health in humans [C52, F21, S6]. An overall perspective of their relative contributions can be gained by relating the incidence frequencies recorded in new-born surveys, perinatal deaths and in spontaneous abortions. Figure I taken from the paper of Sankaranarayanan [S6] and modified to take into account the frequencies of different kinds of anomalies discussed in this Annex provides a summary of these data. In drawing this figure, it has been assumed that the level of spontaneous abortions is of the order of 15% and that 2% of the children die perinatally. Some other important aspects of aneuploidy and structural aberrations in humans, not covered in Figure I, will be briefly dealt with in the following paragraphs.

50. For monosomy-X, there is indirect evidence that maternal meiotic non-disjunction may not be the main underlying cause. It has been shown [C53, K30, W23] that maternal age is not elevated in the mothers of XO conceptuses; in fact, the incidence of XO appears to be highest among young women, a finding which suggests either that there is an increase in events leading to meiotic or early cleavage errors in younger women, or possibly that a greater proportion of their XO conceptuses survive to a stage of becoming recognizable pregnancies [W23].

51. For women with Turner's syndrome, Sanger et al. [S87] have estimated that 77% of the propositae have a maternal X chromosome. Garron and Lindsten [G34] found that X monosomic patients have, on the average, more brothers than sisters. This finding suggested to the authors that the X chromosome is more often lost during spermatogenesis than the Y chromosome. Paternal sex-chromosome loss from XX or XY zygotes at early cleavage could also play a role in the genesis of X monosomy in humans.

52. With respect to their reproductive potential, the chromosomally abnormal types can be roughly divided into four major categories [C52]: the viable steriles (XO, XXY conditions, all male and some female reciprocal X-autosome translocation heterozygotes, Y-autosome translocation heterozygotes and some purely autosomal translocation heterozygotes), viable semi-steriles (most balanced structural heterozygotes, mainly the translocation and inversion carriers), viable but non-repro-

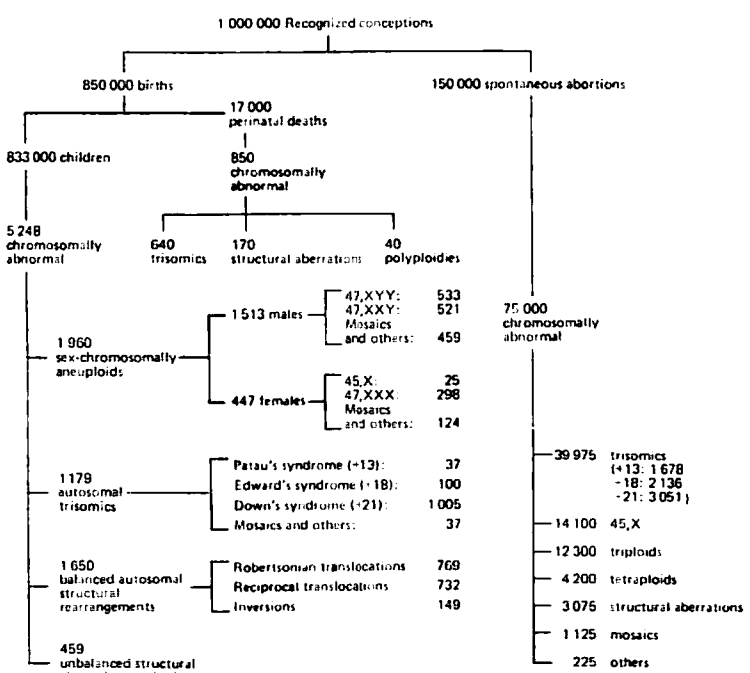


Figure I. A summary of the estimates of chromosome anomalies (per 10^6 conceptions) in spontaneous abortions, perinatal deaths and in children. Modified after [S6]

ductive types (viable trisomy 21 individuals and viable carriers of unbalanced structural rearrangements) and viable fertile types (XXX and XYY conditions). A recent workshop [B78, S91] was devoted to chromosomal aspects of male sterility in mammals including humans.

53. The defect in XO women and XXY men appears to be related to germ cell survival and sex-chromosomal make-up [B61]. Germ cells are present in the ovaries of human XO foetuses [S88], but loss begins late in foetal life and by birth few oocytes remain [C54]. The generally observed sterility of XXY males both in man and in many other mammalian species investigated in this respect has led to the postulate that the presence of two X chromosomes in a testicular germ cell results in its perinatal death [B61]. In female carriers of balanced reciprocal X-autosome translocation, the risk of infertility seems to be brought about by gonadal dysfunction in a proportion of the cases. Summitt et al. [S89] reviewed the literature on this subject and found that each female carrier in which the X breakpoint falls between bands Xq13 and Xq27 is liable to show infertility, with primary amenorrhoea in most cases, while carriers with X breakpoints in other regions are fertile.

54. In male carriers of an X- or Y-autosome reciprocal translocation, and in some cases of autosome-autosome translocations in humans [C55, C70] as in the mouse [S90] the infertility seems to be associated with spermatogenic arrest. For the purely autosomal reciprocal translocations, those with one point of exchange close to the centromere and the other fairly distal seem to be associated with infertility [C55] and this is true also in the mouse [C56, S90, S92]. In humans, among the cases so far described, an acrocentric chromosome frequently seems to be involved in such male-sterile translocations [C55]. The sterilizing effects of these autosome-autosome translocations in both mice and humans appears to be limited to male heterozygotes. In humans, where the translocation has been shown to be familial [B62, C57, L39], sterility and azoospermia have been reported in more than one male heterozygote, but no effects on gamete production in females carrying the same translocation have been apparent.

55. A sizeable proportion of structural heterozygotes are effectively semi-sterile since these individuals produce gametes carrying unbalanced segregation products that can lead to zygotic loss, spontaneous abortions and birth of congenitally malformed children. Each individual translocation, however, is likely to be unique with regard to the level of imbalance produced and its consequences. Very little is known about the reproductive potential of unbalanced translocation heterozygotes, but where meiotic studies have been performed on occasional males, they have shown severe impairment of the spermatogenic sequence [F22].

7. Progress in work with Down's syndrome

56. *General considerations.* Down's syndrome is the best known autosomal aneuploidy in man on which a large amount of literature exists (see [B10, L3, P5, S16, S93] for comprehensive reviews). The incidence is between 1 and 2 per 1000 births among various populations [H6, H7, H8, K31, K32, L40, M5, M54, M55, N22, S94, T1]. Three cytogenetic types of Down's syndrome are known: trisomy 21, translocation and mosaics. Trisomy 21 accounts for over 95% of the cases; about 2–5% are due to translocation, the most frequent being a translocation of a chromosome 21 with a D or G group chromosome. Chromosome 14 is the one most frequently involved in the D group [H5] although chromosome 15 is also rarely involved [N6]. G/G translocations are either t(21q21q) or t(21q22q). About 50% of the D/G and 90% of the G/G translocations are de novo ones, and the remainder are familial. Between 1 and 2% of Down's syndrome patients are mosaics, the most common being 46/47, +21.

57. Although there are no clinical differences between patients carrying the standard trisomic type and those with translocations, there are some important differences regarding their actual or potential family history. Rare exceptions apart, the standard trisomic condition arises by non-disjunction during gametogenesis in one of the parents, more often in the mother. It has been known for a long time that the risk of bearing a child with Down's syndrome increased with advanced maternal age. After the parents have had one child with Down's syndrome the risk of recurrence appears slightly elevated above the risk for the general population. Carter and Evans [C18] estimated the recurrence risk in Britain as 1–2% irrespective of maternal age.

58. If chromosome 21 is translocated to another chromosome, the situation is different because such translocations may be transmitted from generation to generation in the balanced state. The actual risk of producing a child who is effectively trisomic varies, depending on which chromosomes are involved and on whether the father or mother is the translocation carrier. As stated earlier, the majority of D/G translocations involve chromosomes 21 and 14 and it has been estimated on the basis of family data that a mother who carries the translocation has a 10% chance of producing a child with Down's syndrome; if the father is the carrier of the balanced translocation, the risk of Down's syndrome is thought to be only 2–3%. These estimates, however, are preliminary and it is likely that the real risk of having children with Down's syndrome may be higher at least in some families [M6].

59. The recurrence risk of Down's syndrome in families with a G/G translocation also varies depending on the sex of the carrier and on the chromosomes involved. Although the data are not extensive, in the case of a t(21q22q), the female carrier has about 9% chance of producing a child with Down's syndrome. Reliable data are not available for carrier fathers, but the risk appears to be small [M7, S9]. With a t(21q21q), the risk is 100% irrespective of the sex of the carrier, since all gametes will be either disomic or nullisomic for chromosome 21, which means that all children surviving to term will be affected.

60. *Parental origin of the extra chromosome in trisomy 21 and in translocation Down's syndrome.* In the first publication using chromosome heteromorphisms to study the origin of the extra chromosome 21, Licznerski and Lindsten [L4] traced it to the mother. Since then, a number of studies have been conducted [B11, M9, M10, M56, L5, R2, S10, U2, W4]. These studies have established that the extra chromosome can be either maternal or paternal in origin and furthermore, that the disjunctional errors arise in either of the two meiotic divisions. Verma et al. [V2] compiled the results of banding analysis of 67 "informative" cases of Down's syndrome and their parents. Non-disjunction was maternal in 44 cases (65.7%) and paternal in 23 cases

(34.3%). In 37 of the 44 maternal-origin cases, non-disjunction occurred in meiosis I and in the remainder, in meiosis II. In the paternal origin group, in 14 cases, it occurred in meiosis I and in the remaining 9, in meiosis II. These conclusions are similar to those of Langenbeck et al. [L5] and of Magenis et al. [M19].

61. In a more recent paper, Mikkelson et al. [M56] have compiled data from the literature (including some of their earlier ones) in addition to presenting some new data for two areas of Denmark, on the parental origin of trisomy 21. Considering first the literature compilation, out of 145 informative cases, the extra chromosome was maternal in origin in 112 (72.8 %) and paternal in origin in 33 (22.8%). In the first group, 96 out of the 112 cases (86%) were due to division I errors, the remainder being due to division II errors. In the second group, 20 out of 33 cases were due to first division errors and the remainder due to second division errors.

62. The new data of Mikkelsen et al. [M56] pertain to Down's syndrome children born in the Danish islands of Funen and Zealand (the earlier paper of Mikkelsen et al. [M9] was on Down's syndrome in Zealand). The total material comprised 125 families with Down's syndrome children out of which 95 were informative (76%). In 77 children (81%), the extra chromosome could be traced to the mother and 18 (19%), to the father. In the new material alone, paternal failures were observed in 11% of the cases in Funen (5/45) and 23.5% of the cases in Zealand (8/34).

63. Jacobs and Morton [J4] have argued that the methodology used in many of the reports and/or the way in which the data are recorded, leads to the loss of much of the potentially useful information. For instance, Mikkelsen et al. [M9] and Wagenbichler et al. [W4] summarized their results, without giving the actual observations, for those "informative" cases for whom the origin of the chromosome(s) could be established. By not reporting all the observations, the authors have introduced a bias into their series and have made the calculation of the relative probabilities of the different mechanisms of origin of the extra chromosome difficult. By applying a maximum likelihood analysis to the data available to them, Jacobs and Morton [J4] reached the conclusion that "... it appears that trisomy 21 is due to first division maternal non-disjunction although there are case reports of second division non-disjunction, both paternal and maternal..." and suggested the need for complete reporting of the data and large systematic samples.

64. Data on the parental origin of translocation Down's syndrome are limited. The information summarized by Mikkelsen et al. [M56] and by Chamberlin et al. [C58] suggest that in about two-thirds to three-quarters of the cases the translocation was maternal in origin.

65. *Maternal age.* Maternal age has long been known to be an important factor in Down's syndrome (see [P5] and references given therein). This correlation between increasing maternal age and Down's syndrome applies to 95% of the cases which are primary trisomies for chromosome 21 and which result from non-disjunction [P5, M11]. For other types such as translocation Down's syndrome, both spontaneous and inherited, and for mosaics, no age-dependency has been proved [G2, R3]. Thus, among all the cases of Down's syndrome, there is a predominantly maternal-age-dependent and a maternal-age-independent class.

66. If the mother is less than 20 years of age at the time of conception, the risk of producing a child with standard trisomy 21 is about 1 per 2500 livebirths [P5, C7]. The risk gradually increases until 35 years of age, after which there is a more steep increase in the frequency such that a mother over 45 years of age has about 1 in 50 chance of having a child with Down's syndrome [P5, S11]. In more recent papers, Hook and Fabia [H6], Hook and Chambers [H7] and Hook and Lindsjö [H8] have analysed the data on the incidence of Down's syndrome in livebirths by single year intervals in maternal ages for, respectively, the State of Massachussetts (1958–1965), the State of New York excluding New York City, (1963–1974) and for Sweden. The main finding is that the increase in the incidence of Down's syndrome is gradual from maternal age 20 to about 30–31 and more pronounced thereafter. The effect of maternal age has also been confirmed by the results of the second Baltimore case-control study [C8].

67. In their 1980 paper, Lamson and Hook [L41] analysed the data published in the literature in which the rates for Down's syndrome had been given by 1-year maternal age intervals to define the shape of the curve describing maternal-age-specific rates. There were a total of 3613 Down's syndrome cases born to mothers of ages ranging from 20–49. Cases born to mothers below 20 years of age were excluded because the analysis suggested that some factors operative at ages 15–19 are not pertinent to rates at higher ages. Age 49 was chosen as the upper limit because of concern about the accuracy of reporting and coding of data for higher ages.

68. The statistical model used for analysis ("The constant plus exponential model" in the authors' terminology) is represented by the equation

$$y = a + \exp(b + cx)$$

where y is the rate of Down's syndrome in live births, x is the maternal age and a, b and c are constants. The authors point out that the above model gives a good fit to the data "about as well as the approach that used separate equations", and that it does not postulate a sharp transition in biological processes around maternal age 30, but rather a process continuously accumulating at a constant exponential rate, superimposed upon a constant background rate. The equation predicts that there is one group of conditions that occur with a pooled constant rate a (maternal-age-independent?) and a second group of conditions that operate over the entire age-spectrum 20–49, its contribution increasing at an exponential rate with slope c (maternal-age-dependent?). They caution, however, that although their model may be more appealing statistically (and perhaps biologically as well, because its equation has fewer parameters), this does not imply that this model is necessarily more likely to be correct than the others. Furthermore, the calculations of the maternal-age-independent and dependent categories are consistent with the observed distributions, but are not the only possible inferences from them.

69. *The effect of paternal age.* Although it is widely accepted that the most important variable in the incidence of Down's syndrome is maternal age, the possible association with paternal age has also been considered. A number of investigations [L3, P5, S12], however, have failed to detect any significant effect of advancing paternal age in addition to that accounted for by maternal age.

70. Stimulated in part by a number of case reports on the paternal origin of the extra chromosome 21 detected through the use of the quinacrine banding techniques mentioned earlier, the search for paternal-age-effect has once again begun. Stene et al. [S13] have reported the results of an investigation conducted in the Copenhagen Metropolitan area to study the effects of paternal age on the incidence of Down's syndrome. Two hundred and twenty-four Down's syndrome patients born during the period 1960–1971 provided the material. The control was a random sample of 6053 births from the same period. By developing and applying a new statistical technique (detailed in [S14]), the authors found that: (a) there was an increasing incidence of Down's syndrome with advancing paternal age for a given maternal age; and (b) men above the age of 55 years have a significantly increased risk of begetting children with Down's syndrome. The Japanese data presented by Matsunaga et al. [M13] are supportive of the Danish findings: there was an excess of Down's syndrome infants born to fathers $\geq$ 55 years of age.

71. The regression analysis of Hook et al. [H51] of Down's syndrome cases born in 1964–1976 and reported by the British Columbia Registry for Handicapped Children showed that, after adjustment for maternal age effects, the data were consistent with an increase of about 1.024-fold for each year of paternal age throughout the entire age range (thus differing from the results of Stene et al. [S13] and Matsunaga et al. [M13] where the evidence was found only in men of 55 years and over). Among Down's syndrome cases for the period 1952–1963, however, for which ascertainment appears likely to be less complete, there was no evidence for a significant paternal age effect.

72. Erickson [E2] has published the results of an analysis of the data collected from 29 states and two large cities in the United States by the National Cleft Lip and Palate Intelligence Service (NIS) during 1961–1966. The data pertain to 4000 white infants with Down's syndrome and about 86 000 normal white babies. His analysis confirmed the maternal-age association with Down's syndrome with a high degree of statistical significance but did not demonstrate any independent effect of paternal age; in fact, the rates at paternal ages over 45 years appeared to be nearly the same. Erickson's conclusions, however, have been disputed by Stene and Stene [S15]. The latter authors have argued that the NIS data contain too few Down's syndrome cases with older fathers and thus are less suited for an investigation of a possible paternal age effect. Furthermore, they point out that the statistical tests used by Erickson have relatively low resolving power.

73. In a more recent paper Erickson [E3] examined again the question using two new sets of data derived from two sources: the Metropolitan Atlanta Congenital Defects Surveillance Programme and the National Centre for Health Statistics; the former pertained to the period 1968–1976 and the latter to 1973–1975. Analysis of these data (taking into account the criticisms of Stene and Stene [S15] and improving the methods of statistical analysis) showed however no overall excess of Down's syndrome infants born to older fathers in either case. The Atlanta data suggested an increased number of Down's syndrome infants born to older fathers who had children by women $<$ 34 years; however, there was a small deficiency of Down's syndrome infants born to older fathers by women $\geq$ 35 years. Erickson concluded that the possibility of a paternal age effect remains open, but the available data suggest that, if it exists, it is quite small.

74. *Effect of radiation.* In its 1977 report, the Committee reviewed the results of surveys designed to inquire whether parental (in particular, maternal) irradiation may increase the risk of producing Down's syndrome (see also [U3]). The main findings of all the retrospective and prospective surveys are recapitulated in Table 8 which includes also the recent results of the Baltimore Case-Control study [C8]. This study, however, in contrast to earlier findings [S19], found no significant effect of maternal irradiation on the incidence of Down's syndrome. (The Indian study [K4] has been excluded from Table 8 owing to problems of statistical analysis, as discussed in the 1977 report [U1].) Thus the only studies that show a positive effect are those of Alberman et al. [A5], Sigler et al. [S19] and Uchida et al. [U4, U5]. In conclusion, as Uchida [U6] stated "... it may still be premature to say with conviction that radiation as a cause of non-disjunction, increases the frequency of 21-trisomy. However, it seems logical to avoid unnecessary exposure to mutagens that might add to the genetic burden of humans".

8. Satellite associations: their possible functional significance and relevance for autosomal trisomies

75. The satellite regions of human acrocentric chromosomes (Numbers 13, 14, 15, 21 and 22) are frequently located near one another in metaphase chromosome preparations. This relationship called "satellite association" (SA) was first described by Ferguson-Smith and Handmaker [F3] and Harnden [H9] and has been found to occur both in mitosis and in meiosis [F4]. The length of the satellite stalk or secondary constriction, rather than the size of the satellite, is correlated with the frequency of associations [E4, S21, Z1].

76. SA is thought to be the result of the involvement of the acrocentric chromosomes in nucleolus formation [F4, H10, O3] and the connectives between the satellite regions which can sometimes be observed in stained mitotic preparations [Z2] represent remnants of the nucleolus. Both the secondary constrictions of acrocentric chromosomes and the connectives have been shown to contain DNA (rDNA) coding for 18S and 28S ribosomal RNA (rRNA) [E4, H11, H12, C10]. According to a recent estimate [Y1] there are approximately 50 such genes, i.e., about 5 ribosomal genes on each acrocentric chromosome. It is recognized that the number of RNA genes on a given chromosome is variable [e.g., E4, D1, H12] and it has been suggested that such variations may be related to the frequencies with which particular chromosomes are found in satellite associations [H12, M15, W5].

77. The frequency of SA may vary within the population and a variety of in vivo and in vitro conditions (e.g., age, sex, thyroid autoantibodies, viral infection, chromosome culture methods, etc.) have been shown to have an effect on the frequency of SA (see Houghton [H16] for a citation of the relevant papers). There is a recent report showing that SAs are distorted when colcemid is used to collect metaphases [R64]. In part, interest in the problem of SA has been stimulated by the finding that the majority of the chromosomal abnormalities in liveborn children involve the acrocentric chromosomes and that these aneuploidies are

caused by non-disjunction and by structural rearrangements such as reciprocal translocations and Robertsonian translocations; and are also stimulated by the speculation that SA, if it occurs in germ cells, may have an aetiological role in the development of these abnormalities [F3, H9, C11, C12, R5, O3, Z3].

78. Several workers have concluded that participation in SA is random [e.g., C13, C14, H18, J5, N7, R6, S22] while a number of others found that some particular associations were more frequent than others [e.g., C15, N8, A6, P7]. For instance, Cohen and Shaw [C13] found that there was a distinct tendency for G group chromosomes to be associated more frequently than D group elements; in multiple associations of specified size within a given number of D and G chromosomes, the type of associations appeared to be random. Jacobs et al. [J5] noted that there was very significant heterogeneity among individuals in the frequency with which different chromosomes entered into associations and were unable to obtain evidence for preferential association between any particular chromosomes, either homologous or heterologous. The existence of differences between individuals has also been recorded by a number of investigators [e.g., M15, H17, Z2]. On the other hand, Patil and Lubs [P7] found that the chromosomes most frequently involved in Robertsonian translocations[6] (i.e., 14, 21 and 13) were also most frequently involved in satellite associations. The observations of Ardito et al. [A6] show that while the pattern of association of D-D, D-G and G-G groups seem to be random, there exists some preferential association particularly between pairs of 13–14, 13–13, 13–21 and 21–21.

79. The results of studies on Down's syndrome patients and their parents have also yielded conflicting results. Some studies have shown a significant increase in SA in blood cultures of Down's syndrome children [e.g., R7] and it has been reported that the parents of Down's syndrome children showed significant deviations from random association even though there was a random distribution for the children themselves [e.g., C12, R5]. Other workers could not demonstrate any difference between Down's syndrome patients, their relatives and normal controls [e.g., K37, T5]. Mattei et al. [M18] studied SA patterns in a large sample of parents of normal children and parents of Down's syndrome children. In the latter group, more SAs and more complex associations were found. There were also significant differences in the composition of the association complexes: in parents of Down's syndrome children, chromosome 15 was less frequently involved than normal and all associations involving chromosome 22 were increased except for 22–15. For chromosome 21, 21–22 was more frequent than normal.

80. Houghton [H16] investigated the effects of gamma or neutron irradiation of blood derived from normal males and females, Down's syndrome males and females and the parents of both normal and Down's syndrome children on satellite association. In the range of gamma exposures employed (0.05 to 0.6 Gy) no effects on SA were apparent; the results obtained using the silver staining technique (which permits a more precise evaluation) were also the same. With neutrons however, while there was no change in the overall frequency of SAs, there was a change in the composition of the SA complexes: there appeared to be a preferential participation of chromosome 13 in SA over the dose range of 0.05 to 0.6 Gy. The author has no explanation for this observation.

81. In a similar study involving blood from four healthy persons and with x-ray doses of 0.05 to 0.5 Gy (4 levels), Stenstrand [S95] found that the pattern of SA (the involvement of specific chromosomes) varied between the different individuals and that in two cases, irradiation seemed to have a definite influence on this pattern although the chromosomes involved were not the same ones. The changes in the SA tendency were almost opposite to each other.

82. In summary, in spite of the considerable amount of work that has gone into studies on satellite associations, no clear conclusions can be drawn with respect to their relevance in the context of the aetiology of trisomies. Furthermore, the spectrum of chromosome abnormalities in spontaneous abortuses does not support the idea that acrocentric chromosomes are preferentially involved in non-disjunction; the data suggest, rather, that there may be differences in the extent to which the different resultant trisomies (for acrocentric and non-acrocentric chromosomes) survive foetal life.

9. Non-disjunction in the human male studied through direct examination of the germ cell stages

(a) Spermatozoa

83. The 1977 report considered some data bearing on the detection of aneuploidy in human spermatozoa. Briefly, the findings were:

(a) The Y chromosome appears as an intensely fluorescent dot in interphase nuclei after staining with quinacrine dichloride [P2];
(b) With similar staining, the Y chromosome can be seen throughout the male germ cell series [P3] including the spermatozoa [B5, S7].

These findings raised hopes that these F (fluorescent) bodies may be potentially useful for estimating non-disjunction rate of the Y chromosome. In initial studies, it was found that between 1 and 3% of human spermatozoa contained two F bodies [P3, B6] and these frequencies were confirmed in a subsequent study [P4]. As was pointed out in the 1977 report, the assumption that each F body in 2F spermatozoa corresponds to a Y chromosome yields very high estimates of non-disjunction rate for the Y which are inconsistent with the number of XYY individuals (zygotes) found in the liveborn (or abortion) studies.

84. Further work by Beatty [B7, B8, B9] and Sumner and Robinson [S8] has clearly demonstrated that not all Y chromosomes are represented by F bodies and that not all F bodies represented Y chromosomes. In one study [B8], only 83% of the Y chromosomes were represented by F bodies; 7% of the haploid heads and 14% of the diploid heads contained one or more "adventitious bodies" indistinguishable from true F bodies. Indirect DNA estimates of Sumner and Robinson [S8] also lend credence to the idea that a one-to-one correspondence between 2F and YY is unlikely and that many of the

[6] Analysis of the data pertaining to over 10 000 patients examined (for various reasons) at the Institut de la Progenèse in Paris, gives the following frequencies of involvement of the different chromosomes: total Robertsonian translocations detected: 84; 13/14: 27 cases; 14/21: 21 cases; 21/21: 15 cases; 13/21: 7 cases; 21/22: 5 cases; 13/13: 3 cases; 15/21: 2 cases; 13/22, 14/22, 15/22, and 22/22: 1 case each. A similar analysis of published data from newborn surveys pertaining to over 42 000 infants gives the following results; 13/14: 21 cases; 14/21: 5 cases; 13/22, 14/22, 15/22 and 14/15: 1 case each (total 30 Robertsonian translocations) [D6].

2Fs are not YYs. Furthermore, it is known that single Y chromosomes may have a bifid structure and extra dots in spermatozoa may be explained by single Y chromosomes being bifid (see also [B9] for a treatment of the problem).

85. All these lines of evidence strengthen the conclusions reached in the 1977 report namely, that the F bodies may not at present provide a useful means of estimating the rate of Y chromosomal non-disjunction.

86. Notwithstanding these considerations, Kapp [K3] has argued for the use of Y bodies as a tool to monitor Y chromosome non-disjunction in males. His data pertain to a normal male with no known exposure to mutagens, two patients (one who underwent adriamycin treatment for osteogenic sarcoma and who had a prior history of chemo- and radio-therapy and the other who underwent serial x-ray therapy for seminoma), a physician who began fluoroscopy residency, an individual with intestinal amoebiasis who underwent diagnostic irradiation 9 days before starting on a 10-day regimen of Flagyl, a group of 18 men who had experienced occupational exposure to dibromochloropropane (DBCP) and 50 unexposed controls. In the case of the normal male, the average frequency of "2F" sperm was 1.3% (30 samples over 400 days; range: 0.7 to 2.2%). Likewise, 43 out of 45 controls from the DBCP study had "2F" sperm in the range from 0 to 2%. In individuals undergoing chemical or radiation treatment, the frequency was in general elevated reaching levels of between 3 and 6% in about a month after the beginning of the treatment. In the case of DBCP workers (duration of exposure not specified), 16 of the 18 had frequencies of "2F" sperm over 2% while for 2 of them, the frequency was in the range of 0 to 2%.

(b) Meiotic stages

87. Holm and Rasmussen [H13, H14], Holm, Rasmussen and von Wettstein [H15] and Rasmussen and Holm [R4, R65] carried out a detailed analysis of the meiotic prophase and metaphase I of human spermatocytes through three-dimensional reconstructions of the meiotic nuclei from electron micrographs of serial sections. The reconstructions comprise 4 leptotene [H13], 4 early-mid zygotene [R4], 10 late zygotene [R4], 21 early pachytene [R4], 22 mid-late pachytene [H13] and 3 metapahse [H14] nuclei and elucidate details of chromosome pairing, chiasma formation and disjunction in man. Of interest in the present context is their finding which suggests that primary non-disjunction can arise in either of two ways. The first is the failure of homologous chromosomes to form a chiasma, their entering the metaphase plane as univalents with the possibility of orientation of the centromeres towards the same spindle pole. The second is premature dissolution of the synaptinemal complex or chromatin chiasma[7] leading to univalents in the metaphase plane with the possibility of their subsequent movement to the same spindle pole. Holm et al. [H15] suggest that the retention of the synaptinemal complex chiasmata until metaphase I provides the opportunity to study causes of non-disjunction and that the method used holds potential to investigate the effects of radiation and chemical agents on human meiosis.

[7] Chromosome pairing and synaptinemal complex formation are intimately related events in meiotic prophase. With the exception of the Drosophila male (and probably other dipteran males as well) which lack synaptinemal complexes, the regular disjunction of homologues appears to be connected with the presence of synaptinemal complexes. In organisms with achiasmatic meiosis and/or lacking crossing over, the entire synaptinemal complex complement is retained until the separation of homologous chromosomes at anaphase I. In most organisms however, the bulk of the synaptinemal complexes is shed from the bivalents after pachytene leaving only short fragments behind. It is generally believed that these retained fragments are the ultrastructural counterparts of the sites where crossing over has occurred (the chiasmata) and that the fragments stabilize the cross overs, thereby holding the two homologues of each bivalent together (see [R4, R65] for details and pertinent literature).

10. Detection of chromosome anomalies in human sperm through direct cytological analysis: interspecific cell-fusion studies

88. Rudak et al. [R1] described a technique for a direct analysis of the chromosome constitution of human spermatozoa. In this method, human spermatozoa (in semen samples) are fused with zona-pellucida-free eggs of the golden hamster (Mesocricetus auratus) using the eggs as "reactivating vehicles". To obtain large numbers of eggs, adult female hamsters were induced to superovulate by i.p. injection of 25 IU pregnant mares' serum gonadotrophin on day 1 (the day of ovulation) of the animals' oestrous cycle, followed by an i.p. injection of 25 IU human chorionic gonadotrophin on day 3. The animals were killed 17 h after the second injection, their oviducts dissected out and the cumulus mass containing the ova removed; after suitable washing and clearing of the ova, the zonae pellucidae were digested off with 0.1% trypsin at room temperature. Approximately 40–50 eggs were recovered from each superovulated female and eggs from 4 animals were routinely used for each semen sample. The zona-pellucida-free eggs were subsequently transferred to sterile petri dishes containing the medium and mineral oil.

89. To effect sperm penetration, two to three drops of the preincubated sperm suspension were dropped from a Pasteur pipette onto the surface of the oil in each dish and mixed with the eggs. The dishes were incubated at 37°C in 5% CO_2 in air for 3 h. Under the conditions of the experiment, approximately 75% of the eggs which had been incubated with sperm reached the fixation stage. Of the fixed eggs, slightly more than half contained discrete haploid sets of both the hamster and the human metaphase chromosomes. Of the 60 sperm analysed, 31 had a 23,X and 23,Y constitution while 3 were aneuploid (with 22,X, –G; 22,X, –F, and 24,X, +mar, +ace complements). The frequency of aneuploidy in this sample is therefore 5%. The authors suggest that their technique for the first time permits the preparation and analysis of sperm chromosomes with the same precision as has been achieved for the chromosomes of somatic cells and that "... the way is now open to studying directly the chromosome constitutions of a population of sperm ... and to assessing the effects of various natural and experimentally induced phenomena on the chromosomes of mammalian gametes".

11. Cytogenetic studies in offspring of atomic bomb survivors of Hiroshima and Nagasaki: further data

90. Somatic chromosomes of the children of atomic bomb survivors and controls have been examined since 1967 in an attempt to determine whether atomic bomb exposure of parental germ cells may have led to an

increased risk of genetic damage expressed as an increased frequency of children with induced chromosomal abnormalities. The data of Awa [A7] presented in the 1977 report showed that among 2885 children of atomic bomb survivors, a total of 18 individuals (0.62%) with chromosome anomalies were found. In the matched controls (1090 subjects) there were 3 individuals with chromosome anomalies (0.28%). There was a suggestive, but statistically non-significant increase in the frequency of sex-chromosomal anomalies in the children of exposed parents (0.31 versus 0.09%). Finally, the total frequency of chromosomally abnormal children of atomic bomb survivors was in the same range as that which has been reported in several newborn surveys (see Table 2).

91. Awa et al. [A8] have now updated this information (see also Ref. S131). Chromosome analysis has been completed for a total of 10 820 children comprising 5058 controls (children of distally exposed parents) and 5762 children of proximally exposed parents with an estimated conjoint gonadal exposure of 0.87 Sv. The results are that in the controls, 25 (0.49%) were identified as having an abnormal chromosome constitution (11 with balanced autosomal rearrangements, 1 unbalanced rearrangement and 13 sex-chromosomal aneuploids). Among the children of the exposed parents, there were 30 chromosomally abnormal individuals (0.52%) the break-down being, 11 balanced autosomal rearrangements, 3 unbalanced autosomal rearrangements, and 16 with sex-chromosomal anomalies. The present data, based on more than twice the sample size, suggest again no significant difference in the frequencies between controls and the children of exposed parents.

12. New chromosomal abnormalities and birth defects

92. The 1966 report of the Committee [U7] dealt with some of the well-known chromosomal anomalies in humans such as trisomy 21, trisomy 18, trisomy 13, Cri-du-chat syndrome (deletion of the short arm of chromosome 5), partial trisomy for chromosome 21, deletions particularly involving the short or the long arms of chromosome 18, D/D and D/G translocations and the sex-chromosomal anomalies. In the 1972 report [U8], further information on chromosomal anomalies particularly on reciprocal and Robertsonian translocations was presented including methods of ascertainment (through a balanced or an unbalanced proband) and their relationship to the transmission of the translocations.

93. The application of banding techniques (reviewed by Dutrillaux [D5] and Dutrillaux and Lejeune [D2]) to study human chromosomes has revolutionized the field of human cytogenetics and has led to major advances. Among these, the following may be listed:

(a) The confirmation of well-established chromosomal syndromes (e.g. +8, +13, +18, +21, 4p–, 5p–, 18p–, 18q–, etc.);
(b) A precise identification of previously suspected trisomies (e.g., trisomy 8 and monosomies such as those involving chromosomes 21 and 22);
(c) A sub-division of classical chromosomal syndromes according to the chromosomal segments involved (e.g., partial deletions involving the proximal one-third to one-half and the distal one-third to two-thirds of the long arm of chromosome 13; partial deletion of chromosome 18: 18p- and 18q- syndromes; the 21q- syndrome);
(d) The delineation of new chromosomal syndromes involving practically every segment of the different chromosomes of the human complement;
(e) A more precise definition of known chromosomal anomalies (e.g., the identification that the relevant chromosomal segment in the Cri-du-chat syndrome (5p-) is in the mid-position of 5p15 band);
(f) The discovery of fragile sites in certain chromosomes;
(g) The demonstration of extensive chromosomal heteromorphisms in humans and their applications;
(h) The demonstration of an association between (i) certain genetic diseases and specific chromosomal anomalies (e.g., retinoblastoma: specific loss of band 13q14) and (ii) certain neoplasias and chromosomal aberrations (e.g., chronic myeloid leukaemia (CML) and the Philadelphia (Ph^1) chromosome);
(i) Progress in gene mapping;
(j) Evolutionary studies in primates.

94. Most of the above items have been adequately covered in several recent reviews [G2], [G3], [S16], [N9, N10], [R8, R9], [V4], [P8], [Y2], [F5], [W6], [H19],[8] [K5], [S23], [C19], [M21], [L8], [B12], [D3] and [D4]. In what follows therefore, only certain important features will be summarized with particular reference to partial monosomies and trisomies and fragile sites.

(a) Partial monosomies and trisomies

95. As mentioned earlier, new chromosomal defects, particularly deletions and duplications involving almost every chromosome of the human complement have been discovered during recent years (see Table 2 in [S23] and Table 1 and Figure 1 in [L7]). The rate at which information is accumulating justifies the conclusion that the incidence figures for chromosomal anomalies summarized in Table 2 may need upward revision. Most of the currently available information on these partial deletions and duplications, however, is in the nature of case reports. For some such as Cri-du-chat syndrome, the recent review of Niebuhr [N9] shows that the incidence rate may be of the order of 1 in 45 000 and among mentally retarded individuals the rate may be of the order of 1.5 per 1000. There was a significant excess of females with this syndrome.

96. Several chromosome deletions with distinctive features have counterparts in single gene defects which are inherited as autosomal dominants. This seems to be the case with retinoblastoma which is associated with an interstitial deletion of the long arm of chromosome 13, specifically, band 13q14 [Y3]. Lewandowski and Yunis [L7] have cited several other possible instances of this kind.

97. In general, partial trisomies seem to be more frequent that partial monosomies, presumably because the former are less deleterious. Roughly two-thirds of the reported cases (83 out of 129) summarized by Sanchez and Yunis [S23] are partial trisomies and the rest, monosomies. From their detailed analysis of 95 balanced reciprocal translocations (the break-points, the chromosomes and the chromosomal segments

[8] It is worth mentioning here that what have hitherto been considered cases of trisomy-22 are really translocations involving chromosomes 11 and 22 with 11q being the predominant trisomic segment [D6].

involved, the type of segregation observed in the families ascertained, etc.) Aurias et al. [A3] reached a similar conclusion, that trisomies are relatively better tolerated than monosomies. Their results show that in the case of 1:3 segregation (leading to monosomies), there is an average imbalance of 1.68 U[9] whereas in the case of 3:1 segregations (leading to trisomies) the average imbalance is 4.22 U. Furthermore, with 2:2 segregations, the segment in triplicate is generally longer than the monosomic segment (TM[10] translocations: 3.85 U long trisomy for a 0.47 U long monosomy; non-TM translocations: 2.63 U trisomy for 1 U long monosomy). The authors point out, however, that there are some exceptions and that other causes in addition to length may therefore be involved in influencing the severity of chromosome disorders.

98. Another finding of interest that emerges from the work of Aurias et al. [A3] is that there is an excess of breakpoints for chromosome arms 4p, 9p, 10q, 21q and 22q and a deficiency of breakpoints in 1p, 2p and 6p.[11] With the exception of chromosome 22, all the others (4, 9, 10 and 21) are implicated in the aetiologies of relatively frequent chromosomal disorders (for reviews see [G2, R8, R9, Y2]). As one plausible explanation, the authors suggest that monosomies and trisomies of these segments may be relatively well tolerated and that the translocations involving these chromosomes are therefore more readily ascertained, especially in children carrying unbalanced karyotypes.

99. Although trisomies and monosomies may involve any chromosome, the amount of excess or deficient material does not generally exceed 5% of the total genome (see table 2 in Sanchez and Yunis [S23]). A concept that seems to be gaining increasing currency in recent years is that duplications or deletions of late replicating regions are less harmful than those involving earlier replicating regions. Positive Q- and G-bands are now known to represent late replicating regions [G4, C17, C16, D5] and the chromosomal segments generally involved in the chromosomal syndromes are particularly rich in Q- or G-positive bands.

100. In contrast to "classical" chromosomal syndromes (e.g., trisomy 21, 18, 13, etc.) which are relatively well-defined entities (and which can be recognized on clinical grounds alone) some partial deletions and duplications are presently difficult to diagnose either because of the absence of a specific relationship between certain phenotypes and chromosomal segments or because of overlapping phenotypic effects. In addition, the chromosomal segments involved may vary from patient to patient and consequently, the phenotype may show considerable variation. For instance, offspring from carriers of balanced reciprocal translocations may receive derivative chromosomes. This leads not only to partial monosomy or trisomy, but usually to a combination of both which can be translated into various mixtures of two given syndromes.

(b) Heritable fragile sites

101. A class of chromosomal entities that currently engages the attention of human cytogeneticists is constituted by the so-called "heritable fragile sites". Dekaban [D18] first reported on a fragile site on the long arm of a C group chromosome and Lejeune et al. [L42] demonstrated that such a site on the long arm of chromosome 2 (2q1) was heritable. Sutherland [S96] has proposed that a fragile site is a specific point on a chromosome which is liable to show the following features: "(i) a non-staining gap of variable width which usually involves both chromatids; (ii) the site is always at exactly the same point on the chromosome in the cells examined from any individual patient or kindred; (iii) the site is inherited in a Mendelian dominant fashion; and (iv) fragility must be evident by the production (under appropriate conditions) of acentric fragments, deleted chromosomes, triradial figures and the like" (in metaphase preparations).

102. Heritable fragile sites have been found on a number of metacentric or sub-metacentric chromosomes (2, 10, 11, 16, 20) and at least one is known on the X; however, they have so far not been found in any of the five acrocentrics (13–15, 21, 22) or the Y. They are never seen in 100% of the cells examined.

103. Lubs [L43] examined DNA replication by autoradiography in a female with a site Xq27 (or 28) and found that the X with the fragile site did not appear to be selectively inactivated. Fraccaro et al. [F23] similarly studied a site at 2q1 and found that in most cells there was no detectable asynchrony in DNA synthesis between homologues. Sutherland and Leonard [S97] showed that the chromosomal gaps associated with the fragile sites at 2q11, 10q23, 11q23, 12p11, Xq27 (or 28) do not stain with silver nitrate as the nucleolar regions of the acrocentric chromosomes do.

104. Sutherland [S96] demonstrated that the expression of fragile sites in metaphase chromosomes obtained from lymphocyte cultures occurred only when culture medium 199 (which is relatively deficient in folic acid) was used, compared to several other media i.e., their expression depends on the composition of the culture medium. This was true for sites 2q11, 10q23, 11q13, 16q124, 20p11, Xq27 (or 28) but not for the site at 16q22. The expression of these sites (except that at 16q22) was inhibited by folic acid, thymidine, folinic acid and probably BUdR. The inhibition, however, could be reversed by a folic acid antagonist, methotrexate. In addition, there was a correlation between the frequency of the sites and the pH of the medium for the sites at 2q, 10q and Xq. It was therefore postulated that there may be at least three different biochemical classes of fragile sites, as judged by their response to pH, folic acid and methotrexate. In a recent report, Schmid et al. [S98] showed that the presence of the antibiotic distamycin A in the medium can reveal the fragile site at 16q22 although there were interfamilial differences in its appearance.

105. In a recent study, Glover [G38] confirmed the findings of Sutherland, namely that folic acid and thymidine inhibited the expression of the fragile site on the X-chromosome and further showed that the inhibiting effect of folic acid, but not that of thymidine, can be negated by the addition of 5-fluorodeoxyuridine (FUdR) to the culture medium. He suggests that this observation can be explained by the fact that FUdR is intra-cellularly converted by thymidine kinase to 5-fluorodeoxyuridine monophosphate (FdUMP) which in turn, is a potent inhibitor of thymidylate synthetase. In the absence of exogenous thymidine, the pool of deoxythymidine monophosphate (dTMP) is depleted,

[9] U is the unit length of the autosome (total length: 280 units).

[10] TM: breakpoints in the telomeric and median regions.

[11] p and q refer, respectively, to the short and long arm of the chromosome.

thus arresting DNA synthesis. Exogenous thymidine bypasses this block by conversion to dTMP catalysed by thymidine kinase in the "salvage pathway". In other words, the observations are consistent with the hypothesis that the fragile X is expressed by limiting the dTMP pool and, thus, the deoxythymidine triphosphate (dTTP) pool available for DNA synthesis. The data do not support the notion that there is a deficiency in thymidylate synthetase in individuals with the fragile X since inhibition of this enzyme does not result in fragile X expression in control males.

106. In 1980, Sutherland et al. [S99] reported finding a new fragile site at 10q25. This site differed from others in that it required BUdR (at a concentration of 5–10 mg/litre) in the medium for maximum expression frequency, and was not inhibited by folic acid concentrations of up to 20 mg/litre or by pH. High concentrations of thymidine however, tended to inhibit expression. The finding of BUdR-requiring fragile site at 10q25 has also been reported by Scheres and Hustinx [S100].

107. Most of the fragile sites discussed above have been found either in the course of population cytogenetic studies or in individuals suggested to be chromosomally abnormal. Sutherland [S101] points out that with autosomal fragile sites, there is no association with abnormal phenotypes and that the detection in the instances mentioned earlier is probably a reflection of the material analysed. However, the fragile site at Xq27 seems to be associated with, and may even be the cause of, the form of mental retardation with macro-orchidism [e.g., G37, H52, H53, H54, J17, S99, S101, S102, S103].

108. In a study of 21 mentally retarded males with macro-orchidism, 13 obligate carrier females and 26 potential carrier females, Sutherland [S102] found that in the males, the frequency of cells showing the fragile site Xq27 ranged from 4 to 56%. Among the obligate carriers, only 5 showed any evidence of the fragile site and all of them were younger than 35 years; in 7 of the remaining 8 and who were older than 35, the fragile site could not be demonstrated. In the last case, the fragile site was readily demonstrated at age 30, but not at age 32. In only 9 of the potential carriers could the fragile site be shown to occur. The ages of these individuals ranged from 2.5 to 21 years. After reviewing these and other data published in the literature, Sutherland [S102] concluded that the diagnosis of X-linked mental retardation with macro-orchidism remains difficult; that not all the retarded males with the fragile site have macro-orchidism; that the fragile site can often be demonstrated in only a small proportion of metaphases from some retarded males even when the diagnosis is virtually certain on clinical grounds and from a study of the family history including other affected relatives; and that the detection of the fragile site in females is still inadequate despite the methods developed to manipulate the culture medium.

109. A recent report by Daker et al. [D19] has raised the possibility that an X chromosome with a fragile site typical of X-linked mental retardation can occur in normal individuals; the Xq28 was found in a male patient (referred to for cytogenetic examination for other reasons) and in his brother, both of whom appeared to be of normal intelligence. The authors point out that "... although one case can hardly undermine the importance of fra(X) in the diagnosis of X-linked mental retardation, nevertheless, the knowledge that this fragile site may occur in individuals of normal intelligence will make genetic counsellors feel a little uneasy, especially if prenatal diagnosis of the fra(X) becomes a reality ... this case therefore clearly indicates the need for more information about fragile sites, especially in the 'normal' population".

13. Summary and conclusions

110. The available results of 10 cytogenetic surveys of neonates (carried out in different parts of the world) show that 0.63% of the babies (424/67 014) are chromosomally abnormal; 158 children (about one-third) carried sex-chromosomal anomalies, 95 children (about one-quarter) numerical autosomal anomalies, 134 children (about one-third) balanced structural anomalies of the autosomes and the remainder (37/424) unbalanced structural anomalies. The incidence of sex-chromosomal anomalies alone is about 3 per 1000 male births and 1.5 per 1000 female births.

111. Of the autosomal numerical anomalies (about 1.4 per 1000 births), trisomy 21 constitutes the predominant group. Among the balanced autosomal structural anomalies (about 2 per 1000 births) reciprocal translocations and Robertsonian translocations are about equally frequent. Among the latter, those involving two D group chromosomes are more common (48 out of the 60) than those involving D and G group chromosomes.

112. About one-half of all the abnormalities detected at birth may be deemed to be clinically significant (about 3.3 per 1000 births). These abnormalities include all the non-mosaic XXY and 45,X cases, XXX, XYY and XX (male) conditions, all autosomal trisomies and all unbalanced structural rearrangements reported to have been associated with congenital malformations at birth. There are several reasons why this frequency is likely to be an underestimate.

113. The data on the incidence of chromosomal anomalies in newborn infants and other results bearing on whether these are familial or newly arisen, have been used to arrive at estimates of mutation rates. For those abnormalities resulting in livebirths, the estimated rates are the following: numerical errors of autosomes, 6.9 10^{-4}/gamete/generation; sex-chromosomal numerical errors, 8.3 10^{-4}/gamete/generation; balanced Robertsonian translocations, 0.40 10^{-4}/gamete/generation; balanced reciprocal translocations, 1.3 10^{-4}/gamete/generation; unbalanced Robertsonian translocations, 0.23 10^{-4}/gamete/generation; and unbalanced non-Robertsonian structural rearrangements, 0.58 10^{-4}/gamete/generation.

114. In perinatal deaths, the frequency of chromosomal anomalies has been estimated to be of the order of 5 to 6%. Among the anomalies found, trisomies predominate.

115. Further data on the incidence of chromosomal anomalies in spontaneous abortuses (published subsequent to the 1977 report) confirm and extend the conclusions reached in the 1977 report: about 50% of spontaneous abortuses are chromosomally abnormal and trisomies as a group account for over one-half of all chromosomal anomalies recorded in the abortuses. The trisomies have been found to show a maternal-age dependence and the latter is pronounced for those involving the small chromosomes, both acrocentric and non-acrocentric. Trisomy 16 is different from the other

trisomies in that there seems to be no demonstrable maternal-age dependence.

116. Insights into the origin of the extra chromosomes in some trisomies have been gained through the use of chromosomal heteromorphisms as cytogenetic markers. The conclusions that may be drawn from the data are that in the abortus material, for trisomy 16, non-disjunction can occur at any one of the meiotic divisions in either sex, with meiotic I error in the female predominating. For others (trisomy 13, 14, 15, 21 and 22), non-disjunction seems to occur almost exclusively at division I in the female. Trisomy 21 in livebirths seems to arise primarily (in over 70–80% of the cases) as a result of non-disjunction in the mother (division I).

117. There are now extensive data demonstrating that in the case of Down's syndrome, there is an increase in the frequency with increasing maternal age. There are also some reports suggesting that increased paternal age may also play a role.

118. The question of whether there is an increase in the frequency of Down's syndrome children among the progeny of irradiated mothers is not yet settled: the several prospective and retrospective epidemiological studies carried out thus far to specifically investigate the problem have not provided unequivocal evidence in this regard.

119. Studies aimed at testing whether or not satellite associations between acrocentric chromosomes seen in metaphase preparations of lymphocytes may be related to the aetiology of trisomies for these chromosomes, have not provided evidence for such a relationship. Irradiation was found to cause changes in the pattern of satellite associations, but the significance of such changes is not amenable to any satisfactory interpretation.

120. The use of banding techniques to study human chromsomes has led to a number of major advances among which are the discovery of new chromosomal defects particularly partial monosomies and trisomies, and heritable fragile sites. In general, partial trisomies seem to be more frequent than partial monosomies. Heritable fragile sites have been found on a number of metacentric or sub-metacentric chromosomes and at least one is known on the X. Their expression depends on the composition of the tissue culture medium. The relationship between the heritable fragile sites and birth defects is not yet clearly established. However, the fragile site on the X (Xq27 or 28) is usually associated with the form of mental retardation with macro-orchidism in males; there is however one recent report which raises the possibility that an X chromosome with a fragile site typical of X-linked mental retardation can occur in normal individuals.

D. GENES, CHROMOSOMES AND CANCER

1. Monogenic disorders and neoplasia

(a) Introduction

121. Many single gene traits predispose to, or are complicated by, neoplasia [G5, J6, K6, L9, M22, M23, S24]. From the fourth edition of McKusick's [M17] Catalogue, Mulvihill [M23] could extract over 200 conditions with neoplastic tendencies, i.e., with benign or malignant neoplasia or tumour as the sole feature, a frequent concomitant or just a rare complication (see table 1 in [M23]). Among these 200 conditions, about one-half are autosomal dominant, one-third autosomal recessive and one-sixth, X-linked; for some, evidence for Mendelian behaviour is clear-cut while for others such evidence is inconclusive. Some of the traits, because of their rarity, are represented by only single case reports. Notwithstanding these limitations, Mulvihill's analysis shows that a substantial number of all known single gene traits in humans can be manifested as neoplasias; that a large number of gene loci might be involved in cancer susceptibility, and by inference, the number of "normal" genes contributing to resistance to neoplasia is large, and nearly all bodily systems and histological types of tumours are represented including the commonest malignancies of skin, breast, colon and lung.

122. The better known of these traits include xeroderma pigmentosum (XP), ataxia telangiectasia (AT), Fanconi's anaemia (FA), Bloom's syndrome (BS) and retinoblastoma. All these except retinoblastoma are inherited as autosomal recessives. In AT, FA and BS, spontaneous breakage of the chromosomes occurs in peripheral blood lymphocytes and in cultured fibroblasts. On this basis, these syndromes are collectively referred to as "chromosome instability syndromes". In recent years, other disorders such as porokeratosis of Mibelli (autosomal dominant), nevoid basal cell carcinoma (autosomal dominant), incontinentia pigmenti (X-linked) and scleroderma (multifactorial) which may fall under chromosome instability syndromes have come to light. German [G35, G36], Hecht and McCaw [H21] and Paterson [P33] have reviewed the main findings. A workshop [W24] recently held in England was entirely devoted to progress in research with AT. In what follows, some salient features of XP, AT, FA, BS and retinoblastoma will be summarized with special reference to neoplasia.

(b) Xeroderma pigmentosum (XP)

123. The main feature of XP is a marked sensitivity of the skin to sunlight-induced damage, manifested as sunburns, freckling, hyperpigmentation and keratoses, eventually leading to multiple skin carcinomas and melanomas which are the final cause of death usually before the age of 30 [R10]. The disease has now been successfully diagnosed in utero [R11]. Clinical heterogeneity of XP is manifest by a subgroup characterized by mental retardation and neurological abnormalities (De Sanctis-Cacchione syndrome). The basis for predisposition to cancer is a metabolic abnormality in the repair of UV-induced damage to DNA and is considered in a later section.

124. XP patients do not show increased numbers of chromosomal aberrations, although there are isolated reports of a pseudodiploid clone [G6] and of an increase in abnormalities in fibroblasts from XP individuals at late but not at early passage in culture [H22]. The levels of sister chromatid exchanges (SCEs) appear normal [B13, K7, W7].

125. XP individuals have been found in all geographic groups although their freqency seems to vary in different populations. For the populations from North America and Europe, the frequency has been estimated at about 1 in 250 000 [R10]; in Japan this has been estimated to be higher, being 1 in 40 000 to

1 000 000 [T27]. While homozygotes are very sensitive to sunlight-induced cancer (and die due to this), the situation in heterozygotes is not yet clear [S25, T27].

(c) Ataxia telangiectasia (AT)

126. The major findings associated with AT are progressive cerebellar ataxia, conjunctival and cutaneous telangiectasia, frequent sinopulmonary infections with abnormal immunity (not in all patients), a generally hypoplastic lymphoid system and a predisposition to cancer (see [B14, H21]). Most of the cancers reported in AT patients involve the lympho-reticular system; less frequently, epithelial tumours and leukaemia have also been reported [H23]. Death often occurs before the age of 20 either from sinopulmonary infections or from malignancies so that it is difficult to estimate the absolute risk of malignancy (AT patients with cancer are more likely to be reported). There is however no doubt that the risk of malignancy, at least of the reticuloendothelial system, is greatly increased in AT [H21, S25]. An extensive comparison of the many clinical aspects of XP and AT has been made by Kraemer [K8].

127. In many, but not all, AT patients, increased chromosome breakage is evident in lymphocytes, and less strikingly, in fibroblasts [G16, H21, H23, H29, L11]. The SCE frequencies are in the normal range, although there is some variation between different patients [G7, B13, H24]. The non-random chromosomal changes that have been recorded in AT individuals are discussed in the next section.

128. Homozygotes for the AT gene may occur as often as 1 in 40 000 births [S25, S26]. From this, the frequency of heterozygotes (assuming Hardy-Weinberg equilibrium) can be estimated to be about 1% of the population (the latter calculation assumes that AT is genetically homogeneous which it probably is not; see, for instance, [H21, P37]). One report about AT patients (cited in [S25]) noted a number of cancers in family histories in their clinical records. The relatives had no signs of AT and many may have been heterozygous for the AT gene. Swift et al. [S27] found that for blood relatives of AT individuals (27 families) there was an increase in deaths from all types of malignancy, primarily in younger persons ($\leqslant$ 45 years). Below age 45, there were 15 deaths due to malignancy (5.2 expected) and below age 75, there were 59 deaths (42.6 expected). There were actually fewer deaths from cancer than expected in persons dying after 75 years of age. Furthermore, the ratio of observed to expected deaths from malignant neoplasms increased with an increase in the probability of heterozygosity for the AT gene [S25, S27].

129. The estimates of risks for heterozygotes dying of cancer (relative to normal controls) varies by factors of between 2 and 10 depending on how the data are analysed. For instance, the relative risk factor is 2 when death due to all malignancies is considered; it is 5.5 when cancers occurring below age 45 years alone are considered and it rises to 10 when ovarian tumours in women of $\leqslant$ 55 years are taken into consideration. These values of relative risks multiplied by the estimated heterozygote frequency give a value which is a useful measure of the proportion of all cancer patients who carry the AT gene. For instance, over 5% of all persons dying before age 45 from any malignancy may carry the AT gene [S25].

(d) Fanconi's anaemia (FA)

130. Fanconi's anaemia, also termed Fanconi's pancytopaenia or Fanconi's constitutional infantile panmyelopathy is a chromosome instability syndrome associated with progressive marrow failure [F6]. The clinical features include progressive underproduction of red cells, white cells and platelets leading to anaemia, leukopaenia and thrombocytopaenia, hypoplasia or aplasia of the radius and thumb, growth retardation and brownish pigmentation of the skin [B15, G6, H21]. Other skeletal malformations and anomalies of the heart and kidney also occur. Death occurs mainly in the early years, but those who survive longer have an increased risk of acute leukaemia, especially myelomonocytic. Affected patients are also at a greater risk for developing squamous cell carcinoma of mucocutaneous junctions, such as around the mouth and anus and for hepatic adenoma, especially following prolonged androgen therapy for their pancytopaenia [H21].

131. FA patients show increased chromosome breakage and rearrangement, most evident in fresh bone marrow preparations and in lymphocytes cultured for short periods of time such as two to three days; these occur also in fibroblasts cultured for longer periods. The breaks are usually of the chromatid type [S38, S39, S40, W12] and the chromatid interchanges observed (unlike in Bloom's syndrome patients) are mainly between non-homologous sites. The levels of sister chromatid exchanges are normal [H25, K7, L16].

132. Dutrillaux et al. [D11] made a study on the localization of chromatid breaks in lymphocytes of three FA patients using three consecutive stains (Giemsa, Q and R banding). The breakpoints were almost exclusively located in the interbands between R and Q bands, the only true exceptions being the secondary constrictions. The breaks seemed over-represented in the larger autosomes 1–13 (excepting 4, 8 and 10) and under-represented in the smaller ones (excepting chromosome 17); the sex-chromosomes were only rarely affected. There was a clear over-representation of breaks at three sites: 1q12, 9q12 and the interband between 6p21 and 6p22. The remaining breaks were randomly distributed.

133. The incidence at birth of FA is about 1 in 350 000 for the North American population [S25, S31] and may be higher (1 in 70 000) in mid-Europe [W8]. For the former population, a heterozygote frequency of about 0.33% can be estimated. In eight families of patients, 25 deaths from malignancy (among 102 deaths) were found, a frequency which is significantly higher than the 15.6 expected [S25, S31, S32]. This finding of increased cancer risk for FA heterozygotes does not appear to have been substantiated in some other families studied by Swift.

(e) Bloom's syndrome (BS)

134. Three main clinical features of BS are: severe growth retardation, a telangiectatic erythema on exposed areas and sun-sensitivity [B16, G6, G9, G10, H21]. Many patients have serious respiratory and intestinal infections and the immune system is impaired. The risk of cancer is increased in BS patients. Primary cancer develops in approximately 1 out of 6 patients. About half of the cancers are leukaemias of the non-lymphocytic type [H21, G11]. Roughly half of the cases recorded in the literature have been Ashkenazi Jews. A

founder effect is evident and the affected Ashkenazi Jews have been traced to a small area at the border of Poland and the Ukrainian Soviet Socialist Republic. It is not known whether relatives of patients have an increased risk of malignancy.

135. The cytogenetic hallmark of BS is the symmetrical quadriradial figure, which is rarely seen in other chromosome instability syndromes. Lymphocytes and fibroblasts show an increase in quadriradials. The quadriradials involve homologous chromosomes [G10, G12, S30]. This is so characteristic of the disease that, according to German [G10], BS is not diagnosed unless these quadriradials are found. The exchanges occur preferentially near the centromere [G6, G13, S33] and are distributed non-randomly along the chromosomes. In the bone marrow such interchanges have not been found though other aberrations have been detected in some patients [G6, S33, S34].

136. The cells from BS patients contain highly elevated frequencies of sister chromatid exchanges (approximately 90/cell; leucocytes, fibroblasts and bone marrow [B13, C20, G14, S34, S35]). The only known defect in cultured cells is a reduced rate of DNA chain elongation [H55]. However, this impairment does not alter synthesis past pyrimidine dimers in template DNA i.e., post-replication repair is normal [G22].

137. Some reports suggest that the characteristically high level of spontaneous SCEs in BS cells can be reduced. In studies involving co-cultivation of BS and CHO cells, van Buul et al. [B21] showed that the SCE frequencies in BS cells can be reduced by about 20%; the effect was observed only when cell-to-cell contact was present with CHO cells without any effect on the SCE frequencies in CHO cells. Bryant et al. [B22] reported more dramatic results: in euploid cell hybridization studies, they were able to demonstrate that the high SCE frequencies in BS cells could be reduced to normal levels thus resulting in a complete "correction" of the mutant phenotype.

(f) Retinoblastoma

138. Retinoblastoma, an embryoma of the precursors of the rod and cone cells in the retina, is a malignant eye tumour of children [B17, D10]. Mortality is associated with direct extension of the tumour into the cranial cavity to involve the brain and leptomeninges. The incidence figures for this condition reported in the literature (reviewed in ref. [V5]) range from about 1 in 34 000 (Holland, 1927–1929) to about 1 in 10 000 (two African populations; recent figures). Vogel [V5] considers that the most reliable estimates range between 1 in 28 000 and 1 in 15 000 and are based on studies which involved a more complete ascertainment.

139. Retinoblastoma is often considered a classical example of a dominantly inherited tumour. As is now well-known, this is not true of all retino-blastomas. Analysis of the data indicates that about 60% of all retino-blastomas are unilateral and non-hereditary, 15% are unilateral and hereditary and 25% are bilateral and hereditary. In hereditary cases, the tumours tend to appear a year earlier than in non-hereditary cases [K9]. For hereditary cases, the penetrance is of the order of 90 to 95% [K10, V5]. Patients with bilateral, and possibly in general with hereditary, retinoblastoma run an increased risk of becoming afflicted with other tumour diseases, such as bone sarcomas in later life [F24, F25].

140. The idea that retinoblastoma is a direct effect of an autosomal dominant gene has been challenged [Z7]. Knudson [K10, K11] proposed a two-mutation model for both the hereditary and non-hereditary retinoblastoma, i.e., the first event a germinal mutation that makes all of the cells susceptible and the second event a somatic mutation that transforms this mutant cell into a tumour cell. Vogel [V5] has suggested that in the non-hereditary variant, a single mutational step, possibly a small chromosome deletion, may be enough to produce a tumour.

141. The possibility that at least in a minority of retinoblastoma cases, there may be an association with a partial deletion of the long arm of a D group chromosome has long been surmised [L10, T6, W11]. Orye et al. [O5] used the banding techniques to the chromosomes of a patient with retinoblastoma and a deletion of a D group chromosome and identified the chromosome as number 13. This finding has been confirmed in several cases [O6, P13]. Six of the ten cases with an interstitial deletion of chromosome 13 reviewed by Niebuhr [N10] had bilateral tumours and one with bilateral tumours had a ring chromosome.

142. Cytogenetic evidence suggests that the locus for retinoblastoma is on the long arm of chromosome 13 (the proximal part of 13q21 or the adjacent 13q14 region [L7].) Most recently, Yunis and Ramsey [Y3] have refined the localization to a portion of band q14 of chromosome 13.

143. Czeizel et al. [C59] examined lymphocyte chromosomes from 12 of the 43 cases included in their survey of Hungarian patients [C60]. These cases were selected solely for technical feasibility of examination. The breakdown of the selected cases was seven sporadic unilateral cases that had been treated with surgery only, two sporadic unilateral cases, two sporadic bilateral cases treated with surgery and x-irradiation and one familial unilateral case treated surgically and with x-irradiation. It was found that there was a significantly higher number of aneuploid cells and cells carrying structural chromosome anomalies such as chromatid and iso-chromatid breaks and stable chromosome-type aberrations. The increase was found not only in the x-irradiated cases, but also in the seven unirradiated ones (the latter sporadic and unilateral). More recent studies by Knight et al. [K33] on twelve patients with matched controls failed to show any increase in chromosome instability in lymphocyte cultures of retinoblastoma patients.

144. There is at least one report [T28] of increased sister chromatid exchanges in fibroblasts from a child with del(13) retinoblastoma. The skin biopsy was performed before the clinical onset of the tumour. The observed frequency of 19.7/cell was significantly higher relative to that in a normal control.

(g) Aniridia-Wilms' tumour-urogenital abnormalities association

145. Aniridia (absence or defect of the iris; specifically congenital hypoplasia of iris) is usually bilateral and is transmitted as an autosomal dominant trait; it affects about 1 in 50 000 of the general population [M57, M58]. About 30% of the cases are sporadic and

are presumed to represent new germinal mutations [B17]. Wilms' tumour is an embryoma of the kidney derived from metanephric blastema. The incidence rate has been estimated to be of the order of 1 in 10 000 live births or 6–7 per year per million in children under age 15 [Y7]. Wilms' tumour is discovered most often between ages 3 and 4 at which time it is extremely malignant [G39]. These tumours are bilateral in 5 to 10% of the cases, and the bilateral tumours may develop simultaneously or sequentially [B17].

146. Familial Wilms' tumour occurring in siblings has been reported by a number of investigators [B63, B64, K34, M59]. Knudson and Strong [K34] reviewed and summarized data on 58 familial cases. They concluded that bilateral tumours are more likely to be familial, that familial tumours result from two mutations, one germinal and one somatic and that sporadic tumours result from two somatic mutations.

147. It has been found that the presence of aniridia somehow renders the affected child prone to the development of Wilms' tumour [B17, M60]. Aniridia is present in 1 out of 80 Wilms' tumour cases. The sporadic cases seem more at risk, as about a third of these develop Wilms' tumour. The risk of developing Wilms' tumour seems highest when sporadic aniridia is accompanied by genito-urinary tract malformations and mental retardation. Approximately 6% of patients with Wilms' tumour exhibit upper urinary tract anomalies [J18, K35].

148. Since the original report that the aniridia-Wilms' tumour association with mental retardation and genito-urinary abnormalities in males is caused, at the cytological level, by an interstitial deletion of the short arm of chromosome 11 [F26, R66], there have been several confirmatory observations [A26, F27, Y8]. Francke et al. [F27] concluded that a specific deletion of 11p13 appears to cause aniridia with a 1 in 3 risk for the development of Wilms' tumour and an even greater risk for mental retardation. It is interesting to note that the gene coding for catalase has been recently mapped, on the basis of enzymatic studies, to the same region of chromosome 11 (band 11p13) [J19]. Junien et al. [J19] have pointed out that "from a practical standpoint, an assay of catalase activity would thus become a useful complementary test in patients with aniridia appearing to be new mutations. A low catalase activity would then demand surveillance of the kidneys and gonads, even in the absence of a visible chromosome deletion".

2. Specific chromosomal defects in cancer

149. It is quite common to find that cancerous cells have a highly aberrant chromosome number, but this aneuploidy probably results from the rapid uncontrolled mitotic activity of such cells, rather than being the cause of it. Banding techniques have permitted to gain some insights regarding the possible role of some chromosomes (or chromosomal changes) in the origin of some neoplasias. More data, however, would be needed for a precise definition of the relationships between specific chromosomal changes and cancer and for an understanding of the mechanisms involved. Mitelman and Levan [M24], Sanchez and Yunis [S23], Harnden [H26], Rowley [R12] and Hecht [H20] have summarized most of the available information in this area.

(a) Chronic myeloid leukaemia and the Philadelphia (Ph^1) chromosome

150. In 1960, Nowell and Hungerford [N11] reported the first consistent chromosomal abnormality in a human cancer when they described the abnormally small G group chromosome that they observed in leukaemic cells from patients with chronic myeloid leukaemia (CML). This chromosome, which appeared to have lost about half of its long arm, was called the Philadelphia (Ph^1) chromosome from the city of its discovery. A number of laboratories subsequently reported that 100% of patients with CML showed the Ph^1 chromosome in their bone marrow cells. Others reported that up to 30% of patients with CML were Ph^1 negative. In a number of the early cases, only peripheral blood was studied and this might explain why some of the patients were classified as Ph^1 negative (see Rowley [R12] for a review and citation of the early references).

151. By using banding techniques, Caspersson et al. [C21] and O'Riordan et al. [O4] independently reported that the Ph^1 chromosome was no. 22 and that it should be identified as 22q–. The question regarding the nature of the Ph^1 chromosome was answered in 1973 when Rowley [R13] reported that the Ph^1 chromosome represented a translocation, rather than a deletion as many investigators had previously assumed. The first report presented data on 9 Ph^1 positive patients all of whom had additional dully fluorescent chromosomal material at the end of the long arm of one no. 9 (9q+). It was therefore proposed that the abnormality in CML was an apparently balanced translocation t(9;22)(q34;q11). Subsequent measurements of the affected pairs (9 and 22) showed that the amount of DNA added to number 9 is equal to that missing from the Ph^1 [M25].

152. The original report on the translocation, and a number of reports confirming the observation, noted that the translocation occurred only between number 9 and number 22 (see for instance [D8, P9, P10, P11, W9, W10]). However, subsequently, translocations between number 22 and other chromosomes (numbers 2, 13, 16, 17, 19 or 21) were also reported [e.g., F6, H27, H28, M26, R14].

153. When patients with CML enter the terminal acute phase, about 30% appear to retain the 46,Ph^1-positive cell line unchanged, whereas other chromosomal changes also occur on the Ph^1-positive cell lines in 70% of patients (see table 2 in Rowley [R12]). A change in the karyotype is a grave sign and, with rare exceptions, heralds the acute blast phase.

154. In a workshop [D9] which was organized to review the clinical and cytogenetic data in CML and acute non-lymphocytic leukaemia (ANLL), data on 223 patients with Ph^1-positive CML were compiled and analysed. The prerequisites for inclusion of patients in the series were that bone marrow mitoses had been studied by banding and that sufficient clinical data were available. Of the 223 patients, 122 were studied in the chronic phase, 59 in both the chronic and acute phases, 37 (who were known to have CML) only in the blast phase and 5 (with no prior history of CML) in the blast phase.

155. The major findings were that the translocation between chromosomes 9 and 22 was found in 92% (205) of all patients; that of the remainder, 8 had a two-way translocation involving chromosome 22 and another

chromosome, and 9 had three- or four-way translocations, all of which involved both chromosomes 9 and 22 and some other chromosome(s) (see also [P34]); that one patient with a 22q– lacked an obvious translocation; that fewer than 10% of the patients in the chronic phase had other karyotypic abnormalities. In contrast, at least 75% of those in the acute phase showed changes in their karyotype. In some instances, such changes preceded the onset of clinically apparent blast crisis by up to 18 months, although the usual interval was 1 to 4 months. It was found that the additional abnormalities seen in the chronic phase, most often a double Ph¹ chromosome (5%) or +8 (2.4%) were also those most frequently seen in the blast phase. Also, the possible isochromosome for the long arm of 17 [i(17q)] was considered to be a reliable marker for the blast phase, and other structural rearrangements independent of the Ph¹ translocation occurred in about 10% of the patients.

156. Reports of patients with CML whose cells have been analysed with banding have included those who are Ph¹-negative. The Ph¹-negative patients account for about 18% of the cases studied in chronic phase [R12]. These patients tend to be older, with a large percentage of males. They show a smaller elevation of the white blood cell count than do Ph¹-positives [W10], and respond poorly to treatment and therefore have a much shorter mean survival (15 months as compared to 42 months for the Ph¹-positive patients). A number of investigators have suggested that the Ph¹-negative variant could represent a different disease. At present, the tendency is to include both the Ph¹-positive and Ph¹-negative patients within the category of CML.

(b) Acute leukaemias

157. In contrast to the observations discussed in the preceding section on CML in which a specific chromosomal abnormality, the Ph¹ chromosome, is found in over 90% of the patients, the chromosome patterns in acute leukaemias (either myelogenous (AML) or lymphoblastic (ALL)) are quite variable, although chromosomal abnormalities have been detected in about 50% of the cases. Sandberg et al. [S36] first suggested that patients with AML are more likely to have diploid or hypodiploid chromosome numbers whereas those with ALL are more likely to have hyperdiploid chromosome numbers. Although chromosomal changes in bone marrow cells of acute leukaemic patients are diverse, an extra C group chromosome (8 or 9 or sometimes 10 or 11) had been repeatedly reported in bone marrow cells of leukaemic patients as well as in patients with other haematopoietic disorders [J7, R15]; a missing or deleted chromosome 7 [P12, R16] or an isochromosome for the long arm of chromosome 17 has also been found [F7, M27].

158. Rowley [R12] recently analysed the banding patterns of chromosomes of 60 patients with AML, acute myelomonocytic leukaemia (AMMoL) or erythroleukaemia (EL) (see table 8 in reference [R12]). It was found that there is a surprisingly narrow range of modal chromosome numbers, with 22 individuals having 45 chromosomes, 16 having 46 and 15 having 47; 5 had 42–44 and 4 had 48–50 chromosomes; the chromosomal abnormalities can be grouped into three major types: gain of one autosome, loss of one autosome and balanced translocation. It was further found that 13 patients had one extra autosome identified as number 8 in ten cases. Nine showed loss of one autosome, identified as number 7 in six cases. Five patients had an 8;21 translocation.

159. The summary report of van den Berghe et al. [D9] on acute non-lymphocytic leukaemia (ANLL) in 279 patients is in general confirmatory of Rowley's analysis. They found that out of the 279 patients with ANLL, 140 had an apparently normal karyotype and 139 were chromosomally abnormal. Among the latter group, 22 cases had +8, 20 cases were –7, 11 cases had t(8q–;21q+), 9 cases had 5(15q+; 17q–) and 5 cases were t(9q+;22q–). Of the remaining 139 patients 72 had modal chromosome numbers as follows: less than 46 (19 cases); equal to 46 (30 cases) and higher than 46 (23 cases). The survival of patients was related to the karyotypes of the marrow cells. Patients with only normal cells (NN), with a mixture of normal and abnormal cells (NA) and with only abnormal cells (AA) had median survival times of 6, 5 and 4 months, respectively. The correlation between karyotype and survival was most significant for patients with AML in which the median survival was 8 months for NN patients, but 2 and 3 months for AN and AA patients, respectively.

160. It would thus appear that AML and CML in the acute phases have some chromosomal changes in common, namely, an additional number 8 and, less frequently in the former, an i(17q). Other changes appear to be relatively specific for one disease or another. The Ph¹ chromosome is restricted to CML and an extra F, shown to be number 19, is found in CML and not in AML. Loss of Y may occur in up to 10% of Ph¹-positive males, but is rare in AML. The absence of number 7 or an X in females or the (8;21) translocation appears to be limited to AML [R12].

(c) Testicular tumours

161. In 1967, Martineau [M28] reported the occurrence of a long submetacentric marker in 8 out of 9 patients with testicular tumours (seminomas) but so far no banding studies have been reported on these tumours.

(d) Burkitt's lymphoma

162. Burkitt's lymphoma is a sporadic disease of children. First described in Africa, it is also known to occur in virtually epidemic proportions in New Guinea. It shows involvement of the peripheral lymph nodes (e.g., in the jaw) or with a lymphomatous mass in the lower abdomen. The course of the disease is usually short resulting in death within a few years. Burkitt's lymphoma is now known to occur worldwide, including the Americas and Europe. In such areas, the children tend to be a little older when they contract the disease, to be more resistant to drug therapy and to die even more quickly after diagnosis than in Africa or in New Guinea [W6].

163. The most interesting difference between the African (and New Guinean) (AfBL) and the American types (AmBL) is related to the close association with the Epstein-Barr virus in the majority of the cases of the former type whereas this is not true of the latter. Biopsies and cell cultures from patients with AfBL show an abnormal chromosome 14 with an additional terminal band [J8, M29] in many cases. Zech [Z4] and Zech et al. [Z12] have provided evidence suggesting that the extra R band at the distal end of the long arm of

chromosome 14 is the result of a balanced translocation from chromosome 8, i.e., t(8q−;14q+).

164. Studies of cells cultured from two children with AmBL showed that in one there was no detectable Epstein-Barr virus while in the other, it was present. In both cases, the t(8q−;14q+) was found and was indistinguishable from that observed in the AfBL [E5].

(e) Meningiomas

165. Cytogenetic studies of human meningiomas have shown that the majority have a hypodiploid cell line and the G group chromosome missing in many cases is number 22 [M30, Z5]. In addition, the loss of chromosomes 8, 9, X and Y have also been reported in a few cases [M31, Z6].

(f) Ataxia telangiectasia

166. In blood lymphocytes and fibroblasts from patients with AT, increased spontaneous chromosome breakage has long been known [H21, H23, H29, G16, L11]. More recently, chromosomal rearrangements of the translocation type have been described in association with chromosome breakage [B18, P14]. Banding studies have shown the specific involvement of chromosomes 7 and 14 in translocations, generating in particular, t(14;14) and t(7;14) [H30, M32, O7, R17]. The involvement of chromosomes 7 or 14 with other chromosomes has also been reported [M32, O7].

167. In their study, McCaw et al. [M32] found translocations involving 14q in lymphocyte clones obtained from 7 out of 8 AT patients; the other patient had a ring 14 chromosome. The breakpoints in chromosome 14 involved in the translocation were in the q12 band whereas those in the recipient chromosomes were at or near the end. The breakpoints and the extent of probable deletion in the ring 14 chromosomes were not determined. The authors had an opportunity to study the chromosomes of one patient before and after the onset of chronic lymphocytic leukaemia. Before leukaemia was diagnosed, the patient had a lymphocyte clone with a 14q translocation in about 20% of the lymphocytes sampled. After the onset of the leukaemia, 100% of the cells sampled from peripheral blood were leukaemic and showed only one of the two number 14 chromosomes, namely one with extra material on its long arm (14q+). The authors consider that the evolution of the leukaemic clone from the pre-existing translocation clone was not fortuitous and that the leukaemic transformation was intimately related to the structural rearrangement of 14q. They also believe that the increasing evidence provided by others for the non-random involvement of 14q in African-type Burkitt lymphoma and other lymphoid neoplasms support their hypothesis.

168. Aurias et al. [A9] have reported the results of a study on R-banding of lymphocytes and fibroblasts from 11 AT patients and 6 relatives (parents, siblings) of the patients. Among a total of 927 lymphocytes analysed, there were 158 chromosomal rearrangements and out of 187 fibroblasts examined, 33 were chromosomally abnormal giving frequencies of 0.17% for lymphocytes and 0.18% for fibroblasts. The most frequent rearrangement is a pericentric inversion of chromosome 7 and this is true of both lymphocytes and fibroblasts. The relative frequencies of inv(7) and other rearrangements are: 29,inv(7); 8,t(7q;14q); 9,t(7p;14q); 6,inv(14); 24 other rearrangements involving chromosomes 7 or 14; 104 rearrangements involving other chromosomes and a few other rearrangements of a complex type involving chromosomes 7 or 14. The 191 rearrangements detected corresponded to 316 recognizable breakpoints, 35% of which involved chromosome 7, 15% involved chromosome 14, the remainder involving other chromosomes. Among the 112 breakpoints in chromosome 7, 41 seemed to affect band p14 and 40, band q35; an analogous non-random situation existed with respect to chromosome 14: bands q12 and q32.3 are predominantly affected.

169. These results thus demonstrate that inv(7) is the most common single type of rearrangement in AT patients and are at variance with those reported by other investigators who had found t(14;14) and t(7;14) to be the predominant types. The basis for the difference is not clear at present, but may possibly be related to methodological problems (the present work is the first one to use R banding systematically for all cells examined), geographical differences, age, severity of the disease, etc.

170. Turning now to the results from the study of the relatives of AT, in two of the three parents, 2 rearrangements of chromosome 7 and 14 (one, an inv(7) and another a t(7p;14q)) were found in 225 cells. Among 2 of the 3 siblings, 6 rearrangements of chromosomes 7 and 14 were found in 205 cells. In a further study of 17 AT heterozygotes, Aurias et al. [A9] confirmed the above finding with respect to the specificity of rearrangements and their rate of occurrence.

171. It is worth pointing out here that several investigators have independently reported the occurrence of t(7;14) in lymphocyte cultures of apparently normal individuals [A10, B19, H31, W13, Z8]. The apparent breakpoints on each of the two chromosomes were nearly similar in all these cases (chromosome 14: q12 or q(1–2); chromosome 7: q13 or qter). Aurias et al. [A9] stress that in most of the other studies on non-AT patients, inversions had not been detected and this could have been due to biased analyses. Inversions of chromosome 7 and 14 were among the most common if not the most common chromosomal change, both in cells from AT patients and in cells from presumed normal individuals. In both categories the frequency of inversions was probably underestimated because of the difficulty in detecting them. Their data lend credence to the possibility that in AT individuals and AT heterozygotes, the frequencies of rearrangements involving chromosomes 7 and 14 may be, respectively, 40 and 9 times higher than in presumed normal cells.

172. The specific chromosomal defects in cancer discussed in this section and some others not discussed are summarized in Table 9.

3. Summary and conclusions

173. Many single gene traits (autosomal dominant, autosomal recessive and X-linked) predispose to or are complicated by neoplasia. The well studied ones are exemplified by xeroderma pigmentosum (XP), ataxia telangiectasia (AT), Fanconi's anaemia (FA), Bloom's syndrome (BS) and retinoblastoma. All these except retinoblastoma are inherited as autosomal recessives. Conditions such as AT, FA and BS are collectively

referred to as "chromosome instability syndromes" on the basis of the fact that spontaneous breakage of the chromosomes occur in peripheral blood lymphocytes and in fibroblasts from these patients cultured in vitro.

174. The most notable abnormality in XP is hypersensitivity of the skin to solar radiation and is reflected by pigmentation changes, elevated erythema and multiple neoplasms; basal and squamous cell carcinomas are the most prevalent types. Clinicians distinguish two forms of XP: the classical XP displaying skin (and ocular) complications only and neurological XP in which a wide range of central nervous system defects accompany the skin lesions. XP heterozygotes do not seem to be at any increased risk for developing cancers.

175. AT is a complex neurovascular and immunodeficiency syndrome with a predisposition to cancer of the lymphoreticular system. Increased spontaneous chromosome breakage is evident in lymphocytes and less strikingly, in fibroblasts. More recently chromosome rearrangements of the translocation type involving chromosomes 7 and 14 and inversions in chromosome 7 have been described. There is evidence that the presence of the translocation containing clones in peripheral blood lymphocytes may herald the development of cancer; in one AT patient with chronic lymphocytic leukaemia, the neoplastic lymphocytes appeared to descend directly from a pre-malignant clone marked by a 14q translocation. Heterozygotes for AT appear to be at an increased risk for the development of cancer.

176. The predominant clinical features of FA are haematological disturbances involving all elements of the bone marrow, diverse anatomical malformations, cutaneous lesions and growth retardation. The affected individuals usually die in childhood from excessive bleeding or overwhelming infection and those who survive to adulthood are prone to acute leukaemia (particularly myelomonocytic), squamous cell carcinoma of mucocutaneous junctions surrounding the oral and anal cavities and hepatic adenoma. The modal karyotype is normal in FA (this also holds true for XP and AT). Both blood lymphocytes and dermal fibroblasts are characterized by a high spontaneous frequency of chromatid-type breaks and gaps. The chromatid rearrangements are mainly between non-homologous sites. Heterozygotes do not seem to be at an increased risk for cancer.

177. BS is characterized clinically by severe growth retardation, a telangiectatic erythema on exposed areas, increased sun-sensitivity and impairment of the immune system. The risk of cancer is increased in BS patients and about half of the cancers are leukaemias of the non-lymphocytic type. The cytogenetic hallmark of BS is the symmetrical quadriradial figure which is rarely seen in other chromosome instability syndromes. The cells from BS patients show highly elevated frequencies of sister chromatid exchanges in leucocytes, fibroblasts and in bone marrow cells. There are no data on whether heterozygotes are at an increased risk for cancer.

178. Retinoblastoma is a malignant eye tumour of children. About 60% of the retinoblastomas are unilateral and non-hereditary, 15%, unilateral and hereditary and 25%, bilateral and hereditary. The mode of inheritance of the hereditary variety of retinoblastoma is autosomal dominant with over 90% penetrance. Cytogenetic evidence suggests that the locus for retinoblastoma is on the long arm of chromosome 13 at band q14.

179. There is good evidence for the association between aniridia (an autosomal dominant trait), Wilms' tumour and urogenital abnormalities and a specific deletion of chromosome 11 (11p13) appears to cause aniridia with a 1 in 3 risk for the development of Wilms' tumour and an even greater risk for the development of mental retardation. The gene coding for the enzyme catalase has been mapped to the same region as that which is involved in the aniridia-Wilms' tumour association.

180. Over the last two decades, the thesis that some specific chromosomal changes may be involved in neoplasia has gained increasing support. Thus for instance, in chronic myeloid leukaemia, a translocation between chromosomes 9 and 22 has been diagnosed in a majority of the cases. In acute leukaemias, the chromosomal patterns are variable although chromosomal abnormalities (some specific) have been detected in about 50% of the cases. In Burkitt's lymphoma, the main chromosomal change seems to be a translocation involving chromosomes 8 and 14.

E. HUMAN DISORDERS SHOWING INCREASED SENSITIVITY TO THE INDUCTION OF GENETIC DAMAGE BY PHYSICAL AND CHEMICAL MUTAGENS; THE ROLE OF DNA REPAIR

181. In the 1977 report, some aspects of the sensitivity of cells derived from individuals suffering from certain inherited disorders to UV and ionizing radiation and the role of DNA repair processes were dealt with. This section will be devoted to an updating of the information in this area. For more extensive reviews, see [A11, A27, C22, C61, H32, P33, P36, P37, P38, S41, S42].

182. The disorders that have been extensively studied from the standpoint of increased sensitivity to DNA damaging agents are XP, AT, BS and FA. Besides, some information is available for some other disorders. The increased sensitivity of affected individuals to a physical or chemical agent has been a useful indicator of a possible cellular defect in the ability of the cells to recover from induced DNA damage. Thus for instance, the increased sun sensitivity and the finding that XP individuals developed skin cancer at early ages prompted Cleaver's work with XP cells. This led to the discovery that XP cells are deficient in DNA repair [C23] of UV-induced damage and catalysed the search for other disorders that may show repair defects, not only with respect to UV-induced damage but also with regard to damage induced by other mutagens.

1. Sensitivity at the individual level

183. It is now known that, in addition to XP, BS and Cockayne's syndrome patients show increased sun-sensitivity although the repair defects may be of a different nature. The same is also true of FA patients. There are three reports [C24, G18, M33] of AT patients showing unusual radiosensitivity. Gotoff et al. [G18] reported a ten-year-old boy with AT and a malignant lymphoma who, after receiving a maximum dose of 3000 rad to the nasopharynx (out of a planned tumour dose of 4000 rad) was noted to show marked symptoms

of cutaneous erythema and clinical signs indicated deep tissue damage. Following his death eight months later autopsy revealed deep tissue necrosis and it was concluded that the radiation was directly responsible for his death. The second report [M33] concerned a nine-year-old boy with AT and Hodgin's disease who received a partial dose of 2843 rad (out of a planned dose of 4000 rad) to the mediastinum. The patient developed severe oesophagitis, skin damage and respiratory problems and died four months later. Lastly, Cunliff et al. [C24] reported a seven-year-old boy with AT and a malignant lymphoma in the upper lobe of the right lung. After 20 Gy, dysphagia and erythema were noted and, at 30 Gy, the treatment was stopped because of worsening symptoms. He died three weeks later. Again, death appeared to be due to the radiation treatment.

184. There are reports (e.g., [B23]) of patients with basal cell naevus syndrome showing severe responses to radiation therapy (the syndrome is an autosomal dominant condition characterized by multiple basal naevi, which frequently develop into carcinomas and a variety of minor malformations). In the case of familial retinoblastoma, it is known that the gene carriers are susceptible to other tumours, especially osteogenic sarcoma; the latter may affect 1% of gene carriers [J10, K17]. When gene carriers are irradiated, this risk rises sharply; with very large doses of x rays to the orbit, the incidence of osteogenic sarcoma of the orbit may rise to 30% [S51].

2. Sensitivity at the cellular level

185. A number of studies have been carried out to examine the sensitivity of cells derived from these patients to the lethal, chromosome-breaking and mutagenic effects of radiation and of chemicals. These studies have revealed that the patterns are complex and not all of them are amenable to simple interpretations as will be discussed below.

(a) Cell-killing effects

186. In the work of Arlett and Harcourt [A28], the gamma-ray sensitivity to killing of over 50 lines of human diploid fibroblasts (including some derived from individuals suffering from one or another of the diseases mentioned above) was examined. It was found that the normal sensitivity could be described by a range of D_o values of 0.97 to 1.80 Gy. All ten AT strains tested proved radiosensitive and gave a mean D_o value of 0.57 ± 0.15 Gy and these represent the most radiosensitive human skin fibroblasts currently available. Representative cell strains from familial retinoblastoma, FA, Hutchinson-Gilford progeria occupied positions of intermediate sensitivity, as did one of the two AT heterozygotes. Six XP cell strains together with two Cockayne's syndrome cell strains (all known to be sensitive to UV) fell in the normal range, indicating an absence of cross-sensitivity between UV and gamma-irradiation.

187. In the x-ray study of Weichselbaum et al. [W26], again involving over 50 cell strains, the sensitivity of six cell strains from normal individuals was described by D_o values in the range from 1.4 to 1.52 Gy with an overall range, based on the extremes of their standard errors, of 1.28 to 1.64 Gy. About three-quarters of those studied (including those derived from patients with one or another condition associated with a predisposition to malignancy) fell in this range. Cell strains identified as sensitive came from AT patients (D_o: 0.46 to 0.52 Gy), progeria (D_o: 0.96 to 1.39 Gy), the two genetic forms of retinoblastoma (D_o: 0.94 to 0.98 Gy) and partial trisomy for chromosome 13 (D_o: 0.75 to 0.95 Gy).

188. If the sensitivity of AT cell strains is expressed in terms of a dose-reduction factor (DRF) relative to normal strains, this corresponds to a value of about 3 [P36, P37, P38, P39]. This is true irrespective of whether the cells are irradiated under oxic or hypoxic conditions. AT cell strains also display a uniform response to inactivation by 14 MeV neutrons; however they are only from 1.6 to 2 times more sensitive to this densely ionizing radiation than are normal strains [P37, P38].

189. While AT strains are consistently hypersensitive to killing by ionizing radiation, their response to many chemical carcinogens is less uniform. AT strains in general seem to be sensitive to those chemicals whose biological effects mimic those of ionizing radiation such as methylmethane sulphonate (MMS) and N-methyl-N'-nitro-N-nitroguanidine (MNNG); AT cells are inactivated at a normal rate by far UV (chiefly 254 nm) light or UV-mimetic chemicals, such as N-acetoxy-acetylaminofluorene (N-acetoxy-AAF) (see [A11, P37, P38] and references cited therein). There is however, much more interstrain variability in response to treatment with radiomimetic chemicals than is observed for ionizing radiation.

190. XP cells, with the exception of the XP variants, are very sensitive to the lethal effects of UV-irradiation (reviewed in [C25]). XP variants in contrast, are only slightly more sensitive than normal cells [L13]. XP strains display cross-sensitivity to certain chemical carcinogens, including reactive forms of polycyclic hydrocarbons (e.g., "K-region" epoxides of benzo(a)pyrene) and aromatic amides (e.g., 4-NQO; [T12]) but respond normally to ionizing radiation, monofunctional alkylating agents (e.g., MNNG) and the DNA-cross-linking agent (mitomycin-C) [A18, F9, M38, S41].

191. The pattern of sensitivity of FA fibroblasts to different physical and chemical agents is somewhat different than that of XP or AT fibroblasts. FA cells are hypersensitive to bifunctional alkylating agents (e.g., mitomycin-C, nitrogen mustard) or to psoralen-plus-black light, but are at most only slightly more sensitive to far-UV or gamma-irradiation, 4-NQO or MMS [F9, S104].

192. Fibroblasts from BS patients are not unusually sensitive to UV- or x-ray-induced killing, but there are results [K13] showing that BS lymphocytes may be highly sensitive to EMS-induced killing. Fibroblasts from Cockayne's syndrome patients are also hypersensitive to UV-induced killing [M37, S45] but show normal sensitivity with respect to x rays.

193. Some of the main findings discussed in this subsection are summarized in Table 10.

(b) Host-cell reactivation

194. Several cell strains derived from patients with hereditary disorders such as XP, AT, etc., have been assayed for ability to support the reproduction of mutagen-inactivated viruses, a phenomenon known as

host-cell reactivation (HCR). The XP cells have a reduced capacity to reactivate UV-irradiated adenovirus 2 assayed on the basis of either plaque-forming ability [D21] or production of viral structural antigens [R67]. Similar results have been obtained with UV-irradiated SV-40 virus, herpes simplex and vaccinia virus [A15, A16, L15; see also S105]. Several AT strains reactivate MNNG or x-ray-damaged adenovirus normally [D22, R67] despite their hypersensitivity to killing by these two agents; however, HCR of far-UV-irradiated virus is slightly reduced, using both plaque-forming ability and synthesis of viral (V antigen) protein as end-points [R67] although AT cells are inactivated at normal rates by far-UV light. These observations suggest that repair functions presumed to be deficient in AT cells are not required to promote survival of x-ray- or MNNG-damaged virus but are required to assist in viral recovery from a component of far-UV damage to DNA. There is some evidence for progeroid fibroblasts showing a reduced capacity to reactivate gamma-irradiated adenovirus [R69] and for FA cells showing a reduced capacity to produce viral structural antigens after infection with UV or gamma-irradiated adenovirus [R68].

(c) Mutation induction

195. Maher et al. [M35, M38, M39] have shown that UV irradiation induces significantly higher frequencies of 8-AG resistant mutations in both classical XP and variant XP cells than in normal cells. Likewise, the XP cells were found to be more susceptible (by a factor of 2 to 3) to the induction of mutations by the "K-region" epoxide of benzo(a)pyrene, 7,12-dimethylbenz(a)anthracene and dibenz(a,h)anthracene; the XP variant cells (from a patient) were also found to be more sensitive to mutation induction by hydrocarbon epoxides [M34]. Thus, at least in the case of the XP cells, there is a reasonably good correlation between cell killing and mutagenic effects of UV. The preliminary results of different investigators mentioned by Arlett and Lehman [A11] for AT cells suggest, in contrast, that these cells may be hypomutable or even immutable by ionizing radiation. A similar lack of correlation between sensitivity to killing and to mutation induction is also observed in the case of AT cells treated with mitomycin-C. It is tempting to speculate that error-prone repair pathways which in normal cells give rise to gamma-ray or mitomycin-C induced mutations may be inoperative in the AT and FA cells, respectively.

(d) Induction of chromosome aberrations and sister-chromatid exchanges

196. XP strains display more chromosome breakage than normal cells upon treatment with UV light or "UV-like" carcinogens but not with "ionizing-radiation-like" chemicals [B13, S43, S106, W17]. The chromosomal sensitivity to UV appears to be insufficient to account for the increased lethality, suggesting that the chromosome aberrations are probably not the principal cause of cell death in XP [M36]. Most, but not all, XP cells show an elevated rate of UV-induced SCEs [D12, P15, S47]. Wolff and co-workers [W17] reported that a virus-transformed XP cell strain from complementation group A showed increased induction of SCEs by a variety of chemical mutagens, even those (such as EMS) to which XP cells exhibit a normal repair and cell-killing responses. The results of Perry et al. [P15] support those of Wolff and co-workers. Heddle [H34] found that elevated levels of SCE induction by EMS were not obtained in three untransformed XP cell strains from complementation group A. In XP variants, UV exposure results in normal levels of SCE [D12, W17].

197. Ionizing radiation produces a much higher frequency of chromosomal aberrations in AT than in normal cells; furthermore, it has been shown that lymphocytes of AT patients when irradiated in G_0 or G_1 show both chromosome-type and chromatid-type aberrations, in contrast to the normal situation of only chromosome-type aberrations [T7]. Natarajan and Meijers [N12] studied the x-ray-induction of chromosome aberrations in peripheral blood lymphocytes as well as in skin fibroblasts from AT patients and found that in G_0, G_1 and G_2, more aberrations were induced in AT cells than in normal cells. These results as well as those of Taylor [T9] demonstrate that base damage which needs an S-dependent repair is not entirely responsible for the increased frequency of x-ray-induced aberrations in AT cells. The frequencies of SCEs induced by x rays (as well as those induced by a number of chemical mutagens) are in the normal range [G20].

198. FA cells show an extreme specific sensitivity to both the lethal and chromosome-breaking effects of DNA cross-linking agents such as mitomycin-C [F8, F9, S44]. The induction of chromatid-type aberrations by mitomycin-C is markedly elevated in FA lymphoctyes [S44] and this is also true of x-ray exposure [H56]. Diepoxybutane, another bifunctional agent, also increases the yield of chromosome aberrations at concentrations that produce no increase in normal cells [A14]. In FA cells, a lower than normal number of SCEs are induced in blood cells (but not fibroblasts) by mitomycin-C [L16].

199. It has been reported that cells (erythrocytes) from two unrelated FA patients are deficient in superoxide dismutase [J9] and that treatment with this enzyme reduces the spontaneous level of chromosome breakage in cultured cells [N13]. Raj and Heddle [R19] tested whether or not treatment with superoxide dismutase (among other enzymes chosen) will lead to a greater proportional reduction in chromosomal damage (measured using the induction of micronuclei as the criterion) of mitomycin-C treated FA fibroblasts. The results showed that while the enzyme treatment reduced both the spontaneous and mitomycin-C-induced chromosome breakage, there was no consistent pronounced effect in FA cells.

200. BS cells do not show increased frequencies of chromosome aberrations following UV- or gamma-irradiation [15] but they seem to show an elevated SCE response following exposure to EMS [K13]. Cockayne's syndrome cells show an increased sensitivity to the UV-induction of SCEs [M36, S45]. In the study of Marshall et al. [M36], at any UV dose, approximately 2.5 times more SCEs were induced in Cockayne's syndrome cells than in normal fibroblasts.

201. Some of the main results pertaining to chromosome aberrations and SCEs are summarized in Table 11.

3. DNA repair

(a) Xeroderma pigmentosum (XP)

202. There are now extensive biochemical and biophysical data on the DNA repair properties of UV-irradiated XP strains to support the idea that the abnormal UV response of XP cells is due to a molecular defect in the repair of UV-induced DNA damage. The defect is not complete, however, but may be over 90% in the cells of some individuals and only 50% in others [C25, K8, S41]. Cell strains established from all neurological XP patients and from most classical XP patients are deficient, to varying extents, in excision repair. This conclusion is supported by data on several molecular end-points: removal of dimers [C25, C26], disappearance of UV-endonuclease sensitive sites [P39] and repair synthesis levels as monitored directly by unscheduled DNA synthesis (UDS) or repair replication [C26] or indirectly by photolysis of incorporated bromodeoxyuridine (BrdUrd) [R70].

203. The XP strains that are deficient in excision repair have been subdivided on the basis of complementation analysis, using the technique of somatic cell hybridization [K14]. Two strains are assigned to different complementation groups if, upon fusion, both nuclei of binuclear hybrid cells exhibit near-normal levels of UV-induced UDS; alternatively, if the UDS levels remain reduced in the hybrids, the two strains are allocated to the same complementation group. Thus far, seven complementation groups have been identified [A17, D13, D14, K14, K15]. The strains designated as XP variants constitute a minority of the strains from persons having the classical form of XP; such strains are proficient in excision repair, but are deficient in post-replication repair after UV treatment [L12]. These variants like the excision repair strains possess reduced levels of photolase activity [S107] although the residual levels vary between different variant strains. Table 12 summarizes some of the main DNA repair properties of different genetic forms of XP.

204. There is considerable evidence for the thesis that the defect in most, if not all, of these groups is in the incision step. Firstly, following UV-irradiation of XP cells of groups A–D, only small numbers of single strand breaks (SSB) are observed compared with the number of dimers in the DNA [C26, F10]. Secondly, when T4 endonuclease V is introduced into UV-irradiated XP cells of groups A–E, UDS approaches normal levels and the introduced enzyme increases survival [T10, T11]. Thirdly, Ciarrocchi and Linn [C27] showed that T4 endonuclease restores repair replication activity in a cell-free system obtained from XP–A cells. Smith and Hanawalt [S47] characterized repair replication activity in isolated human cell nuclei, and demonstrated that the activity restored to XP–A cells by addition of T4 endonuclease closely resembled repair replication in normal human cells. The observation that the incision endonuclease can allow cells from several different complementation groups to perform the subsequent steps in excision repair suggests that all are deficient in incision but not in excision-resynthesis.

205. It would thus appear that mutation in any of a number of genes might lead to the loss of incision activity in human cells. However, the existence of seven complementation groups in XP does not necessarily indicate that seven different proteins are required for incision. Some of the groups may represent genes determining polypeptides that interact to form a single functional complex; others may reflect intragenic complementation, mutations in regulatory genes or mutations in genes whose products facilitate the endonucleolytic event [H32].

206. Some support for the last possibility mentioned above comes from the work of Mortelmans et al. [M40]. They found that normal human cells disrupted by sonication were capable of specifically excising pyrimidine dimers both from purified DNA that had been heavily irradiated, and from their endogenous cellular DNA. However, sonicated XP cells from groups A, C and D also excised dimers from purified DNA; but sonicated XP–A cells were unable to excise dimers from their endogenous DNA. This was shown to be a deficiency in enzyme activity rather than a property of the endogenous DNA, as DNA-free sonicates of normal cells were able to promote dimer excision from the XP–A DNA. These findings led to the suggestion that these XP cells are not deficient in the endonuclease activity per se but in some other activity necessary for incision in vivo. Alternatively, the excision of dimers from purified DNA may represent the activity of enzymes not normally associated with excision repair in vivo. Although the inability of sonicated XP–A cells to excise dimers from their endogenous DNA mimics their excision properties in vivo, this is not true of XP–D cells in which excision is observed in vitro but not in vivo.

207. It was mentioned earlier that cells of the XP variant class have normal or near-normal sensitivity to UV light and normal excision repair. These have a defect in post-replication repair [L12], a process which may be defined as "the ability of UV-irradiated cells to achieve the eventual synthesis of high molecular weight daughter strands of DNA despite the presence of unexcised damage in the template strands" [A11]. It has been demonstrated that the molecular weight of newly synthesized DNA in UV-irradiated XP variants is considerably lower than in normal cells [L12]. This suggests that gaps in the daughter DNA strands (presumed to be opposite damage in the template strands) persist for much longer in XP variants than in normal cells. In addition, caffeine has been found to inhibit the sealing of these gaps in XP variants, but to be without effect on normal cells [L12].

208. Park and Cleaver [P16] studied DNA synthesis in normal cells and in excision-defective (group A) and XP-variant cells after irradiation with UV. The sizes of DNA synthesized during brief pulses of tritiated thymidine 1–2 h after irradiation were decreased, the XP variant showing the smallest molecular weight. Once synthesized, however, the labelled DNA increased in size at the same rate as in control in all strains, and the rate was relatively insensitive to caffeine. After 2–3 h, labelled DNA in each cell type reached a maximum size that was less than in the control cells, indicating the presence of long-lived blocks to DNA chain growth. These authors argue that in the studies of Lehman et al. [L12, L13] where one or two chase times were used, the major difference between XP variant cells and normal cells was expressed in the size of the labelled DNA made, not on its subsequent rate of elongation. On the basis of their results, the authors proposed a model alternative to the post-replication repair model; their model assumes normal chain elongation and termination mechanisms in which the dimers and other damaged sites act as all-or-nothing blocks to the progress of the replication forks. Therefore, although the XP variant has a unique

response to UV damage, this does not involve a defect in the bypassing of dimers during a post-labelling chase (i.e., no gaps opposite dimers) but only blocked forks at dimer sites (see also [C61]).

209. The mutation frequency induced by UV in XP variants is well above normal not only when expressed per unit UV fluence but also per survivor [M38, M39]. In contrast, the XP strains deficient in excision repair are only hypermutable when the mutation frequency is given as a function of UV fluence and not survival [M38]. These observations provide good biological evidence that post-replication repair is relatively error-prone whereas, excision repair is error-free, at least in response to UV damage.

210. The fact that all XP cell lines are defective in one or more repair pathways for UV damage have led to the speculation that UV-induced skin carcinogenesis in normal human beings has a low probability because most of the lesions are removed and DNA synthesis beyond any that remain is relatively error-free. In excision-defective XP cells, many dimers remain and replication beyond them, although relatively error-free, makes an appreciable number of mistakes and hence gives a high possibility for neoplastic transformation. In the XP variants, there are a few more dimers than in normals (because of a defect in post-replication repair) but replication beyond dimers is error-prone and, as in the case of conventional XP's, an appreciable number of mistakes is made [S41].

211. XP cells are also defective in the repair of damage induced by a number of chemical agents while they are repair-proficient with respect to the damage induced by certain other chemicals, as well as by ionizing radiation; these are listed in Table 13. It should be realized that the classification of chemical compounds as making reparable or irreparable damage in XP cells, although useful, is complicated by the fact that most, if not all, agents each produce a number of different DNA lesions. The repair of a fraction of these lesions can be impaired in XP cells while the remainder is normal. This seems to be the case with alkylation damage to DNA. Both normal and XP cells are able to remove readily N-7-alkylguanine, but only normal cells can do it for the minor, but biologically more important product O-6-alkylguanine [G21].

212. Earlier studies with 4-NQO demonstrated that XP cells were more sensitive than normal cells for cytotoxic effects [T12] and that XP cells had a relatively low level of DNA repair synthesis [C28, S48]. Ikenega et al. [I2] found that three major stable purine adducts formed by 4-NQO treatment were removed from the DNA of normal cells but such removal was not detectable with the SV-40 transformed XP strain of complementation group A; a less stable guanine adduct however, did disappear from XP DNA, but the rate of removal was lower than in normal cells.

213. The similarity of effects of UV and 4-NQO in XP prompted Zelle [Z9] and Zelle and Bootsma [Z10] to investigate the problem in greater detail. The hypothesis was that if 4-NQO lesions are (predominantly) removed by the same pathway as the pyrimidine dimers and are dependent on the same gene products, then the classification of the different XP strains into different complementation groups should be similar with respect to UV and 4-NQO repair in the strains. DNA repair was studied by determining the extent of UDS in the exposed cells by means of autoradiography. The strains that are classified into the same complementation group on the basis of their repair of UV-damage also did not complement each other after 4-NQO treatment. Strains belonging to different complementation groups (because they do complement each other for the excision of UV lesions), also showed complementation for the repair of 4-NQO-induced damage. In the pure strains, the degree to which UDS after 4-NQO treatment was depressed followed the same pattern as was seen for the repair of UV-damage. From these results, the authors have drawn the conclusion that repair pathways of UV and 4-NQO lesions have steps in common and that the gene products responsible for the repair deficiency in the groups A, B, C, and D are of equal importance for the repair of the majority of the damage induced by 4-NQO.

(b) Ataxia telangiectasia

214. The DNA repair characteristics of AT fibroblast strains after irradiation or other mutagen treatments are summarized in Table 14. The 13 strains examined thus far, can be divided into two broad categories, denoted as exr$^-$ and exr$^+$, on the basis of their capacity (relative to that of normal strains) to execute DNA repair synthesis (i.e., DNA repair replication and UDS) following hypoxic gamma-irradiation [P37]. The diminished level of gamma-ray-induced repair synthesis observed in the exr$^-$ strains does not seem to stem from a defect in strand-rejoining, because all AT strains restitute both single-strand (including alkali-labile lesions) and double strand-breaks with normal kinetics, as judged by several independent criteria [L17, P18, T7]. Instead, the reduction in repair synthesis can be ascribed to a defective capacity to remove alkali-stable radio-products which are detected as sites in DNA sensitive to the strand-incising activity of lesion recognizing enzymes present in crude extracts from Micrococcus luteus [P18, P36].

215. The site removal data imply that certain AT strains lack a fully functional enzyme (endonuclease or DNA glycosylase) or co-factor involved in the initial incision reaction in an excision-repair process. The radioproducts whose removal is presumed to be defective in exr$^-$ AT strains have not been identified: the whole spectrum of base, sugar and cross-link lesions are all candidates with the exception of thymine glycols. AT strains, both exr$^+$ and exr$^-$, apparently repair this numerically important class of modified bases normally [C62, R71].

216. The pattern of DNA repair replication for six AT strains when treated with MNNG resembles that observed after exposure to hypoxic gamma-irradiation; four exr$^-$ strains exhibit diminished levels and two exr$^+$ strains, normal levels [S110]. Recently, Lehman et al. [L45] reported that they were unable to confirm the above observations of Scudiere [S110] regarding defective repair synthesis in AT3B1 (exr$^-$).

217. In spite of the enhanced sensitivity of some AT strains to the lethal effects of MMS, all strains have an apparently normal capacity to repair damage caused by this alkylating agent, at least as reflected by DNA repair replication. In agreement with cell survival studies, the AT cells are proficient in the repair of far-UV light [A18, P17] and AAF-induced [A19] damage.

218. Although considerable success has been achieved in elucidating the DNA properties in AT strains, the

precise biochemical defect responsible for the enhanced radiosensitivity observed at the cellular and cytogenetic levels remains unknown. Enzymological studies have provided little insight into the nature of the underlying defect: cell extracts of both exr+ and exr− strains contain normal levels of activity of uracil-DNA glycosylase [K36] and AP endonuclease [I3, M62, S111].

219. Inoue et al. [I3, I7] have shown that the ability of cell-free extracts to increase the priming activity (in a DNA-polymerase assay) of gamma-irradiated DNA is severely reduced in several AT strains. A comparison in a similar assay of three AT homozygotes, one heterozygote and normal strains showed that homozygotes had substantially lower activity than normal strains, but no difference between heterozygotes and normal strains was found.

220. Cell fusion analyses have allocated three exr− strains to two complementation groups: AT1BE and AT3B1 to group A and AT2BE to group B [P17; see also I7]. AT is thus genetically heterogeneous as is XP.

(c) Bloom's syndrome

221. The nature of the DNA repair defect in BS is not known, but Hand and German [H35] have demonstrated a lowered rate of DNA chain growth in S-phase fibroblasts which may account for the observation that the sedimentation of pulse-labelled DNA after UV-irradiation is somewhat slower than in normal cells [G22].

(d) Fanconi's anaemia

222. The unusually high sensitivity of FA cells to DNA cross-linking agents has already been mentioned. It has been suggested that FA cells are defective in the repair of DNA cross-links [F9, S50]. The DNA of FA cells analysed on alkaline gradients immediately after treatment with mitomycin-C sediments more rapidly than that from normal cells [F9]. This fact may be consistent with the explanation offered by Latt et al. [L16], namely, that mitomycin-C damages one polynucleotide chain (as do monofunctional alkylating agents) but removal of the fragment connected to the other chain by an inter-strand cross-link cannot be effected normally. The steps for the removal of such a fragment in mammalian cells are not defined and this is true also of the fundamental molecular lesion in FA. Poon et al. [P18] observed defective removal of thymine dimers following large UV doses; with 4-NQO, normal endonucleolytic strand scission, and normal levels of UDS were obtained. Remsen and Cerutti [R72] found that in two out of four FA strains, the ability of cell nuclear preparations to excise thymine glycols from gamma-irradiated exogenous DNA was reduced. For all FA strains thus far investigated, the repair of x-ray-induced single-strand breaks is not deficient. A recent report [K16] has described a significant decrease in DNA ligase activity observed in fibroblasts and lymphocytes of a patient with FA and his mother (following UV-irradiation). No differences were found in the other steps of repair.

(e) Cockayne's syndrome

223. The nature of the molecular defect in Cockayne's syndrome is not yet known. Wade et al. [W18] have reported that the fibroblasts derived from seven Cockayne's syndrome patients show increased UV- but not x-ray sensitivity; reduced amounts of *UDS* following UV-irradiation; reduced incorporation of ^{3}H-thymidine into small molecular weight single-stranded DNA after UV; normal excision of UV-induced pyrimidine dimers; and complementation of the ability to repair UV-induced DNA damage in cell hybrids formed between some of the fibroblast strains. Assays on crude extracts of 5 of the 7 strains examined thus far show that all 5 contain less than 50% of the normal DNA polymerase activity.

4. Summary and conclusions

224. The best studied human genetic disorders from the standpoint of sensitivity to mutagens (both at the individual and at the cellular levels) and DNA repair aspects are xeroderma pigmentosum (XP), ataxia telangiectasia (AT), Fanconi's anaemia (FA), Bloom's syndrome (BS) and Cockayne's syndrome. XP, BS and Cockayne's syndrome patients show increased sun-sensitivity and AT patients are highly sensitive to ionizing radiation.

225. XP cells (with the exception of the so-called variants) are very sensitive to the killing effects of UV and of certain chemicals such as some derivatives of acetylaminofluorene (AAF) and nitroquinoline oxide (4-NQO) which form large adducts to DNA. Their response to ionizing radiation and to relatively simple alkylating agents such as MMS and EMS is normal. XP cells are deficient in host-cell-reactivation of viruses. XP cells are also more sensitive to mutation induction (8–AG^R) by UV and chemicals such as the "K-region" epoxide of benzo(a)pyrene, 7, 12-dimethyl-benz(a)-anthracene and to the UV-induction of chromosome-breakage events and sister-chromatid exchanges (SCEs).

226. There is now a substantial body of evidence supporting the premise that the XP strains are defective in the repair of UV-induced DNA damage; all strains (with the exception of the XP variants) are deficient, to varying extents, in excision repair. The variant strain is excision-repair proficient, but post-replication repair deficient.

227. When unscheduled DNA synthesis (UDS) after UV irradiation was examined in the nuclei of heterokaryons formed by fusing cells from different XP patients (their cells being deficient in excision repair), certain combinations appeared normal in excision repair capacity. On this basis, seven complementation groups designated A to G have been defined.

228. The AT cells represent the most radiosensitive (to ionizing radiation) human cells known but their response to many chemical carcinogens is not uniform. In general, the AT cells are more sensitive to those chemicals whose biological effects mimic those of ionizing radiation. Host-cell reactivation as well as response to far-UV are normal in AT cells. Preliminary results suggest that AT cells are less mutable than normal cells by ionizing radiation.

229. Ionizing radiation produces a much higher frequency of chromosomal aberrations in AT than in normal cells. AT cells display an unusual pattern of chromosome aberrations following irradiation in either G_0 or early G_1 phases in the sense that the aberrations

produced are both chromosome-type and chromatid-type. On the basis of their capacity to perform UDS following hypoxic gamma-irradiation (relative to normal cells), the AT strains can be divided into two broad categories, those which are excision-repair proficient and those which are deficient in this respect. Three excision-repair deficient strains have been allocated to two complementation groups A and B, on the basis of complementation studies. The precise biochemical defect responsible for the enhanced radiosensitivity observed at the cellular and cytogenetic levels still remains unknown.

230. FA cells are hypersensitive to bifunctional alkylating agents and to psoralen-plus-black light, but are only slightly more sensitive than normal cells to far-UV, gamma-irradiation, 4-NQO or MMS. The induction of chromatid aberrations by mitomycin-C is elevated in FA lymphocytes and this is also true of x-ray exposure; diepoxybutane also elicits a higher response in FA cells.

231. Fibroblasts from BS patients are not unusually sensitive to UV- or x-ray-induced killing, but there are some data showing that BS lymphocytes may be more sensitive to EMS-induced killing. Fibroblasts from Cockayne's syndrome patients are hypersensitive to UV-induced killing, but show normal sensitivity with respect to x rays. There are some data which suggest that some Cockayne's syndrome strains may have reduced levels of DNA polymerase activity (in crude extracts).

F. OTHER RELEVANT DATA

232. Although a detailed review of the data bearing on the radiation-induction of chromosome aberrations in somatic cells per se is not within the scope of this Annex, the following data are discussed in view of their topical interest and importance.

1. Chromosome aberrations in lymphocytes of individuals living in an area of high radioactivity

233. Pohl-Rüling and Fischer [P20] have summarized the results of their studies on chromosome aberrations in peripheral blood lymphocytes of individuals living and working in Badgastein, Austria, an area known to have a high natural radioactivity. The thermal radon-containing springs constitute the main source of this radioactivity. Five million litres of hot water containing high levels of radon are delivered daily and most of the water is conducted to big reservoirs and from there to hotels and spa houses where it is used for treatment. Almost all of the ^{222}Rn is discharged into the air. In addition, radon emanates from the ground in the whole region. The air activity is lower in the periphery (zone II: 80–150 mR a^{-1}, open air; 100–190 mR a^{-1}, room air) than in the vicinity of the springs (zone I: 80–170 mR a^{-1}, open air; 120–300 mR a^{-1}, room air). Higher levels occur in the various rooms with treatment facilities and the highest air activity is found in the "thermal gallery" (1500 mR a^{-1}), a former gold mine near Badgastein in which more than 5000 patients are treated per year. The radiation burden of the population is derived from inhaled radon and daughters in addition to external gamma irradiation. However, the alpha dose differs widely, being dependent on site of habitation and occupation and type of work. The total dose is lower for inhabitants of zone II than for inhabitants of zone I, higher for attendants at the thermal baths and administrative personnel of the spa house, and highest for the train drivers and doctors who spend several hours a day in the thermal gallery.

234. Chromosome studies were carried out in 180 blood samples from 122 persons grouped into five categories with increasing radiation doses, according to their geographical position within the Badgastein area and their occupations in the thermal baths, spa house or thermal gallery. Category A comprised members of the population living and working in Badgastein and its surroundings who were continuously irradiated by the background radiation; category B consisted of individuals who received occupational irradiation daily six times per week for 4 to 6 h (B1, bath attendants) or 8 to 10 h (B2, thermal gallery personnel) in addition to the Gastein area background irradiation; category C included doctors and train drivers (miners) who received the dose pattern B2 and in addition a high alpha dose six times per week during one (C1) or two (C2) 2 h period of duty within the mine. In addition, there were other individuals who were considered a special group (caretaker who lived on the premises and others who had received diagnostic irradiation etc.). The different groups of individuals studied had accumulated "blood burdens" of 110 to 340 mR a^{-1} of gamma ray dose and 1 to 1600 mR a^{-1} of alpha dose.

235. The main findings are:

(a) Even at these very low dose levels, dose-effect relationships were observed with the mean values of aberration frequencies (fragments, dicentrics and interstitial deletions) increasing from A to C;

(b) There was a weak dependence of aneuploid cells on both age and dose only within groups A and B;

(c) The frequency of fragments showed an age-dependence for all groups. When these were normalized to an age of 50 years, the age-corrected mean values increased from groups A to C, although the dose-response patterns within each group showed differences (the slope was flatter in C than in A and B). At comparable doses, the number of fragments was higher in group A than in B and in B than in C. Within A, there was a strong dependence on alpha dose (expressed as mR per month), but no gamma-ray dose dependence. In group B, a weak dependence on both dose components was present and in group C, only to the gamma-ray dose;

(d) The results for dicentrics and interstitial deletions within groups A and B were similar to those for the fragments, namely, alpha dose dependence in group A and dependence on both alpha- and gamma-ray dose in group B. No linear relationship between dose and two-break aberrations could be established for group C as a whole although a weak alpha dose dependence was present in group C1 (in group C2, there was a decrease in aberration frequencies at the highest dose levels).

2. Chromosome aberrations in lymphocytes of nuclear dockyard workers

236. Evans et al. [E6] published the results of a study on the incidence of chromosome aberrations in peripheral blood lymphocytes of 197 dockyard workers followed up over a 10-year period. These workers had been exposed to mixed neutron + gamma irradiation during the refuelling of nuclear reactors, but most

exposures were below the internationally accepted maximum permissible level of 0.05 Sv per year. Details about the study population and methods of analysis are summarized in the following paragraphs. When the facility for refueling of nuclear-powered submarines was started in England in 1968:

(a) The majority of the workers who joined the establishment had not received previous occupational exposure to radiation;
(b) Blood samples were taken before their classification as "radiation workers" to give background control samples and serial blood samples were later obtained at periodic intervals as the dose accumulated;
(c) The blood was cultured using procedures standard to their laboratory; the cells were orcein-stained and those with 45 or more centromeres were scored for dicentrics, rings, acentric fragments, minutes, abnormal monocentrics, additional or absent monocentrics (aneuploidy), a medium-sized chromosome with abnormal centromere separation (almost certainly an abnormal X chromosome) and chromatid aberrations;
(d) Dose estimates in rems, from film badges, were provided by the Admiralty Radiation Records Centre;
(e) The radiation sources were nuclear submarines undergoing refit and emitting mixed neutron + gamma radiation, although the exposures were stated to involve "almost exclusively gamma radiation".

237. The main results are:

(a) When the cumulative doses over the ten-year period were grouped into 0.05 Sv intervals, there was a positive correlation between the incidence of cells containing all types of aberrations with dose;
(b) In view of evidence from a variety of populations for an increase in the spontaneous frequency of aberrations (in the absence of known radiation exposure) with increasing age it was expected (and in fact found) that older workers and samples from later years contributed more to the higher dose categories, i.e., there was a positive correlation between dose and age, and dose and year of culture and aberration frequency;
(c) In view of the evidence from radiotherapy patients and from individuals accidentally exposed to high doses of radiation that the frequency of unstable aberrations decreases with time following the exposures, it was expected that, for a given time of blood sampling, an exposure a few days or weeks prior to sampling would result in higher detected incidence of induced unstable aberrations than an equivalent exposure received a year or more prior to sampling; this was in fact found;
(d) When all these considerations were taken into account, significant effects of dose were evident for the incidence of dicentric aberrations, acentric fragments and cells with unstable aberrations (Cu cells), but not for cells with symmetrical rearrangements; for the former type of aberrations (Cu), all data are consistent with a linear dose response;
(e) A significant age-effect (but no dose-effect) was found for aneuploid cells, for chromatid aberrations and for X chromosomes with abnormal centromere separation, as expected (the majority of peripheral lymphocytes are G_1 at the time of exposure and consequently no chromatid type of aberrations would be expected);
(f) For all categories of Cu aberrations, the dependence on "recent dose" is greater, although not significantly so, than on "early dose". These data are compatible with the conclusion that considered overall, the rate of increase of dicentric aberrations is 1.4 10^{-4} dicentrics per cell per 0.01 Sv.

238. The authors have stressed the point that the population examined is small in number, subject to very low levels of radiation exposure for periods of up to a maximum of ten years and is therefore unlikely to provide useful data on the incidence of malignant disease. But it is clear that the yield of dicentric aberrations in cells from individuals obtained prior to occupational exposure (or following exposure to less than 0.01 Sv) was about 1 in 700 cells rising approximately four-fold after accumulated doses of 0.2 to 0.3 Sv; the observed increase is not large, but is believed to be a direct expression of damage to genetic material consequent to radiation exposure. As the relationship between the yield of dicentrics in blood lymphocytes and reciprocal translocations in the germ cells varies between species, these data cannot also be used for predicting genetic hazards in the progeny of exposed individuals.

3. Chromosome aberrations in lymphoctyes of nuclear power plant workers

239. In a study similar to that of Evans et al., Bauchinger et al. [B65] made chromosome analyses of 57 healthy male employees of six German nuclear power plants; they were metal workers, technical engineers or radiation protection workers mainly in maintenance or refuelling crews. All of them had received annual doses below the maximum permissible limit of 0.05 Sv a^{-1} and had worked with radiation for periods ranging from 1 to 14 years. The exposure was mainly to external sources of gamma rays and higher energy x rays. The controls for this study were 11 healthy males with no radiation history except natural background.

240. The frequencies of dicentrics and acentrics in the radiation workers were significantly higher than in the controls; and there was no evidence for a positive correlation between the aberration yields and the accumulated total dose, even when only the recent annual dose of the workers was considered. Furthermore, multiple regression analysis of aberration frequencies on dose and age did not show any significant dependence on these. These observations are thus not in agreement with the findings of Evans et al. In addition, although the total dose-ranges were similar in these studies, the observed frequencies of aberrations (the data arranged in 0.05 Sv intervals) in the nuclear power plant workers were in general lower than those in the dockyard workers. The authors attribute the different nature of their findings to a combination of several factors such as the limited number of individuals studied, lack of adequate data on the dose accumulation patterns in the years preceding blood sampling etc.

4. Chromosome aberrations in lymphocytes of classified radiation workers

241. Lloyd et al. [L49] have also compared the frequencies of dicentric and acentric aberrations in unirradiated control subjects and classified radiation workers exposed to gamma irradiation within permis-

sible limits at a nuclear establishment in the United Kingdom and routinely monitored with film badges and thermoluminescent dosimeters. All those exposed had consistently recorded doses in the range of 0.015 to 0.05 Sv per year for at least the four years immediately preceding sampling, and in many cases for more than ten years. The incidence of both dicentrics and acentrics was significantly higher in the exposed workers than in the controls. When allowance was made for the turnover of lymphocytes for the period over which each worker had worked with radiation, a linear dose-response relationship was found. The rate of induction of dicentrics was (2.22 ± 0.94) 10^{-4} per 10^{-2} Gy and for all unstable aberrations, (8.24 ± 2.8) 10^{-4} per 10^{-2} Gy. These rates are in reasonable agreement with dose-response data obtained in vitro.

5. Chromosome aberrations in lymphocytes of uranium miners

242. Brandom et al. [B66] have studied the incidence of chromosome aberrations in peripheral blood lymphocytes of 80 underground uranium miners and 20 controls (in Colorado). The exposure estimates were based on mine-air measurements and underground working time. One working level (WL) is defined as any combination of radon and radon daughters in 1 litre of mine air which will result in the emission of 1.3 10^5 MeV of alpha-particle energy. One working level month (WLM) is 1 WL times 170 working hours. Alpha particles from short-lived ^{218}Po and ^{214}Po deliver the main radiation dose to the tracheobronchial epithelium and excess long-lived ^{210}Pb in bone and blood is reported to be related to the WLM estimates.

243. The difference between miners and controls in the incidence of dicentrics and rings is not significant although, collectively, there is a three-fold increase in the frequency of these aberrations in the lymphocytes of the miners. The frequencies of inversions and translocations, as well as those of terminal and interstitial deletions were higher in the miners. The frequencies of all aberrations (other than dicentrics and rings), showed a dose-dependent increase in the miners up to an estimated dose of 3000 WLM. Finally, in the most highly exposed group of miners (> 3000 WLM), there was a marked decrease in the prevalence of dicentrics and rings, relative to other exposed groups.

6. Chromosome aberrations in lymphocytes of workers with internal depositions of plutonium

244. In another study, Brandom et al. [B67] conducted chromosome analyses of peripheral blood lymphocytes of 343 workers from the United States Department of Energy facility at Rocky Flats, Colorado, and 68 non-exposed controls from Rocky Flats and the Greater Denver area. The radiation dose to the workers derives mainly from internal depositions of a mixture of $^{239}PuO_2$ (93–94%), ^{240}Pu (6%) and ^{241}Pu (0.5%). Physical dose estimates of incorporated plutonium were derived by two methods, urine assay ("systemic burden") and lung counters ("lung burden"). External doses (x, gamma rays and neutrons) were estimated with x-ray film badges until 1970 and from 1970–1979, by thermoluminescent badges. Although plutonium enters the body primarily through inhalation, because of its differential organ distribution, the investigators did not have any individuals with only lung burdens. There were workers with estimates of solely systemic burdens and those with both systemic and lung burden estimates. The systemic burden estimates ranged from about 37 Bq to 370 Bq in the different workers with only systemic burdens and from about 37 Bq to more than 1.5 kBq in those with both systemic and lung burdens. The average external radiation estimates varied from 0.002 to 0.02 Sv for the different individuals and the average years of exposure from 11.8 to 15.2; the mean cumulative Sv value in each exposure group varied from 0.03 to 0.33 Sv.

245. The individuals were classified into a number of sub-groups based on estimated exposures. Approximately 100 cells were analysed for each subject. The chromosomes were trypsin-banded and C-banded for karyotypic examinations and all chromosomes in every cell were analysed for numerical and structural aberrations. The data were categorized into: complex aberrations (dicentrics + rings + inversions + translocations); and total aberrations (complex aberrations + deletions).

246. In the group with only systemic burden estimates, there was no measurable increase in the frequency of aberrations relative to controls. The authors point out however that caution must be exercised in interpreting these data since the dose estimates are subject to some uncertainty; consequently, the lack of significant increase in aberration frequency may be due to limitations in the sensitivity or accuracy of the urine assay for systemic burden estimates, or may reflect a true biological indication of no response at these relatively low dose estimates.

247. In the group with both systemic and lung burden estimates, there were significant increases in aberration frequencies from the least to the most highly exposed persons, in both the complex aberrations and total aberrations (up from 0.5 per 100 cells in controls to about 3.5 per 100 cells, complex aberrations; up from about 1 per 100 cells in controls to about 5 per 100 cells, "total" aberrations). The frequencies of deletions strongly contributed to the total yield of aberrations, especially in the lowest estimated exposure group.

248. When the data were appropriately pooled based on total burden estimates and re-analysed, there was again, a significant increase in the incidence of complex and "total" aberrations with increasing dose. While the increase in aberration frequency with dose was statistically significant ($P < 0.01$), it was not marked, rising from an average of about 1% of cells with some category of structural aberrations among the controls to about 5% of cells affected in the highest exposure group.

249. Stepwise linear regression analyses demonstrated that lung burden estimates, cumulative external irradiation and age entered as significant independent variables. The relative contribution of cumulative doses of external irradiation to the aberration yields cannot be accurately estimated. For instance, the frequency of aberrations in the categories "complex" and "total" was markedly higher in a group with an estimated external dose of 0.15 Sv than in another with more than twice (0.33 Sv) that dose. The mean plutonium burden estimate for the first group was 4.4 kBq and for the second, 1.3 kBq. It would thus seem that the difference in aberration yields noted above is probably primarily due to the amount of internal plutonium.

7. Chromosome aberrations in atomic bomb survivors of Hiroshima

250. In earlier investigations on the somatic chromosomes of atomic bomb survivors of Hiroshima and Nagasaki, it was shown that cells with radiation-induced chromosome aberrations persisted among the circulating lymphocytes for at least three decades after radiation exposure and that the frequency of aberrant cells was in general proportional to dose. The majority of such aberrant cells were identified as having symmetrical exchanges (reciprocal translocations and inversions) while the frequency of unstable aberrations (dicentrics and rings) was an order of magnitude less frequent [A20, A21].

251. Sofuni et al. [S52] made a further analysis of radiation-induced chromosome aberrations in atomic bomb survivors by comparing the results derived from a conventional staining and a trypsin-Giemsa banding method. Twenty-three atomic bomb survivors from Hiroshima were selected for this investigation. Their estimated doses ranged between 1 to 8.5 Gy of mixed gamma and neutrons; however, these dose estimates are subject to revision. Lymphocyte cultures were established for each individual and the chromosome preparations were made using both the ordinary (O) staining and the trypsin-Giemsa banding method (G). The data are summarized in Table 15 from which it can be seen that:

(a) In general, there is a dose-dependent increase in the frequency of aberrant cells;
(b) The frequencies are clearly higher in the G (banding stain) than in the O (ordinary stain) series. Not shown in the table is the finding that the asymmetrical aberrations constituted only 5% of the total aberrations (17 348 cells identified as having aberration by one or the other method). In addition to easily detectable interchanges involving two breaks, the symmetrical aberrations identified included paracentric inversions, several types of insertional and reciprocal translocations and some quite complex translocations involving more than three breaks.

8. Summary and conclusions

252. Chromosome studies in peripheral blood lymphocytes of people living and working in an area of high natural radioactivity in Austria (radiation burdens from inhaled radon and daughters in addition to external gamma radiation); and of workers exposed to radiation in a number of different occupational settings (nuclear dockyard workers in the United Kingdom, nuclear power plant workers in the Federal Republic of Germany, uranium miners in the United States, workers in the United States with internal depositions of plutonium) have been carried out. Further results from continuing studies of the atomic bomb survivors of Hiroshima have also become available.

253. In the Austrian study, where the different groups studied had accumulated "blood burdens" of 110 to 340 mR a^{-1} of gamma-ray dose and 1 to 1600 mR a^{-1} of alpha dose, the mean frequencies of aberrations (dicentrics, interstitial deletions and fragments) increased with increasing dose, even at these relatively low exposure levels.

254. In the British nuclear dockyard workers (primarily gamma-ray exposures below the maximum permissible limits), significant effects of dose (linear dependence) were evident for the incidence of dicentric aberrations, acentric fragments and cells with unstable aberrations; for all categories of unstable aberrations, the dependence on recent dose was greater (but not significant) than on early dose.

255. In the case of the nuclear power plant workers of the Federal Republic of Germany (external gamma ray and higher energy x-ray exposures; also below maximum permissible limits), although the frequencies of dicentrics and acentrics were significantly higher in the workers than in controls, there was no evidence for a positive correlation between aberration yields and the accumulated total dose even when only the "recent" annual doses were considered. However, in a survey of United Kingdom radiation workers, a linear dose-response relationship was found after appropriate weighting of results to allow for turnover of lymphocytes. The rates of induction of dicentrics and of all unstable aberrations were in reasonable agreement with in vitro dose-response data.

256. In uranium miners in the United States exposure to radon and daughters up to and exceeding 3000 WLM (1 WL is defined as any combination of radon and daughters in 1 litre of mine air which will result in the emission of 1.3 10^5 MeV of alpha-particle energy; one WLM is 1 WL times 170 working hours) the frequencies of all aberrations (including inversions, translocations, terminal and interstitial deletions, but excluding dicentrics and rings) showed a dose-dependent increase up to an estimated dose of 3000 WLM.

257. In the case of workers in the United States with internal depositions of plutonium (mean cumulative exposures in the range from 0.03 to 0.33 Sv), there was a significant increase in the frequencies of complex (dicentrics + rings + inversions + translocations) and total (complex aberrations + deletions) aberrations.

258. The results of the study of chromosome aberrations in lymphocytes of the survivors of the atomic bomb in Hiroshima confirm those obtained earlier, namely, a dose-dependent increase in the frequency of aberrant cells (dose range: 1 to 8.5 Gy; mixed neutron and gamma-ray exposures). Furthermore, with the use of Giemsa banding techniques, around 20% more aberrations could be identified, relative to conventional orcein staining technique.

II. EFFECTS IN EXPERIMENTAL MAMMALS AND OTHER SYSTEMS

A. DOMINANT LETHALS AND REPRODUCTIVE CAPACITY

259. The 1977 report considered in some detail the data on the radiation induction of dominant lethals in mice and other experimental mammals. A modest amount of data including those from a comparative study of the effects of ^{239}Pu, fission neutrons and gamma irradiation in male mice have since accumulated; these are reviewed in the following paragraphs.

1. The mouse

260. Grahn et al. [G23] conducted a large-scale study to assess the induction of dominant lethality (among other things) in male mice by incorporated ^{239}Pu and by

external gamma and fission neutron irradiation. Hybrid B6CF$_1$ male mice 100–120 days old received injections of monomeric ^{239}Pu citrate in the tail vein at dose levels of 0.19 and 0.37 MBq/kg body weight. Following the injections, they were mated to 100–150 day old female B6CF$_1$ mice (1 male x 2 females per week up to 45 weeks). In the neutron series, the male mice were exposed to 0.8 MeV neutrons from the Janus Biomedical Research Reactor (this neutron source has a gamma-ray contamination of less than 3%); single exposures in the range from 0.1 to 1.6 Gy were administered at rates of 0.04 to 0.12 Gy per minute. Weekly exposures (for a total of 6 to 24 weeks) were in the range of 0.008 to 0.13 Gy and were delivered during a 45 minute exposure period weekly; the dose rates ranged from 2 10^{-4} Gy to 3 10^{-3} Gy min^{-1}. All doses were midline tissue absorbed doses (MDL) as measured in a tissue equivalent phantom. Dose to the testes may have been up to 10% higher.

261. All gamma irradiation exposures employed ^{60}Co sources. Single gamma irradiation dose levels, in terms of MLD, were in the range of 0.45 to 5.7 Gy and were delivered at 0.3 to 0.4 Gy min^{-1}. Weekly doses of between 0.08 and 2.1 Gy were delivered in a 45 minute period each week concurrently with the weekly neutron exposures and dose rates were 2 10^{-3} to 4.7 10^{-2} Gy min^{-1}. Continuous (22 h d^{-1}) exposures were given at two MLD levels, 0.03 and 0.06 Gy d^{-1} delivered at 2.5 10^{-5} and 4.5 10^{-5} Gy min^{-1}.

262. The extent of dominant lethality in the different experiments was assessed by dissecting pregnant females from 10 to 17 days after conception and counting the numbers of corpora lutea, uterine implants (IMP), live implants (LE) early deaths occurring at or around the time of implantation, late deaths and pre-implantation losses. However, only the data on post-implantation foetal survival are given in the paper, since the aim of this study was to compare the effects of ^{239}Pu with the other radiations and Pu exposure was not found to influence pre-implantation losses.

263. Concerning first the retention and microdistribution of ^{239}Pu in the testis which was also assayed in this work (a total of 19 mice at the 0.19 MBq/kg and 23 mice at the 0.37 MBq/kg levels), it was found that Pu was retained in the testes with no change over the 420-day observation period, with the average retention (both dose levels) being about 0.05% of the initial injected dose. In autoradiographs, about one-half of the alpha tracks were in the interstitial tissue, the remainder occurred in the tubule, mostly originating from plutonium deposited along the basement membrane of the spermatogenic tubule. The heterogeneity of deposition was such that more than 83% of the gonad was radiation-free. In an earlier study from Harwell, Green et al. [G24] examined the inherent heterogeneity of this distribution and concluded that the spermatogonia within a 10 μm concentric ring inside the basement membrane would receive a dose 2.5 times higher than the whole-organ absorbed dose. Russell and Lindenbaum [R21] have recently confirmed this value and noted that the localized dose to the gonia may be up to 4 times higher than the integrated dose. Initially, a 0.37 MBq/kg dose produces a total testicular burden of about 5 Bq or about 20 Bq/g equivalent to a daily exposure of about 1.5 10^{-3} Gy or about 1 10^{-2} Gy per week to the whole gonad.

264. One important observation related to the finding that the testes continued to decrease in weight, while retaining 0.05% of the initial dose. Therefore, the actual dose rate to the gonad would slowly increase with age and duration of exposure. For the purpose of their analysis, the relevant genetic dose had been assumed to be the whole gonad dose and to remain unchanged during the course of the study. This dose was taken to be 1.5 10^{-3} Gy d^{-1} at 0.37 MBq/kg and 7.5 10^{-4} Gy d^{-1} at 0.19 MBq/kg.

265. The data on plutonium-induced dominant lethals are presented in Table 16. These data were examined for evidence of statistical heterogeneity within mating time sequences; it was found that the weekly variation in LE/IMP proportions were not significant. There was however a dose effect, as shown by the difference between the 0.19 and 0.37 MBq/kg data. A linear regression analysis of these data within and across mating time sequences and within dose levels, demonstrated that the regression of post-implantation survival on time after injection (an indicator for accumulating dose) was not significantly different from zero slope. Therefore, the dominant lethal rate was concluded to be independent of accumulating dose and to principally reflect dose rate. Searle et al. [S53] had discussed these aspects in connection with their ^{239}Pu work and had concluded that the observed dominant lethality was mostly induced in meiotic and post-meiotic cell stages. The gonadal doses for these latter stages of germ cell development were estimated to be 0.021 and 0.042 Gy for the 0.19 and 0.37 MBq/kg regimes. Under these conditions, the dominant lethal rate could be estimated as (64 ± 11)10^{-4} gamete/10^{-2} Gy of alpha irradiation to the whole gonad.

266. The results from chronic gamma-irradiation together with estimates of doses are given in Table 17. These data yield a rate of dominant lethality of (5 ± 0.6)10^{-4}/gamete/10^{-2} Gy, for post-meiotic germ cells. The estimates of rates from other data (single and weekly gamma-ray exposures, single and weekly neutron exposures) are summarized in Table 18. Also shown in the Table are the estimates for ^{239}Pu and chronic gamma-irradiation.

267. Inspection of Table 18 will reveal that, for post-meiotic stages:

(a) There are no statistically significant differences in dominant lethal rates for gamma-irradiation delivered either singly or weekly; for chronic gamma-irradiation, however, the rate is only about one-half of the above rates;
(b) There are no significant differences with fission neutron irradiation delivered singly or weekly;
(c) Single gamma-irradiation exposures are more efficient than weekly or chronic exposures in inducing dominant lethality in pre-meiotic stages;
(d) The effects of single or weekly neutron exposures of pre-meiotic stages are not significantly different.

The RBE estimates for these data are given in Table 19 from which it can be seen that alpha irradiation of post-meiotic stages is nearly as efficient as fission neutrons; for pre-meiotic stages, fission neutrons are 19 times more effective than chronic gamma irradiation.

268. In subsequent work, Grahn, Frystak and Lee [G25] have compared the induction of dominant lethality (among other things) by low single doses of neutrons (1 10^{-2} to 40 10^{-2} Gy) and of gamma rays (0.23 to 1.45 Gy) in male mice. The strain of mice used, age, etc., are the same as those of the study discussed in the preceding paragraphs. The data pertain to the first five

weeks of mating following irradiation. The average number of live implants/pregnant female was slightly reduced and this effect was significant after 0.2 and 0.4 Gy of neutrons and 1.45 Gy of gamma rays. Pre-implantation mortality was slightly increased (significant at all neutron doses except at 0.01 and 0.1 Gy); the increases in the gamma ray series did not reach statistical significance. Post-implantation mortality was slightly higher in all irradiated groups except after 0.01 Gy of neutrons. There were some indications that at the very low doses employed (0.01 and 0.025 Gy of neutrons and 0.23 and 0.45 Gy of gamma rays), post-implantation mortality was higher than expected on the basis of extrapolation from higher doses in earlier work.

269. In an extension of the ^{239}Pu studies to ^{241}Am, another transuranic element presumed to have a slightly different metabolic behaviour, Grahn et al. [G26] injected a single dose of 0.37 MBq/kg of ^{241}Am (intravenous) and examined the testicular distribution pattern and dominant lethality. It was found that the gonadal retention was only 50 to 60% of that seen for ^{239}Pu. Retention through the first 100 days after injection remained unchanged (as for plutonium) and preliminary autoradiography indicated that the microdistribution was similar to that seen for plutonium. The estimated testicular dose for the measured burden of about 13 Bq per gm of tissue was 9.2 10^{-4} Gy d^{-1}, slightly above the dose delivered by ^{239}Pu dose of 0.19 MBq/kg. The results of a 10-week dominant lethal series conducted between 125 and 195 days after injection suggested that the amount of intrauterine mortality was low and not significantly different from that in controls.

270. Shevchenko et al. [S133] studied the induction of dominant lethals in mice by incorporated ^{14}C. Labelled glucose solution (5.4 10^4 Bq/g, 12.4 10^5 Bq/g and 25 10^5 Bq/g) was administered orally to adult hybrid (CBA x C57BL) male mice. The midline absorbed doses in the testes were, respectively, 0.22, 0.5 and 1.0 Gy. It was found that the amount of dominant lethality in post-meiotic germ cells increased linearly with an increase in dose. The authors estimated that the RBE for beta rays from incorporated ^{14}C (relative to x or gamma rays) was not significantly different from 1.

271. In a series primarily designed to study the induction of autosomal recessive lethals and to assess the length of the sterile period, Lüning et al. [L18] irradiated 60–70-day old CBA male mice with 14 MeV neutrons at 1.5 and 2.5 Gy. The irradiated males were mated to unirradiated females of the same strain (1 male x 3 females) for three consecutive weeks. The pregnant females were killed and examined for intrauterine deaths on the 17th day after the beginning of the matings. The frequency of dead implants was between 8 and 9.5% in the controls (week 1, 9.5%; week 2, 8.5% and week 3, 8.3%). With 1.5 Gy, these frequencies increased from 21.1% (week 1) to 25.3% (week 2) and to 37.8% (week 3). At 2.5 Gy the corresponding figures were: 23.4% (week 1), 32.4% (week 2) and 49.5 % (week 3). As no parallel experiments with x-irradiation were done, no RBE values could be calculated. However, in comparison with previous experiments with the same strain [F12], the authors concluded that 14 MeV neutrons may be between one and two times as effective as x rays.

272. Yusof [Y9] compared the yields of dominant lethals in caffeine-fed hybrid (C3H x 101) male mice irradiated with 2 Gy of either x rays (0.7 Gy min^{-1}) or ^{60}Co gamma rays (0.002 Gy min^{-1}) and mated to females on either the eighth or fifteenth day after x- and gamma-irradiation, respectively, to sample treated spermatids. The live embryo/corpus luteum ratio in pregnant females killed on about the fourteenth day of pregnancy was 0.51 for x rays and 0.67 for gamma rays. These corresponded to rates of induction of dominant lethals of about 17 10^{-4} and 10 10^{-4} per gamete per 10^{-2} Gy, respectively. Caffeine had no significant effect.

273. The above differences in induction rates might have been due to dose rate and/or to quality effects. In order to investigate this, Searle and Beechey [S54] gave (C3H x 101) hybrid male mice doses of 3 Gy of x- or gamma-irradiation at the same high and low dose rates of about 0.6 and 0.002 Gy min^{-1}. All litters were conceived 12–16 days post-irradiation and so were derived from treated spermatids as in the previous experiment. Live embryo/corpus luteum ratios were 0.59 and 0.52 for protracted and acute gamma-irradiation, 0.40 and 0.38 for protracted and acute x-irradiation. These ratios correspond to rates of induction of dominant lethals per gamete of 0.39, 0.50, 0.77 and 0.83, respectively. Although for both x- and gamma-irradiation, acute exposures were more effective than protracted ones (protracted/acute ratios of 0.92 and 0.78, respectively), the differences were not significant. However, there were significant quality effects, the relative effectiveness of x- versus gamma-irradiation being 2 at low and 1.7 at high dose rates. In both experiments of Yusof and of Searle and Beechey, the frequencies of abnormal spermatozoa were significantly increased 7 to 8 weeks after irradiation, but there was no consistent effect of radiation intensity or quality. In the experiment of Searle and Beechey, there was no significant effect of dose rate on either testes mass or sperm count in the x-ray series but there was a significant effect in the gamma-ray series, with greater survival at the lower intensity. This result is in line with other evidence which suggests a greater effect of dose rate after gamma-irradiation than after x-irradiation over the same range.

274. Generoso et al. [G27] have recently reported on an experiment designed to examine whether the oocytes in female mice are capable of carrying out repair of genetic damage induced in the male genome. Such experiments although known for a long time in Drosophila (see [S55] for a review) have so far not been carried out in mammals with this specific objective. In the present work, 12-week old males of one stock (either (101 × C3H)F_1 or the reverse hybrid (C3H × 101)F_1) were irradiated with 5.5 Gy of acute x rays (or treated with one of four chemicals) and mated to females from different stocks (T, (SEC × C57BL)F_1, (C3H × 101)F_1 and (C3H × C57BL)F_1). Dominant lethality was assessed through dissection of pregnant females in the usual manner, focusing attention on pregnancies that occurred during 0.5 to 3.5-day mating interval (x-ray series), 3.5 to 7.5-day mating interval (IMS), 6.5 to 9.5-day mating interval (TEM), etc. The results showed that, while there was no difference in the yield of dominant lethals in the x-ray series, marked differences were noted in the experiments with chemicals, particularly with IMS: the frequencies ranged from 9% ((C3H × C57BL)F_1), to 50% ((SEC × C57BL)F_1) and to 81% (T stock), all at 65 mg/kg body weight (the dominant lethal frequencies were calculated from the ratio of live embryo per pregnant female in the experimental group to those in the controls).

275. Favor et al. [F11] used a modified dominant lethal test to assess the extent to which dominant lethals

were expressed during the later stages of gestation (i.e., late dominant lethals). In this study, 10-week old B6D2F$_1$ hybrid male mice were irradiated with 600 R of x rays and then mated to females of the same genotype and age (1 male × 2 females) for seven days. The females were checked daily for the birth of new litters and the numbers of live and dead at birth were recorded. The progeny were weaned at three weeks of age after which the parental females were sacrificed and their uterine horns examined and scored for live and dead implantation scars according to the method described by Soares [S56, S57]. Unirradiated controls were run concurrently. The data showed that the radiation treatment caused a significant increase in the number of late deaths (defined as the difference between the number of "live scars" and the number of "live born"): the percentage of late deaths increased from a control mean of 7.32% to 28.6% in the irradiated series. The scar method used in this work has the advantage that the females need not be killed at mid pregnancy and that the incidence of dominant lethality can be assessed after the birth of litters.

276. The authors are aware of the fact that the method of assessing live and dead implantations by the scar technique underestimates dead implantations and overestimates live implantations. Using an estimate of error rate (the calculation of which is outlined in their paper) the data collected by the scar technique can, however, be corrected to be more accurately representative of the live and dead implantations.

277. Goldstein and Spindle [G28] studied the x-ray-induction of dominant lethals in male germ cell stages which are expressed from the cleavage stage to the early (trophoblast) outgrowth stages in cultured mouse embryos. Random-bred male mice of the Dub:(ICR) strain aged 10–12 weeks were irradiated with 4.5 Gy of high dose rate x rays (0.6 Gy min^{-1}) and mated to females of the same strain sequentially (1 male × 1 female twice a week for the first four weeks after irradiation of the males and once a week for the next four weeks). The females, prior to mating, received injection of pregnant mares' serum gonadotrophin and human chorionic gonadotrophin for induction of superovulation. In each group, on day 2 of pregnancy, the females were killed and the oviducts were flushed out to obtain uncleaved and two-celled embryos. The ratio of uncleaved ova to two-celled embryos provided a measure of fertilization. The embryos were cultured and mortality at various stages of development was recorded (Table 20).

278. The data show that:

(a) In the irradiated group, there is a higher incidence of developmental failures in early cleavage, at the late morula stage and at the late blastocyst stage than in the controls;

(b) Dominant lethals[12] are induced more frequently in germ cells exposed as early spermatids and spermatocytes and next most frequently in germ cells exposed as spermatozoa: of the experimental two-cell embryo fertilized 14–28 days after irradiation (spermatids-spermatocytes), 35.9% are arrested during cleavage, primarily at the two- or three-cell stage and this is more than twice the proportion found in controls for the same period. Furthermore, of those fertilized 14–28 days after irradiation that developed to the morula stage, 26.8% did not form blastocyst after 72 h in culture while only 7.8% of the control embryos failed at this stage;

(c) The germ cells irradiated as early spermatids and spermatocytes manifest about equal proportions of dominant lethals at each developmental stage whereas those irradiated as sperm manifest dominant lethality predominantly at the blastocyst. The overall pattern of stage sensitivity as observed in this study agrees well with what has been known from conventional dominant lethal studies [B24].

279. In subsequent work with the same strain of mice and techniques, Goldstein et al. [G29] used four lower x-ray doses (0.9, 1.8, 2.7 and 3.6 Gy). The main observations were the following:

(a) When the germ cells used for fertilization were spermatozoa or spermatids at the time of irradiation, the fertilization index (i.e., the ratio of 2-cell embryos to uncleaved eggs) was not affected at any dose level; with spermatocytes, however, the fertilization index was significantly lower than in the controls at all doses except the lowest one;

(b) With spermatozoa, there was no significant increase in the frequency of embryos arrested in development before blastocyst formation but there was a small, dose-independent increase in these frequencies (between 5 and 9%) after blastocyst formation;

(c) Embryos derived from germ cells irradiated as spermatids showed increased developmental arrest both before and after blastocyst formation; furthermore, the dominant lethals manifesting before blastocyst formation were about equally distributed at all cleavage stages. This latter observation, however, is in contrast to that noted at 4.5 Gy (paragraph 278) by the same workers: at this dose, developmental failures were found primarily at the 2-cell stage. The overall frequencies of dominant lethals[13] over the range 0.9–4.5 Gy gave a satisfactory fit to a model which incorporates a linear and quadratic component.

280. Eiche [E7] conducted a study to examine the effects of low x-ray doses (0.04 and 0.08 Gy) given to young (1-, 2- and 3-week old) female mice and to female foetuses irradiated in utero (at two weeks of age) on intrauterine death. The choice of these groups was dictated by the fact that oocytes in very young females are very sensitive to killing [R22] and the oocytes in the 15-day old foetuses are at a stage when the DNA synthesis is most conspicuous [P21]. Young females or foetuses (CBA × CBA and CBA × A$_{Jax}$) were irradiated and, when 63–64 days old, were mated to CBA or C57BL males. On the 18th day after the beginning of the matings, the animals were killed and examined for intrauterine contents (live foetuses, early deaths and late deaths).

281. The data showed that there were no significant differences in intrauterine death rate between the

[12] Percent dominant lethals:

$$1 - \left[\left(\frac{1-\text{fraction arrested at a given stage, experimental}}{1-\text{fraction arrested at the same stage, control}}\right)\right] \times 100.$$

The stage may be early cleavage, late morula or late blastocyst.

[13] Total dominant lethality =

$$\left[1 - \frac{\left(1-\text{fraction of experimental embryos arrested before trophoblastic outgrowth}\right)}{\left(1-\text{fraction of control embryos arrested before trophoblastic outgrowth}\right)}\right] \times 100.$$

control and irradiated groups within any experiment, although the controls in two out of the three experiments gave low values; however, these latter values were within the range of intrauterine death rate of non-irradiated series in earlier experiments from the same laboratory. In the experiments in which similar type of females were mated to males of two different strains, there was a considerable difference in the mean number of implants as well as in their distribution. The observation that the mean number of implants per female in the two series in which the females had been irradiated during the first week was considerably lower than in the other series, however, was not borne out in a subsequent study [E8].

282. Baev et al. [B25] exposed adult female mice of the H strain to whole-body chronic gamma-irradiation from a ^{137}Cs source over a 35-day period at a mean dose of about 1 10^{-4} Gy min^{-1} (total dose: 5 Gy). After the completion of the exposure the animals were mated (2 females × 1 male) to males of the same strain and age for a 7-week period. The females were checked from the 13th mating day onwards and those found to be pregnant were killed and the numbers of corpora lutea, live and dead embryos were counted.

283. It was found that the frequency of pregnant females was lower in the irradiated groups (58%) than in the controls (96%). There was a marked fall in fertility beginning with the second week; from week 3 through week 7, fertility rates varied between 3 and 9% versus 27 and 58% in the controls. Mean corpora lutea counts in the irradiated females were normal at week 1, but declined progressively thereafter through week 7. Counts of implants showed the same pattern of decline, with the rate of decrease even more marked. These data and estimates of dominant lethality [B25] show that:

(a) The induced post-implantation mortality rate is rather low, varying from 2.6 to 6.1% (apart from week 6 where the estimated rate has a negative sign) with no statistically significant difference between the different weeks;
(b) The induced pre-implantation mortality rate, on the other hand, varies over a wide range: (3.1%, week 1; 5.1%, week 2; 15.9%, week 3; 3.2%, week 4; 7.5%, week 5; 17.7%, week 6; 3.9%, week 7; 0.3%, week 8 and 14.9%, week 9);
(c) Consequently, the increase in total dominant lethal rate can be accounted for primarily by pre-implantation loss.

However, the latter (c) is known to include non-genetic effects, such as unfertilized eggs and it is a less reliable index.

284. A comparison of these data with the results of Searle and Beechey [S58] for weeks 1 and 3 after acute x-irradiation exposures in the range of 0–4 Gy (0.7 Gy min^{-1}) shows that a decrease in dose rate to 1 10^{-4} Gy min^{-1} reduces the rate of post-implantation mortality. The rate observed in the present study with 5 Gy of chronic gamma irradiation is of the same magnitude as that after 1 Gy of acute x-irradiation.

285. Searle et al. [S59] compared the breeding performance of hybrid (C3H/HeH female × 101/H male) F_1 female mice given ^{239}Pu (0.19 or 0.37 MBq/kg body mass in 1% trisodium citrate by the tail vein) or kept in a 0.1 Gy d^{-1} or 0.2 Gy d^{-1} ^{60}Co-gamma-irradiation field for up to six 4-week periods (but mated in the control area) or unirradiated. The injected (or gamma-irradiated) females and the contemporaneous control females were mated to males of the PT stock. In the plutonium series, most of the females were mated 24 h after injection and were allowed to breed until they failed to produce any live-born litters within two months of the previous one; some other females were killed 24 h after injection or at later intervals for radiochemical or autoradiographical studies. In the gamma-ray series, the mice were initially put together as trios (1 male to 2 females) in the control area and a female was moved into the radiation field when a vaginal copulation plug was found; she was removed to the control area on the 18th day of gestation and the appropriate male added to allow a mating at post-partum oestrus. One day after the birth of the litter (or on the day of birth if a vaginal plug was recorded then) she was returned to the radiation field and only removed when the litter was 18 days old and ready to be weaned. She was then paired with the male again and the procedure was repeated until sterility ensued.

286. The ovarian dose rates from the injected plutonium were initially 8 10^{-3} and 1.7 10^{-2} Gy d^{-1}, respectively in the two groups, changing little thereafter. Actual gamma-ray dose rates averaged around 8 10^{-2} and 16 10^{-2} Gy d^{-1}, respectively; the highest dose received was in the first 4-week period 2.6 or 5.2 Gy, declining to about two-thirds of these values by the fourth 4-week period. As mentioned earlier, the females were irradiated until the onset of sterility.

287. The results show that both gamma-ray treatments affected the reproductive performance more than the plutonium injections with respect to duration of fertility and offspring per litter in successive 4-week periods, though the overall mean litter sizes were not significantly less than controls. In the gamma-ray series, the percentage of fertile females dropped to zero by the fifth and eighth 4-week periods (respectively, in the 0.2 Gy and 0.1 Gy d^{-1} groups). In the plutonium series, a similar drop was noticed after 12 and 15 4-week periods, respectively in the 0.37 and 0.19 MBq groups. The mean number of offspring per litter in the gamma-ray series dropped to one-third of that in controls in the 0.1 Gy d^{-1} group and to one-sixth in the 0.2 Gy d^{-1} group. In the plutonium groups, this drop was less pronounced reaching only two-thirds of the control level even in the 0.37 MBq group. From these and other data, the authors estimated that the RBE for the effects on reproduction attributed to germ-cell killing is about 2.5 for the alpha particles relative to gamma rays, a value which is lower than that found for testis mass reduction (10–15) in an earlier study [S53]. They suggest that this low RBE may be connected with the inhomogeneity of the alpha-particle dose within the ovary.

2. Other species

288. Chambers and Chapman [C29] studied the induction of pre- and post-natal lethality (among other things) in rats that were given testicular x-ray exposures of either 600 R or 450 R, using litter size and the number of progeny alive after birth at day 1 and at day 21 as criteria. Male rats of the yellow Cu_2 strain were irradiated (either with a single acute exposure of 600 R at 10 weeks of age or with a fractionated exposure of 450 R given in three fractions of 100, 150 and 200 R at 10, 12 and 14 weeks of age, respectively; 85–90 R min^{-1}). Nine weeks after irradiation (a period of time sufficient to ensure that irradiated spermatogonia will be sampled) the males were mated to females and the numbers of progeny born alive and those that survived

until day 1 and day 21 were recorded. The data show that:

(a) There is a reduction in litter size following spermatogonial irradiation;
(b) Based on the litter sizes in the progeny, the rate of induction of such effects can be estimated to lie between $(2.0 \pm 1.4)10^{-4}$/gamete/R to $(3.0 \pm 2.3)10^{-4}$/gamete/R.

These values are in agreement with those calculated by Taylor and Chapman [T13] in an earlier study with rats, $(1.4 \pm 0.8)10^{-4}$/gamete/R, and also with those in mice: Luning's [L19] mouse data yield estimates of $1.8\ 10^{-4}$ and $2.2\ 10^{-4}$/gamete/R based on litter size at birth and weaning, respectively. Estimates based on the same traits from the mouse data of Lyon et al. [L20] are $1.4\ 10^{-4}$/gamete/R for both traits.

289. Caine and Lyon [C30] reported on the effects of x-irradiation on reproductive capacity and dominant lethal induction in female guinea pigs and in the Djungarian hamsters (Phodopus sungorus). The latter species resembles the mouse in body size, is physiologically closer to the hamsters, has a relatively low chromosome number (2n = 28) and is easily maintained under laboratory conditions. Female random-bred, albino guinea pigs and Djungarian hamsters were irradiated with 4 Gy of x rays at 3–5 months or 8–12 weeks of age, respectively (bilateral irradiation, each side being exposed in turn; 0.5 Gy min^{-1}). The irradiated females were mated to males (guinea pigs: 4 females × 1 male; hamsters: pair-mating) 24 h after irradiation and left to reproduce for two years, litters being expected at approximately 2–3 month intervals for guinea pigs and 3–4 week intervals for the hamsters. Dominant lethal studies were carried out only with the guinea pig at the first oestrus and at 3 months, while in both species the reproductive capacity was assessed.

290. The following results were obtained:

(a) In the guinea pig, the irradiated females produced fewer offspring in the first litter, but the difference from the controls was not significant;
(b) The mean litter size of irradiated guinea pigs was reduced in the first six months (2.9 versus 4.6 in the controls), but this reduction was barely significant; in the 6–12 month interval and in the remainder of the period there were no differences; there was no significant alteration in the overall mean number of litters per female during the 2-year period, although the irradiated females produced a smaller mean number of offspring than the controls (22.4 versus 31.2 in the controls);
(c) In the guinea pig again, irradiation caused a significant increase in dominant lethals at the first oestrus matings with a lower non-significant induction at three months; the dominant lethal yield at first oestrus matings was due primarily to pre-implantation loss while at three months, post-implantation loss was higher; most of the post-implantation death occurred soon after implantation;
(d) In the Djungarian hamster, irradiation produced a dramatic sterilizing effect, i.e., a lowering of both the total number of litters and litter size; only 12 out of the 48 females in the irradiated group were fertile and these produced only one litter each (in contrast to controls with a mean of 11.8 litters/female) as a consequence of which the total reproductive capacity was drastically reduced (3.3 versus 43.3 offspring per female in the controls).

291. These data demonstrate that the female Djungarian hamsters are at least as sensitive to the sterilizing effect of radiation as the mouse, and considerably more sensitive than the Syrian hamster (Mesocricetus auratus) in which some animals may remain fertile for three months after a dose of 4 Gy [C31]. The Djungarian hamster thus represents another species for the study of the differences in sensitivity of oocytes to irradiation.

292. In Mikamo's experiments [M49], mature female Chinese hamsters were x-irradiated with 50, 100 or 200 R and mated to unirradiated males to assess the amount of dominant lethality in oocytes at the first, third or fifth oestrous cycle after irradiation. The uterine contents of pregnant females were examined at 18.5 days of gestation. There were a total of 436 females (80 controls, 88 for the 50 R group, 121 for the 100 R group and 147 for the 200 R group). The results showed that, with one possible exception, there was no statistically significant increase either in pre-implantation mortality (range: 6.5 to 8.5% in the different irradiation series versus 6.4% in the controls) or in the frequency of abnormal foetuses (range: 8.8 to 10.7% versus 10.8% in the controls). In the third oestrous cycle after 100 R, the frequency of abnormal foetuses was slightly higher (12.8%) and this was correlated with an increase in chromosomal abnormalities in oocytes of females cytologically examined in parallel experiments (see paragraph 378).

3. Summary and conclusions

293. Further data on the radiation-induction of dominant lethals and on the effects of radiation on reproductive capacity have become available from studies with some experimental mammals. Male mice were injected with ^{239}Pu (0.19 and 0.37 MBq kg^{-1}) and mated at weekly intervals to unirradiated females and the amount of dominant lethality was assessed by dissecting the pregnant females at mid-pregnancy and scoring live and dead implants. It was found that the weekly variation in the ratio of live implants to the total number of implants did not show significant differences for the different weeks, but there was a dose-effect as shown by the differences between the 0.19 and 0.37 MBq kg^{-1} data (estimated gonadal doses of 0.021 and 0.042 Gy). The amount of dominant lethality observed (mostly induced in meiotic and post-meiotic germ cell stages) was consistent with a rate of $64\ 10^{-4}$ per gamete per 10^{-2} Gy.

294. In the gamma-ray experiments, the rates of dominant lethality were nearly the same irrespective of whether the exposures were administered singly (in the range of 0.45 to 5.7 Gy) or as weekly doses of between 0.08 and 2.1 Gy (sampling of post-meiotic male germ cell stages); for chronic exposures (at the rate of $3.36\ 10^{-2}$ Gy d^{-1} and $5.98\ 10^{-2}$ Gy d^{-1} with total accumulated exposures of between 0.59 and 1.06 Gy and between 1.05 and 1.89 Gy), the rate of induction of dominant lethals is $5\ 10^{-4}$ per gamete per 10^{-2} Gy which is one-half of that after single or weekly exposures. However, single gamma-ray exposures were more efficient than weekly or chronic exposures in inducing dominant lethality in pre-meiotic stages. The rates (per gamete per 10^{-2} Gy) are, respectively, $1.1\ 10^{-4}$, $0.35\ 10^{-4}$ and $0.14\ 10^{-4}$.

295. With fission neutron irradiation of male mice, there were no significant differences in rates in post-

meiotic cells between single exposures (in the range from 0.1 to 1.6 Gy) or weekly exposures (in the range from 0.008 to 0.13 Gy for a total of 6–24 weeks). Furthermore, the effects of single or weekly neutron exposures of pre-meiotic stages were not significantly different.

296. In terms of relative biological effectiveness, alpha-irradiation of post-meiotic stages is nearly as efficient as fission neutrons; for pre-meiotic stages, fission neutrons are 19 times more effective than chronic gamma-irradiation.

297. With low single doses of neutrons (2 to 40 10^{-2} Gy) and of gamma rays (0.23 to 1.45 Gy) to males (sampling of germ cells during the first five weeks), there were slight but measurable increases in post-implantation mortality.

298. Fourteen MeV neutrons (1.5 and 2.5 Gy) may be between one and two times as effective as x rays in inducing dominant lethals in post-meiotic male germ cell stages.

299. The frequency of dominant lethals induced in spermatids by acute x-irradiation (2 Gy) is 1.7 times that induced by protracted (0.002 Gy min^{-1}) gamma-irradiation. Pre-treatment of the males with caffeine prior to irradiation did not affect the dominant lethal yields with either kind of irradiation. Irradiation of spermatids (3 Gy) with low dose rate (0.002 Gy min^{-1}) or high dose rate (0.6 Gy min^{-1}) x or gamma rays showed that the relative effectiveness of x- versus gamma-irradiation was 1.9 at low and 1.6 at high dose rates. There were no statistically significant effects of dose rate on testes weight or sperm count in the x-ray series, but there were significantly less severe effects on both with protraction of the gamma-irradiation.

300. The extent to which oocytes in female mice are capable of carrying out repair of genetic damage induced in the males (sampling of mutagenized spermatozoa) has been investigated by irradiating (or treating with one of four chemicals) males of a given strain and mating them to females of different strains and assessing the amount of dominant lethality. It was found that, while with x-irradiation, there were no significant differences between the different female strains, with chemicals, particularly with isopropyl methane sulphonate, the frequencies of dominant lethals were markedly different with certain strains of females.

301. In one study with mice, a modified dominant lethal method was used to assess the extent to which dominant lethals were expressed during the late stages of gestation. The results (600 R of x rays; sampling of spermatozoa) showed that radiation caused a significant increase in the number of late deaths. In experiments designed to examine x-ray induction of dominant lethals in male germ cell stages of the mouse which are expressed from cleavage stages to the early trophoblast outgrowth stages, it was found that the stage at which the embryos die (early cleavage, late morula, late blastocyst) varied depending on the radiation dose and the germ cell stages that were sampled; for instance, with 4.5 Gy, embryos derived from germ cells that were spermatids at the time of irradiation showed developmental arrest primarily at the 2-cell stage. With lower doses, however, (0.9 to 3.6 Gy) and with sampling of the same germ cell stages, the dominant lethals manifesting before and after blastocyst formation were about equally distributed at all cleavage stages. The overall pattern of stage sensitivity as observed in this study agrees well with what has been known from conventional dominant lethal studies.

302. When adult females were exposed to chronic gamma-irradiation over a 35-day period (total dose: 5 Gy), mated to males and the pregnant females analysed for intra-uterine mortality of the embryos, it was found that the induced post-implantation mortality was rather low (2.6 to 6.1%) in the different mating weeks; the induced pre-implantation mortality varied over a range from 0.3% to 18% in the different weeks. The increase in dominant lethality can thus be accounted for primarily by increase in pre-implantation losses.

303. When female mice were injected with ^{239}Pu or chronically irradiated with gamma rays and then tested for breeding performance, it was found that there was an adverse effect with respect to the duration of fertility and the number of offspring per litter, although the overall mean litter sizes were not significantly less than in the controls. In the gamma-ray series (0.1 and 0.2 Gy d^{-1} for up to six 4-week periods), the percentage of fertile females dropped to zero by the fifth and eighth 4-week periods (respectively in the 0.2 and 0.1 Gy d^{-1} groups). In the plutonium series, a similar drop was noticed after the twelfth and fifteenth 4-week periods, respectively, in the 0.37 MBq and 0.19 MBq groups. From these and other data, it has been estimated that the RBE for the effects on reproduction attributed to germ cell killing is about 2.5 for alpha-particles relative to chronic gamma rays.

304. When rats were given testicular exposures of 450 and 600 R and germ cells irradiated as spermatogonia were sampled, there was a significant reduction in litter size and this was consistent with a rate of induction of such effects of between 2 and 3 10^{-4}/gamete/R.

305. Irradiated (4 Gy of x rays) female guinea pigs produced fewer offspring in the first litter and the mean litter sizes were slightly reduced in the first six months; from this time onwards up to two years, there was no pronounced alteration in the overall mean number of litters per female, but the irradiated females produced a smaller mean number of offspring than controls.

306. In the female guinea pig, irradiation caused a significant increase in dominant lethals at the first oestrus matings, one that was mainly due to an increase in pre-implantation losses. Post-implantation losses were higher 3 months after irradiation.

307. In the female Djungarian hamster, x-irradiation (4 Gy) produced a marked sterilizing effect, i.e., a lowering of both the total number of litters and litter sizes.

308. In experiments involving irradiation of mature female Chinese hamsters (50–200 R) it was found that the amount of dominant lethality in oocytes at the first, third or fifth oestrus cycle matings was not significantly increased, relative to controls, with one exception: in the third oestrus cycle after 100 R, the frequency of abnormal foetuses was slightly higher relative to controls and this was correlated with an increase in chromosomal abnormalities in oocytes of females cytologically studied in parallel experiments.

B. TRANSLOCATIONS

1. Introduction

309. Since the publication of the 1977 report, some new data have become available on the radiation-induction of translocations and other exchange type aberrations in male and female germ cells of the mouse and in spermatogonia of the rhesus monkey. These data pertain to the induction of reciprocal translocations in spermatogonia following irradiation of males (and analysed cytogenetically in descendant spermatocytes), of chromatid aberrations in meiotic stages of male and in oocytes of female mice (also analysed cytologically), of heritable translocations in females (studied using genetic techniques and subsequently verified using cytological methods) and of reciprocal translocations in spermatogonia of the rhesus monkeys (studied cytologically in descendant spermatocytes).

310. Ford et al. [F14] compiled most of the relevant cytogenetic data that bear on the induction of reciprocal translocations in mouse spermatogonia (eight different studies involving examination of a total of over 70 000 spermatocyte preparations of irradiated males and examination of spermatocyte preparations of 681 sons of irradiated fathers). In one of the two studies [S113] involving cytogenetic analysis of spermatocytes of 531 sons of irradiated fathers (spermatozoal irradiation), one male progeny heterozygous for an induced reciprocal translocation was also a mosaic for a Robertsonian translocation: about half of the spermatocytes examined contained a typical "Robertsonian trivalent" which was replaced by two normal bivalents in the remainder.

311. Ford et al. point out that mosaicism indicates that the Robertsonian translocation would have originated during embryonic development, possibly as early as the first cleavage division and that this was presumably a spontaneous event. Apart from this, there were no instances in any of the other studies for the radiation-induction of Robertsonian translocations. The authors point out that, although it is likely that some cases of Robertsonian translocations could have been misclassified as reciprocal ones on the basis of metaphase I configurations (and all the investigations referred to in their paper were carried out before the C-banding procedure was introduced), the number of Robertsonian translocations so missed could have been only very few. As they stated "... it can be concluded with confidence that if Robertsonian translocations are induced by ionizing radiation at all, they are formed with negligible frequency compared to reciprocal translocations".

2. Reciprocal translocations in male germ cells of the mouse

(a) Spermatogonia

312. Brewen et al. [B26] compared the yields of translocations obtained at low exposure rates of ^{60}Co gamma-irradiation in the range of 1–0.001 R min^{-1} (range: 100–800 R; spermatogonial irradiation) with those after x-irradiation at 100 R min^{-1}. Adult CD1 male mice which were 8–10 weeks old at the start of the irradiations were used throughout the study with the exception of a few animals that were 40 weeks old which served as an aged control. The animals were killed at different times after the end of the irradiations depending on the exposure and exposure rate and the testes were processed for cytological preparations.

313. The data are presented in Table 21 and show that the yield of translocation decreases over the range of 100–0.003 R min^{-1} with no significant difference between 0.001 and 0.003 R min^{-1}. These data are very similar to those of Pomerantzeva et al. [P22, P23] and Searle et al. [S53] discussed in the 1977 report and permit the conclusion that there is no increase in translocation yield at very low exposure rates. The rate per R at the high exposure rate of 100 R min^{-1} is about 16 times that at the lowest rate of 0.001 R min^{-1} when a correction is made for the relative biological efficiency of gamma rays relative to x rays. The finding of a lack of increase in the rate of translocation recovery at very low exposure rates is also qualitatively in line with that from specific locus experiments [R23, R24] discussed in the 1977 report.

314. In the work with plutonium alpha rays, gamma rays and neutrons reported in the section on dominant lethals, Grahn et al. [G23] also studied the induction of reciprocal translocations in spermatogonia. Testes preparations were made from 8 to 60 weeks after injection of plutonium and the spermatocytes at metaphase I were screened for translocations. The frequencies of translocation configurations observed were such that when they were plotted against total accumulated dose (minus the 13 days of meiosis preceding metaphase I) no dose-effect relationship was evident. However, there was a suggestive indication that a peak response may be obtained at 0.15–0.20 Gy and this possibility is being tested at present.

315. In contrast, weekly doses of fission neutrons up to total doses of 1.2 Gy produce a linear response with a slope of $(6.8 \pm 0.6)10^{-4}$ per 10^{-2} Gy for cells with translocations. The response to single doses of neutrons was non-linear and was best fitted with a power function with a coefficient of 0.79 ± 0.04. For gamma rays, the weighted linear regression coefficients for the effects of single weekly and chronic gamma irradiations are $(1.53 \pm 0.074)10^{-4}$, $(0.76 \pm 0.077)10^{-4}$ and $(0.175 \pm 0.017)10^{-4}$, respectively. The decrease in effectiveness with decreasing dose rate is consistent with earlier studies of Searle et al. [S53]. The lowest coefficient from the chronic exposure data is almost identical to the values recorded by Searle [S53] and Pomerantzeva et al. [P22, P23] for comparable low dose rate exposures.

316. In their other study discussed earlier, Grahn, Frystak and Lee [G25] obtained suggestive evidence for translocation induction after single neutron doses of 0.025 to 0.40 Gy and 0.225 to 1.45 Gy of gamma rays. The increases were small but significant at all doses employed except at 10^{-2} Gy of neutrons.

317. In the same work reported in the section on dominant lethals, Shevchenko et al. [S133] also obtained cytogenetic data on the induction of reciprocal translocations in mouse spermatogonia by incorporated ^{14}C. The frequencies were 0.34%, 0.84% and 0.60% at the estimated absorbed doses of 0.22, 0.5 and 1.01 Gy, respectively. Comparing the yields of translocations recorded in this study with those published in the literature (chronic gamma irradiation experiments), the authors concluded that the RBE value for ^{14}C beta rays is about 1.

318. In the study of Yusof [Y9] discussed in the section on dominant lethals, translocations were also

scored in the spermatocytes (descended from irradiated spermatogonia; 2 Gy of high dose rate x rays or 2 Gy of ^{60}Co gamma rays at low dose rate) of males which had been given 0.1% caffeine in their drinking water for eight weeks. As expected, the frequencies of translocations were significantly lower in the gamma-irradiation group (2.8% versus 5.2% in the x-ray group). Caffeine treatment did not have any measurable effect, but in the gamma-ray group, the caffeine-treated males tended to have a somewhat higher incidence of translocations, although the effect was non-significant. The frequency of autosomal univalents was higher after acute x-irradiation than after gamma-irradiation and the univalent frequency tended to be lower in the irradiated groups that had received caffeine (2.9% versus 5.6%, x rays and 1.7% versus 2.0%, gamma rays).

319. In the 1977 report, the work of Cattanach et al. [C32] on the induction of translocations in mouse spermatogonia by fractionated (unequal fractions) x-ray exposures was discussed. In these experiments, the yield of translocations depended on the size and sequence of the exposure fractions. Thus, when a 1000 R exposure was administered as 100 R followed by 900 R 24 h later, the yield of translocations (22%) was similar to that which can be obtained by extrapolation from lower exposures (assuming linearity) and also to that after a 500 + 500 exposure, 24 h apart. However, when the 900 R exposure preceded the 100 R exposure, the response was much lower (7.4%) yet still higher than that produced by a single 1000 R exposure (4.5%). The same order of effectiveness was observed for the length of the sterile period.

320. From these results, the authors concluded that 24 h after the initial exposure the surviving stem cells are more sensitive than earlier, both to killing and to the induction of translocations; and they are no longer heterogeneous in their radiosensitivities so that increasing yields of translocations may be obtained with increasing exposures. Evidence for this loss of heterogeneity came from the observation that numbers of spermatocytes with 0, 1, 2 ... translocations gave a good fit to a Poisson distribution in the 100 + 500 R, 100 + 700 R, and 100 + 900 R series, but often showed an excess of cells with two or more translocations (suggesting heterogeneity with a more sensitive sub-population) in other series [C33].

321. In further experiments aimed at studying the radiation-induced loss of heterogeneity of the spermatogonial stem cell response to the induction of translocations, Cattanach and Crocker [C33] obtained results at two further exposure levels, namely at 600 and 800 R. The main observation was that the yield of translocations was highest after fractionation (24 h interval) when the treatment regime comprised the 100 R as the "conditioning" exposure followed by the larger "challenging" exposure. The results thus substantiate the earlier observations [C32] and also support the 100 + 500 R data of van Buul and Léonard [B27] in showing that the elevated response also occurs at lower exposures. All these data are thus consistent with the thesis that the stem cell spermatogonia surviving a radiation exposure become sensitized to genetic damage 24 h later and at this time, little of the original heterogeneity in radiosensitivity typical of the unirradiated testis remains [C32, P24].

322. In another study, Cattanach et al. [C63] reported that if the chemical mutagen triethylenemelamine (TEM) was given to male mice as a "conditioning" exposure, followed 24 hours later by 900 R of x rays, then high translocation yields were obtained as with 100 + 500 R. TEM + 500 R 24 hours later gave a small but non-significant increase above normal response to 500 R, while TEM + 500 R four days later gave a sub-additive yield (as did the reverse order treatment), as had 100 + 500 R five days later in a previous study [C64]. The authors thought it unlikely that TEM and x rays would both synchronize the cell cycle of surviving stem cell spermatogonia in a similar fashion.

323. Cattanach et al. [C63] therefore postulated that the common mediating cause was the depletion of the stem-cell population, probably by preferential killing of cells actually in cycle [C65]. This might have "triggered" the long cycling survivors from a static out-of-cycle condition or G_0 phase which may be highly radioresistant [C65] into a more active and shorter cell cycle (see also [P24]). The authors consider that 24–48 hours later, a very high proportion of these cells may have been synchronously brought into either a sensitive stage of the cell cycle proper or a sensitive longer lasting transitional phase, before having begun a series of rapid cell divisions to repopulate the germinal epithelium. The sharply reduced translocation yields with the fractionation intervals of 3–16 days after 500 R may have then typified the response of the rapidly cycling cells, which seems similar to that found in the actively proliferating mouse testes [C65].

324. In an extension of their earlier study [B27], van Buul and Léonard [B28] gave unequal fractionated x-ray exposures to male mice (spermatogonial irradiation) to define the magnitude of the conditioning exposure that would sensitize the A_s spermatogonia to the challenging exposure 24 h later. In this work, a total exposure of 1000 R was administered in the following way: 100 + 900 R; 75 + 925 R; 50 + 950 R and 25 + 975 R. Appropriate single exposure controls were done concurrently. The results showed, however, that when the conditioning exposure is below 100 R, there was no enhancement of the translocation frequencies. The frequencies recorded were the following: 25R: 0.4%; 50 R: 0.76%; 100 R: 1.3%; 1000 R: 2.5%; 25 + 975 R: 3.3%; 50 + 950 R: 5.0%; 75 + 925 R: 5.0% and 100 + 900 R: 16.1%. These results support the idea that depletion of the stem-cell population is the important cause in triggering survivors into the more active cycle as has been postulated by Cattanach et al. [C63] because at exposures below 100 R, stem-cell depletion would be relatively slight though there would still be major killing effects upon differentiating spermatogonia.

325. Van Buul et al. [B29, B69] studied the response of four different stocks of mice (with the Swiss random-bred genetic background (Cpb(SE)S)) to the x-ray-induction of reciprocal translocations in their spermatogonia. The stocks were the following:

(a) Normal mice;
(b) Mice heterozygous for a reciprocal translocation involving chromosomes 1 and 13;
(c) Mice that were trisomic for the translocated chromosome but with normal phenotypic appearance;
(d) Mice that were trisomic for the same translocated chromosome, but characterized by severe underdevelopment, skull malformations and abnormal growth of the upper and lower incisors ("*teeth* trisomics").

326. In the first experiment (which involved the first three stocks) the irradiation exposure was 3 Gy. The

frequencies of translocation recorded were: 8.8 ± 3.5% (normal mice); 6.1 ± 1.9% (translocation heterozygotes) and 9.6 ± 2.6% (normal trisomic mice) showing that while the normal and trisomic mice have similar sensitivities, the translocation heterozygote may have a lower sensitivity. The latter observation has been confirmed in experiments involving 2.5 and 5.0 + 5.0 Gy (24 h interval) in which it was found that the translocation heterozygotes had a lower sensitivity than normal mice (11.4% versus 19.7%, 700 cells scored in each and 24.9% versus 33.8%, 800 cells scored in each). In the second experiment (with a different radiation set-up) in which the comparison was between normal and "teeth trisomic" mice after 3 Gy, the frequencies of translocations were 5.8 ± 2.3% in the normal mice and 5.6 ± 2.2% in the latter showing no significant difference.

327. In another study, van Buul [B30] examined the radiosensitivity of male mice descended from a mouse population which had been exposed to 2 Gy of whole-body x-irradiation every generation (at 26 ± 2 days after weaning) for 69 generations. Non-irradiated male descendants of the 69th generation were obtained from Spalding and at the age of 12 weeks were given a whole-body 400 R x-ray exposure. Control mice of the same strain without radiation history received the same x-ray exposure. After 10–13 weeks, the mice were killed and meiotic chromosome preparations were made. The results showed that the frequencies were the same in both the groups (8.7 and 8.8%) as were the nature of the translocation configurations. The ratio of ring versus chain configurations was somewhat higher in the group with radiation history (1.5) relative to controls (0.9). However, the mean chiasma frequencies were similar in both groups. Van Buul concluded that the radiation history did not alter the radiosensitivy of the males to the x-ray induction of reciprocal translocations in their spermatogonia. These results are in agreement with those reported by Sheridan [S60, S61] in the mouse and by Sankaranarayanan [S62] in Drosophila.

(b) Meiotic stages

328. Adler [A23] investigated the sensitivity pattern of different stages of meiotic prophase of spermatocytes for gamma-ray-induced chromatid aberrations. Ten- to twelve-week-old hybrid male mice (C3H × 101) were irradiated with 300 R of gamma rays (60 R min^{-1}) and primary spermatocytes were sampled on day 1 (diplotene), 5 (mid-pachytene), 9 (zygotene) and 11 (leptotene). The results show that:

(a) Zygotene is the most sensitive stage for the induction of rearrangements, the rank order being zygotene > pachytene > diplotene > leptotene;
(b) The frequencies of fragments as well as those of autosomal and sex-chromosomal univalents did not vary significantly between the different stages;
(c) At zygotene, the exposure-frequency relationship for chromatid interchanges was consistent with a more-than-linear increase with exposure ($Y = aD + bD^2$) and this was also true for fragments.

329. These results are at variance with some others published in the literature. For instance, Tsuchida et al. [T14] found that with 300 R of gamma-irradiation at a lower exposure rate (29 R min^{-1}), diplotene and pachytene were equally sensitive to the induction of rearrangements, but the pachytene stage was less sensitive than diplotene (10.5% versus 16.0%) for the induction of fragments and breaks outnumbered rearrangements. The picture that emerges from the work of Walker [W19] shows that radiosensitivity progressively increases during prophase, diakinesis being the most sensitive (this stage was not investigated in the work of Adler) with respect to both rearrangements and fragments. Her work also showed that acute x-irradiation (0.72 Gy min^{-1}) and protracted gamma irradiation (2 Gy; 1 10^{-4} Gy min^{-1} over 13 d) were equally effective in inducing structural aberrations if the mean frequencies were weighted for each stage with respect to their time span.

(c) Relationship between partial sterility of translocation heterozygotes and the length of the translocated segment

330. It has long been known that the degree of partial sterility of male translocation heterozygotes may vary from substantially lower than 50% to substantially higher than 50% of normal fertility. The former is mainly dependent upon the proportions in which balanced and unbalanced gametes are represented in the ejaculate, which in turn is a function of meiotic segregation. On the other hand, the formation of multivalent associations observed in meiotic preparations is assumed to be dependent upon the size of the translocated chromosome segment, which influences the possibility of chiasma formation between the translocated segment and its homologous segment in the intact chromosome.

331. Generoso et al. [G41] tested the possibility that the degree of partial sterility of a male translocation heterozygote is correlated with the frequency at which multivalents are observed in the diakinesis-metaphase I spermatocytes. The index of partial sterility used is the percentage of dead implants in females that have been mated to translocation heterozygotes. Only males that carried single reciprocal translocations were included in the analysis (45 males identified from analysis of 25 metaphase I spermatocytes). The percentage of dead implants was based upon 6 pregnancies from each of 41 males, 9 pregnancies from each of 2 males, 5 pregnancies from 1 male and 4 pregnancies from another. The percentage of multivalents was determined from 25 cells scored for each male.

332. The results demonstrate a significant positive correlation between the degree of partial sterility and the frequency of multivalents in meiotic preparations; this means that the length of the translocated segment has some influence on the proportion of unbalanced gametes in the ejaculate. When the translocated segment is short, the probability of scoring a cell with multivalent is reduced, but the proportion of sperm in the ejaculate with balanced translocation is increased. The reverse is true when the translocated segment is long. What this means is that cytological scoring may be biased in favour of translocations with translocated segments which have a lower probability of transmission. However, it should also be remembered that if the translocated segment is short, there is more chance of post-natal survival of unbalanced zygotes.

3. Heritable reciprocal translocations in female mice

333. In the 1977 report, the results of Searle and Beechey [S63] and of Krishna and Generoso [K18] on the x-ray induction of heritable reciprocal translocations in female mice were presented. In the study of Searle and Beechey, none out of 386 sons of females

given 3 Gy of x rays showed evidence of translocation heterozygosity, although there were 3 confirmed translocations in 294 female progeny. With the same radiation exposure (300 R), Krishna and Generoso found that 4 out of 800 male progeny were partially sterile (and subsequently confirmed cytologically as translocation carriers) and 2 were sterile (and were cytologically normal).

334. The testing of the female progeny from the same experiment has now been completed [K19]. The results show that out of 935 sons tested, 4 are partially sterile (and have been shown to be translocation heterozygotes through cytological analysis), 2 fully sterile (cytologically normal); in addition, 1 daughter with an XO constitution is also semi-sterile. Besides, 7 XO females and 1 XO/XX mosaic have been recovered. These results demonstrate that reciprocal translocations can be recovered in both male and female progeny of irradiated females. If one restricts attention to semi-sterile males alone, a total of 8 translocations have been recovered among 1735 progeny (males + females) which gives a frequency of 0.46% or a rate of 0.15 10^{-4} per R per gamete, about one-half of that after spermatogonial x irradiation [U1]. The control rate in the work of these authors is 1 in 4392 [G40] such that correction for controls will not affect the rate appreciably.

4. Chromatid-interchanges and other aberrations in mouse and Chinese hamster oocytes: in vitro studies

335. Other studies on aberration induction in oocytes have used the technique of culturing oocytes in vitro. In these, at different times after irradiation, the female mice are killed, the oocytes with germinal vesicles recovered and cultured in vitro and then screened for aberrations in metaphase I. The general findings were that:

(a) The frequency of chromosomally abnormal oocytes increased with time after irradiation;
(b) The variation in the yield of aberrations as a function of time between irradiation and ovulation agreed well with the variation in sensitivity to dominant lethal induction over the same period;
(c) From the frequency of aberrations observed in the oocytes, it was possible to predict the frequency of transmissible reciprocal translocations. Studies of this kind reported in the 1977 report included among others, those of Brewen et al. [B31] and of Searle and Beechey [S63].

336. Since then, the results of three studies on the same general problem have been published. Caine and Lyon [C34] conducted experiments to compare the effects of x rays and some chemical mutagens on the yields of aberrations. The x-ray dose was 4 Gy and was given to mature females that were 8–12 weeks old. The oocytes were recovered after one and three weeks, cultured in vitro and processed for examination of aberrations. The results confirm the earlier findings, namely, that the yield of aberrations is significantly higher in week 3 than in week 1 and this is true of the proportion of abnormal cells in the two sampling times (59.5% versus 41.5%). The aberrations studied included chromatid gaps and breaks, isochromatid gaps, fragments and rearrangements. Fragments, usually isochromatid, were the most common aberration type and more aberrations were found in week 3 (all four categories) with the frequency of rearrangements being more than twice that in the first week (22% versus 8.5%).

337. Brewen and Payne [B32] conducted a study to analyse in detail the radiosensitivity of mouse oocytes from the standpoint of the induction of aberrations. Four x-ray exposures (50, 100, 200 and 300 R) were used. Eight- to ten-week-old female mice of the CD1 strain were irradiated and the oocytes were collected at various intervals ranging from 1.5 days to 28.5 days. The types of aberrations scored were chromatid deletions, isochromatid deletions and chromatid interchanges. The results showed that, as expected, the sensitivity was different depending on the degree of maturation of the oocytes: the least sensitive oocytes were those that were 0.5–1.5 days from ovulation (probably corresponding to stages 7 and 8); the sensitivity gradually increased with longer intervals between irradiation and ovulation until a stage of peak sensitivity was reached at 9.5 days. From this time, the aberration yield remained relatively constant until the females became functionally sterile.[14]

338. The data were analysed by the authors in three ways. Firstly, the data from all time intervals at each exposure were pooled. Secondly, the data from the least sensitive time intervals at each exposure were pooled. Thirdly, the data from the period of uniform sensitivity at each exposure were pooled. Exposure-frequency regression analyses were done on these pooled data and the best fits were to the models $Y = a + bD + cD^2$ and $Y = a + cD^2$ for both deletions and interchanges (the terms a, b and c correspond to the coefficients of the spontaneous, one-track and two-track terms, respectively). These analyses have thus demonstrated that the aberrations under consideration result from a predominantly two-track process. The data on which these calculations were made are summarized in Table 22.

339. Brewen, Payne and Adler [B33] carried out a study to examine the induction of chromosome aberrations in mouse dictyate oocytes after fractionated x-ray as well as after chronic ^{60}Co gamma-ray exposures using procedures similar to those employed in their earlier work [B31]. In the first series, a total exposure of 400 R of x-rays was split into two fractions separated by time intervals of 90, 135, 180 and 1440 min. In the second one, the same total exposure was administered in unequal fractions (100 + 300 R or 300 + 100 R) separated by 90, 135 and 180 minutes. In the third series, chronic gamma-ray exposure was given to female mice over an eight-day period, 8–16 days prior to ovulation and the exposures were 117, 240, 348 and 483 R. Appropriate single exposure controls were concurrently run. The frequencies of interchanges and deletions were determined in metaphase I oocytes.

340. Considering first the results of series I, it was found that with 90- and 135-minute intervals between fractions, the yields of interchanges did not significantly deviate from those expected on the basis of interaction of chromosome breaks produced by the two fractions (the yield with the 90-minute fractionated interval was identical to that after the single exposure; with the 135-minute interval, it was lower). With intervals of either 180 min or 24 h, the observed frequencies of interchanges were similar but lower than those with shorter intervals between the fractions and

[14] The authors have defined functional sterility as the inability to super-ovulate a sufficient number of oocytes to make slides. For instance, after 300 R, only about 35 *oocytes* were obtained from 100 females at the 28.5-day interval. This degree of oocyte killing makes cytogenetic studies difficult, but does not preclude the possibility of some females being capable of producing a few offspring.

were not significantly different from the expectation based on additivity. With deletions, the frequency was consistent with interaction with the shortest interval (90 minutes) but not at other intervals.

341. The results of the second series of experiments indicate that there was no difference in aberration yield and thus in the rejoining time, irrespective of whether the first fraction was 100 or 300 R. For interchanges for instance, the frequencies were the following: 100 + 300 R, 90 min: (74.7 ± 5.0)%; 300 + 100 R: (62.4 ± 7.1)%; 100 + 300 R, 135 min: (62.8 ± 5.6)%; 300 + 100 R: (61.5 ± 5.1)%; 100 + 300 R, 180 min: (52.9 ± 4.3)%; 300 + 100 R: (52.5 ± 4.3)%. The authors consider that these data "... argue strongly that the mouse oocyte's repair systems, at least for chromosome aberration formation, are not drastically altered by the magnitude of the x-ray dose, and that this repair occurs within hours and not days or weeks".

342. The data from the chronic gamma irradiation series show that the frequencies are much lower than after acute irradiation and this is true for both interchanges and deletions; and the frequencies observed are consistent with a linear increase with exposures. These data demonstrate that when the exposure rate is reduced from 100 R min^{-1} (x rays) to 0.04 R min^{-1} (gamma rays), the yield of exchanges is reduced to one-tenth at a total exposure of 478 R. The magnitude of reduction in the yield observed in this study is lower than that observed in specific locus work involving maturing oocytes. The combined data from the fractionation and low exposure rate exposures led the authors to conclude that the exposure-frequency relationships for both exchanges and deletions induced by x-irradiation are due to the involvement of two-track processes.

343. In the Chinese hamster, Mikamo [M49] conducted a study to assess the chromosomal radiosensitivity of the oocyte stages sampled from x-irradiated 5-month-old mature females. Oocytes sampled from females irradiated at 85, 59, 35 and 19 hours before ovulation (and analysed at metaphase II) manifest a relatively low level of sensitivity to the induction of chromosome aberrations (mainly chromatid breaks from 0.3 to 4.1%). From 17 hours before ovulation, the sensitivity begins to rise (10% breaks) reaching a peak at 11 hours before ovulation (43.3%); the stage of peak sensitivity corresponds to diakinesis just prior to the onset of prometaphase I. Prometaphase I and metaphase I stages (9 and 7 hours before ovulation) retain a relatively high level of sensitivity (aberration frequencies of 31.4 and 25.3%) although this is not as high as diakinesis. The exposure-frequency relationships for chromatid breaks at the most sensitive diakinesis stage appears consistent with a greater than linear increase in yield with increasing exposures (50–200 R range).

5. Reciprocal translocations in spermatogonia of the rhesus monkey and comparison with results from other mammalian species

344. In the discussion of the data on the induction of reciprocal translocations in the spermatogonia of the rhesus monkey in the 1977 report, it was pointed out that:

(a) The frequencies in the rhesus monkey are much lower than in man, marmoset and the mouse;
(b) Peak yields of translocations are obtained at around 1–2 Gy in the monkey, levels that are much lower than in the mouse;
(c) There are significant differences in the response between the different animals even at the same dose level and in the frequencies recorded by Lyon et al. [L23] on the one hand and by van Buul [B34] on the other.

345. Van Buul [B35, B36] has now collected more data on translocation induction in the spermatogonia of the rhesus monkey and these are presented in Table 23 (the translocations were scored in C-banded preparations). It can be seen that:

(a) The spontaneous frequency of translocations in the rhesus monkey is low and comparable to that recorded for other mammals studied so far in this respect such as the mouse, marmoset, rabbit, guinea pig and golden hamster;
(b) The dose-response curve is humped with a maximum around 1 Gy and a humped curve has been found for all mammalian species studied;
(c) The chiasma frequencies in the rhesus monkey are much higher than in the mouse, rabbit, golden hamster, etc., and consequently the ratio of ring versus chain configurations is much higher in the rhesus monkey than in other species.

346. Van Buul [B36] fitted the translocation data to linear and linear-quadratic equations (0, 0.5 and 1 Gy data) and found that these gave a good fit to the linear model $Y = a + bD$ and the fitted values of a and b are, respectively, 0.0233 and 0.0086. A comparison of the values of the slopes for the data of the rhesus monkey and those of other species (mouse, rabbit, guinea pig, marmoset and man) show that the value for the monkey is significantly lower than that of other species except the guinea pig (see also [B68]). These comparisons are summarized in Table 24.

347. In a cytogenetic study, Benova et al. [B79] compared the sensitivities of the spermatogonia of the mouse, rabbit, Syrian hamster and the rat to the gamma-ray induction of reciprocal translocations. The doses were in the range of 0.5 to 5 Gy and the dose rate was either 1.23 Gy min^{-1} or 10^{-4} Gy min^{-1}. It was found that for exposures given at the high dose rate, the sequence (in decreasing order of radiosensitivity) was the following: rat, rabbit, mouse and the Syrian hamster. For low dose rate exposure, the sequence was: rabbit, rat, Syrian hamster and the mouse.

6. Summary and conclusions

348. Reciprocal translocations are the predominant kind of structural aberrations induced by ionizing radiation in mouse spermatogonia. An examination of all the relevant cytogenetic results that bear on the radiation-induction of translocations in mouse spermatogonia support the thesis that, if Robertsonian translocations are induced, they are formed with a negligible frequency relative to reciprocal translocations.

349. In a cytogenetic study, a comparison was made of the yields of reciprocal translocations after spermatogonial irradiation of mice at different exposures and at high and low dose rates (x- and gamma-irradiation). The results showed that the yield per unit dose decreases over the range of exposure rates from 100 to 0.003 R min^{-1} (a maximum of 16-fold difference) with no further decrease at still lower exposure rates. These

results support those from earlier studies discussed in the 1977 report.

350. With plutonium alpha-ray irradiation of mouse spermatogonia, there are indications that the peak yield of reciprocal translocations may be obtained at doses of between 0.15 and 0.2 Gy. Caffeine treatment of male mice prior to irradiation (spermatogonial x- or gamma-irradiation) does not affect the yield of translocations.

351. A number of additional experiments (subsequent to those reported in the 1977 report) involving irradiation of mouse spermatogonia with unequally fractionated x-ray exposures (100 + 900 R, 100 + 500 R etc., in this or reverse order with a 24-hour interval between the fractions) have been completed. The yield of translocations was found (as has been the case in earlier studies) to depend on the size and sequence of the exposure fractions. With a small fraction preceding a large one, the yield is high and is equal to that linearly extrapolated from lower exposures. With the reversed sequence of exposures, the yield is low, but higher than that after a single acute exposure. These observations have been interpreted on the assumption that 24 hours after the first fraction, the surviving stem cells are in the more sensitive stage than before, both to killing and to translocation induction and that they are less heterogeneous in their radiosensitivities at the time they receive the second fraction (the degree of synchrony is dependent on the magnitude of the first fraction). In other fractionation experiments involving unequal x-ray exposures (100 + 900 R, 40 + 950 R, 25 + 950 R and the single exposures) it was found that when the conditioning exposure was below 100 R, there was no enhancement of translocation yields. These results support the idea that depletion of the stem-cell population is the important factor in triggering survivors into the more active cycle and that at exposures below 100 R, stem-cell depletion would be relatively slight.

352. Heterozygosity for a specific reciprocal translocation involving chromosomes 1 and 13 in mice appears to decrease the radiosensitivity (relative to normal mice) for the x-ray induction of reciprocal translocations in their spermatogonia. But tertiary trisomic mice (trisomic for the same translocated chromosome) however, do not differ in radiosensitivity from normal mice, with respect to the same end-point.

353. When male mice descended from a population that had a previous radiation history (for 69 generations; exposed to 2 Gy per generation at 26 days after weaning) were tested for their radiosensitivity (translocation induction in spermatogonia) and compared with non-irradiated descendants, no differences could be discerned.

354. A study has been conducted to examine whether reciprocal translocations induced in mouse spermatogonia are subject to selection between the stage at which they are induced and the spermatocyte stage at which they are scored. The results are consistent with the view that there is probably no selection against spermatogonia carrying translocations in the exposure range from 50 to 300 R.

355. There are results which document the premise that in male mice which are heterozygous for a reciprocal translocation, there is a significant positive correlation between the degree of partial sterility of these males and the frequency of multivalents in meiotic preparations.

356. The completed studies on the x-ray induction of heritable translocations in female mice demonstrate that reciprocal translocations can be recovered in both male and female progeny of irradiated females and that the rate of 0.15 10^{-4}/R/gamete is about one-half of that after irradiation of spermatogonia.

357. Subsequent to the publication of the 1977 report, further studies on x-ray induction of aberrations in female mice (using the technique of culturing the irradiated oocytes in vitro) have been conducted. The results obtained confirm those discussed in the 1977 report in showing that the frequency of chromosome aberrations in oocytes recovered three weeks after irradiation were significantly higher than those in oocytes recovered in week 1. In another investigation, it was found that the least sensitive oocytes were those that were 0.5–1.5 days from ovulation and that the sensitivity gradually increased, reaching a peak around 9.5 days from ovulation; from this time onwards, the aberration yield remained relatively constant until the females became functionally sterile.

358. Again in studies using in vitro culturing of irradiated mouse oocytes, when the x-ray exposures were fractionated with intervals of between 90 and 180 minutes and of 24 hours between the fractions, it was found that with 90 and 135 minute intervals, the yields of interchanges did not deviate from those expected on the basis of interaction of chromosome breaks produced by the two fractions; with intervals of either 180 minutes or 24 hours, the yields of interchanges were consistent with the additivity expectation. With deletions, the frequency was consistent with interaction with the shortest interval (90 min), but not at other intervals. Similar studies with chronic gamma-irradiation of female mice and scoring for aberrations in their oocytes in vitro demonstrated a pronounced dose rate effect: at an exposure of 478 R, the yield of chromatid interchanges was only one-tenth after chronic than after acute exposures.

359. In the Chinese hamster, oocytes sampled from females irradiated 11 hours before ovulation (and analysed at metaphase II) manifest the highest level of radiosensitivity to the induction of chromatid breaks relative to other stages. The stage of peak sensitivity corresponds to diakinesis prior to the onset of prometaphase. In this stage, the frequencies of chromatid break increase faster than linearly with an increase in x-ray exposures.

360. More extensive data on the induction of reciprocal translocations in the rhesus monkey spermatogonia have now become available. These confirm the conclusion reached in the 1977 report in showing that the rhesus monkey is much less radiosensitive than most of the mammalian species studied in this respect. The peak yield is obtained at around 1 Gy.

C. LOSS OR ADDITION OF CHROMOSOMES: NON-DISJUNCTION

1. Introduction

361. The 1977 report considered the importance of experimental models to study non-disjunction together with the data that were then available in the mouse, mouse-tobacco mouse hybrids and in the northern field vole, Microtus oeconomus. In this section, the information that has accumulated since then will be

discussed and placed in perspective with the earlier work that has been done in this area. Useful reviews on this subject with particular reference to the mouse [R25] and to experimental mammals in general [H39, H40] have been published.

2. Methods to study aneuploidy

362. The methods that have so far been used can be broadly divided into cytogenetic and genetic ones. The cytogenetic methods, which are currently in extensive use in several laboratories, involve chromosome analysis of second meiotic metaphase in oocytes [H41, R26, R27, U10, U11] or spermatocytes [B42, O8, S67]; pre-implantation embryos at the first cleavage stage [D15, F15, F16, K20, M45] or morulae and blastocysts [F17, G30, Y4]; post-implantation embryos [F17, S68, T17, Y4, Y5, Y6]; and newborn offspring (in mice) [G31].

363. Methods for chromosome preparations from oocytes and from pre-implantation cleavage stages involve modifications of Tarkowski's air-drying technique [T18]. The technique of Evans et al. [E10] for early post-implantation embryos has also been modified and "banding techniques" have been employed for a better identification of the chromosomes. Chromosomes from spermatocytes at metaphase II are usually prepared according to the method of Evans et al. [E11]. All these methods make use of direct chromosome analysis to assess the amount of aneuploidy in male or female germ cells or in embryos at various developmental stages.

364. Some of the genetic methods, particularly those aimed at studying sex-chromosomal non-disjunction have been in use since the early 1960s [K21, R25, R28, R29, R30] and involve studying the segregation of sex-linked marker genes in genetic crosses of appropriate stocks. The genetic method described by Lyon et al. [L30] in 1976 using Robertsonian translocations has not yet been employed in any further published study, neither have other possible methods that would use marked autosomes [R25].

3. Spontaneous incidence of aneuploidy

365. Data on the spontaneous incidence of some numerical chromosome anomalies of interest in different mammalian species are summarized in Tables 25 and 26. It can be seen that in most species, the incidence of aneuploidy in early embryos is rather low in contrast to the situation obtained in humans. Not mentioned in the tables is the finding that the incidence of aneuploidy in the first cleavage stages of the embryos varies between different strains of mice and is generally higher when fertilization is effected in vitro than in vivo [F15].

4. The mouse

366. Chandley and Speed [C35] and Speed and Chandley [S114] have recently reported their results on x-ray-induced non-disjunction in male and female mice. In the male series, random-bred Q strain adult mice were irradiated with 1 Gy of x rays and mated to females five weeks after irradiation (to sample spermatocytes) or seven weeks after irradiation (to sample spermatogonia). Appropriate unirradiated controls were also run. Pregnant females from week 5 and week 7 and control matings were killed at 9–10 days of gestation and chromosome preparations made from all viable foetuses or their membranes. The data to be discussed below are from the paper of Speed and Chandley [S114] since the earlier paper [C35] was a preliminary report.

367. In the above investigation, the overall frequency of abnormalities in the controls was 1.1% (6/571) and included 2 trisomics (41,XXY), 1 triploid (60,XXY) and 3 mosaics (39/40); the frequency of trisomies alone is 0.35%. In week 5 of the irradiated series, the frequency of abnormalities was 2.0% (20/1005) and included 2 monosomies (39,X), 1 trisomy (41,XY,+16), 1 triple-trisomy (43,XXY,+10,+17), 5 triploids, 2 tetraploids, 8 mosaics and 1 with miscellaneous aberration (40,XY,1q+). In week 7, the frequency of chromosomally abnormal embryos was slightly higher being, 2.8% (20/688; 2 monosomies, 7 trisomies, 8 mosaics, 1 triploid and 2 tetraploids). The frequencies of trisomies alone were, respectively, 0.20% (2/1005) and 1.0% (7/688) in weeks 5 and 7 and were not significantly different from the control frequency of 0.35%.

368. In the female series, there were three irradiated groups (6–8 week old females irradiated with 5 10^{-2} Gy; 9 month old females irradiated with the same dose and mated; and 6–8 week old mice irradiated with the same dose and mated when 9 months old) and two controls (young and aged). Techniques for making chromosome preparations were the same as those mentioned earlier.

369. When young females were irradiated, the frequency of chromosomally abnormal embryos was 1.5% (2/129; 1 trisomy and 1 mosaic) and not significantly higher than in controls (1.1%; 6/571; same as given in paragraph 367). When young females were irradiated, aged and then mated, the frequency was 2.1% (3/145; 1 monosomy, 1 trisomy and 1 mosaic); the corresponding frequency for irradiation of aged females was 3.6% (6/168; 3 trisomies, 3 triploids). The frequency of chromosomally abnormal embryos in the aged female control group was also 3.6% (6/168; 1 monosomy, 1 trisomy, 2 mosaics, 1 triploid and 1 tetraploid). Thus, apart from a general increase in the frequency of chromosomally abnormal embryos with an increase in maternal age, there is no measurable effect due to irradiation at this dose level.

370. Max [M63] irradiated virgin female mice (from an inbred CBA strain) of 6, 15 and 46 weeks of age (groups 1, 2 and 3, respectively) with 2, 4, 8 or 16 R of x rays and mated them to young males of the same strain when the irradiated mice were, respectively 16 or 32–35 weeks old (groups 1 and 2). Group 3 mice were mated soon after irradiation. The foetuses were examined for chromosomal abnormalities, particularly aneuploidy. There were concurrent controls. In the controls (all age groups pooled), there were 2 trisomic and 2 triploid embryos out of 213 screened; the former were found in group 3 controls (2/27) while the latter were in group 2 (2/78). In the irradiated series (all radiation groups) there were 1 trisomic and 6 triploid embryos among 642 embryos; the single trisomic was found in group 2 (1/289) and the triploids were in groups 1 (4/307) and in group 2 (2/289). Thus in these experiments, while there is some suggestive evidence for an increase in chromosome abnormalities with increasing maternal age, no radiation effects could be demonstrated.

371. In the experiments of Strausmanis [S68] virgin inbred C57BL females aged eleven months were

irradiated with 4, 8 or 16 R of x rays and placed with young untreated males of the same strain, five days after irradiation. The pregnant females were killed 10 days after vaginal plugs were observed and the conceptuses processed for chromosome analysis. Aneuploid embryos classified as alive (heart beats observed while dissecting) were 1 monosomic in the control group (out of 496 embryos) and 2 trisomics in the irradiated groups together (out of 568 embryos). The number of aneuploid embryos classified as dead was 4 trisomics in the control and 3 trisomics in the irradiated groups. These data show that trisomic embryos are not uncommon in the mouse but die after implantation. In any case there is no evidence for an increased frequency of chromosome abnormalities in embryos of aged female mice x-irradiated before mating as compared to non-irradiated ones.

372. In the study of Hansmann et al. [H39, H40] female mice of the NMRI/Han strain (8–12 weeks old) were x-irradiated with 20 R or 200 R and mated to unirradiated males. Cytological preparations of foetuses were carried out 9.5 days after detection of vaginal plugs on the morning after irradiation. The results showed no evidence of aneuploidy among 90 karyotyped control foetuses and among 95 embryos in the 20 R series. However, one embryo out of the 22 karyotypes in the 200 R group was monosomic (chromosome 19) and another trisomic (chromosome 17) and these findings were confirmed in all metaphases examined after banding.

373. In another experiment, Hansmann [H39] and Hansmann et al. [H42] irradiated 8–12 week old male mice with 20 or 200 R and mated them from day 2 to day 36 after irradiation to unirradiated females of the same age and strain. Foetal preparations were made on day 9.5 post coitum. Out of 211 karyotyped foetuses in controls, there were no aneuploids. In the 20 R series, there were 3 aneuploids among a total of 216 foetuses analysed (1.4 %) and in the 200 R series, there were 7 aneuploids among 385 foetuses analysed (1.8%). The genetic constitutions were (with the origin in terms of the day of mating given in parentheses): 20 R: 41,XX,+11 (21); 41,XY,+2 (21) and 41,XX,+11 (31); 200 R: 39,XO (4); 39,XY,–8 (5); 41,XX,+14 (7); 41,XY,+13 (16); 39,XO (25); 41,XYY (28); 40,XO,+13 (32). It is worthy of note that the induction of aneuploidy is not significantly enhanced by the higher exposure relative to the lower one. Irradiation did not seem to enhance the incidence of polyploidy in this study.

374. In 6 of the 10 observed aneuploid foetuses, the mal-segregation could be allocated to meiosis I or II; the other 4 foetuses, however, were derived from sperm irradiated in the vas deferens (39,XO and 39,XY,–8) or the epididymis (41,XX,+14) or irradiated as mid-spermatids (41,XY,+13). A chromosome loss most probably may explain the XO karyotype. Mitotic non-disjunction during early cleavage stages could lead to the two trisomic foetuses (trisomy 13 and trisomy 14) generated 7 and 16 days after irradiation [H42].

375. Russell et al. [R75] have used a genetic method to determine whether advancing age affects non-disjunction in irradiated or unirradiated female mice. Sex-chromosome markers were built into the cross so that maternal non-disjunction (X^MX^MY or OX^P) could be distinguished from paternal non-disjunction (X^MX^PY or X^MO) (any XXX types would be only questionably detectable by phenotype; and XO can result from breakage-related chromosome loss as well as from non-disjunction). Irradiated (200 R; x rays; 1 day before mating) or control females ranged in age from 2.5 to 12 months at conception. Over 13 000 offspring have been scored with only one case of maternal trisomy (X^MX^MY/X^MY mosaic) derived from a 12-month old irradiated female and one of paternal trisomy (X^MX^PY), and no clear-cut differences in either OX^P or X^MO frequencies with age.

5. Other species

376. Although the Chinese and Syrian hamsters have been used for the study of oocytes and pre- and post-implantation embryos in recent years [B43, H43, H44], radiation data are very scanty. The unpublished observations of Hansmann quoted in his paper [H39] show that following x-irradiation of female Chinese hamsters and examination of metaphase II oocytes there is not a single case of aneuploid oocytes either in the group irradiated with 20 R or 200 R (147 and 131 oocytes, respectively, were examined) or in the control group (121 oocytes).

377. In the Chinese hamster study of Mikamo [M49] discussed earlier, chromosome analyses were also carried out (at metaphase II) in oocytes of 5-month-old virgin females that had received 50, 100 or 200 R of x-irradiation; of 16–19 month old females irradiated with 50 R. In the first series, in each of the first, third and fifth cycles after irradiation, unfertilized eggs were collected and processed for chromosome analysis at metaphase II; in the second series the oocytes collected were those in the first cycle after irradiation.

378. In the first series, 8197 oocytes from 1200 females were chromosomally analysed (1747 eggs from 254 control animals, 1812 oocytes from 309 females in the 50 R group, 2300 oocytes from 336 females in the 100 R group and 2338 oocytes from 301 females in the 200 R group). The data showed no significant increase in the frequency of aneuploid eggs except in the 200 R, first-cycle group where there was a slight but significant increase in the frequency of aneuploid eggs (3.4 versus 2.1% in the controls). With respect to structural abnormalities, again there were no significant increases except in one group: in the third cycle eggs of the 100 R group, the frequency of these anomalies was 1.1% versus 0.2% in the controls (see also subsection II.A.2). The author has no explanation for the statistically significant increase in these two particular samples.

379. In the second series (with aged females irradiated with 50 R), there was a demonstrable effect of maternal age with respect to the production of spontaneous aneuploids (4.1% in the aged controls versus 2.1% in the young controls of the first series), but no effect of irradiation was detected in the treated group (4.0%). With respect to structural aberrations, there was no measurable effect of either maternal age or irradiation (0.2% in the young controls, 0.4% in the aged controls, and none in the treated group).

380. The other results obtained by Mikamo [M49] relate to the induction of aneuploidy in oocytes sampled from irradiated Chinese hamster females irradiated at 85 to 7 hours before ovulation. In these experiments (200 R), the frequencies of hyper-haploid eggs fluctuated around a mean of 1.5% (1526 oocytes sampled in 10 different periods before ovulation) with a range from 0% (35, 15 and 7 hours before ovulation) to

3.4% (59 and 11 hours before ovulation). The mean frequency of hypo-haploid oocytes was slightly higher (2.4%) with a range of between 0% (13 hours before ovulation) and 5% (11 hours before ovulation). The control frequencies of hyper- and hypo-haploid oocytes were, respectively, 0.8% and 1.3% (1839 oocytes sampled). In one stage (oocytes sampled 11 hours before ovulation; as will be recalled, this stage showed the highest sensitivity to the induction of chromatid aberrations), which was studied in detail, the data at exposure levels of 50, 100 and 200 R show small but non-significant increases (the latter probably due mainly to the small numbers of oocytes that could be sampled) in the frequencies of hyper- and hypo-haploid oocytes at 50 R (2.1 and 4.2%, respectively; 1/48 and 2/48 versus the control rates of, respectively 0.8 and 1.3%) with no consistent increase at higher exposure levels.

381. In the 1977 report, the preliminary results of Tates [T19] from studies on non-disjunction in the Northern field vole, Microtus oeconomus, were reported. In this species, C-banding techniques have shown that the X chromosomes have large blocks of centromeric heterochromatin and the Y chromosome is C-band positive along its entire length. This permits the identification of spermatids having single Xs, two Xs and two Ys. Using this technique, Tates obtained good evidence for the induction of non-disjunction (in pre-spermatid stages) at x ray exposures as low as 50 R, but the calculation of the exact frequencies was complicated by the frequent variability between animals within exposure levels and within and between sampling intervals.

382. In their 1979 paper, Tates et al. [T20] presented the results on the x-ray induction of sex-chromosomal non-disjunction and of diploidy induced in pre-spermatid stages of Microtus, and scored cytologically in the descendant spermatids. The following conclusions may be drawn:

(a) In controls, the frequency of non-disjunction spermatids is about one-fifth of that of diploid spermatids ($0.5\ 10^{-4}$ versus $2.6\ 10^{-4}$);
(b) In irradiated animals (range 0.25 to 2 Gy), particularly in those given relatively high doses, there is a pronounced induction of non-disjunction and of diploid spermatids at most of the sampling times; the exposure-frequency relationships for non-disjunction spermatids show, however, no uniform pattern at the different sampling times. On days 1 and 12, the frequencies increase with increasing exposures, but at days 2, 4 and 8, the pattern is irregular, particularly at lower exposures. The induction of diploid spermatids shows in general a better exposure-frequency relationship;
(c) At any given exposure level, the mean frequencies of non-disjunction spermatids and of diploid spermatids vary at different sampling time;
(d) The induction of non-disjunction spermatids and of diploid spermatids occurs during the first as well as the second reduction division.

383. Tates et al. [T20] noted that the induction of non-disjunction of sex-chromosomes and of diploid spermatids are not necessarily linked, in the sense that sometimes there is a significant induction of one kind of event and not of the other. The usefulness of this system for the study of non-disjunction is to some extent marred by the occurrence of significant heterogeneities between animals, within exposures and between experiments and sampling times.

384. In a relatively large-scale extension of this work involving 4 different x-ray doses (0.25, 0.50, 1.00 and 2 Gy), 6 different sampling times (1, 4, 6, 7, 9 and 12 days after irradiation) and 6 animals per dose point, Tates and de Vogel [T21] were unable to demonstrate any significant increase in the frequencies of non-disjunctional (for the sex-chromosomes) spermatids over the control level. However, the frequencies of diploid spermatids increased linearly over the range of doses tested, but the slopes for the different sampling times were different. The cell stages most sensitive to the induction of diploid spermatids were sampled on days 4 and 9 after irradiation (day 4: primary spermatocytes in late pachytene, diakinesis or metaphase and possibly some secondary spermatocytes at the time of irradiation; day 9: leptotene, zygotene and early pachytene at irradiation).

385. The lack of response to the induction of sex-chromosomal non-disjunction is puzzling. The animals used in this and in the earlier studies were derived from a colony initiated in 1974 with 2 pairs of animals and 3 young. No specific breeding scheme was used except that in every generation, breeding pairs were usually formed by taking into account factors such as fertility, fecundity and absence of cannibalism. It may be that increased inbreeding might have selected against presumed non-disjunction-prone individuals. Current studies with a new colony established from new wild animals which are under way, may help to throw light on this possibility.

6. Summary and conclusions

386. A number of cytogenetic and genetic methods are currently available to study spontaneously-arising and radiation-induced chromosome losses and gains in the germ cell stages of experimental mammalian species. Most of the recent data have come from the use of cytogenetic methods (e.g., chromosome analysis of early cleavage stages, embryos at 9–10 days of gestation, oocyte stages at metaphase II, etc.).

387. The spontaneous incidence of monosomics and trisomics in early embryonic stages of most mammalian species studied in this respect is quite low, being of the order of about 0.5 to 1%. This is in contrast to the situation obtained in humans.

388. When male mice are exposed to x irradiation (100 R), mated to unexposed females and the embryos derived from irradiated meiotic and spermatogonial stages are analysed for aneuploidy, there is no measurable increase in the frequency of either monosomic or trisomic embryos over the control level. One study with a lower exposure of 20 R provides some evidence for a possible increase in the total frequency of aneuploids (monosomy and trisomy) and for the possibility that non-disjunction may occur at meiosis I or II; in the same study, at the higher exposure of 200 R, there seems to be no further increase in aneuploidy.

389. The problem of whether small x-ray exposures to female mice (in the range from 2 to 16 R) will lead to an increase in the frequency of non-disjunctional gametes leading to monosomic and trisomic embryos has been investigated by a number of workers. The available data suggest that this effect could not be demonstrated in either young or aged female mice.

390. The results of a genetic study in the mouse have provided no convincing evidence for irradiation

causing an increase in the frequency of X-chromosomal non-disjunctional progeny in irradiated young or aged females.

391. Studies involving irradiation of female Chinese hamsters (young and old; 20–200 R range) and subsequent culturing of their oocytes in vitro have provided no clear-cut evidence for an increase in the frequency of aneuploid eggs; there was no demonstrable effect of maternal age either. Other experiments with the same species aimed at ascertaining the oocyte sensitivity to the x-ray induction of aneuploidy (irradiation of females 85 to 7 hours before ovulation; 10 different time periods) show that there may be an increase in the frequencies of hyper-haploid and hypo-haploid eggs after irradiation with 200 R; the increases for any individual stage, however, are not significant in view of the relatively small sizes of the samples. In oocytes sampled 11 days before ovulation (and which manifest a high sensitivity to the induction of chromatid structural aberrations) for which data at 50, 100 and 200 R are available, there are indications that there may be an increase in the frequency of hyper-haploid and hypo-haploid eggs, but it is by no means as striking as it is in the case of chromatid aberrations.

392. In the Northern field vole, Microtus oeconomus, contradictory results have been obtained on the radiation-induction of sex-chromosomal aneuploidy in male meiotic stages: earlier experiments provided positive evidence while the later ones showed no significant induction (dose of up to 2 Gy); however, there is good evidence for the induction of diploidy and the cell stages sampled on days 4 and 9 after irradiation seem to be most sensitive in this respect.

D. POINT MUTATIONS

1. Specific-locus mutations in male mice: effects of ^{3}H and ^{239}Pu

393. In the 1977 report, the preliminary results of Cumming et al. [C36, C37] on the induction of specific locus mutations by tritiated water in the germ cells of male mice were presented. More complete results from this work have now become available [R31]. Briefly, (101 x C3H) F_1 wild type male mice were injected intraperitoneally with tritiated water (1.85 or 2.78 10^{-2} MBq per gram of body weight) and mated to females of the tester stock. The offspring were scored for presumed mutations at the seven loci and the presumed mutants were bred to establish allelism of the mutations and to determine the viability of the mutations in the homozygous condition. Both post-spermatogonial and spermatogonial stages were sampled. The weighted mean dose for the experiments with irradiated post-spermatogonial stages was calculated by estimating the accumulated dose for each succeeding day after HTO injection and weighting by the number of offspring conceived that day. For the experiments with irradiated spermatogonial stages, the weighting was by weekly, rather than daily, intervals. The data are presented in Table 27. These data permit an estimate of an induction rate of 4.4 10^{-7}/locus/10^{-2} Gy for post-spermatogonial stages and of 1.5 10^{-7}/locus/10^{-2} Gy for spermatogonia after correction for control rate (historical control: 28 mutations in 531 500 offspring).

394. An examination of the distribution of the mutations in the offspring (Table 28) shows the following features:

(a) For spermatogonial irradiation, the pattern is not significantly different from that which has been recorded for x- or gamma-irradiation where a low frequency has always been observed at the a and se loci;
(b) The mutations in the offspring from irradiation of post-spermatogonial stages appear to be more evenly distributed among the loci, a characteristic of those obtained in x-irradiation experiments involving these stages [R32];
(c) Although no deficiencies involving d and se loci simultaneously has been recorded in the present study (these are common after x-irradiation of post-spermatogonial stages [R32, R33]) there is other evidence for the association of some of the mutations with aberrations: three of the mutants were sterile and an s locus mutant listed as "untested" had a high frequency of sterility in her offspring;
(d) In the spermatogonial series, 10 out of the 18 tested mutants were viable in the homozygous condition and this proportion was 3 in 11 in the post-spermatogonial group.

Altogether, these data present no evidence for any striking disparity from the spectrum and properties of mutations recovered in x-irradiation experiments.

395. Russell et al. [R31] have estimated the RBE values for mutation induction by ^{3}H relating the mutation rates observed in the present work with those recorded in earlier investigations with x- or gamma-irradiation. For post-spermatogonial stages, the results of experiments with 300 R of x rays (90 R min^{-1}) was chosen as the standard although the dose rate in the ^{3}H study was much lower than the rate of 90 R min^{-1}. The justification for this is that the mutation rate in post-spermatogonial stages appears to be independent of dose rate or at least not markedly affected by it [R34]. The x-ray data (based on the progeny from the first two weeks of mating) yield a rate of 6.1 10^{-7}/locus/10^{-2} Gy (25 mutations in 18 693) after correction for controls [R35]. (The reason for using these data is that in the ^{3}H experiments 95% of the progeny were conceived in the first two weeks after injection.) The rate in the ^{3}H experiments namely 4.4 10^{-7}/locus/10^{-2} Gy divided by the rate cited above for x rays gives an RBE of 0.7 (after making a correction from R to Gy) for the induction of specific locus mutations in post-spermatogonial stages. With the limited number of mutations scored in the ^{3}H series, the above RBE values are not significantly different from 1.

396. For spermatogonial stages, as is well known, dose rate is very important [R34, R36]. In the ^{3}H experiment, the dose rate is relatively high in the first few days after injection as compared to what it is later, but even in the first half day, it probably does not average much more than about 0.001 Gy per minute. Consequently, the data most suitable for comparison are those obtained with gamma rays at 0.8 R min^{-1} and below. The recent calculations of Russell and Kelly [R77, R78] show that for all such data, the straight line of best fit is described by $Y = (8.04\ 10^{-6} \pm 1.19\ 10^{-6}) + (7.34\ 10^{-8} \pm 0.83\ 10^{-8})D$ in which Y is the mutation frequency per locus and D is the exposure in R. This result does not differ greatly from the regression formula $Y = (8.34\ 10^{-6}) + (0.659\ 10^{-7})D$ calculated by Searle [S69] who restricted his analysis to the data then available at exposure rates of 0.009 R per minute and lower. Dividing the rate obtained with ^{3}H ($1.5\ 10^{-7}$) by the rate for gamma rays estimated by Russell and Kelly (with correction for the change from R to Gy), one obtains an RBE value of 2

for ^{3}H relative to chronic gamma ray exposures of spermatogonia. Because of the limited number of mutations in the sample, uncertainty as to the number of independent events involved when clustering occurs, and some uncertainty as to the true doses, Russell et al. [R31] believe that it is unlikely that the RBE value of 2.0 differs significantly from 1. They, however, stress the point that "it would seem prudent at this time to assume that the RBE for exposure of stem cells in the testis to tritiated water might be approximately 2" and that this value might be used in the context of risk evaluations.

397. In the 1977 report, a review was made of the available data on the induction of dominant lethals [L33, S53] and cytogenetic damage [S53, B44] in male mice by ^{239}Pu. Experiments have been initiated in Oak Ridge [R37] to study the induction of specific locus mutations with this radioactive isotope. In this work (101 x C3H)F_1 male mice were injected intravenously with 0.37 MBq/kg body weight (~ 0.925 MBq/mouse) of monomeric ^{239}Pu citrate. Thirteen weeks after injection, the males were mated with untreated females of the tester strain and the offspring are being scored for mutations at the seven specific loci. Until now, 11 presumed mutations have been observed in 54 679 offspring. This is highly significantly above the control frequency.

2. Specific-locus mutations in female mice

398. In earlier work discussed in the 1977 report, Lyon and Phillips [L31] investigated the mutational response of maturing mouse oocytes to x-irradiation with a total dose of 2 Gy given in 20 fractions of 0.1 Gy each.[15] The offspring conceived within the first seven weeks (and later) after the last irradiation were scored for mutations at the seven loci of the PT stock. Appropriate controls with 2 Gy given acutely were run. The results showed that the yields with the fractionation regimes were lower than that after acute irradiation. Based on those data and earlier fractionation data of Russell [R39] Lyon and Phillips concluded that "... it seems reasonable to suppose that in our work, the effect of each 0.1 Gy dose was low, and equal to 1/20 of the observed effect of twenty such doses ... it seems probable that the effects per unit dose of a 0.1 Gy dose is indeed less than that of 0.5 Gy and hence the dose-response relationship is highly curved. There is a suggestion in Russell's data that the mutation rate per unit dose is still increasing at dose levels of 200 R to 400 R, but this needs further work". The experiments of Lyon et al. [L32] considered below were designed to examine the mutational response at relatively higher doses.

399. Adult female mice were given doses of 2, 4, or 6 Gy of x rays at 0.52 or 0.72 Gy min^{-1} and mated immediately. Offspring conceived in the first seven days (i.e., using oocytes which were mature at the time of treatment) were scored for specific locus mutations at the seven loci. The earlier data from their work at 2 Gy (acute irradiation; conceptions up to 10 days after treatment) were added to the results of 2 Gy in the present work; the control data were taken from Russell [R38].

400. The results are presented in Table 29. Statistical analysis was carried out by fitting the data to a linear model ($Y = c + bD$), a linear-quadratic model ($Y = c + aD + bD^2$) and to a square-law model ($Y = c + bD^2$). With the linear model, the values of slope varied from $(3.13 \pm 0.50)\ 10^{-6}$ to $(3.06 \pm 0.50)\ 10^{-6}$ depending on the control frequency, with the departure from linearity being marginally significant at the 5% level. With the linear-quadratic model, the values of a varied from $(0.42 \pm 1.05)10^{-6}$ to $(0.23 \pm 1.05)10^{-6}$ and those of b from $(6.22 \pm 2.60)10^{-9}$ to $(6.47 \pm 2.60)10^{-9}$ again depending on the control frequency assumed. The P values (from tests of goodness of fit) were from 0.49 to 0.50, showing that the fit of the data to the model was good. It may be noted that the linear term is not significantly different from zero. With the last model, the b values ranged from $(6.99 \pm 1.15)10^{-9}$ to $(7.19 \pm 1.15)10^{-9}$ and the P (goodness of fit) values, from 0.71 to 0.77 showing that the fit to this model is slightly better than that to the previous one.

401. The authors point out that the good fit of the data to the linear-quadratic or to the square-law models does not necessarily imply that these relationships give a good representation of the biological phenomena involved; that the observations are also amenable to interpretations based on dose-dependence of repair processes, as has been suggested earlier by Russell (see [R38] for a recent discussion); and that they prefer the interpretation based on the repair hypothesis. Their reasoning for the last conclusion is discussed in the next section.

402. Other useful information that was obtained in the study of Lyon et al. [L31] pertain to the distribution of the mutations among the different loci, their viability pattern, the induction of dominant or X-linked visible mutations and those with irregular inheritance. The spectrum of mutations resembled that found by Russell et al. [R40] and others [S69] in mouse spermatogonia in that approximately 50% occurred at the s locus, whereas mutations at the a and se loci were rare. There were no simultaneous d-se mutations (presumed to arise as deletions) although Russell [R33] had found such deletions to be common after irradiation of oocytes. The proportion of those which was lethal in the homozygous condition was 78%, in good agreement with that obtained by Russell et al. [R40] for spermatogonia and nearly all the s and d mutations were homozygous lethal. The dominant and X-linked visible mutations included 2 viable repeats of tabby (Ta), two lethal splotch (Sp) alleles and a lethal W allele. In addition there was a new X-linked mutation (broad-headed; Bhd) and two further mutations caused a light coat colour and/or spotting. Six additional mutants with irregular inheritance occurred and these had tail kinks, light coats, behavioural abnormalities and small size either together or in various combinations.

403. Selby et al. [S70] studied the mutational response of the oocyte stages in female mice shortly before birth. These mice were given 300 R of either x-irradiation at high exposure rate (93 R min^{-1}) or 300 R of gamma-irradiation at 0.8 R per minute. At maturity, the irradiated animals were mated to males of the tester stock to score for mutations at the seven specific loci. In the acute x-ray series, 3 mutations were recovered among 16 194 F_1 progeny; in the gamma-ray series, 1 mutation was found among 37 218 progeny. These results are therefore consistent with the existence of a marked dose-rate effect of the kind recorded for maturing oocytes and the possibility that the repair capacity of the oocytes in mice shortly before birth may not be different from that of maturing oocytes in adult female mice.

[15] 4 fractions of 0.1 Gy at 2-h intervals every day for 5 successive days or 20 daily fractions on 5 days of 4 weeks.

3. Nature of specific-locus mutations

(a) Dose-response kinetics and the nature of specific-locus mutations.

404. The 1977 report of the Committee considered in detail the arguments of Abrahamson and Wolff [24] which led these authors to conclude that:

(a) The dose-rate effect for low-LET irradiation found in specific-locus experiments with mouse spermatogonia and oocytes is a consequence of the fact that a large proportion of mutational events at high dose rates are two-track events;
(b) The relative contribution of one-track and two-track events to the mutational yield could be estimated (for oocytes this was done from data on acute x-irradiation at 50, 200 and 400 R and for spermatogonia, the linear component estimated from the available low dose rate data was used to estimate the magnitude of the two-track component after acute x-irradiation);
(c) The coefficients for one- and two-track components so obtained can be used to calculate expected frequencies of mutations in the other experiments;
(d) As the magnitude of the one-track component for oocytes is substantial (and since the oocyte data are used to predict genetic risks for irradiated human females) there is reason to consider that the earlier hazard evaluation (which assumed that the risk to human females from low-LET irradiation of mature and maturing oocytes at low doses or at low dose rates is only one-twentieth of that at high doses and dose rates) is too low and to revise it upwards.

405. In their recent paper on x-ray stage sensitivity of mouse oocytes, Brewen and Payne [B32] have drawn attention to the line of reasoning pursued by Abrahamson and Wolff discussed in the preceding paragraphs, in the interpretation of the mouse oocyte results. Brewen and Payne compared the yields of cytologically-scored chromosome deletions (observed in their study of oocytes irradiated in the intact animals and cultured in vitro with subsequent processing for chromosome aberration analysis) and specific-locus mutations (in Russell's studies). They found that, when appropriate corrections are made for changes in oocyte sensitivity with time after irradiation, both the data on deletions and specific-locus mutations gave good fits to a power law model of the form $Y = kD^n$ where the slope of the line (in a log-log plot) is a first approximation of the dose exponent, n. The exponent n approximated a value of 1.7 when the data were plotted by individual stages of sensitivity, i.e., week 1 for deletions and mutations, weeks 2 to 4 for deletions and weeks 2 to 6 for mutations. The data pooled over the entire time span tested, gave a slope of 1.7 for deletions over the entire exposure range studied; for mutations this was true from 50 to 200 R but between 200 and 400 R n was equal to 1.1 (for deletions too, if the analysis was restricted to week 1 data at the higher doses, the same phenomenon was observed, namely, a lower n).

406. On the basis of these analyses, Brewen and Payne stated "... the similarities in the variations in sensitivity of induction as a function of oocyte maturation and the dose-response characteristics, when this stage sensitivity is accounted for, of both structural chromosome aberrations and specific locus mutations lead us to conclude that they are produced by the same general mechanism following ionizing radiation ... We suggest that this mechanism involves, principally, the interaction of two independently induced lesions when low-LET radiation is employed and consequently follows approximate D^2 kinetics. This proposal does not require any more complicated hypotheses to explain the data and is in accord with other radiobiological theory ... this would explain the very low mutation yields following chronic or multiple small fractionated exposures ..."

407. However, ever since his first discovery of dose-rate effects in spermatogonia and oocytes, Russell [R38] has continued to favour the alternative hypothesis (on the basis of a number of further studies and a solid body of supporting data) that the mutations themselves are single-track phenomena and other track events are involved in damaging or saturating the repair processes at higher doses and dose rates; that the hypothesis that the dose-rate effects observed may be predominantly a consequence of repair of one-track mutational events also fits the data indicating that the dose response for low-LET radiations for induction of point mutations in mammalian cells is probably curvilinear (concave) at high, and linear at low dose rates; and that the approach used by Abrahamson and Wolff is not a reliable one for estimating hazards in man.

408. It may be recalled from subsection 2 that Lyon et al. [L32] consider that their oocyte specific-locus data are biologically more consistent with an interpretation based on repair mechanisms. Their arguments are that W.L. Russell [R38, R41] had shown that in young females, mutation rate varied with time after treatment. Weeks 2–6 were more sensitive than week 1, and from week 7 onwards, no mutagenic effects were obtained. The increased sensitivity of weeks 2–6 does not appear to occur at all doses. A similar variation with time after treatment is found for chromosome aberrations [B45, B46, C34] and dominant lethals [C34]: the frequency rises with time until sterility sets in, and, as with gene mutations, the amount of increase is dependent on radiation dose [C34]. Further there is another factor which had been shown to affect sensitivity of oocytes to mutagenesis, namely, the age of females at irradiation; Russell [R36, R41] found that old females gave a higher mutation rate than young females, particularly in second litters. Females irradiated on the day of birth or as 17.5 day old foetuses however gave a lower mutation rate than those irradiated when adult, but the mutations occurred at later (>7 weeks) intervals. Lastly, it is thus easy to see that all these different responses cannot be easily explained in terms of radiation hit kinetics.

409. Lyon et al. [L32] believe that the assumption of differing activities of compensating error-free and error-prone repair systems in oocytes such as those postulated to exist in microorganisms (see [K22] for a recent review) would provide ample ground for explaining the observed variations in mutability. First, the combination of sensitivity to cell killing and resistance to mutagenesis shown by small oocytes, resting in small follicles (up to stage 3a [P27]) and sampled later than seven weeks [O9] is consistent with the absence of error-prone repair. One may thus postulate that small oocytes are characterized by weak error-free and absent error-prone repair. Any potentially mutagenic insult would lead to death of these cells; such an absence of error-prone repair would protect the germ cells from excessive mutagenesis at the expense of increasing cell death. Second, in growing follicles sampled in weeks 2–6, repair enzymes (including error-prone systems) would be among the proteins becoming functional in the developing oocyte.

The finding of Pedersen and Mangia [P28] that UDS in response to UV treatment was higher in growing than in resting oocytes is in line with this reasoning. The ability of the oocytes to survive mutagenic insults would increase, but at the expense of an increase in mutagenic response. Finally, in the mature follicle, in which UDS is high [M46], error-free repair would become stronger so that resistance to both cell killing and mutagenesis would improve.

410. Lyon et al. [L32] suggest that the above model involving varying levels of error-free and inducible levels of error-free and error-prone repair, although admittedly speculative, would fit the data on mutagenesis in mouse oocytes well. It would also be possible to explain variation among species, or among strains within a species, in a similar way. The details of these phenomena however, remain to be elucidated.

(b) Further data from the analysis of the albino locus "c" region

411. In the 1977 report, some data of L.B. Russell et al. on the c (albino) locus mutations were presented. The study is now completed [R42, R43, R44, R79]. Altogether, 119 presumed mutations involving the c locus were recovered in more than two decades of work by W.L. Russell et al. on the radiation-induction of specific locus mutations in various germ cell stages and with different kinds of irradiations and regimes and these constituted the material for the study of L.B. Russell et al. Of these 107 were fully tested for allelism and for viability in the homozygous condition; of the remaining 12, one was tested for allelism only, four died before they were old enough to reproduce and 7 were not mated.

412. The 107 tested mutations may be subdivided on the basis of

(a) Viability in the homozygous condition (viable, subvital and neonatally or prenatally lethal, designated with v, s and l, respectively, as part of their superscript);
(b) Whether with respect to pigment phenotype in various combinations, they mimicked the "albino" allele (mutants designated with a as part of their superscript) or were intermediate between c and C (designated with ch or x as part of their superscript). Fifty five of the mutations were viable and albino (c^{av}), 13 were viable and of various intermediate pigment types (c^{xv}), 4 were subvital (c^{as} and c^{xs}), 7 neonatally lethal albinos (c^{al}) and 33 prenatally lethal albinos (c^{al}).

413. All the prenatally lethal and at least one of the neonatally lethal c locus mutations (c^{al}) classes are probably deficiencies. Since the absence of the locus mimics albino in phenotype, the intermediates are assumed to result from intragenic changes. There is evidence that the class of viable albino mutants are either intragenic changes or very small deficiencies.

414. The distribution of the major classes of the mutations are given in Table 30 from which it can be seen that:

(a) Among the x- or gamma-ray-induced mutations, 34 of the 51 induced in spermatogonia (67%) are homozygous viable; this frequency is slightly lower for neutron-induced c locus mutations (9 out of 15);
(b) The total number of mutations that were available from other cell stages is relatively small;
(c) The proportion of the mutations that are lethal homozygously is of the order of about 30% for those recovered after spermatogonial irradiation (x- or gamma- or neutron-irradiation); for other cell stages, the overall proportion of lethals is almost twice as high (58%; 14/24);
(d) The proportion of intermediate types among the 34 non-lethal, non-mosaic c locus mutations recovered from irradiated spermatogonia (x- or gamma-irradiation) is 26%, which is nearly the same as that among spontaneous mutations (28%); none of the 9 whole-body non-lethals derived from the neutron-irradiated spermatogonial group was of the intermediate type. It would thus appear that low-LET irradiation of spermatogonia increases the absolute frequency of viable c locus mutations without changing the spectrum from that of spontaneous ones;
(e) The proportion of homozygous viables is highest for the spontaneous c locus mutations.

Not shown in Table 30 is the finding that there was no significant dose rate effect on the relative proportions of c locus mutations that were homozygous lethal. L.B. Russell et al. [R42] consider that these findings support the view that most of the c locus mutations induced in spermatogonia even by high dose rate x- or gamma-irradiations are of a type most likely to result from single-track events (62% c^{xv}, c^{xs} and c^{av} plus 16% presumed deficiencies not involving the closest marker) and that most of the reduction in mutation frequency at low dose rates is not due to a change in relative proportion of two-track and one-track ionizing events.

415. Turning now to fractional c locus mutations, 16 of them were recovered among the total of 119 [R43]. These 16 mutations were distributed evenly among controls and irradiated groups, suggesting that the fractionals observed are all presumably spontaneous in origin. (At the c locus, the bulk of spontaneous mutations have been fractionals.) The overall progeny ratios from the fractional mutants indicated that the mutations could have occurred in one strand of the gamete DNA, in a daughter chromatid derived from pronuclear DNA synthesis, or in one of the first two blastomeres prior to replication.

416. The stage at which homozygotes die was determined for 28 c locus mutations of which 26 had earlier been found to be probably prenatally lethal [R45]. Uterine dissection experiments involving 796 dissected females and 7615 corpora lutea [R44] indicate that the prenatally lethal mutants die either around early preimplantation (13 mutants) or around the time of implantation (13 mutants). None of the c locus mutations kills between the latter time and the time around birth, when the neonatal lethals (7 mutants) die.

4. Autosomal recessive lethals in male mice

417. The primary aim of the work of Lüning et al. [L18] described earlier in the section on dominant lethals was to assess the effectiveness of acute and chronic irradiation with 14.5 MeV neutrons in inducing autosomal recessive lethals in mouse spermatogonia. Adult CBA male mice were irradiated with 1.5 or 2.5 Gy (acute) or 2.5 Gy (chronic: about 7 10^{-3} Gy h^{-1}, 8 hours a day for 5 days a week through 11 weeks). The two important findings from this study are that:

(a) There is no measurable difference in the rate of induction of autosomal recessive lethals in mouse spermatogonia between neutrons delivered acutely or chronically;
(b) The rate of induction is about 2 $10^{-4}/10^{-2}$ Gy/gamete, 14.5 MeV neutrons being about twice as effective as acute x rays.

5. Sex-linked recessive lethals in male mice and rats

418. In the 1977 report, the details of an X-chromosome inversion In(X)1H described by Evans and Phillips [E12] were given. This inversion covers about 85% of the physical length of the X chromosome and, therefore, covers slightly over 5% of the mouse genome. Lyon, Phillips and Fisher [L50] have now reported on the use of this inversion to study the x-ray induction of X-linked recessive lethals in spermatogonia. Males were irradiated as young adults with a fractionated dose of 5 + 5 Gy of x rays (0.9 Gy min^{-1}) with a 24 h interval. It was found that 2/536 irradiated and 0/529 control X chromosomes carried a confirmed lethal. These frequencies correspond to a rate of induction of 1.9 10^{-6} per 10^{-2} Gy per X chromosome for single exposures (allowing for the enhancing effect of fractionation). The results are considered as fully consistent with previous experiments in which X-linked lethals were not detected and indicate the value of using inversions for this work and the need for large-scale experiments. The results are also consistent with those on the induction of autosomal recessive lethals although there were indications that some X-linked lethals may be eliminated in the heterozygous state.

419. Chambers and Chapman [C29] have recently reported on the rate of induction of sex-linked recessive lethals in rat spermatogonia. The total x-ray exposure was 450 R given in three fractions of 100, 150 and 200 R at 10, 12 and 14 weeks of age, respectively. The data used for estimating the rate of sex-linked recessive lethals were those on litter size on day 1 and on day 21. The rates arrived at in their two dose groups are 1.1 10^{-4} and 2.1 10^{-4}/X chromosome/R and in good agreement with the earlier estimate of 1.6 10^{-4}/X chromosome/R by Taylor and Chapman [T13].

6. Autosomal recessive lethals in female mice

420. Lüning and Eiche [L34] have collected data on the induction of autosomal recessive lethals in maturing oocytes of mice of their CBA strain. The procedures and test schemes were essentially those used earlier in connection with work on the determination of radiation-induced autosomal recessive lethals in spermatogonia [L36, L37]. The x-ray exposure was 250 R to sexually mature females; the irradiated females were mated to males immediately after irradiation and were allowed to produce one or two litters conceived during the first six weeks following irradiation. The data are consistent with a rate of induction of 1.3 10^{-4}/R/gamete by one method of calculation [H58] or of 0.8 to 1.2 10^{-4}/ R/gamete by another method [L35]. In any case it is clear that these estimates are about the same as that arrived at for spermatogonia [L47].

421. In other experiments with irradiation of female foetuses [L34] (x-irradiation of pregnant females with a fractionated exposure: 25 R d^{-1} for four days from day 10 to day 13 of pregnancy plus 50 R d^{-1} for a further four days from day 15 through day 18; total accumulated exposure: 300 R) it was found that the mortality in the F_2 crosses was no higher than in controls. This suggests that the germ cells of female foetuses may not be more sensitive than maturing oocytes of adult females and that the risk from foetal exposure is no higher than that from adult exposures.

422. Rönnbäck and Sheridan [R46] irradiated female CBA mice chronically with ^{137}Cs gamma rays in utero during either of two periods, the 10th to 14th days of gestation or 14th to 18th days of gestation. The doses administered were 0.34 Gy/generation in the first group and 1.6 Gy/generation in the second group. The dose rates were 3 10^{-3} Gy h^{-1} in the first and 1.7 10^{-2} Gy h^{-1} in the second group. The irradiation exposures were administered through nine generations and at the end, the female progeny were tested for the induction of autosomal recessive lethals. The data obtained are consistent with rates of induction of 1.5 $10^{-4}/10^{-2}$ Gy/gamete (in the group that received 0.34 Gy/generation during days 10–14) and 0.3 $10^{-4}/10^{-2}$ Gy/gamete in the group that received 1.6 Gy per generation during days 14–18. The rate of 1.5 10^{-4} is in accordance with that reported by Rönnbäck [R47], i.e., 6.3 $10^{-4}/10^{-2}$ Gy/gamete (with a range of 0.7 to 11.8 10^{-4}: 95% confidence limits) after a single chronic gamma irradiation exposure of female foetuses (1.6 Gy) during the 10th to 14th days of gestation.

7. Biochemical mutations detected by electrophoresis

423. In the 1977 report, data on the induction of mutations in mouse spermatogonia, using nine electrophoretically detectable markers [M47] and haemoglobin loci [R48] were discussed. Narayanan et al. [N14] has now obtained some data in a spermatogonial irradiation experiment in which biochemical mutations at 20 loci were studied. Adult C3H males were irradiated with ^{137}Cs gamma rays (100 + 500 R, separated by a 24 h interval) and mated to females of the 101 strain. Liver biopsy was performed on the offspring in order to screen for biochemical variants. Liver extracts were then submitted to isoelectric focusing on polyacrylamide gels, an electrophoretic method that is capable of separating proteins from one another differing in as little as 0.01 pH unit in their isoelectric points. Among 2100 F_1 animals so far screened, three isoenzyme variants (two esterase and one lactic dehydrogenase variants) were recovered. In the controls, two esterase variants were found among 12 800 animals. A puzzling feature of the variants recovered in this work is that they were not transmitted beyond the F_1.

424. In another study, Pretsch [P40] used a thin-layer-chromatographic method to detect the induction of mutations causing hyperaminoacidemias. Adult C3H males or (101 × C3H)F_1 males were given 100 + 500 R of ^{137}Cs gamma-irradiation (24 h interval) and mated to females of the 101 or T strain, respectively. Both pre- and post-meiotic stages were sampled. The blood from the F_1 animals was used for chromatography. No mutants, however, could be detected in a sample of 5786 animals.

8. Dominant mutations

425. In the 1977 report, the unpublished results of Selby and Selby on the induction of mutations causing dominant effects in the skeleton of the mouse were described. These data and discussions about their

relevance for hazard evaluations have now been published [E16, E17, E18, R49, S71, S72, S73, S74, S75, S117]. In this work, adult male mice received a fractionated gamma-irradiation exposure (100 + 500 R, separated by 24 h; 60 R min^{-1}) and were mated with untreated females. The F_1 sons conceived during the post-sterile period were processed for examination of their skeletons after they were allowed to produce progeny. Thirty seven of the 2646 F_1 males were judged to have dominant mutations that caused one or more rare skeletal abnormalities; 31 of these were shown to be mutants by breeding tests and the remaining 6, having no progeny, were counted as mutants based only on criteria supported by the data.

426. In breeding tests, the authors found that the dominant mutations affecting the skeleton showed variable expressivity and incomplete penetrance for many or all of the effects that they caused. A number of them severely affected viability. With the experimental procedure used, both incomplete penetrance and decreased viability would have caused an underestimate of the mutation rate. Thus, some F_1s actually having a mutation might not show it because of low penetrance, some mutant F_1s having defective skeletons might not be classified as mutants if penetrance were too low to permit proof of transmissibility, and mutants that died before examination would not be counted. Note, however, that the first of these three cases does not lead to any underestimation of first generation genetic damage.

427. In order to know if some of the skeletal mutations might actually be gross chromosomal changes such as reciprocal translocations or aneuploids, cytogenetic examination of the testes of mutation-bearing males was carried out on 9 of the skeletal mutants (6 of which were proved mutants and 3 of which were counted as mutants on the basis of presumed-mutation criteria), 2 non-skeletal mutants and one sterile F_1. These were chosen for cytogenetic examination because they were either sterile or had partial sterility. Mutant numbers 1268, 2490 and 2691 were all found to be balanced reciprocal translocation heterozygotes; a heterozygote for a non-skeletal mutation (a belly-spot; mutant number 2971) which was partially sterile was also found to be a translocation carrier [S72]. Subsequent breeding tests involving mutant numbers 1268, 2691 and another mutant (number 1163) revealed that every mouse that had the reciprocal translocation had the skeletal defects and conversely, every one that did not have the translocation did not have skeletal defects. It thus appears that at least for these mutations, the association between the presence of a balanced reciprocal translocation and skeletal defects is strong and suggests that some of the balanced reciprocal translocations are in fact associated with dominant phenotypic effects.

428. In further experiments [S75] Selby tested eight other skeletal mutations for effects in homozygous condition. It was found that all of them were lethal as homozygotes; for seven of them, death occurred after implantation and before birth, and for the remaining one, 10 days after birth. Thus, at least in this limited sample, the majority of mutations having dominant effects on the skeleton in heterozygous carriers also act as recessive lethals. The follow-up experiment in which males known to be heterozygous for a skeletal mutation (mutant number 1629) were mated to normal (+/+) females, showed that the intra-uterine death rate was higher than what would have been expected on the basis that the mutation had no heterozygous effects on dominant lethality. From these results and other considerations, Selby has concluded that recessive lethals often have dominant harmful effects.

429. In addition to the skeletal system discussed above, there is one other system that has already been shown to be useful in studies on the induction of dominant mutations. This concerns dominant mutations causing cataracts in the eye of the mouse. The fact that cataracts can be caused by dominant mutations in mammals (including humans) is known [E19, M16, P30, W21, W27]. The experiments of Ehling and colleagues [E13, E20, E21, E24, K23, K24, K42] have validated the usefulness of the cataract system for both radiation and chemical mutagenesis studies. The paper of Ehling [E24] is the most recent on this subject. The radiation work of these authors consists of three experiments, one involving a total exposure of 910 R given in two equal fractions separated by a 24 h interval and the other two involving single exposures of 534 R and 600 R, respectively. In all experiments, adult (101 × C3H)F_1 male mice were gamma-irradiated at a rate of 53–55 R per minute and mated to females of the seven-locus tester stock (to score, in the same experiment, for specific locus mutations) and the eyes of the F_1 progeny at about 3 weeks of age were examined biomicroscopically with the aid of a slit lamp to detect lens opacities. All the presumed mutants were progeny-tested to confirm the genetic nature of the lens opacity phenotype. Specific locus mutations were scored using standard procedures.

430. The data are summarized in Table 31a which shows that the mutation rate for post-spermatogonial stages is higher than for spermatogonia and that exposure fractionation has an augmenting effect on mutation frequency. These responses have long been known from specific locus work and the present work has demonstrated that similar responses are obtained with cataract mutations. The mutation rate estimates that can be derived from these data are: 0.45–0.55 mutation per 10^6 gametes per R for single high dose rate gamma ray exposures and 1.26 mutations per 10^6 gametes per R for the particular fractionation regime used.

431. Small lens opacities frequently occurred in the offspring of the experimental as well as control groups (opacities of the anterior embryonic suture, opacities of the posterior embryonic suture, small white patches differing in form and location and remnants of the pupillary membrane). The total frequency of offspring with any small lens abnormality was 10% in the control group and 11% in the experimental group. Breeding tests of approximately 300 carriers provided the evidence that these small lens abnormalities are not caused by single dominant genes [K42]. These abnormalities were therefore excluded from the data presented in Table 31a.

432. The properties of the transmissible radiation-induced dominant cataract mutations are given in Table 31b. It can be seen that apart from two mutants which were sterile, the remainder were fertile. The penetrance and expressivity properties of these mutants are similar to those affecting the skeleton.

433. When one compares the overall frequencies of induced cataract and specific locus mutations (columns 4 and 7, respectively, in Table 31a), it is clear that the recessives outnumber the dominants by a factor of

about 2.5 for spermatogonial and 2.7 for post-spermatogonial irradiation. In humans, 20 well-established dominant cataract mutations are currently known [M16]. If the number of loci at which dominant cataract mutations can arise in the mouse is the same as in humans, then one is scoring for events at 20 loci as far as dominant cataract mutations are concerned, compared to events at 7 loci scored in the specific locus experiments (a factor of 3). Thus, on a per locus basis, radiation induces approximately 8 times (i.e. 2.5–2.7 × 3 ≈ 8) more recessive visible mutations than cataract mutations [E24].

9. Histocompatibility mutations

434. In the 1977 report, the studies of Kohn and colleagues on the induction of histocompatibility (H) mutations in mouse spermatogonia were described. As is well known, the H-system in mammals comprises a group of co-dominant genes located throughout the genome, and their action (production of cell membrane alloantigens) determines the acceptance or rejection of dermal grafts. For operational reasons, the H-loci in mice are divided into two classes distinguished from one another in the F_1 hybrids of the B6 and C lines that are used. The class-I loci, at least 30 in number [B73], have different alleles in the parental lines and are therefore heterozygous in the F_1 hybrid. The class-II loci have similar alleles in the parental lines and are therefore homozygous in the hybrid; the number of class-II loci is unkown, but a conservative estimate is of the order of about 50 loci [G42].

435. The procedure to detect new mutations is to exchange tail skin grafts orthotopically between F_1 hybrid mice (derived from mutagenized germ cells) from the two strains mentioned above and classify the progeny as resulting from "gain" type mutations (appearance of a new antigenic specificity, i.e., grafts donated by the putative mutant rejected) or "loss" type mutations (loss of specificity i.e., grafts placed on the putative mutant rejected) or "gain-loss" type of mutations (one specificity replaced by another). Class-I mutations are distinguished from class-II by their "loss" or "gain-and-loss" phenotypes for loci on autosomes and X chromosomes; class-II mutations could produce only "gains" unless the Y chromosome is involved (see [K38] for detailed description of the methods).

436. The earlier results of Kohn et al. [K38, K39] showed that there was no evidence for the recovery of x-ray induced histocompatibility mutations (spermatogonial irradiations). This result was attributed by the authors, not to the failure of the system to detect mutations, but rather to the very low mutability of these loci (relative to the seven or six specific loci that have been used in radiation studies with mice). They surmised that this could happen if the x-ray induced H-mutational lesions failed to result in viable progeny (see also [K40]).

437. In a further study, Dunn and Kohn [D23] tested for the induction of H-mutations in post-meiotic male germ cell stages. The doses used were 3.5, 6.5 or 3.5 + 3.0 Gy with a 24-h interval. Altogether 8 H-mutations were found in nearly 3000 progeny (including 1101 control progeny). Two of them were clusters and therefore could not have occurred in sperm; one class-I mutation was not relevant because it occurred in the B6 genome of the unirradiated mother. Of the relevant five, two were class-I losses (1 from the 6.5 Gy group; 1/565; the other was in the 3.5 + 3.0 Gy group; 1/514) and the remaining three were class-II mutations of the "gain" type: one on the control (1/1101), one in the 3.5 Gy group (1/809) and one in the 3.5 + 3.0 Gy group (1/514).

438. A comparison of these results with those for specific locus mutations in post-meiotic male germ cells and with spermatogonial mutation rate for the H-loci clearly indicates that in the first comparison, the rate for the class-I H-loci is only about 1/9 of the specific-locus rate; in the second comparison, the two rates do not significantly differ from one another. At face value, the spermatogonial rate for the H-loci is only about 1/60 of that for specific-locus mutations. In any case, the very low radiation-induced mutability appears to be a general property of these loci, one which does not depend on germ cell stage.

10. Induction of congenital anomalies and tumours by irradiation of mouse germ cells

439. Recently, Nomura [N23] published a paper in which he demonstrated that congenital anomalies and tumours could be detected in the progeny of irradiated mice and has thus identified a potentially useful model system for the study of these effects following irradiation of germ cells. Mature male or female mice (63–65 days old) were x-irradiated with doses in the range from 0.36 to 5.0 Gy and mated to unirradiated animals. Living foetuses on day 19 and offspring surviving more than 7 days after birth were examined for the incidence of congenital anomalies. (The germ cell stages sampled are not specified.) The results are summarized in Table 32.

440. It can be seen that there is a significant induction of congenital anomalies following germ cell irradiation and that the frequencies decrease (relative to those obtained in living foetuses) in live-born progeny. This is due to the fact that some anomalies (cleft palate, exencephalus etc.) are lethal shortly after birth. Since the data are presented as frequencies pooled over all radiation doses employed, no conclusions can be made with respect to whether there are dose-effect relationships or whether certain specific kinds of anomalies predominate at lower versus higher doses.

441. In the other part of the study dealing with tumours, the progeny of exposed parents (same doses as in the congenital anomalies part of the study) derived from irradiated spermatozoa, spermatids, spermatogonia and maturing oocytes were screened for the presence of tumours in their internal organs. The total yields of tumours in the offspring for all male germ cell stages sampled were significantly higher than in controls. Tumour incidence and lung tumour frequency were slightly higher when x-irradiation was administered 8–14 days before mating than at other intervals. Exposure of oocytes in early follicular stages (8–21 days before ovulation) induced significant yields of tumours while mature oocytes (1–7 days before ovulation) were resistant to 2.16 Gy of irradiation. When the dose was fractionated (2 equal fractions separated by 24 hours), increased yields (relative to single doses) were found for irradiated spermatogonia and mature oocytes, but not for spermatozoa and spermatids.

442. Kirk and Lyon [K43] have now confirmed Nomura's findings with respect to the induction of

congenital anomalies in the offspring of exposed female mice. These were irradiated with 1.08 to 5.04 Gy acute x irradiation and mated at intervals of 1–7, 8–14, 15–21 and 22–28 days, with uterine examination in late pregnancy to detect early foetal deaths (dominant lethality) and late malformations. At each weekly interval, the incidence of abnormalities (with dwarfism and exencephaly the commonest types) tended to rise with increasing dose, and at any given dose the incidence tended to rise with time after irradiation. Changes in incidence of dominant lethals and of abnormal foetuses paralleled each other closely, with highest incidences in week 3 ((59 ± 5)% for dominant lethals and (12.5 ± 3.1)% for abnormal foetuses after 5.04 Gy). This increased radiosensitivity of less mature oocytes is similar to that reported previously for other genetic effects.

11. Summary and conclusions

443. Subsequent to the publication of the 1977 report, more data have been obtained on the induction of specific-locus mutations in the germ cell stages of male mice by tritium (given as tritiated water by i.p. injections). The data permit an estimate of induction rate of 4.4 10^{-7}/locus/10^{-2} Gy of beta-irradiation for post-spermatogonial stages and of 1.5 10^{-7}/locus/10^{-2} Gy for spermatogonia. The RBE estimate (relative to high dose rate x- or gamma-irradiation) for post-meiotic germ cells is not significantly different from unity. For spermatogonia, the RBE value (relative to chronic gamma rays) is about 2.2 although this value may not be significantly different from 1.

444. An examination of the distribution of the mutants among the seven loci reveals that the pattern is not significantly different from that recorded for x- or gamma-irradiation for spermatogonial mutants; the mutants obtained from irradiation of post-meiotic germ cells are more evenly distributed among the loci, a characteristic of those obtained in x-irradiation experiments involving these stages.

445. The preliminary results obtained in studies with ^{239}Pu show that this radioactive isotope is capable of inducing specific-locus mutations in spermatogonia.

446. Further data have been obtained by Lyon and colleagues on the x-ray induction of specific locus mutations in maturing mouse oocytes at dose levels of 2, 4 and 6 Gy. When these data were analysed statistically, it was found that they fitted all three models tried (linear, linear-quadratic, power-law model) although the linear-quadratic and power-law models gave slightly better fits. It has been pointed out that the good fit of the data to the linear-quadratic and power-law models does not necessarily imply that these relationships adequately reflect the biological phenomena involved. Lyon and colleagues have expanded on the repair model originally proposed by W.L. Russell to explain these results.

447. The frequencies of specific locus mutations recovered from irradiation of oocyte stages in female mice shortly before birth at a low exposure rate of 0.8 R min^{-1} (gamma rays: 300 R) were significantly below those obtained after the same exposure given at a high exposure rate (93 R min^{-1}); this observation suggests that the repair capacity in these oocyte stages may not be very different from that in oocytes of adult female mice.

448. Further data on the nature of mutations induced by ionizing radiation in mouse germ cells have been published pertaining to the analysis of the mutations recovered at the c (albino) locus in different radiation experiments. These show that for spermatogonial irradiation, nearly two-thirds of the x- or gamma-ray induced mutations are homozygous viable. The proportion is slightly lower for neutron-induced c locus mutations. Most of the lethal mutations are probably deficiencies. Since the absence of the locus mimics albino phenotype, the intermediate types (with respect to pigment phenotype) which were recovered are assumed to result from intragenic changes. The proportion of intermediate types among the 34 non-lethal, non-mosaic c locus mutations recovered from irradiated spermatogonia (x- or gamma-irradiation) is nearly the same as that among spontaneous mutations (26% and 28%, respectively). The viable albinos (as well as the intermediate types) are concluded to result from one-track events. There was no dose rate effect in the relative proportion of c-locus mutations that were lethal.

449. The 14.5 MeV neutrons are about twice as effective as acute x rays in inducing autosomal recessive lethals in mouse spermatogonia. At dose levels of 1.5 or 2 Gy, there is no dose rate effect for the induction of recessive lethals.

450. The rate of induction of autosomal recessive lethals in mature mouse oocytes after x-irradiation (high dose rate) is about the same as that recorded for spermatogonia; the germ cells in female foetuses (fractionated irradiation from day 10 through day 18 of pregnancy) do not appear to be more sensitive than maturing oocytes in adults.

451. Further studies with the skeletal mutations in mice have shown that some of the skeletal mutations may be associated with balanced reciprocal translocations; put in another way, some of the balanced reciprocal translocations are associated with dominant phenotypic effects. Other data on skeletal mutations show that all the eight tested were lethal in the homozygous condition.

452. New data have become available from studies on the induction of another kind of dominant mutation, namely, those that cause cataracts in the eye of the mouse. The induced cataract mutations are qualitatively similar to those affecting the skeleton in terms of dominance, penetrance and expressivity.

453. New data on the induction of histocompatibility mutations in post-meiotic male germ cell stages of the mouse show that the rate of induction by x-irradiation is much lower than that for recessive specific locus mutations; these data and those on irradiation of spermatogonial stages (in these stages too, the rate is much lower than that for specific locus mutations) confirm the view that the H-loci in general are much less mutable than the specific loci at which mutation induction has been extensively studied.

454. The studies of Nomura have shown that congenital anomalies and tumours can be recovered in the progeny of irradiated male and female mice. It thus appears that the mouse can serve as a useful model for the study of these kinds of effects following irradiation of germ cells.

E. GENETIC EFFECTS OF INTERNAL EMITTERS

455. In earlier reports of the Committee as well as in this Annex, data an the induction of genetic (and some other biological) effects by incorporated radioactive isotopes have been dealt with. The purpose of this section is to present a broad synthesis of all this information (for a recent review, see [S76]).

456. Studies on the genetic effects of incorporated radioactive isotopes present some special problems which are not encountered in other branches of radiation genetics and which, in many ways, are very similar to those encountered in chemical mutagenesis. Thus, for working with radioactive isotopes it is important to know the extent to which the nuclide actually reaches the gonads and how long it remains there, as well as its actual relationship to the germ cells themselves. Except with internal gamma-emitters, track-lengths are usually too short to allow the germ cells to be affected by any extra-gonadal material. Sometimes, the nuclide can become incorporated into the hereditary material itself and then its exact position and what chemical changes follow its decay may affect the likelihood of a mutational event after the transmutational one. These and other complex phenomena associated with the disintegration of a radioactive material mean that its actual effectiveness in mutation induction will not be determined solely by the characteristics of the emitted radiation.

457. Table 33 gives details about some internally deposited radionuclides of special genetic interest. Three of the β-emitters included are of obvious interest because they can be incorporated into DNA. The penetrating gamma radiation from ^{137}Cs will reach the gonads from anywhere in the body, but β-radiation from gonadally deposited material is of importance as well. The three alpha emitters are known to reach soft tissues (including gonads) after being taken into the body and to be retained there for long periods [I4, R51]. Environmental contamination from these three radionuclides arises in various nuclear operations, such as mining and milling and fuel processing, while it has been estimated that thermonuclear reactors would produce 105 times as much tritium per megawatt as fission reactors [S77].

458. A summary of some of the main results obtained with different radioactive isotopes studied in mammals is given in Table 34. It is clear that the work done so far in this area is relatively meagre and diffuse but it has already exposed some intriguing aspects of biological response. For instance, there is the apparent high cytogenetic sensitivity of rat spermatogonia to low doses of certain β-emitters [B47], the later intra-uterine deaths after ^{239}Pu alpha exposures which continued into the next generation [L33] and the declining translocation yield with prolonged exposures of male mice to ^{239}Pu despite high retention [B44, G23]. All these and other problems need more detailed studies.

F. OTHER RELEVANT DATA

1. Biological effects in mice and rabbits kept in an area of high natural radioactivity

459. Léonard et al. [L21] have reported on their observations of biological effects in male mice and rabbits artificially kept in area near Lodève in South-western France. Exceptionally high concentrations of uranium (of the order of 1% and sometimes up to 7–8%) are found at certain sites, giving rise to a very high natural radioactivity. Correspondingly high concentrations of radon occur in the atmosphere. At a site where the dose rate amounts to about $8\ 10^{-5}$ Gy h^{-1}, a rabbit hut was built and cages with laboratory rabbits were placed on its floor. Gamma-ray dose was determined by placing individual lithium fluoride dosimeters around the neck of each rabbit. Air samples inside the hut were taken in spring and autumn for the determination of ^{222}Rn. The rabbits were kept in the hut for a period of 12 months, and blood samples were taken at 4-month intervals to study chromosome aberrations in lymphocytes. Control animals were kept in a nearby site with very much lower level background radiation, as well as in the laboratory.

460. Male mice of the BALB/c strain were also placed in the hut during summer; they could not be maintained for longer periods owing to their sensitivity to climatic variations. Control mice were kept in the same hut as control rabbits. The effects studied included those on fertility and the induction of heritable chromosome aberrations.

461. The external gamma radiation dose received by individual rabbits varied between 0.13 and 0.26 Gy after 120 days, 0.15 to 0.53 Gy after 240 days and 0.21 to 0.71 Gy after 360 days. The concentration of radon in the rabbit hut was ~ 5 kBq l^{-1} in autumn and ~ 90 Bq l^{-1} in the spring. It was estimated that at these radon concentrations, an annual dose of about 5–10 Gy would have been delivered to the bronchial region, the doses to other tissues being much smaller (e.g., gonads: annual dose of about $8\ 10^{-3}$ to $1\ 10^{-2}$ Gy). In mice, the total accumulated gamma dose was estimated to be 0.14 Gy for the 3-month period.

462. The cytogenetic observations on rabbit lymphocytes showed that in those cells sampled prior to radiation exposure, the only aberrations noted were chromatid and chromosome gaps and chromosome fragments and this was true of controls as well. After the exposure, in addition to these aberrations, dicentrics were found; the total frequency of abnormal cells rose to 1.90% by four months, 2.63% by eight months and 3.9% by one year (the control value was one-third of the last mentioned figure after one year). In the mice in which both the irradiated males and their F_1 sons were studied cytologically for the presence of translocations or other aberrations in their spermatocytes, none were found.

463. In a subsequent paper, Léonard et al. [L22] extended these observations to a further eight months for rabbits and also conducted further studies with mice. In rabbits, the lymphocytes of which were sampled at 16 months, difficulties were encountered to stimulate the lymphocytes to divide and the aberration frequencies became very variable between the different animals. In general these frequencies did not exceed the level observed after 12 months and in fact showed a reduction. By 20 months, there were practically no aberrations (1000 cells from 7 animals). Male mice kept in the radiation area for three months showed slight increases in litter size, the mean number of offspring sired and in the mean number of offspring weaned over a 6-month period (estimated external dose: 0.15 Gy). Female mice, whose biological response was also studied, however, showed slight reduction in the mean number of litters, mean number of offspring sired and in the mean number of offspring weaned. Model experi-

ments with radon exposure of laboratory rabbits under controlled conditions (to concentrations that were roughly five times the total exposure of the rabbits maintained in Lodève for eight months) showed no chromosome aberrations, suggesting that the chromosome aberrations observed in the earlier study were probably not due to radon exposure but essentially to gamma irradiation.

2. Further data on the relationship between chromosome arm number and relative radiosensitivity in different mammalian species

464. It may be recalled that in the 1977 report, the "arm number hypothesis" proposed by Brewen et al. [B39] and the data collected by other authors to further examine the validity of the hypothesis were discussed (see also [S64]). It was concluded that the arm number relationship (i.e., the linear relationship between the yield of dicentrics and the effective chromosome arm number after low-LET irradiation) was not adequately documented to be used at present to predict from lymphocyte data of one species the expected frequencies of dicentrics in lymphocytes of another, or to estimate the frequencies of reciprocal translocations in spermatocytes of one species from those of another. Furthermore, the two-fold higher sensitivity of human lymphocytes to the induction of dicentrics (relative to the mouse) could not be confirmed.

465. Subsequent to the publication of the 1977 report, some new data have become available. Considering first the comparison of the sensitivities of human and mouse lymphocytes to the induction of dicentrics, the earlier data of Brewen et al. [B39] had been collected using culture times of 60–63 h for the mouse and 54 h for human lymphocytes. The work of de Boer et al. [B40] demonstrated that, in the above investigation, the frequencies of dicentrics scored in mouse lymphocytes were based on cells that were both in the first and second division after irradiation; when a 36 h culture time was used (scoring only first division cells), the frequencies of dicentrics were nearly the same as those in human lymphocytes and this was true after 1 Gy as well as after 2 Gy of x rays, i.e., there was no relationship between chromosome arm number and relative radiosensitivity to the induction of dicentrics (mouse: 40 chromosome arms; man: 81 chromosome arms).

466. Preston and Brewen [P26] re-examined the above problem by studying the frequencies of induced dicentrics using different fixation times (42 and 48 h for human and 36 and 48 h for the mouse lymphocytes) and a range of exposures (25–250 R). It was found that:

(a) For human lymphocytes, the dicentric yields with the 42 h fixation time were higher for two donors while these were nearly the same as those from a different donor the lymphocytes of whom were fixed at 48 h;
(b) When the yields at the later fixation times were corrected appropriately by assuming that a cell containing a dicentric without an accompanying acentric fragment was at its second mitosis after treatment, the yields at the 42 h fixation time was still higher; this suggested to the authors that the increased yield at the earlier fixation time was not entirely due to the fact that only the first division cells were being analysed;
(c) In mouse lymphocytes, the dicentric yields were higher at the earlier (36 h fixation time) than at the later one (48 h); when corrections similar to those carried out for human lymphocytes were made for second division cells, again the frequencies were still higher at the 36 h than at the 48 h fixation time;
(d) Considering all data together, it appeared that the dicentric yields in human lymphocytes were from 1.5 to 2 times higher than in those of the mouse, thus substantiating their earlier contention.

467. A further repeat of this work by Van Buul and Natarajan [B74] with blood from 8 different human donors, x-ray doses of 1 or 2 Gy, fixation times of 42 and 48 hours in two experiments and several fixation times (40–60 hours) and FPG-staining in another, demonstrated that the "mixing-up" of first and second cell cycle at later sampling times cannot explain the observed variation in the frequencies of chromosome aberrations, but that donor-donor variation is a predominant factor influencing aberration yields. In fact, the condition of the donor seemed to be most important since repeats on the same donor showed marked variability in sensitivity. Whether the inter-donor variations are due to different proportions of sub-populations of lymphocytes with different radiosensitivities could not be answered. Confirmatory results showing that the frequencies of radiation-induced dicentrics were nearly the same at different fixation times when corrected for cells in their second and third mitoses were also obtained by Léonard and Decat [L26] and Scott and Lyons [S116]. In using blood from four different donors, the latter authors noted that in one donor, the frequencies of radiation-induced dicentrics were significantly different between two experiments.

468. In the study of de Boer et al. [B40] dealing with radiosensitivity of mouse and human lymphocytes to the induction of chromosome aberrations considered earlier, some results on the induction of dicentrics in lymphocytes of normal mice, mice heterozygous for a translocation between chromosomes 1 and 13, tertiary trisomic mice carrying the same translocated chromosome and either normal or abnormal in appearance were also presented. One of the findings was that these abnormal ("teeth trisomic") mice manifested a higher level of radiosensitivity than normal mice. However, in their recent work, Van Buul and de Boer [B69] could not confirm the above observation. They point out that since the tertiary trisomic mice occur in a variety of phenotypes and the splitting up into "normal-looking" and "teeth trisomics" is based on some phenotype properties only, it is likely that the genetic factor(s) that might have caused the high frequencies in the earlier study were missing in the "teeth trisomic" mice used in the later experiments.

469. Another mammalian species from which conflicting results had been obtained in the past is the rabbit. Scott and Bigger [S65] and Muramatsu and Matsuoka [M44] observed that the yields of x-ray induced dicentrics in the rabbit lymphocytes were less than one-half of those in human lymphocytes; Bajerska and Liniecki [B41] found however, that the sensitivities were the same (both species have the same effective chromosome arm number). With a fixation time of 48 h Léonard et al. [L29] found that the sensitivity of rabbit lymphocytes is in fact less than one-half of that of human lymphocytes. This finding was confirmed by Liniecki et al. [L28] who had earlier reported similar sensitivities of rabbit and human lymphocytes (1 to 4 Gy of x rays; 40 h fixation time for the rabbit and 44–48 h fixation time for human lymphocytes). In the same study Liniecki et al. also assessed the sensitivity of pig

lymphocytes to the induction of dicentrics (1–4 Gy of x rays) and found (despite the fact that the chromosomes of the pig have 64 effective arms) that this was similar to that of rabbits (31 h fixation time for pig lymphocytes).

470. The recent and more decisive experiments of Fabry and Léonard [F13] using BUdR-Giemsa techniques (which permit unequivocal distinction between cells in M_1, M_2 and M_3) demonstrated that there exists no significant differences in the frequencies of dicentrics in human and rabbit lymphocytes (200 R of x rays) provided that only cells in the first division were included in the calculations. Their results further show that at 48 h (the fixation time used in most of the studies on rabbit lymphocytes published in the literature and referred to in the preceding paragraph) around 50% of the cells are in the second and about 30% of the cells in the third division.

471. The finding of Muramatsu and Matsuoka [M44] discussed in the 1977 report, namely, that the lymphocytes of cat (arm number: 71) manifested only about one-fifth of the radiosensitivity of human lymphocytes to the radiation-induction of dicentrics, has now been confirmed by Stephan et al. [S66]. These authors found that the ratio of the yields of dicentrics in human as compared to cat lymphocytes is 1.0 : 0.27 (100–400 R).

472. In primates, Léonard et al. [L29] studied the chromosomal radiosensitivity of lymphocytes from the chimpanzee (Pan troglodytes), a hominoid ape phylogenetically and chromosomally closely related to man (48 chromosomes and 81 chromosome arms). No significant differences were observed in the radiation-induced frequencies of dicentrics and fragments (100–400 R; 48 h fixation time for both). The mean areas covered by the lymphocyte nuclei are, however, very different for the two species: 48.4 μm^2 for man and only 23.3 μm^2 for the chimpanzee. In the gorilla (Gorilla gorilla) however (chromosome arm number: 81) the sensitivity to the induction of dicentrics appears higher than in humans [D24].

473. Takahashi et al. [T15] compared the yields of dicentrics after acute and low dose rate gamma irradiation of the lymphocytes of man and the crab-eating monkey (Macaca fascicularis; 83 chromosome arms). Doses of 1–4 Gy were administered to heparinized whole blood samples at dose rates of either 0.5 Gy min^{-1} or 0.17 Gy h^{-1} (0.0029 Gy min^{-1}). With acute irradiation, the yields of dicentrics were similar in both species as had been found in an earlier study [H38].[16] At the low dose rate, the yields were lower in both species, as would be expected from the kinetics of induction of dicentrics ($Y = aD + bD^2$). The surprising result was that, except at 1 Gy, the yields were significantly lower with monkey lymphocytes. A comparison of the values of the a and b coefficients after acute and low dose rate irradiation showed that:

(a) The magnitude of the linear components was not significantly different either between the species or between the radiation regimes;
(b) There was a drastic decrease in the magnitude of the quadratic component in the monkey (by a factor of about 30) whereas this reduction was much less with human lymphocytes (by a factor of 4).

[16] This study showed in addition that the yields of induced dicentrics (as well as dicentrics and rings) were similar to those in man, crab-eating monkey, squirrel monkey (Saimiri sciureus; 77 chromosome arms) and slow loris (Nycticebus cougang; 99 chromosome arms).

These results permitted the authors to conclude that the chromosomal damage leading to dicentrics can be repaired in unstimulated (G_0) lymphocytes and that such repair capacity is different in the two species.

474. Takahashi et al. [T15] also looked into the question of whether there was any preferential elimination of cells with dicentrics during the course of low dose rate irradiation. This was carried out by incubating the cells for varying periods in the medium (2, 4, 6 and 24 h) after acute or chronic irradiation with 4 Gy prior to PHA stimulation. It was found that:

(a) With lymphocytes of both species, there was a decrease in mitotic indices and dicentric yields with post-irradiation incubation, although the time when these reached their lowest values was different (2 and 4 h after irradiation for mitotic index and dicentric yields, respectively); with the 24 h interval, the reduction was by one-quarter for dicentric yields for both the species while that for mitotic indices was by about 30% and 60% for man and monkey, respectively;
(b) At comparable time intervals between irradiation and PHA stimulation, the yields of dicentrics were similar in both the species;
(c) There was no evidence for preferential elimination of cells with multiple dicentrics in either species.

These results, particularly those showing species-independence for the elimination of aberrations with time (post-irradiation incubation prior to PHA stimulation), strengthen the view that the different yields of dicentrics obtained after low dose rate irradiation in the two species may be a reflection of primarily a species-specific G_0 repair mechanism.

475. Takahashi et al. [T16] have now extended their studies to the induction of chromosome aberrations at low gamma-ray doses (0.05 to 0.5 Gy; 6 levels). The methods used (48 h cultures; BUdR technique) were the same as in the earlier work. The results showed that as in the earlier work, there were no differences between the monkey and human lymphocytes with respect to the induction of dicentrics. The human data gave a satisfactory fit to a linear model (i.e., a linear increase in aberration frequency with dose), whereas this was not the case with those for the monkey. There was some suggestive evidence for the existence of a plateau in aberration yields between 0.1 and 0.3 Gy for the monkey and between 0.2 and 0.3 Gy for human lymphocytes, but more data would be needed to verify this suggestion, particularly for human lymphocytes.

3. Molecular mechanisms involved in the production of chromosome aberrations

476. In the 1977 report, some of the available information on the relationship between radiation-induced lesions in the DNA, their repair and their relationship to mutations and chromosomal aberrations was reviewed. Some new data have been collected since then which shed further light on the mechanisms involved in the formation of chromosome aberrations in eukaryotic systems, and these will be reviewed in this section.

477. Kihlman et al. [K26] used the 5-bromodeoxyuridine labelling technique to explore the mechanisms involved in the formation of chromosomal aberrations. The rationale for using this technique is the following: the incorporation of BUdR into the DNA of a chromatid alters its staining properties and its sensi-

tivity to chromosome damage by UV and x rays. A chromatid that has incorporated BUdR into both strands of its DNA stains more weakly with the fluorescence plus Giemsa (FPG) technique than a chromatid that has incorporated the BUdR into only one strand of its DNA, and such a single-substituted chromatid in turn does not stain as strongly as a completely unsubstituted chromatid. The same dose of x rays produces about three times more breaks in unifilarly substituted chromatid than in an unsubstituted one. The extreme case is represented by long-wave UV (i.e., wavelengths of between 310 and 350 nm) which produces aberrations exclusively in chromatids having BUdR-substituted DNA.

478. Although the thesis that two lesions are required to produce one exchange aberration is not a new one in radiobiology (it was arrived at long ago on the basis of dose-effect relationship for radiation-induced exchanges [L38, M67, S78]) direct evidence has been lacking. The experiments of Kihlman et al. [K26] were designed to obtain such evidence.

479. Root-tip cells of Vicia faba were exposed in the G_2 phase to long-wave (320–380 nm) UV radiation or to x rays (40 R); before the irradiation exposures, BUdR had been substituted for thymine in various numbers of DNA strands in these chromosomes. The experiments involved cells with chromosomes of the following constitutions: TT-TT (both chromatids of the chromosome containing unsubstituted DNA), TT-TB (one chromatid with unsubstituted DNA and one with unifilarly substituted DNA). The sister chromatids in chromosomes of the TT-TB and TB-BB constitution could be distinguished by differential staining with the FPG technique.

480. The results show that:

(a) Long-wave UV induced no aberrations in chromosomes with unsubstituted DNA;
(b) In chromosomes with BUdR-substituted DNA, long wave UV, like x rays, induced subchromatid and chromatid aberrations; because these aberrations were found in the first mitosis after exposure of G_2 cells, the effect of long wave UV was of the S-independent, ionizing-radiation-type;
(c) The sensitivity to the production of aberrations by x rays increased with increasing number of BUdR-substituted DNA strands, i.e., TT-TT < TT-TB < TB-TB < TB-BB;
(d) The increased sensitivity of TB-TB chromosomes over the TT-TB chromosomes was particularly striking.

481. The question of whether a damaged chromatid may interact with an undamaged one to form an exchange (as has been suggested in the model of Resnick [R54]) was studied by making use of the finding that in cells with chromosomes of the TT-TB constitution, long wave UV produced no breaks in TT chromatids, whereas x rays produced about three times as many breaks in the TB chromatids as in TT chromatids. In the latter case, if the assumption that two lesions are required to form one exchange is true, then, there should be nine times more exchanges between TB chromatids than between TT chromatids. If, on the other hand, one lesion can give rise to an exchange, there should be three times as many exchanges between TB chromatids as between TT chromatids. The results were in line with the first assumption. These results provide direct evidence that two lesions are required to produce one exchange.

482. Natarajan and Obe [N15] tested the hypothesis whether or not double-strand DNA breaks are responsible for radiation-induced chromosome aberrations. They made use of the finding of Tanaka et al. [T10] who demonstrated that the introduction of T_4 endonuclease in Xeroderma Pigmentosum (XP) cells in vitro in the presence of inactivated Sendai virus led to the ability of these cells to perform unscheduled DNA synthesis. This indicated that, as XP cells are deficient in the first (incision) step of excision repair, this first step can be mediated by the endonuclease and when this is done, the other steps in the sequence can be carried out by the cells' own enzymatic machinery. According to the accepted model of excision repair, following treatment with a mutagen causing direct breaks (x rays) or where the repair processes generate single-strand breaks (UV), transient short stretches of single-strand regions should be present in the chromosomal DNA of the treated cells. If single-strand-specific endonuclease, such as Neurospora endonuclease, is introduced in these cells, one would expect to induce double-strand breaks in the single-stranded regions of the DNA. If double-strand breaks are responsible for radiation-induced chromosome aberrations, under these conditions, there would be an increase in the frequency of aberrations for a given dose in the ensuing mitosis.

483. CHO cells were irradiated with x rays or short-wave UV or treated with chemicals (MMS, bleomycin, mitomycin-C) in G_2 stage in the presence of the inactivated Sendai virus and Neurospora endonuclease and the aberrations were scored in the ensuing mitosis. In the x-ray series, the above treatment led to an enhancement of the frequencies (by a factor of about 2 at the lowest exposure of 50 R and much higher at 100 and 200 R) of breaks, exchanges and gaps. These results have been interpreted by the authors as due to the conversion of some of the x-ray induced single-strand DNA breaks into double-strand breaks by the enzyme. Similar results were obtained after treatment with MMS and bleomycin but not after UV or mitomycin-C; with the latter two, however, there was a clear increase in the frequency of gaps.

484. The possible reasons for the difference in response between x rays, MMS and bleomycin on the one hand and UV and mitomycin C on the other are the following: ionizing radiations produce chromatid aberrations in G_2 and the effect is S-independent. It does not require DNA and chromosome replication to be expressed as chromosomal aberrations. Bleomycin is known to act like x rays, i.e., to be S-independent. Although the aberrations induced by MMS are S-independent, MMS is known to behave more like x rays with regard to excision repair, namely, "small-patch" repair [R55]. MMC, on the other hand, is a cross-linking bifunctional alkylating agent and the aberrations are of the delayed type and S-dependent. Short-wave UV induces dimers which are implicated as being responsible for UV-induced chromosome aberrations; these are of the S-dependent type. It is known that in addition to dimers, UV induces strand breaks. During excision repair of UV-induced lesions, long patches of single strand regions are expected to occur. It would appear that single-strand stretches following the "long patch" repair even if initiated in G_2 are not converted into double-strand breaks by the endonuclease and it may be that this type of repair relevant to initiation of chromosome aberrations is confined to the S phase only.

485. In a subsequent study, Natarajan et al. [N16] extended their observations to CHO cells irradiated in

the G_1 stage of the cell cycle, in addition to examining the duration of availability of single-strand gaps for action by Neurospora endonuclease in irradiated G_2 cells. The results show that after G_2 irradiation, (50–200 R) all classes of chromatid aberrations increased, as noted in the earlier study. In G_1 cells (75–300 R) an increase in chromosome-type of aberrations was found but there was also a marked induction of chromatid aberrations. The increase in chromosome-type aberrations in irradiated G_1 cells treated with Neurospora endonuclease has been interpreted as due to the conversion of DNA single-strand breaks or gaps to double-strand breaks by the enzyme; the induction of chromatid aberrations in G_1 was assumed to be due to conversion of some of the damaged bases into strand-breaks by the enzyme. The authors have provided evidence for the conversion (by the enzyme) of single-strand breaks induced by x rays into double-strand breaks using neutral sucrose gradient centrifugation.

486. The data from experiments designed to determine how long the single-strand breaks or gaps produced in G_2 by x rays remain available for action by the enzyme show that immediate post-irradiation treatment with the enzyme leads to a marked increase in the frequencies of chromatid gaps, breaks and exchanges. Later post-treatments, i.e., after 60 or 90 min, increase the frequencies only of breaks, but not of exchanges. It would thus seem that single-strand regions are available even 60 min after irradiation, but the induced double-strand breaks are not able to interact effectively to produce chromatid-type aberrations. This may be due to changes in spatial arrangements of chromosomes in later G_2 or prophase cells prior to mitosis, which restrict interaction of breaks.

487. Kato [K27] demonstrated that the frequencies of UV-induced sister chromatid exchanges (SCE) in rat kangaroo cells were reduced on photoreactivation with visible light, suggesting that pyrimidine dimers are involved in the production of SCEs. Reynolds, Natarajan and Lohman [R56] irradiated CHO cells with far UV and near UV (broad-spectrum) and determined the frequencies of SCEs over a range of doses; in parallel experiments, enzymatic assays were performed to assess the numbers of pyrimidine dimers making use of dimer-specific endonuclease from Micrococcus luteus. It was found that both types of UV irradiation induced SCEs, which showed a linear increase with exposure time (dose); in addition, the enzyme specific sites (ESS) showed a similar increase and the ratios of SCEs to ESSs were nearly the same over the dose range studied. These data thus suggest that dimers are related to SCE induction. However, a substantial number of dimers need to be produced in the DNA of CHO cells before one SCE can occur and their calculations show that about 20 000 pyrimidine dimers need to be induced for each additional SCE.

488. Recently, in experiments with chick embryonic fibroblasts (which possess photoreactivating enzymes), Wolff [W22] found that photoreactivation (PR) following UV irradiation leads to the disappearance of dimers but not of SCE's. The interpretation was that some other minor photoproduct and not the dimers may be responsible for the induction of SCE's. Similar results were obtained by Natarajan et al. [N17] after 5 and 10 J/m^2 UV irradiation followed by PR; there was a reduction in the number of dimers (i.e., ESS) but no reduction in the frequencies of SCEs. The frequencies of SCEs seemed to saturate around 20 per cell.

489. An examination of the chromosome preparations showed that at these UV doses, there was a considerable mitotic delay and a high frequency of chromosome aberrations in cells which were still in their first mitosis. This would indicate that only a small proportion of cells came through to a second cell cycle. In subsequent experiments therefore, Natarajan et al. used lower UV fluences (1 and 2 J/m^2). The results showed that:

(a) There was a considerable amount of dimer removal (by about 95%) after PR;
(b) There was a reduction in the frequencies of SCEs by about 50%.

490. In order to investigate the effect of fixation time on the frequency of SCEs, an experiment with 2 J/m^2 was conducted and the cells were fixed at 5 h intervals between 24 and 35 h. The data clearly demonstrated removal of dimers with PR (to the extent of about 85%) and that, at all fixation times, there was a significant reduction in the frequencies of SCEs which varied between 25 and 40%. These results, therefore, show that there is a relationship between SCEs and pyrimidine dimers. The discrepancy between these data and those of Wolff [W22] is probably due to the possibility that high UV fluences were used in his study.

491. Using Potorous cell line PtK2, Ishizaki et al. [I8] found that the frequency of UV-induced SCEs could be reduced by post-irradiation exposure to visible light. In their experiments, UV fluences of 5 and 10 J/m^2 were used. Moreover, the effect of PR light was temperature-dependent; the authors therefore concluded that the reduction in the frequency of SCEs is probably mediated through an enzymatic reaction.

492. In more recent work, van Zeeland et al. [Z11] conducted experiments with fibroblasts from Xenopus laevis which possess photoreactivating enzyme to study the influence of photoreactivation on UV-induced pyrimidine dimers, sister-chromatid exchanges, cell-killing and point mutations to ouabain resistance. The results clearly showed that the frequencies of all the biological end-points studied were reduced on photoreactivation and this was paralleled by a decrease in the frequencies of pyrimidine dimers (determined as endonuclease sensitive sites). However, an absolute quantitative relationship could not be established between the photoreactivation-mediated reduction in the amount of pyrimidine dimers and the decrease in the frequencies of SCEs, chromosomal aberrations, point mutations and the extent of cell killing and this could be due to a number of causes. Nonetheless, these studies show a direct relationship between biological effects and UV-induced pyrimidine dimers in this system.

4. A test of the hypothesis of whether there is proportionality between spontaneous and induced rates of mutations

493. One of the main assumptions involved in the use of the doubling-dose method for risk evaluations in man is that of proportionality between the average spontaneous and induction rates of mutations. An example will serve to illustrate this point. Suppose that in species A, the average spontaneous rate is 10^{-5} per gene and the average rate of induction is 10^{-7} per unit dose per gene. The doubling dose then is 100 dose units and the mutational risk per unit dose of radiation exposure is 1/100 of the spontaneous incidence. Suppose that in a related species B, the average

spontaneous rate is lower, say 10^{-6} per gene. It will be valid to apply the doubling dose of 100 dose units to species B only when it is assumed that the average rate of induction in species B is also lower, say, 10^{-8} per unit dose per gene such that $10^{-5}/10^{-7} = 10^{-6}/10^{-8} = 100$. If for instance in B, the rate of induction is 10^{-7} (i.e., the same as in A), the doubling dose will be 10 dose units and the mutational risk will be an order of magnitude higher, namely 1/10 of spontaneous incidence (instead of 1/100 of the spontaneous incidence) in spite of the fact that the amount of damage induced will be the same in both cases.

494. One way to test the validity of the assumption of proportionality between spontaneous and induction rates is to examine the average induction rates of mutations in related species or strains of organisms that differ from one another in their spontaneous rates and see whether such a proportionality is in fact obtained. Another method is to examine within a species whether or not such a proportionality between spontaneous and induction rates is obtained on a locus-by-locus basis for a number of gene loci. Shukla, Sankaranarayanan and Sobels [S79] adopted this latter approach to study this problem in Drosophila melanogaster. These investigators collected data on the induction of specific-locus mutations at 14 X-chromosome loci following spermatozoal irradiation (x rays; 3000 R). The mutational spectrum obtained in the radiation work was compared with the spectrum that Schalet [S80] has observed in his work on spontaneous mutations using the same set of loci and stocks. The conclusion that emerged from their work was that the data were not out of line with the assumption of positive correlation between spontaneous and induction rates of mutations for the loci under study but that more extensive data, both on spontaneous and induction rates would be required before the evidence could be considered conclusive. Furthermore, a proportionality across the spectrum of mutations for spontaneous and radiation-induced mutations in spermatozoa may not hold for spermatogonia, since it has been shown in the mouse that the spectra for induced mutations in these two germ cell stages are not the same.

495. In another study, Racine, Langley and Voelker [R57] accumulated enzyme mutants by exposing a balanced lethal strain of Drosophila melanogaster (heterozygous at seven allozyme loci) to chronic gamma irradiations (0.07 Gy h^{-1}) for 14 generations (196 days; total accumulated dose: 335.52 Gy). Following the 14 generations of exposure the flies were screened by gel electrophoresis for newly-arisen null mutants and/or mobility variants. Among other things, the rank order of mutability observed in this work was compared with the one recorded by Mukai and Cockerham [M3] and their own unpublished results on spontaneous mutations at the same set of loci. This analysis revealed the following rank order for radiation-induced mutations (the numbers of mutants are shown in parenthesis): αGpdh (6); Hex-C (4); cMdh (2); Got-2 (1); Adh (0); Dip-A (0) and αAmy (0). For spontaneous mutations, the order was the following: αGpdh (7); Hex-C (5); cMdh (2); αAmy (1); Got-2 (1); Dip-A (0) and Adh (0).[17] It can be seen that there is a good correspondence between the two rank orders suggesting that these data are consistent with the assumption of proportionality between spontaneous and induced mutations.

496. Glickman et al. [G33] conducted a study on gamma-ray induction of mutations in the lacI gene of Escherichia coli, a locus which codes for the lac repressor. Exposures from 5 kR to 40 kR were used and the lacI mutants recovered (among which were nonsense mutations ranging from 1.4 to 10.8% in the different experiments) were analysed for changes at more than 70 nonsense sites (amber and ochre) within the lacI gene. Contemporary controls were run and the conclusions drawn pertained to 98 and 135 independent nonsense mutations isolated in the controls and 30 kR radiation experiments, respectively.

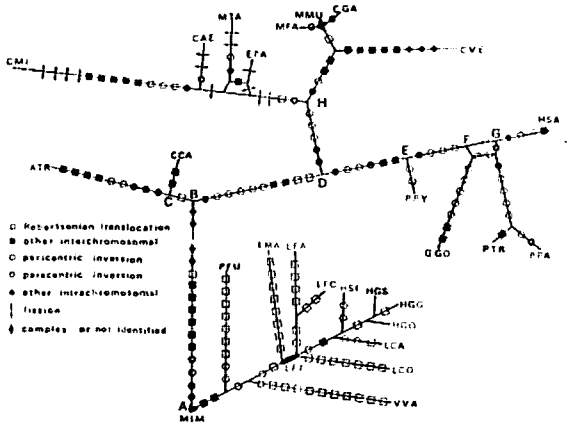
497. Among the spontaneous mutants, both transitions and transversions were frequent and there were three "hot spots" in the amber spectrum at sites 6, 15 and 34. These sites had previously been shown by Miller et al. [M48] to correspond to the location of 5-methylcytosine residues in the DNA; this naturally-occurring modified DNA base gives 5-methyluracil (thymine) by spontaneous deamination and therefore occasionally results in errors in the DNA that go uncorrected by uracil-N-glycosidase [C39]. Gamma rays also induced both transitions and transversions but the prominent amber "hot spots" seen with the spontaneous mutants were absent, suggesting that gamma rays presumably do not cause extensive deamination. Transitions constituted 55.6% of the gamma-ray induced amber mutants compared with 71.4% transitions among the spontaneous amber mutants; the difference is statistically significant at the 5% level. When the amber data were analysed again with the amber "hot spots" excluded, the distribution of transition and transversion events in the spontaneous and induced mutants was similar. The authors have drawn the conclusion that the spectra of induced and spontaneous mutations are similar with the exception of the spontaneous "hot spots".

5. Chromosomal evolution in primates and its possible relevance for inter-specific comparisons and for assessing the chromosomal basis of human pathology

498. Dutrillaux [D4] has published an exhaustive review of the chromosomal evolution in primates and has proposed a tentative phylogeny from Microcebus murinus (a Prosimian which seems to have retained a rather primitive karyotype) to man. The chromosome studies were carried out after whole blood culture or fibroblast culture after skin biopsy. Detailed comparisons of the karyotype of man with those of about 60 species (of the approximately 200 species of the order of primates) were made, on a band-by-band basis for every chromosome using all the available banding techniques. Almost all the data used for these comparisons have been collected by the author and his colleagues. The major conclusions of use to the Committee that emerged from this work are summarized in the following paragraphs.

499. To facilitate discussions, the reconstructed evolutionary tree showing the sequence of chromosomal changes that have occurred is diagrammed in Figure II. An examination of the above figure shows that the pattern of chromosomal evolution is not the same in the different lines. The types of rearrangements that have occurred vary from one group (suborder, family, genus)

[17] αGpdh: α-glycerolphosphate dehydrogenase; Hex-C: hexokinase-C; cMdh: cytoplasmic malate dehydrogenase; Got-2: mitochondrial glutamate oxaloacetate transaminase; Adh: alcohol dehydrogenase; Dip-A: dipeptidase-A; αAmy: α-amylase.



Legend: Each species is designated by a three-letter code:

HSA:	Homo sapiens	(man)	Pongidae
PTR:	Pan troglodytes	(chimpanzee)	
GGO:	Gorilla gorilla	(lowland gorilla)	
PPY:	Pongo pygmaeus	(orangutan)	
MMU:	Macaca mulatta	(rhesus monkey)	Cercopithecidae
MFA:	Macaca fascicularis	(crab-eating macaque)	
PPA:	Pan paniscus	(pygmy chimpanzee)	
CGA:	Cercocebus galeritus		
EPA:	Erythrocebus patas	(patas monkey)	
MTA:	Myopithecus talapoin		
CAE:	Cercopithecus aethiops	(several species)	
CMI:	Cercopithecus mitis		
CVE:	Colobus vellerosus		Colobidae
CCA:	Cebus capucinus	(capuchin monkey)	Cebidae
ATR:	Aotus trivirgatus	(owl monkey)	
MIM:	Microcebus murinus		Lemuridae
LFF:	Lemur fulvus fulvus	(red-fronted lemur)	
LFA:	Lemur fulvus albocollaris		
LFC:	Lemur fulvus collaris		
LMA:	Lemur macaco		
LCO:	Lemur coronatus	(crowned lemur)	
LCA:	Lemur catta	(ring-tailed lemur)	
HSI:	Hapalemur simus		
HGO:	Hapalemur griseus occidentalis		
HGG:	Hapalemur griseus griseus	(gentle lemur)	
HGS:	Hapalemur griseus subspecies		
VVA:	Varecia variegata		
PFU:	Phaner furcifer		

Figure II. Reconstruction of the sequence of chromosomal changes that have occurred during primate evolution from the most ancestral karyotype seen in Microcebus murinus [D4]

to another. For instance, Robertsonian translocations are preponderant among the Lemuridae (44 of the 57 changes are of this type), but are non-existent among the Pongidae. Chromosome fissions are very frequent among the Cercopithecinae (26/51, including new information), but are not found elsewhere, and pericentric inversions are preponderant in the evolution of Pongidae and the human species (17/28).

500. There is a very close similarity of chromosome banding patterns between the simians studied and man. All the quantitative and some of the qualitative variations detected involve the heterochromatin. Approximately 70% of the bands are common to the simians and to the lemurs (prosimians). In the remaining 30%, technical difficulties prevented a meaningful comparison but this does not exclude the possibility that a complete analogy may exist. It thus appears that the chromosomal evolution of the simians (and probably of all the primates) has occurred without detectable duplication or deficiency of the euchromatin.

501. The reasons why particular kinds and/or sequence of changes have occurred in one but not in another line can only be conjectured but the answers presumably lie in the breeding structure and size of the evolving populations, the selective advantages or disadvantages of given rearrangements, the genic contents of the chromosomes concerned, the functional alterations that may accompany structural alterations (position effect), etc. The available data suggest that of all these considerations, evolution by structural-change-mediated position effects appears least likely.

502. As mentioned earlier, the kinds and relative frequencies of the different rearrangements are different in the different lines of evolution. For instance, a closer look at Figure II, segment B→HSA will reveal that from the last common ancestor of all simians to man, 50% of the changes are pericentric inversions, 13% complex intrachromosomal rearrangements and 16% complex, imprecisely-defined interchromosomal ones. In the direct ancestors of man (segment D→HSA; Figure *II*) again, 8 of the 15

changes are pericentric inversions, the remainder being made up of others (3 other intrachromosomal, 3 interchromosomal and 1 paracentric inversion) with no Robertsonian translocations.

503. In contemporary human populations, as was discussed in chapter I, the two kinds of rearrangements that are predominant are the Robertsonian and reciprocal translocations; the pericentric inversions constitute a minor class. It would thus appear that the categories of rearrangements most frequently observed in humans are not those that occurred in the evolution of our ancestors.

504. Some of the types of chromosomal changes that have been noted during the evolution of primates are also known in chromosomally abnormal human individuals. Apart from the Robertsonian and reciprocal translocations mentioned earlier, pericentric inversions appear to be common to both human evolution and human pathology, although the relative frequencies are different. It would therefore appear instructive to examine whether these inversions that are rarely observed in man are not those that are "frequently" observed in evolution. In the work reported [D4], Dutrillaux could identify 44 pericentric inversions among which 21 occurred either on chromosomes that were already identical to those of man or on those which were at the last stage before giving rise to human chromosomes. Two-thirds of the latter could be considered as possible "convergent mutations" (in this context, referring to the occurrence of similar structural changes in species belonging to different lines of descent) and one-third, "reverse mutations" (the occurrence of structural change leading to ancestral chromsome(s)). From the data available for patients (over 10 000 of them) at the Institut de Progénèse, Dutrillaux could extract 26 independent pericentric inversions; in addition, there were three independent cases of paracentric inversions.

505. A comparison of these 29 inversions with those detected during evolution permitted the conclusion that 8 of the former could be considered as possible "reverse mutations" and 1 a possible "convergent mutation". Of these 8, 7 were pericentric inversions and 1 a paracentric inversion; out of the first 8, 1 was observed 3 times and another 2 times. Considering the fact that the number of breakpoints and consequently the number of different inversions is theoretically very large, it would appear that the correlation between changes that have occurred in human pathology and in human evolution is more than mere coincidence.

506. The implications of these findings for interspecific comparisons of chromosomal sensitivity to radiation (or other mutagens) to the induction of different kinds of aberrations can only be speculated on at present. Two questions, yet unresolved, are: "can the evolutionary history provide any clue with respect to the inducibility of a given kind of chromosomal aberration in different species and in man and the pathological consequences that may derive from such induced aberrations in man?" and "can quantitative and qualitative comparisons be based on the induction of one kind of aberration in different species provide a proper perspective and a basis for predicting the relative radiosensitivity of human chromosomes to damage that is relevant in the context of induced pathological states?"

6. Summary and conclusions

507. Experiments were conducted in which mice and rabbits were kept in huts in sites of high concentrations of uranium in the soil. The radiation exposures were from external gamma-irradiation and from inhaled radon. Periodical blood samples were taken from the rabbits to assess the amount of chromosome damage; the mice were used in tests on fertility and for cytogenetic studies on induced reciprocal translocations (spermatocyte analysis).

508. In the rabbits, the frequency of dicentrics in the lymphocytes rose from zero per cent (at the beginning of the experiment) to 1.9% after 4 months exposure (gamma-ray doses in the range from 0.13 to 0.27 Gy for individual rabbits), to 2.6% after eight months (gamma-ray doses of between 0.15–0.53 Gy for individual rabbits) and to 3.9% after one year. After a 16-month period, there was no further increase in the frequency of aberrations and after a 20-month period, the frequency actually dropped to zero. The radon exposure estimates were 5–10 Gy per year to the bronchial region and about $1\ 10^{-2}$ Gy per year to the gonads. From model studies with radon exposures alone to rabbits, it was concluded that the chromosome aberrations observed were all due to gamma irradiation.

509. Male mice kept in the radiation area for three months showed slight increases in litter size, the mean number of offspring sired and in the mean number of offspring weaned. Female mice (also kept in the radiation area) showed slight reductions in all the above three indicators of radiation effects. Neither the irradiated male mice nor their sons showed any evidence for the presence of translocations or other aberrations in their spermatocytes. The estimate of the external gamma-irradiation for the 3-month period was 0.15 Gy.

510. Additional data on the radiation-induction of aberrations in lymphocytes (dicentrics) that have become available since the publication of the 1977 report confirm the conclusion reached by the Committee in its 1977 report, namely, that there is no simple relationship between the effective chromosome arm number of the species and its relative radiosensitivity to the induction of these structural aberrations. The mammalian species studied in this respect included the rabbit, the cat, the chimpanzee, the gorilla and the crab-eating monkey. Furthermore when it is ensured that only cells in their first mitosis after irradiation are scored for dicentrics, there are no differences in sensitivity between mouse and human lymphocytes, and between rabbit and human lymphocytes.

511. Whereas after acute gamma irradiation the frequencies of radiation-induced dicentrics in the lymphocytes of man and the crab-eating monkey are similar (at similar doses) after chronic irradiation, the yield in monkey lymphocytes was lower. The difference after chronic irradiation has been explained on the assumption that chromosomal damage leading to dicentrics can be repaired in unstimulated (G_0) lymphocytes and that such a repair capacity may be different in the two species.

512. Direct evidence for the thesis that an exchange aberration is the result of interaction of two lesions has been obtained using root-tips of Vicia faba in which prior to irradiation with long-wave UV or x rays, BUdR

was substituted for thymine in various numbers of DNA strands in the chromosomes with a consequent change in radiosensitivity, this increasing with increasing numbers of substituted strands.

513. Data demonstrating that double-strand breaks in the DNA are responsible for radiation-induced (x rays) chromosome aberrations has been obtained in CHO cells in vitro. The experiments involved the introduction of Neurospora endonuclease into cells made permeable prior to the x-ray exposure. The results showed a marked increase in the frequency of aberrations under these conditions relative to controls which were not treated with the enzyme. Similar results were obtained with bleomycin and MMS, but not with UV or mitomycin-C. Possible reasons for these differences are discussed. In the x-ray work, there is evidence showing that the single-strand breaks produced by irradiation are available for action by the enzyme even 60 minutes after irradiation, but the induced double-strand breaks are not able to interact effectively to produce chromatid-type aberrations as the interval between irradiation and the enzyme treatment increases.

514. The frequencies of UV-induced sister-chromatid-exchanges in rat kangaroo cells and in a potorous cell line are reduced on photoreactivation with visible light, suggesting that UV-induced pyrimidine dimers are involved in the production of SCEs. Using another technique, the involvement of dimers in UV-induced SCEs has also been demonstrated in CHO cells.

515. In chick embryonic fibroblasts (which have the PR enzyme), PR following UV-irradiation led to the disappearance of the dimers but not of SCEs in some studies. The reason for this has now been clarified: higher UV fluences which were used in these studies led to a considerable mitotic delay and, consequently, only a small proportion of cells came through to a second cell cycle. With lower UV-fluences, clear evidence has been obtained for removal of dimers by PR treatment after UV as well as for a reduction in the frequencies of SCEs.

516. The hypothesis of whether there is proportionality between spontaneous and radiation-induced mutation rates (an assumption which is central to the use of the doubling-dose method for risk evaluations) has been tested in Drosophila and in E. coli. In Drosophila, the data on spontaneous and induced mutation rate estimates for a number of individual loci are consistent with the hypothesis. In E. coli where the comparison was between spontaneous and induced mutation rates at more than 70 sites in the lacI gene, if the three amber "hot-spots" (predominant in the spontaneous mutation spectrum) were excluded, there was correspondence between spontaneous and induced mutation rates for the different sites.

517. Extensive data on chromosomal evolution in primates have been published in which detailed comparisons of the karyotype of man with those of about 60 primate species have been made (on a band-by-band basis for every chromosome using all the available banding techniques). It has been found that the pattern of chromosomal evolution is not the same in the different branches of the evolutionary tree (i.e., the types of rearrangements that have occurred vary from one group to another). From the last common ancestor of all simians to man 50% of the changes are pericentric inversions. However, in contemporary human populations, the pericentric inversions constitute a minor class. The possible implications of the finding of pericentric inversions in chromosomally abnormal individuals are briefly outlined within the framework of the evolutionary history of our species.

III. EFFECTS OF X-IRRADIATION ON SURVIVAL KINETICS OF SPERMATOGONIAL CELLS IN MICE AND RATS

518. Oakberg [O10] conducted a study to investigate the effects of x-irradiation on the survival of stem cell spermatogonia in the mouse and to obtain dose-response curves for both single and fractionated exposures in order to determine if the cell populations surviving these treatments are qualitatively different. This study is an extension of the author's earlier work [O11] discussed in the 1972 and 1977 reports of the Committee.

519. One group of adult C3H x 101 hybrid male mice received three injections of 0.46 MBq or ^{3}H-thymidine at 9 h intervals and x-irradiation (100, 300, 500, 600, 1000 R or the first half fraction of a 1000 R exposure) 24 h after the last injection. The mice were killed 120 h and 207 h (in one experiment, 414 h) after irradiation. The rationale for choosing 120 and 207 h is that it is known from previous work [O12] that some surviving stem cells will divide between these two intervals, although intervals of five days or more are required for the process of degeneration to run its course. A second group of mice received a single injection of 0.46 MBq of ^{3}H-thymidine one hour before x-irradiation at levels similar to those mentioned above. Appropriate controls were maintained. Testes preparations were made for autoradiography and for scoring of survival of the stem cells: cell survival was measured by counting stem cells in 99 tubule cross sections per slide (198 per mouse) distributed among the stages of the cycle of the seminiferous epithelium; labelling was scored by counting 100 A_s spermatogonia per slide (200 per mouse).

520. The stem-cell survival data 120 and 207 h after x-irradiation are given in Table 35. The mean number of A_s cells in the unirradiated mouse is reduced by the injection of ^{3}H-thymidine and likewise, irradiated mice given ^{3}H-thymidine show lower cell counts than mice that received radiation alone. Compared to the 120 h data, the number of cells scored in the unlabelled group (experiment 1) after 207 h is higher at 300, 500 and 600 R, lower at 1000 R and the same for the 500 + 500 R exposure; in the mice receiving ^{3}H-thymidine survival after 207 h is higher than after 120 h at 300, 500 and 600 R, and lower for both 1000 R and 500 + 500 R exposures. At both intervals, with and without ^{3}H-thymidine, the data fit a curvilinear relationship with no evidence of discontinuity over the 100–1000 R range, though it should be noted that there are no points between 600 and 1000 R.

521. The data from experiments on the labelling of A_s spermatogonia are summarized in Table 36. The percentage of labelled cells at 207 h is markedly influenced by the total exposure and by exposure fractionation; for instance, in the 3 x 0.46 MBq group, the percentage of labelled cells does not differ significantly between controls and the 100–600 R groups, is significantly lower in the 1000 R group and significantly high in the 500 + 500 R group. At 414 h, there is no significant difference between 100, 300, 500, 600 and 500 +

500 R groups (all are higher than controls) while the single 1000 R exposure is lower than in the controls just as at 207 h. When irradiation is given 1 h after ^{3}H-thymidine injection, very few labelled cells survive any of the exposures used with values ranging from 2.2% to 6.6% compared with 21% for controls.

522. From these results, Oakberg [O10] has concluded that the surviving stem cell population is qualitatively the same for that portion of the dose-response curve giving a linear increase in mutation frequency, but different for both 1000 R single and fractionated exposures. This parallelism between survival of labelled cells and mutation frequency in spermatogonial stem cells summarized in Table 37 suggests that a stage in the cell cycle 24–42 h after DNA synthesis is resistant to cell killing but sensitive to mutation induction. The mutation rate after a single 1000 R exposure is low because labelled mutation-sensitive cells have been selectively killed. The mutation frequency after the 500 R exposure is increased because of synchronization induced by the first fraction combined with the selective killing of unlabelled cells by the second one. Irradiation one hour after the labelling with ^{3}H-thymidine demonstrated that the S phase of the spermatogonial stem cell cycle is sensitive to radiation-induced cell killing.

523. There are some interesting differences between the dose-response relationship reported by different authors for effects of low-LET irradiation on some direct measures of spermatogonial survival. As already stated, Oakberg [O10] found a curvilinear (quadratic) response for survival of type A_s spermatogonia scored 207 h after x-irradiation, with no sign of discontinuity at 600 R. De Ruiter-Bootsma et al. [R76] reported an exponential relationship over the 4–12 Gy range for spermatogonial stem-cell survival measured 3 weeks after irradiation by the tubule repopulation method, again with no sign of discontinuity around 6 Gy.

524. Cattanach [C40], however, reported an exceptionally high 600 R point (giving a plateau between 600 R and 700 R) in the otherwise exponential dose-response curve for the median day of return to fertility (i.e., length of the sterile period which results from spermatogonial killing) after 300–1000 R x-irradiation. He interpreted this as due to the presence of two stem-cell populations with different radiosensitivities to radiation killing. Lu et al. [L48] assayed levels of the X-isozyme of lactate dehydrogenase, LDH-X (providing a measure of the number of spermatocytes plus spermatids) and numbers of sperm-heads in testicular homogenates 56 days after 0–14 Gy of acute gamma-irradiation. Both curves had very large shoulders with inflection points at 5 and 6 Gy. The authors concluded that there was a radioresistant subpopulation of stem-cells which predominated after doses greater than 6 Gy.

525. Thus, results of the two histological assays are in agreement with each other, as are those of the two functional assays. As the former two assays measured the stem-cell survivors at an earlier post-treatment stage than the latter two, the possibility arises that some temporal factor (possibly connected with a feed-back mechanism) alters the form of the response between the initial phase of spermatogonial proliferation and the final phase of sperm production. Oakberg [O10] suggested that the 600–700 R plateau in return to fertility found by Cattanach might be connected with the dynamics of repopulation at higher doses when the number of surviving colonies is low. This might affect the return to sperm numbers adequate for fertility in a manner which is dose-dependent. However, this hypothesis may need modification in view of the more recent results of Lu et al. [L48] already discussed.

526. Huckins and Oakberg [H59, H60, H61] have recently carried out further analyses of the behaviour of stem-cell spermatogonia in normal and irradiated rat and mouse testes, mainly using whole mounts of seminiferous tubules. When their conclusions are compared with those of Cattanach and co-workers [C32, C63, C64, C65] derived from translocation studies and already discussed in section II.B., a consensus seems to emerge. The only spermatogonia which survive an acute exposure of 100 R or more (apart possibly from some A_1 cells) are some of the radioresistant long-cycling stem cells.

527. According to Huckins and Oakberg [H61] these survivors are likely to be in a prolonged "protective" G_1 phase, while Cattanach and Crocker [C63] have described it as G_0 phase. Probably as the result of the depletion of other spermatogonial stages, these long-cycling surviving cells are triggered from the indeterminate "A-phase" into the determinate "B-phase" [S118] of active mitotic proliferation, with nearly synchronous entry into DNA synthesis 2 to 3 1/2 days later [H61]. Most stem-cells then go into a short cycle, as the results of de Ruiter-Bootsma and colleagues indicate [R76]. Some stem-cells start to differentiate into subsequent stages before the complete rebuilding of the undifferentiated population [H61].

528. At 24–48 h after irradiation the surviving A_s spermatogonia synchronously arrive at what is probably a transitional phase sensitive to the induction of mutations and chromosome aberrations, but in which some cells could still survive a large radiation dose. The sub-additive mutational response at longer fractionation intervals (3–15 days) presumably reflects the sensitivity of the short cycling stem-cells. These are the only type found in the immature testis, which also has a reduced radiation response [C64, E22, S119]. The exact relationship between the long-cycling and the short-cycling stem-cell spermatogonia is still obscure. It is possible that the short cycle precedes differentiation, or that short-cycling cells periodically and randomly enter a longer cycle [H61].

529. Although the long- and short-cycling cells can be regarded as more resistant and more sensitive subpopulations, it seems difficult to equate them with the entities thus described by Cattanach et al. [C40] and Lu et al. [L48] since the shorter cycling cells seem to disappear at doses which are decidedly lower than the > 6 Gy postulated. However, it seems clear that heterogeneity in sensitivity to killing and to mutation induction must remain within the long-cycling A_s cells at stage G_0 or G_1 which would alone survive doses of 6 Gy or more, since otherwise it would be very difficult to explain the humped type of dose-response curve for the induction of point mutations or translocations. The exact nature of the mechanism which triggers active stem-cell proliferation after irradiation is still unknown, but it should be noted that neither Cattanach et al. [C64] nor Cunningham and Huckins [C66] have been able to demonstrate a chalone effect in the irradiated testis.

530. In the 1977 report, the work of Hsu and Fabrikant [H45] on the cellular response and cell population kinetics during spermatogonial cell renewal

in the mouse testis exposed to continuous gamma irradiation at 1.8 10^{-2} Gy d^{-1} and at 0.45 Gy d^{-1} was described. The results were that:

(a) At the lower dose rate for seven days, the A_s spermatogonial cells showed no reduction in cell number; at the higher dose rate, the number of A_s cells was reduced to 50% of that in controls during the first three days of continuous irradiation and from day 4 to 10, this figure was 80%. From day 11 onwards, control levels were reached;

(b) In the group irradiated at the higher dose rate for two weeks, the repopulation of the seminiferous epithelium commenced with increased cell proliferation in the A_s cells. This was supported by the finding of an increase in the A_s mitotic index. Labelling with ^{3}H-thymidine was used in this study for the analysis of cell population kinetics.

531. Erickson [E14] has recently reported the results of a similar study in rats with a broader spectrum of low dose rates but without using any radioactive label. Sprague-Dawley rats were irradiated continuously with ^{60}Co gamma rays at dose rates of 1 10^{-2}, 3 10^{-2} or 6 10^{-2} Gy per 23 h day (7 10^{-6} Gy min^{-1}, 2.1 10^{-5} Gy min^{-1} and 4.2 10^{-5} Gy min^{-1}) for periods ranging from one month to six months. At the termination of the radiation treatments in the different groups, the animals were killed and testes preparations were made. Spermatogonia were counted in whole mounts of seminiferous tubules that were isolated from the testes.

532. At 1 10^{-2} Gy d^{-1}, there was no statistically significant effect on stem cell number and this was so irrespective of the duration of exposure (i.e., irrespective of the total dose delivered); at 3 10^{-2} and 6 10^{-2} Gy d^{-1}, there was an initial drop (after one and two months of irradiation, respectively) to about 80 or 60% of the control level, followed by a slower decrease reaching values of 60 and 40% of the controls.

533. One month after irradiation, counts of differentiating spermatogonia were reduced to a dose rate dependent level that remained essentially unchanged during the succeeding five months of irradiation; the production of A_4 spermatogonia (a population whose size depends on spermatogonial generations A_1-A_3) was not significantly affected by 1 10^{-2} Gy d^{-1} and average values for dose rates of 3 10^{-2} Gy and 6 10^{-2} Gy d^{-1} were 60 and 30% of controls, respectively; testicular weight was also not significantly affected by 1 10^{-2} Gy d^{-1}, but 3 10^{-2} Gy d^{-1} resulted in a final value of 73% of control and that for 6 10^{-2} Gy d^{-1} was 49% of control. Erickson concluded that a reduction of stem cell mitotic activity may be the principal effect of continuous low-level irradiation on spermatogenesis in the rat.

IV. TIMING OF OOCYTE MATURATION IN THE MOUSE AND ITS RELEVANCE TO RADIATION-INDUCED CELL KILLING AND MUTATIONAL SENSITIVITY

534. In the 1977 report, the preliminary results of Oakberg and Tyrell [O14] from their autoradiographic studies on the timing of oocyte development in the adult mouse were briefly discussed. Oakberg [O9] has now published these results and has also compared the nuclear morphology of arrested and stage 3 oocytes in the mouse, guinea pig and the human female. The results of Oakberg and those of some others not considered in the 1977 report are summarized in this section.

535. The importance of this problem derives from the fact that in specific-locus experiments with irradiated female mice, the mutation rate drops to zero in the progeny derived from conceptions that occurred after six weeks and it had not been possible so far to relate specific oocyte (and follicular) stages to specific post-irradiation litters. Pedersen's extensive analyses of follicular dynamics in the female mouse [P31] were based on ^{3}H-thymidine labelling of follicle cells: his results showed that it took 19 days for a stage 3b with about 20 cells to reach ovulation. Duration of stages 7 and 8, however, could not be measured by this technique. Other difficulties in using ^{3}H-thymidine labelling are that beta rays from the tritium kill follicle cells [B48]. Follicle cells have different cell cycle times, as a consequence of which undue weight may be given to rapidly dividing cells, thereby shortening the estimate of transit times.

536. In their earlier work using N-^{3}H-thymidine-acetyl-D-glucosamine, Oakberg and Tyrell [O15] estimated that 35 days were required for maturation of stage 3b follicles. Although the problem of oocyte timing was not discussed by Haddald and Nagai [H46], the results of these authors with labelled L-fucose gave results similar to those of Oakberg and Tyrell, showing that the estimated time for maturation of 3b oocytes was longer than that in the work of Pedersen [P31].

537. In the work recently reported by Oakberg [O9] the question was asked whether the drop in mutation rate after six weeks might be attributed to the sampling of arrested stage 1 oocytes or whether it did occur after the initiation of follicular growth when species differences in chromosome morphology are minor. Four labelling experiments were performed, the first two with N-^{3}H-acetyl-D-glucosamine, the third with D-1-^{3}H-glucosamine and the last one with L-1-^{3}H-fucose. In experiment 1, the mice were given labelled acetyl-D-glucosamine (3 x 925 kBq at 9 h intervals) and killed at intervals ranging from 6 h to 25 days. In experiment 2, the females were irradiated with 50 R of x rays (group 1) or given single intraperitoneal injection and 50 R of x rays 24 h later (group 2) or the labelled compound alone (group 3). While some of the mice from these three groups were used for histological studies of the ovaries, some were pair-mated with 101 x C3H males. In experiment 3, the mice received D-1-^{3}H-glucosamine (either in a single injection of 925 kBq or in three equal fractions spaced 9 h apart) and killed at intervals ranging from 24 h to 28 days after injection. Labelling with L-1-^{3}H-fucose was achieved by two 925 kBq injections given 4 h apart and the animals were killed 1, 7, 14, 21 and 28 days after injection. The progressive appearance of unlabelled oocytes (unlabelled in zona pellucida) were used to compute the transit and the maturation time of the different stages.

538. The results show that:

(a) Of the three compounds tested, L-1-^{3}H-fucose gave the best labelling with the lowest dosage;

(b) Approximately four weeks are required for stage 4a oocytes (with a second layer of follicle cells) to reach ovulation, thus confirming the earlier finding [O14]; the duration of stage 3b, however, is about two weeks instead of one week as suggested earlier;

(c) Adding these two estimates gives six weeks as the time interval from initiation of stage 3b to ovulation;

(d) Although there was some evidence for a reduction in the numbers of stage 3 and 4 oocytes in the N-

^{3}H-acetyl-D-glucosamine-injected females, an extensive ten-week breeding test showed no effect on breeding behaviour or litter size of females given the labelled compound;

(e) There was no evidence that either 50 R or pregnancy had any effect on the progression of labelled follicles.

539. Thus, conceptions within six weeks after irradiation sample oocytes exposed in stages 3b–8 and litters conceived after six weeks are derived from stages 1–3a. The numbers of surviving stage 1 and stage 2 oocytes are so low (after irradiation) that no more than one or two litters are produced from these and at least one litter must be derived from stage 3a. The nuclear morphology of both stages 3a and 3b are similar to one another and also to stage 3 of guinea pig and human oocytes and yet there are striking differences in mutational sensitivity of the 3a and 3b stage oocytes in the mouse; furthermore, the change in mutational sensitivity of the mouse oocyte with time after irradiation as shown by Russell [R38, R60] occurs in a cell with "typical" diplotene chromosome configuration, i.e., it does not parallel the change from the arrested dictyate to the more characteristic diplotene of oocytes contained in a follicle with a single layer of cuboidal cells. These findings demonstrate that the degree of chromosome condensation does not appear to be a reliable criterion of oocyte sensitivity to either cell killing or mutation induction.

540. The high sensitivity to cell killing and the more diffuse (dictyate) condition of the chromosomes of the arrested mouse oocyte compared to the radiation resistant "typical" diplotene of the arrested human oocyte has raised doubts concerning the relevance of genetic data in the mouse for the estimation of radiation hazards to the human female. The data of Caine and Lyon [C30] and of Cox and Lyon [C41], however, show that the guinea pig, where the oocyte is arrested in a condensed diplotene, with a high resistance to cell killing, also shows a low incidence of radiation-induced dominant lethals, just as the arrested dictyate oocytes of the mouse and hamster.

541. There is therefore no consistent correlation, either negative or positive, between sensitivity to cell killing and the frequency of mutation observed [C30, R38]. The evidence so far suggests that low mutational sensitivity may be a general property of arrested mammalian oocytes (irrespective of nuclear configuration) but the number of species studied from this point of view is still small. Moreover, it should be pointed out that although the usual pattern for dominant lethal induction is one of high sensitivity of the maturing oocyte and low sensitivity of the immature one, Caine and Lyon [C30] found a somewhat higher frequency of post-implantation dominant lethals in the immature guinea-pig oocytes than in the mature, although the yield was still low.

542. As the authors point out, a considerable part of the high pre-implantation loss in first oestrus matings may have been due to oocyte damage rather than to dominant lethals. The evidence for dominant lethal induction was accompanied by a reduction in litter-size, lasting for many months after irradiation. The extent to which this reduction was the result of genetic damage is not yet clear. Caine and Lyon emphasize the need for further work on this, pointing out that "if genetic damage were detectable in guinea-pig oocytes several months after irradiation it would not be safe to conclude that such damage would not persist in human females". Therefore it would seem incorrect to assume that the mutational radiosensitivity of the immature human oocyte is necessarily as low as that of the immature mouse oocyte. Obviously, more data are needed.

V. SENSITIVITY OF MAMMALIAN FEMALE GERM CELLS TO KILLING BY IRRADIATION

543. The 1972 report of the Committee [U8] considered in some detail the sensitivity of oocytes to radiation-induced cell killing in different species of mammals. In this chapter, the main findings recorded in the above report will be first summarized before considering new data.

544. Female mammals are born with a finite number of oocytes formed already during embryonic development. These so-called primordial oocytes are surrounded by a single layer of follicular cells. With maturation, the oocytes grow and multi-layered follicles are formed. In young adults of both the rat and rhesus monkey, the number of growing oocytes amounts to about 10% of the total population, the remaining 90% being primordial follicles [B49].

545. In the oocytes, the sequence of nuclear changes comprising meiosis is arrested at the diplotene stage which lasts until the time of ovulation. The nuclear morphology of the arrested oocytes varies between species. Thus, a typical diplotene is characteristic of man, the rhesus monkey, the goat and the dog. A synizesis-like diplotene (chromosomes clumped into a dense knot) is characteristic of the guinea pig and a diffuse interphase-like diplotene (dictyate) is present in the mouse and a few related species of rodents such as the hamster, the deermouse and the gerbil.

546. The chromosomes in the nucleus of the primordial oocytes in man and the rhesus monkey are of the so-called lampbrush type, similar in form to those of amphibia and other lower vertebrates. The oocytes in the growing follicles in all the species examined possess lampbrush-type chromosomes.

547. In humans, there is evidence [S81] that the oocyte chromosomes synthesize a large body of nucleolar material and that the synthesis is amplified during the diplotene stage. In pachytene, the oocyte nucleus shows 1 to 2 main nucleoli (connected with the satellites or secondary constrictions of D and G group chromosomes) and micronucleoli are rare. In diplotene however, the main nucleoli (2 to 3) become voluminous and numerous, micronucleoli appear and do not seem to be connected with the acrocentric chromosomes. They arise at the contact zones of the heterochromatic regions and differ from the nucleolar organizers on acrocentric chromosomes; they are connected in part to centromeric heterochromatin including various secondary constrictions.

548. In terms of radiation-induced killing of primordial oocytes, there are drastic differences in sensitivity between the different species. The response of the oocytes in the growing follicles, however, is not strikingly different. Information on these is summarized in Table 38.

549. A few papers (among them two reviews) dealing with the effects of irradiation on mammalian female germ cells have been published during the last few years [B48, B50, B51, H47]. Some of the information contained in the review papers [B50, B51], although not necessarily new or recent, covers a broader spectrum of mammalian species than was the case in the Committee's 1972 report. These data, however, strengthen the Committee's earlier conclusions, namely, that the sensitivity of the human oocytes to the killing effects of x-irradiation is more similar to that of the rhesus monkey than to that of rats or mice. In what follows, those aspects of radiosensitivity to killing not covered in the 1972 report will be presented with particular emphasis on the data from the rhesus monkey and man.

550. Oogonia in the ovaries of the rhesus monkeys and humans [B52, B53, B54] are more resistant than the corresponding cells in rodents. For example, Baker and Beaumont [B52] showed that the exposure of foetal rhesus monkeys aged 4–4.5 months to 350–600 R of x rays caused a 7% reduction in the population of oogonia; when the post-irradiation interval was extended to 10–14 days, the depletion of the germ cells was only 4%, reflecting the repopulation of oogonial cells by mitotic divisions. The proportion of oogonial killing was exposure-dependent; by increasing the exposure to 1000 R, the population was reduced to 43% of that in controls.

551. Baker and Neal [B54] showed that the sensitivity of oogonia in the ovaries of mice, rats and rhesus monkeys remains virtually the same irrespective of whether they are exposed to x-irradiation in organ cultures in vitro, or in vivo. Furthermore, they showed that exposure of 2000 to 4000 R eliminates only a proportion (80% during the sixth month of gestation) of the oogonia in human ovaries in vitro. This finding suggests that the human oogonia may be even more resistant than those of the rhesus monkey.

552. Data on the radiosensitivity of oocytes in foetal rhesus monkey are scanty. The available ones show that exposures between 200 and 400 R have no measurable effects on the population of oocytes [O16]. Baker and Beaumont [B52] found that none of the foetuses aged two months to full term (six months) was completely devoid of germ cells after 350–600 R of x rays and that a severe reduction of the number of oocytes occurred only after 1000 R or more. The most marked effect was found after exposure during the fifth month of gestation, a period associated with a high rate of spontaneous atresis and with the cessation of mitotic activity in oogonia [B52, B55].

553. Baker and Neal [B54] and Baker [B53] compared the structure of the irradiated and control human ovaries (from foetuses aged 2–7 months post-coitum) at various intervals after the onset of organ culture. Exposure to 2000–4000 R affected the germ cells at all stages in their development, although oogonia undergoing mitosis appeared to be the most sensitive. Quantitative studies of a foetal ovary from a six-month old foetus showed that 4000 R x-irradiation caused a 65% reduction in the number of germ cells within 7 days of treatment. A similar response was obtained in foetal rhesus monkeys after exposure to 2000 R and confirms that human oogonia and oocytes are very radioresistant.

554. The radiosensitivity of the oocytes of some juvenile and adult mammals has already been considered (Table 38). Most of the other mammalian species for which quantitative data are available suggest that they are intermediate between the mouse and the rhesus monkey. The $LD_{50/30}$ for primordial oocytes in the guinea pig is about 500 R, although 15 000 R is required for 100% killing ([I5], see also [O17]). This vast difference between the LD_{50} and LD_{100} values is presumably due to the fact that there are two distinct populations of primordial oocytes: one, a "large" type, with appearance similar to those of other species such as the monkey and man and the other, a "contracted" type, in which the chromosomes appear to be condensed toward the centre of the nucleus. "Contracted" oocytes are radiosensitive: they are either killed by exposure to x rays or are transformed into the larger types [I5].

555. Only qualitative data are available for the rabbit and the hamster. Oocytes in these species seem to have radiosensitivities comparable to those in the rat [B56, M50]. Thus, doses of less than 7 Gy destroy the majority of primordial follicles and also a proportion of those that have completed their growth phase. Females of species that have relatively long foetal or post-natal development, in contrast to those of rapidly developing species (such as rodents), are not sterilized by acute radiation exposure. This is owing to the greater asynchrony of oocyte stages in the former species. Even in the slowly developing species, however, continuous or fractionated exposure has revealed a highly sensitive developmental stage of limited duration. This has been found to be the case for bonnet monkeys (Macaca radiata) [A31], squirrel monkeys (Saimiri sciureus) [D25], and juvenile dogs [A32], species in which the arrested oocyte is resistant to radiation-induced cell death. Continuous exposure of foetal squirrel monkeys to tritiated water indicated a sensitivity of developing oocytes even higher than that observed for the mouse. The finding that primates, as well as mice, have oocyte stages that are vulnerable to radiation suggest that the human oocyte may also pass through highly sensitive stages in development. The general pattern of sensitivity of oocytes to radiation among mammalian species may be more similar than is commonly thought.

556. Preovulatory maturation of oocytes within Graafian follicles commences with the onset of the so-called "LH surge" (Luteal hormone) which occurs, for example, about 13 hours before ovulation in the mouse and 36 hours before ovulation in man [B50]. Thereafter, radiosensitivity varies according to the stage of meiosis attained by the oocyte and increases by a factor of 10 as the cell passes from the dictyate stage to metaphase I in the mouse [M51].

557. Hobson and Baker [H47] studied the effect of ovarian x-irradiation in the rhesus monkey on menstrual cycle length, duration of menstrual bleeding, excretion of gonadotrophin in the urine, concentration of gonadotrophin in the pituitary gland, ovarian histology and breeding performance. It was found that at exposure below 4000 R, there was no significant effect on any of the above parameters measured. However, exposures of between 400 R and 6000 R rapidly induced amenorrhoea in most animals, but no increased excretion of gonadotrophin was observed. The reproductive capacity of the animals used in the study was poor. No births occurred before irradiation and only three confirmed pregnancies thereafter.

558. Baker and McLaren [B48] conducted experiments to measure the cell-killing effects of ^{3}H-thymidine on the developing oocytes of mice using

a multiple injection method similar to that in the work of Callebaut [C42]. Pregnant Q strain mice received seven injections of ^{3}H-thymidine (148, 1480 kBq and 14.8 MBq per injection) between the 13th and 16th day of pregnancy at about 12 h intervals. The animals were either killed on the 17th day of pregnancy and the foetal gonads removed for analysis or they were allowed to give birth and the ovaries of the progeny were studied.

559. It was found that:

(a) The ovaries of the foetuses on the 17th day of gestation and on the day of birth contained oocytes which were predominantly at the zygotene or pachytene stage of prophase I and the majority of these cells were labelled;
(b) The highest intensity of silver grains was over the oocytes;
(c) Ovaries from experimental mice aged up to one month appeared normal, although smaller than in the controls; the proportion of the oocytes undergoing degeneration was higher than in the ovaries of control mice and in the treated ovaries, the atretic oocytes being more heavily labelled;
(d) In 5-months old experimental mice, the primordial follicles were mostly normal in appearance in ovaries from the low dose group (148 kBq); in the high dose groups, however, there was an increase in the proportion of grossly abnormal follicles and some ovaries were devoid of oocytes;
(e) There was a reduction in the total number of oocytes in the ovaries of experimental mice and this was proportional to the dose of the isotope used and affected primordial follicles more than multilayered follicles: by 5 months of age, the numbers of oocytes in the 1480 kBq and 148 kBq groups were reduced to about 1% and 50% of the control values, respectively;
(f) At 13 months of age, ovaries from mice in the 14.8 MBq group were devoid of oocytes and corpora lutea, while in the 1480 kBq group some corpora lutea remained, but virtually no oocytes. These results permitted the authors to conclude that the mouse oocytes are highly sensitive to internal beta-radiation from ^{3}H-thymidine incorporated during embryonic life.

VI. SOMATIC CELL GENETICS

560. Only a limited amount of data has accumulated since the publication of the 1977 report on mutation induction in somatic cells by ionizing radiation. The papers concerned and some others dealing with other kinds of radiations will be briefly reviewed in the following paragraphs.

A. MUTATION INDUCTION AT THE HG-PRT LOCUS

1. Chinese hamster ovary (CHO) cells

561. It is known that several factors, such as the analogue used, its concentration, cell-seeding density, time of addition of the analogue to the mutagen-treated cells (expression time), the source of serum used in the selective medium, interclone metabolic co-operation etc., affect the recovery and type of mutants obtained. Jostes et al. [J11] investigated the role of de-amination of 8-azaguanine (8-AG) to 8-azaxanthine (8-AX) by serum under conditions where cell density and expression time were controlled. It was found that the reduction in toxicity of 8-AG which results from its de-amination to the non-toxic product 8-AX leads to the selection of many mutants which are resistant only to drug concentrations lower than that added to the selecting medium. That is, at lower concentrations one may be selecting preferentially for mutants with partial enzyme activity or for non-mutant cells. In fact, an analysis of mutant clones selected under conditions where drug toxicity was maintained revealed that most of the mutants having partial enzyme activity were eliminated. The elimination of partial mutants agreed well with the approximately 2-fold reduction in frequencies of spontaneous and x-ray induced mutants when drug toxicity was maintained by single 30 μg AG/ml and by changing the drug medium once.

562. Burki [B80] found that when exponentially growing CHO cells are exposed to 50-kVp x rays, the survival curve shows a shoulder and the induction of 6-TG^R mutations is curvilinear with dose (2–10 Gy), responses similar to those reported by other investigators for exposures of CHO and V-79 cells to more energetic x rays. When the cells are synchronized without the use of drugs, the x-ray-induced cell killing and induced 6-TG^R follows a characteristic pattern. For cell killing, the sensitive periods of the cell cycle are the G_1, G_2, M and early S periods, as others have reported. For mutation induction, the sensitive stage is the G_1 period with the maximum sensitivity near the boundary between G_1 and S; other periods of the cell cycle appear to be very refractory to the induction of 6-TG^R mutations.

563. Jostes et al. [J20] conducted a study in which synchronous CHO cells were x-irradiated (300-kVp x rays) at various stages in the cell cycle and analysed for the frequency of 8-AG^R mutants. The induced mutant frequencies were highest in mitosis (40 10^{-5} after 5 Gy), in early G_1 (30 10^{-5}) and at the G_1/S border (30 10^{-5}); were low in mid-to-late G_1 (15 10^{-5}) and were lowest in S phase (6 10^{-5}). Qualitatively, the variation in sensitivity during the cell cycle for induction of mutants corresponded with that reported for the induction of chromosomal aberrations. However, a quantitative comparison of the two end-points and plots of the logarithm of survival versus mutant frequencies or aberration frequencies indicated that the mutant frequencies were much higher than expected when the cells were irradiated in mitosis or at the G_1/S border. The mutants recovered were classified as complete (i.e., failing to survive in azaserine-hypoxanthine medium and incorporating tritiated hypoxanthine at a rate less than 1% of that for wild-type cells) or as partial (i.e., surviving in azaserine-hypoxanthine medium at a rate greater than 1% of that for wild-type cells). The percentage of mutants classified as partial was 0–22% for selection in 30 μg/ml 8-AG and 15–60% for selection in 5 μg/ml 8-AG. However, the number of partial relative to complete mutants had little or no dependence on radiation dose or phase of the cell cycle irradiated.

564. In another investigation [J21], CHO cells were given two 4.5 Gy doses of x rays separated by 1 or 2 h, during which interval the cells were held at room temperature to minimize progression through the cell cycle. The frequency of induced mutations to 6-TG^R was compared with that of mutations induced by a single dose of 4.5 or 9 Gy. Mutation frequencies induced by the split dose were intermediate between

those induced by the two single doses, suggesting that "premutational" lesions were repaired.

565. In the study of Cleaver [C43] cultured CHO cells were labelled with 6-^{3}H-thymidine or 5-methyl-^{3}H-thymidine, frozen and allowed to accumulate damage from ^{3}H decays for varying periods of time. Two series of experiments were carried out with each of these. At the end of various "dose accumulation periods", the cells were thawed to 37°C and used for the determination of 6-TG^R mutations. Appropriate controls were maintained. In parallel experiments, mutation induction by UV (up to 24 J/m^2) and x rays (up to 10 Gy) was also studied.

566. The results showed that, in the range of doses employed, the dose-response curves were linear for all three experiments. ^{3}H in the 6 position produced 2–3 times more 6-TG^R mutants than ^{3}H in the 5-methyl position, indicating that a local effect associated with transmutations at the 6 position in the DNA produces mutations more efficiently than the emitted beta particle does. No difference between ^{3}H decays at the 6 position and the 5-methyl position was observed when DNA damage in the form of single-strand breaks was measured. In another study, Cleaver [C44] examined whether or not x-irradiation would induce an error-prone repair process that would increase the frequency of 6-TG^R mutants in CHO cells. The cells were x-irradiated at times from 0 to 17 h before being irradiated with UV. Only one x ray dose (3 Gy) and one UV dose (13 J/m^2) were used. No synergism however, was observed.

2. Chinese hamster V-79 cells

567. Thacker, Stretch and Stephens [T23] examined the induction of 6-TG^R mutants in the V-79 Chinese hamster cells after gamma irradiation. After irradiation, the cells were grown in non-selective medium for different time intervals before respreading into medium containing 0.5 to 0.7 μg/ml 6-TG; in some experiments, colonies arising in 6-TG medium were counter-selected in medium containing the glutamine-analogue azaserine, which distinguishes mutants with very little HG-PRT activity. Only these mutants were found to be increased in frequency by irradiation, the maximum measured frequencies occurring in cells respread after two days of growth in non-selective medium. The results showed that over the range from 1–8 Gy the dose-effect relationship for induced mutations per viable cell was non-linear (induction rates of 5 10^{-8} per 10^{-2} Gy to 3 10^{-7} per 10^{-2} Gy). However, a plot of the induced mutation frequency against log surviving fraction gave an approximately linear relationship. The same linear relationship holds for recently published data on human and mouse cell cultures, so that all three mammalian cell types exhibit the same fixed probability of mutation induction relative to the extent of inactivation caused by ionizing radiation (about 4 10^{-5} mutants per lethal event) (see also [T33]).

568. Asquith [A25] studied the mutagenic and lethal effects of single and fractionated doses of gamma irradiation in the same cell line. The induction of 8-AG^R mutants was scored. The results showed that:

(a) The dose-effect curve after single doses (0.5 to 10 Gy) was non-linear;
(b) The lethal and mutagenic effects of fractionated doses were always less, relative to those after single exposures;
(c) When the cells were exposed to graded single doses of up to 6 fractions (each of about 3.5 Gy), the rate for fractionated doses always was lower than that for the corresponding single doses; and
(d) When a total dose of 8.34 Gy was administered either singly or in 2, 3, 4, 6 or 12 fractions of equal size, there was an increase in survival with increasing number of fractions paralleled by a concomitant decrease in mutation frequency, such that there appeared to be a constant relationship between mutation and survival.

569. Thacker et al. [T24] studied mutation to 6-TG resistance in V-79 Chinese hamster cells after irradiation with accelerated helium, boron or nitrogen ions covering a LET range from 28 to 470 keV μm^{-1}. It was found that for all radiation qualities, a dose-dependent increase in mutation frequency was obtained for doses giving surviving fractions greater than about 0.20. The effectiveness per unit dose for both inactivation and mutation induction increased with increasing LET of the radiation to a maximum in the range of 90–200 keV μm^{-1}. However, the maximum mutagenic effectiveness (relative to gamma rays) was about 2 or more times that for inactivation.

570. Unique RBE values cannot be given for these data because of the differences in the shapes of the dose-effect curves at different LETs. The linear coefficient taken from the quadratic fit to each set of data gives one estimate of RBE which emphasizes the difference in effectiveness at low doses. This "initial slope RBE" for helium ions (for mutation induction) range from 2.9 to 17 in the range of LETs from 20 to 90 keV μm^{-1}; for boron ions, at both LETs tested (110 and 200 keV μm^{-1}) the RBE values are the same, while for nitrogen ions this is 14.

571. In a subsequent paper, Goodhead et al. [G43] used carbon-K characteristic ultrasoft x rays of photon energy 0.278 keV. These x rays produce electrons of "range" $\leq$7 nm which is an order of magnitude smaller than those for aluminium x rays and is only about three times the diameter of the DNA double helix. The effective ranges are less than 7 nm owing to the very tortuous path of such slow electrons; each electron produces a total of only about 14 ionizations and these are not along a clearly defined path. The dose distribution through the cell is highly non-uniform being 100% on the entrance surface and decreasing exponentially with depth in the cell. Under the assumption that the targets are uniformly distributed within the cell of uniform thickness 7 μm, the average dose to the targets is 24% of the dose at the entrance surface. Despite the very low energy and short track length, the authors found that the above ultrasoft x-irradiation caused inactivation and induced 6-TG^R mutants. With certain assumptions about the position of the sensitive sites within the cells, it was concluded that carbon x rays are more effective than gamma rays and are probably at least as effective as long tracks of helium ions of similar LET. These data extend the conclusions previously drawn from the observed effectiveness of aluminium x rays [C67, G44] regarding the sizes of the sub-cellular targets involved in inactivation and mutation induction. They imply that the sensitive sites are smaller than about 7 nm and that highly localized energy depositions consisting of $\leq$ 14 ionizations are sufficient to produce biological effects.

572. The increasing use of photochemotherapy, involving combined treatments with 8-methoxypsoralen

(8-MOP) and long-wave UV light (UVA: emission range: 305–450 nm with a maximum at 355 nm) for treatment of psoriasis in man prompted Burger and Simons to study the effects of similar treatments (PUVA) on mutation induction and cell-killing in V-79 Chinese hamster cells [B57] and in diploid human fibroblasts [B58] this study is considered later in this chapter. Treatment with 8-MOP alone (50 μg/ml, 4 h) or UVA alone (9000 J/m^2) did not cause any significant induction of 6-TG mutants. Combined treatment (PUVA) induced both cell-killing and mutations. This was also observed under conditions approaching patient treatment (PUVA) with respect to the concentration of 8-MOP in the skin and the amount of UVA received by the epidermal cells. A simple relationship proved to be applicable for mutation induction under different conditions: 5.5 10^{-8} per J/m^2 per μg of 8-MOP.

3. Mouse lymphoma (L 5178Y) cells

573. Nakamura and Okada [N18] investigated the gamma-ray (^{137}Cs) induction of 6-TG^R mutations in L5178Y cells at 0.5 Gy min^{-1} and 8 10^{-3} Gy min^{-1}. In addition, they examined cell killing, the relationship between mutation frequencies and variations in dose rate in the range of 0.5 to 8 10^{-3} Gy min^{-1} at a dose of 2 Gy, the effects of temperature (±0°C versus 37°C during irradiation at 0.5 or 8 10^{-3} Gy min^{-1}; 2 Gy) and the effects of adding dimethyl sulphoxide (DMSO) at various concentrations to the medium containing the cells during irradiation.

574. For cell killing from 2 to 8 Gy the dose-response curve was sigmoidal at high dose rate and exponential at low dose rate. In the same dose range, the frequency of 6-TG^R mutations increased faster than linearly with high dose rate irradiation, but was nearly linear at low dose rate. At a dose of 2 Gy, the mutation frequency continued to decline (to about one-half of that after high dose rate irradiation) with a decrease in dose rate until the latter reached about 3.3 10^{-2} Gy min^{-1}, below which there was no further reduction. At 0°C, the frequencies of mutations were nearly the same at both the high (0.5 Gy min^{-1}) and low (8 10^{-3} Gy min^{-1}) dose rates, whereas at 37°C the frequency at the lower dose rate was less than one-half of that at the higher one. DMSO exhibited a radioprotective effect both with respect to survival and to mutation induction; the reduction in mutation frequencies became more pronounced with increasing DMSO concentration following irradiation at 0.5 Gy min^{-1} but were not measurably affected by irradiation at the low dose rate.

4. Human diploid fibroblasts

575. In the experiments of de Ruijter and Simons [R61], human diploid fibroblasts were x-irradiated (100, 200 and 300 R) in suspension and mutation induction at the HG-PRT locus was studied using the 8-AG or 6-TG selection systems; in addition, the length of the expression time for these mutants was ascertained by seeding the cells for selection at 0, 3, 6, 10 and 14 days after x-irradiation. The results showed that:

(a) Direct expression of at least a proportion of the mutants occurred on day 0 followed by an increase in mutant frequency over the entire culture period; the latter, however, was found to be entirely due to an increase in spontaneous mutations, suggesting that for human diploid fibroblasts, culturing after treatment is not necessary for the expression of HG-PRT deficient mutants.

(b) In practice, however, a culture period is needed as the number of clone-forming cells that can be seeded without culture after treatment is very low, and the number of mutants that can be selected is consequently small, even in large-scale experiments.[18]

(c) The exposure-frequency relationship does not appear to deviate from linearity; the mean mutation rate is 2.1 10^{-7} per R which, in the exposure range used, is about twice that obtained in rodent cells.

576. Cox and Masson [C45] studied the induction of cell killing and mutations to 6-TG^R in cultured human diploid lung fibroblasts (HF 19 strain) after exposure to ionizing radiations with LET in the range from 20 to 470 keV μm^{-1}. It was found that, for all radiations studied, the dose-response curves were exponential (range: up to 2.5 Gy). Helium ions of increasing average LET showed increasing effectiveness in the order: He(20) < He(28) < He(50) < He (70) < He (90). The D_o values decreased from 0.92 Gy at 20 keV μm^{-1} to 0.32 Gy at 90 keV μm^{-1}. Correspondingly, the RBE values increased from 1.4 to 4.0. Boron ions of increasing average LET showed decreasing effectiveness in the order B (110) > B (160) > B (200). The D_o values increased from 0.34 Gy at 110 keV μm^{-1} to 0.5 Gy at 200 keV μm^{-1}. The RBE values correspondingly decreased from 3.7 to 2.5. Nitrogen ions of 470 keV μm^{-1} were less effective than B ions of 200 keV μm^{-1}; the D_o was 0.73 Gy and the RBE, 1.7. In view of the fact that the survival curves were exponential, the RBE values for inactivation were not dose-dependent; the RBE maximum lies between LETs of 90 and 110 keV μm^{-1} and is of the order of about 4.

577. The dose-response relationships for mutation induction were approximately linear for all radiation types. Helium ions of increasing average LET showed increasing mutagenic effectiveness in the same order as that for cell killing; the induced mutation rates increased from 3.9 10^{-5} Gy^{-1} at 20 keV μm^{-1} to 22 10^{-5} Gy^{-1} at 90 keV μm^{-1}. Correspondingly the RBEs increased from 1.3 to 7.1. Boron ions of increasing average LET showed similar mutagenic effectiveness; the induced mutation rates were between 17.8 and 20.7 10^{-5} per Gy. The RBE values were between 5.7 and 6.7. Nitrogen ions of 470 keV μm^{-1} were considerably less effective than boron ions, the induced mutation rate being 8.5 10^{-5} Gy^{-1} and the RBE 2.8.

578. The mutation data suggest that the RBE-LET relationship has a humped form similar to that for cell inactivation. However, while the RBE values for inactivation and mutation induction differed only slightly for radiations in the LET range between 20 and 50 keV μm^{-1}, at higher LET these values for mutation were about twice those of the corresponding RBEs for inactivation. The RBE maximum for mutation induction is in the range 90–200 keV μm^{-1}. Although this range is similar to that obtained for the induction

[18] It is instructive to recall that in the work of Cox and Masson [C71] discussed in the 1977 report, it was demonstrated that, with respect to the induction and selection of 6-TG^R mutants, the maximal yield was observed when the cells surviving the irradiation had completed 3–4 doublings (6–7 days of growth) in a non-selective medium.

of 6-TG^R mutations in V-79 Chinese hamster cells [T24], the comparison of RBE is complicated by the fact that the hamster cell RBEs are not unique values.

579. In experiments with aluminium soft x rays and carbon soft x rays, Cox et al. [C67] and Goodhead et al. [G43] demonstrated that these irradiations are capable of causing cell inactivation and inducing 6-TG^R mutations in human cells. The general conclusions are similar to those arrived at using V-79 cells.

580. Burger and Simons [B58] investigated cell killing and induction of 6-TG^R mutations in dividing and non-dividing (i.e., under liquid-holding conditions) human skin fibroblasts (derived from a healthy boy) from treatment with 8-MOP and long-wave UV (UVA). Two 8-MOP concentrations (0.25 and 10 μg/ml) and a range of UVA doses (up to 600 J/m^2 in combination with 10 μg/ml 8-MOP and up to 5333 J/m^2 in combination with 0.25 μg/ml 8-MOP) were used. Under liquid-holding conditions, both the amount of cell killing and the frequency of induced mutations are lower than for dividing cells under the same 8-MOP/UVA conditions; the effect of liquid-holding on cell survival is less pronounced (reduction by 40%) than on mutations (reduction by 80%). The number of mutations induced per unit dose (= per μg 8-MOP/ml per J/m^2) in dividing cells is 3.3 10^{-8}/cell (for 10 μg/ml 8-MOP and UVA dose range up to 100 J/m^2 and for 0.25 μg/ml 8-MOP and UVA range up to 3500 J/m^2) this finding being qualitatively similar to that obtained with V-79 cells [B57]. These data thus suggest that there is a linear relationship between mutant yield and the product of 8-MOP concentration times UVA dose. The cytotoxic effect of PUVA treatment, however, is dependent on the actual concentration of 8-MOP and UVA dose and this result is also in agreement with the results with V-79 cells. Calculations show that, for instance, at 50 and 10% survival levels, the decrease of 8-MOP concentration by a factor of 40 (from 10 to 0.25 μg/ml) can be compensated by an increase of UVA exposure by a factor of 10. This suggests that the increase in UVA exposure needed does not bear a simple proportionality to the decrease of 8-MOP concentration with the combined treatment.

581. Burger and Simons have used the above data to calculate the risk of mutation induction in epidermal cells for PUVA therapy of psoriasis patients under the assumptions that the mutational response of the basal epidermal cells is similar to that of skin fibroblasts; that the concentration of 8-MOP in the skin during a normal PUVA treatment is 0.25 μg/ml; that about 30% of the dose of UVA reaches the basal layer; and that about 10% of the epidermal cells are dividing and 90% are in G_0. In clinical studies, Burger et al. [B55] used a starting dose of 18 000 J m^{-2} for fair-skinned individuals which, for the basal layer of the epidermis would mean a dose of 5400 J m^{-2}. The weighted average frequency of mutations per PUVA session then becomes

$$5400 \times 0.25 \times 3.3\ 10^{-8} \times 0.10 \text{ (for dividing cells)} +$$
$$5400 \times 0.25 \times 0.6\ 10^{-8} \times 0.90 = 1.17\ 10^{-5}$$

Patients given 36 maintenance treatments a year for 30 years will accumulate 30 x 36 x 1.17 $10^{-5} \approx 1.26\ 10^{-2}$ per cell. This figure might be of some relevance in the context of assessing potential risk of cancer induction (on a mutation model) for patients given PUVA therapy if such therapy can be shown to have a carcinogenic effect.

5. Human peripheral blood lymphocytes

582. In 1977, Strauss and Albertini [S120] reported on an autoradiographic method to quantitatively detect 6-TG^R variants in human peripheral blood lymphocytes. In subsequent papers, Albertini [A30] and Strauss and Albertini [S121] discussed in detail the experimental procedures and the results obtained in studies with lymphocytes of normal individuals, from cancer patients treated with cytostatic chemicals or x-radiation therapy and from Lesch-Nyhan syndrome (LN) patients.

583. Albertini [A30] and Strauss [S120, S121] made use of the cytotoxicity of 6-TG to human lymphocytes possessing normal HG-PRT levels to distinguish and select for viable 6-TG^R variants. In autoradiographic studies, such variants were shown to undergo DNA synthesis (incorporation of ^{3}H-labelled thymidine) and survive in the presence of normally toxic levels of 6-TG, following PHA stimulation. Experiments with artificial mixtures of lymphocytes from LN patients and normal individuals showed that the LN cells were virtually all detectable even when present in low frequency (10^{-5}). 6-TG^R lymphocytes were found in healthy normal individuals at median frequencies of 1 10^{-4} and 1.1 10^{-4} when determined at 2 10^{-3} M and 2 10^{-4} M concentration of the selective agent. Their frequencies were not found to be age-related. The distribution of the frequencies of 6-TG^R variants in cancer patients (treated with chemotherapeutics) differed from that for normal controls in that more than half of the patients had the variants in frequencies higher than the highest seen in controls. Such an increase in variant frequency over control levels was also noted in lymphocytes from radiotherapy patients [A30].

584. In their studies, Strauss and Albertini also found that lymphocytes from even LN patients which were resistant to 6-TG at concentrations 10 000 times over those which inhibit normal cells, were not absolutely resistant; thus a marked difference in the apparent frequency of 6-TG^R cells was seen when LN cells were tested at 2 10^{-4} M and 2 10^{-3} M: only the cells at the higher concentration were able to incorporate ^{3}H-thymidine. Secondly, in the chemotherapeutically exposed cancer patients, the 6-TG^R fraction of cells was different at 2 10^{-3} M or 2 10^{-4} M, suggesting that many of the 6-TG^R lymphocytes had properties similar to LN cells. Thirdly, in some of these cancer patients, the levels of 6-TG^R cells were higher even before chemotherapy with further rises either after the initiation of chemotherapy, or after its re-initiation after a non-treatment interval. Fourthly, PUVA treatment for psoriasis also leads to elevated variant frequencies. Finally, the authors have evidence to suggest that some cells that synthesize DNA in vitro under the conditions used for selection may not be mutants but rather may be phenocopies.

585. Considering all the data, Strauss and Albertini suggest that at least some of the variants isolated are somatic cell mutants and that the system in its simplest application may be valuable as a retrospective monitoring system for unknown environmental contaminants, for combination of agents, etc.

586. Evans and Vijayalaxmi [E23] have now collected data on the x-ray and mitomycin-C induction of 8-AG^R variants in in vitro studies with human lymphocytes. In parallel experiments, determinations of chromosome

aberration frequencies (after x rays) and of SCE frequencies (after MMC) were also made.

587. The reason for using 8-AG for variant selection has been stated as follows by the authors: "We were strongly influenced by the fact that 6-TG is incorporated into DNA and that inhibition of DNA synthesis by excess thymidine protects against the toxicity of 6-TG, but not 8-AG. In contrast, 8-AG is incorporated into RNA and inhibition of RNA synthesis protects against the killing effects of 8-AG, but not of 6-TG. The short-term culture of lymphocytes in vitro is inappropriate for selecting for resistance to cell killing post-DNA synthesis, and since the blast formation of lymphocytes by PHA necessitates a considerable amount of RNA synthesis, we elected to use 8-AG ($2\ 10^{-4}$ M) in preference to 6-TG in all the experiments" [E23].

588. The main results are that the incidence of 8-AG^R variants varied from $0.80\ 10^{-4}$ to $3.99\ 10^{-4}$ in the blood samples from 26 donors whose ages ranged from 16 to 82; although there was considerable scatter, there was nevertheless a clear age dependence (the frequencies increased with age); there was no sex-difference in the frequency of these spontaneous variants; significant increases in 8-AG^R variant lymphocytes occur following exposure to quite low doses of x rays and the dose-response over the range 0–2 Gy is curvilinear; the data give a good fit to a quadratic equation with a negligible linear term or to a power-law function with n equal to 2.1. Assuming that $n = 2$, then the linear term is equal to $(6.90 \pm 0.11)\ 10^{-4}$ and the quadratic term, $(6.81 \pm 0.20)\ 10^{-4}$; the kinetics of dose-response for the x-ray induction of 8-AG^R variants is similar to that for x-ray induction of chromosome aberrations; with MMC (treatment times of 1, 5 or 10 h in the concentration range 10^{-9}–10^{-5} M) the frequencies of the variants increased with MMC concentration with each dose-response curve being of the form $y = a + bD$ where y = variant frequency, a = control frequency of $(8.38 + 0.37)\ 10^{-4}$ and D = MMC concentration. The values of b (for treatment durations of 1, 5 and 10 h) are, respectively, 0.83, 0.92 and 1.06; the maximum increase in 8-AG^R variants is around 12-fold at the highest MMC concentration, but significantly increased frequencies are evident following exposure to low doses, of the order of 10^{-8} M over short time periods and the data on SCEs show that these are induced at very much higher frequencies relative to the 8-AG^R variants per cell, but the shape of the dose-response curves for these two end-points are very similar. The authors have suggested that x-ray induced 8-AG^R cells may be true mutants (the spontaneous variants are probably deletions involving the terminal region of the X-chromosome containing the locus for HG-PRT) and that on the basis of their evidence, for every 8-AG^R event in a cell population, there are around 10 visible chromosome breaks in an active X-chromosome. The MMC-induced 8-AG^R variants are considered to represent "cells in which large MMC-guanine adducts have prevented normal transcription of the HG-PRT locus to give functional HG-PRT".

B. MUTATION INDUCTION AT THE THYMIDINE KINASE (TK) LOCUS

589. In the study of Knaap and Simons [K28] mentioned earlier, mutation induction at the TK locus was also investigated in the L5178Y mouse lymphoma cell line heterozygous for TK. The frequency of TK-deficient (bromodeoxyuridine resistant) mutants (following UV or x-irradiation) appeared to reach a plateau two days after treatment, an expression time which is much less than that needed for TG-resistant mutants. The dose-effect relationship was linear (1–4 Gy, x rays; 1.25 to 5 J m^{-2}, UV) and the induction rate for TK-deficiency was higher by a factor of 2 relative to that for TG-resistance.

590. Jacobson et al. [J12] found that unfiltered broad-spectrum radiation emitted by black light (BL), cool white (CW) and black light blue (BLB) fluorescent lamps and a sunlamp (SL) is both toxic and mutagenic to L5178Y mouse lymphoma cells when the cells were irradiated in phosphate-buffered saline. The increase in mutant frequency was linear throughout the range of exposures tested. To facilitate comparisons between the different fluorescent sources, the authors defined a parameter called joule-equivalent mutagenesis (jem) and this was equal to the number of mutants per 10^5 survivors per joule per square meter; jem values were calculated using the integrated irradiance of each lamp. Based on these values, the relative mutagenic efficiency of the various lamps (compared to the germicidal UV lamp) was $3.0\ 10^{-3}$ for the sunlamp; $1\ 10^{-4}$ for the black light and cool white lamps; and $3.0\ 10^{-5}$ for the black light blue lamp. Since some of the lamps have relatively higher emission in the UV spectrum than others, this property may be responsible for the differences observed. Unpublished observations of the authors have shown that filtration of wavelengths shorter than 388 nm effectively eliminates the toxic and mutagenic effects of CW lamps. Although other wavelengths may have effects, a comparison of the spectral radiance of the BLB, BL and CW lamps over 10 nm intervals in the UV region shows that these lamps emit about 100-fold less radiation than the SL from 290–330 nm. This is in good agreement with the 100-fold lower rate of mutagenesis of the BLB and a 30-fold lower rate of the BL and CW lamps compared to the SL. The BLB lamp emits appreciably less radiation than the BL and CW lamps from 290 to 300 nm, which may account for its mutagenesis rate being about one-third of that of the BL or CW lamps.

C. MUTATIONS TO OUABAIN RESISTANCE (OUA^R)

591. Thacker et al. [T25] have reported on their studies on mutation induction to ouabain resistance (OUA^R) in Chinese hamster V79-4 cells by EMS and by gamma-irradiation (ouabain is a specific inhibitor of the plasma membrane enzyme ($Na^+ + K^+$)-dependent ATPase (Na/K ATPase)). With EMS, reproducibly large increases in the frequency of OUA^R mutants were found in cultures treated with various concentrations (1 to 4 mg/ml) and re-spread in 1 mM ouabain for up to 8 days after treatment. The concentration-frequency curve was linear in the range from 1 to 3 mg/ml concentration, followed by a very marked increase to about $30\ 10^{-5}$ at the highest concentrations of 4 mg/ml. In contrast, gamma rays were found to be ineffective in inducing these mutations despite exploration of the role of variables such as radiation dose, ouabain concentration, post-treatment interval before selection, cell density in selective medium and clonal state of the cells at the time of adding ouabain (in situ versus respreading method). A similar result was obtained for accelerated helium ions for which the RBE had been shown to be about 10 (relative to gamma rays) for 6-TG resistance in these cells [T24]. The authors have some

evidence for an interaction between cellular radiation damage and ouabain (irradiated wild-type cells were more rapidly inactivated by ouabain than unirradiated cells) but this damage seems insufficient to account for the inability to detect OUA^R mutations after ionizing radiation.

592. Chang et al. [C47] irradiated Chinese hamster V-79 cells with an unequally fractionated UV dose (UV_1, $3J/m^2 + 17J/m^2$) separated by 4, 6 or 12 h, with or without cycloheximide or caffeine present during the interval between the fractions, for part or whole of the period. Among others, the effects of these different regimes on post-replication repair, survival and mutation induction to OUA^R were studied. The data on post-replication repair (collected using alkaline sucrose density gradient methods) show that irradiating cells with an initial small dose of UV, 4–6 h before a larger UV dose, significantly increases the rate by which small DNA, found immediately after irradiation is converted into high molecular weight DNA; the presence of UV-damaged DNA for at least 1.5 h before UV_2 irradiation appears to be sufficient to enhance the rate of post-replication repair. This enhancement is inhibited by cycloheximide treatment during the interval between fractions; a similar inhibitory effect was observed with caffeine.

593. The data also demonstrate that with fractionated UV irradiation, the colony-forming ability was higher relative to the unfractionated dose; however, the mutation frequencies were either reduced or were not affected. The results from cycloheximide treatments gave two different kinds of effects, depending on the protocol used; a 4 h treatment immediately before the second irradiation increased survival but reduced mutation frequencies whereas a 6 h treatment (or treatment long before UV_2) tended to reduce survival and increase the mutation frequency. While the mechanisms for the two different effects of cycloheximide treatment are not clear, the authors speculate that this chemical may have dual effects, one promoting the action of an error-prone system (i.e., causing the observed increase in mutation frequency) and the other an error-free system (causing the observed reduction in mutation frequency). With respect to caffeine, the results show that caffeine pre-treatment or treatment between the fractionated UV doses always increases the mutation frequency. Since caffeine does not effect excision repair in Chinese hamster cells, these data indicate that caffeine pre-treatment may inhibit an error-free post-replication repair system, while allowing error-prone repair to occur.

594. In Cleaver's studies on the induction of TG-resistant mutants in CHO cells by radioactive thymidine discussed earlier in this chapter OUA^R mutations were also sought for, but none found. His other experiments [C44] on synergism between the effects of UV and x rays for mutation induction to OUA^R provided no evidence for such an effect.

D. RESISTANCE TO METHOTREXATE (MTX^R)

595. In the work of Nakamura and Okada on the gamma-ray induction of $6\text{-}TG^R$ mutations in L5178Y cells the induction of MTX^R mutations was also studied. It was found that the dose-response curve for these mutations was linear, irrespective of the mode of delivery (high versus low dose rate) of the irradiation although the rate of increase with increasing dose was less after low dose rate irradiation. As in the case of $6\text{-}TG^R$ mutations, presence of DMSO in the medium at the time of high dose rate irradiation afforded a radioprotective effect, this effect increasing with increasing DMSO concentration.

E. NATURE OF RADIATION-INDUCED MUTATIONS IN SOMATIC CELLS

596. In 1978, Cox and Masson [C46] presented evidence that gross structural changes involving the X chromosome constitute the genetic basis of a significant proportion of radiation-induced $6\text{-}TG^R$ mutations in human fibroblasts. Gene mapping experiments have assigned the HG-PRT locus in humans to the terminal region of the long arm (q27) of the X chromosome [P41]. Cox and Masson determined the pattern disruption points (PDPs) for 23 $6\text{-}TG^R$ mutants induced by 250 kV x rays, carbon ultrasoft x rays, helium ions of 90 keV/μm, alpha particles from plutonium (~ 140 keV/μm) and nitrogen ions of 470 keV/μm. These mutants were selected by resistance to 3 μg/ml 6-TG, seven days after irradiation at dose levels that gave surviving fractions of 0.2 (about 2 Gy of x rays). The hypothesis was that, if radiation-induced mutations to $6\text{-}TG^R$ arise as a consequence of structural changes of the X chromosome, a proportion of the more extreme changes should be detectable cytologically, using banding techniques.

597. It was found that aberrations (exchanges and deletions) consistent with the mapped position of the HG-PRT locus were apparent in the X chromosomes of up to 40% of TG^R mutants. In the case of exchange aberrations, the independence of the mutants described was clear, since all the exchanges were different. The majority of mutants with X chromosome deletions were detected in a single experiment using nitrogen ions and it is possible that two examples of del(X)(q26) were repeats of a single clone. With a single exception (an Xp exchange probably not associated with the mutant phenotype) all PDPs occurred in the q arm of the X chromosome.

598. Analysis of 20 spontaneous mutant karyotypes failed to reveal any structural abnormalities in the X chromosome. Since a direct association between induced TG resistance and X-chromosomal aberrations would require that such aberrations in non-mutant cells surviving the radiation dose should be rare, 25 non-mutant viable clones were also examined cytologically (alpha particles from plutonium were used); no aberrations were found.

599. The conclusion that structural changes of the X chromosome are associated with the loss of HG-PRT function raises the question of whether the functions of other genes located on the long arm of the X are also affected. As a preliminary test of this possibility, the authors examined the G-6-PD activity using semi-quantitative histochemical staining techniques. As judged by the staining intensity, the variations in G-6-PD activity among the alpha-particle induced TG-resistant mutants were considerably larger than those observed among non-mutant surviving clones, with up to 5% of the mutant clones showing very low activity and a similar number showing hyperactivity. In electrophoretic enzyme assays, two karyotypically defined Xq exchange mutants were completely devoid of HG-PRT activity but were not obviously deficient or super-active in G-6-PD activity. However, because almost all mutant

clones showing atypical G-6-PD activity in histochemical assays showed very poor growth, it has not been possible to carry out truly representative karyotype and electrophoretic analyses and hence the question of multiple gene effects in radiation-induced TG mutants still remains to be answered.

600. Brown and Thacker [B75] stress that the methods of human fibroblast HG-PRT mutant selection and the limited life span of mutant clones preclude precise estimates of the proportion of radiation-induced mutants with recognizable X-chromosome aberrations. The 40% figure quoted in the paper of Cox et al. [C46] was an average figure for a variety of different qualities of ionizing radiation and in these preliminary experiments, no attempt was made to avoid the problems of mutant fitness and consequently there was considerable experimental variation in the proportion of chromosomal mutants detected. However, Brown et al. generally observed that 250-kV x rays generated a lower proportion (5–25%) of such mutants than radiations of high-LET (20–60%). Since the proportion of such mutants observed was influenced by the duration of the post-irradiation growth (for mutant expression) and many mutant clones showed such poor growth that they could not be characterized, these authors are disinclined to put too much emphasis on these figures; instead, a good case for the gross nature of the radiation-induced HG-PRT mutants can be made on biochemical evidence. Such evidence has now been obtained.

601. The evidence comes from HG-PRT mutants in V-79 Chinese hamster cells [B75]. Each of these mutants was independently isolated (the experimental design ensured this) although inevitably, some spontaneous mutants will be included in those isolated after irradiation. The analysis pertains to a total of 50 mutants isolated after a 5 Gy gamma-ray exposure (6-TG^R mutants) and to similar numbers of spontaneous and EMS-induced mutants. All of these were examined in cell-free extracts for HG-PRT activity. Approximately 10% (5/48) of radiation-induced mutants showed measurable (i.e., more than 1% of the activity of wild-type cells) HG-PRT activity while 50% (23/46) of spontaneous mutants showed such activity. Since the radiation treatment gives only a 5-fold increase in mutant frequency over that found spontaneously at this dose, it is possible that all those mutants with measurable activity found after irradiation are of spontaneous origin.

602. Other evidence to support this idea is that the frequency of mutants with measurable HG-PRT activity does not increase with radiation dose, as was demonstrated earlier by Thacker et al. [T30]. In addition, out of a small number (15) of independently-isolated mutants induced by alpha particles at a dose giving a 14-fold increase in mutant frequency, none showed measurable HG-PRT activity.

603. Brown et al. [B75] checked for the presence of HG-PRT protein in those mutants which showed no measurable HG-PRT activity, by producing an antibody to purified HG-PRT. It was found that only 2 (or possibly 3) of the radiation-induced mutants lacking HG-PRT activity showed a cross-reaction to this antibody. However, it is again possible that these cross-reacting mutants are of spontaneous origin, since as many as 4 or 5 of the mutants selected after radiation treatment could be spontaneous mutants with no measurable HG-PRT activity (from the relative mutant frequencies and the fact that 50% of spontaneous mutants show no measurable HG-PRT activity, see above). None of these isolated mutants show loss of G6-PD activity, but a small number show changes in the X-chromosome arm known to carry the HG-PRT locus (see for instance [T31] for a description of a radiation-induced (Pu) mutant which has a clear X-chromosome rearrangement, probably a pericentric inversion of the Xq-X-chromosome with PDPs in the p2–q1 region).

604. Waldren et al. [W28] have presented some results from a study involving a CHO hybrid cell line containing a single human chromosome 11; on this human chromosome are genes for cell surface antigens a_1, a_2 and a_3 and for lactic dehydrogenase-A (LDH-A). The a_1, a_2 and a_3 loci cause the formation of specific cell surface antigens that render the cell sensitive to killing by specific antigens in the presence of the complement. The a_1, a_3 and LDH-A are on the short arm while a_2 is on the long arm. In the mutagenesis experiments, the cells were either x-irradiated (100–600 R) or treated with MNNG and a_1^- mutants were isolated and tested for loss of only a_1, a_1 and up to 2 others and all four markers. The results are summarized in Table 39 which shows that the frequency of single marker loss is quite low after x-rays (as compared with MNNG and controls); limited marker loss (a_1 and up to two others) is higher for both x rays and MNNG (relative to controls). Total marker loss is highest in the x-ray group. These data therefore suggest that at least for the loci studied, the radiation-induced mutational events predominantly involve chromosomal deletions.

F. MUTAGEN-SENSITIVE CELL STRAINS

605. Recent years have witnessed an increasing interest in the isolation of cultured mammalian cell lines which are sensitive to specific mutagens. The impetus came from similar work with human cell strains derived from patients with inherited disorders and it is hoped that the isolation and study of mutagen-sensitive mutants of cultured mammalian cell lines may also contribute to our knowledge of DNA repair processes and their relationship to mutagenesis. A number of mutagen-sensitive mutants have been isolated using replica plating methods [K41, S122], viral suicide method [S123] and others [T32].

606. Sato and Hieda [S82, S83, S84] have reported the isolation and characterization of mutant mouse cell strains isolated from L5178Y cells mutated with nitrosoguanidine, which have been found to be sensitive to physical and chemical mutagens. Thus, for instance, the line designated as M10 [S83] which was originally isolated as being sensitive to methylmethane sulphonate, was later found to be more sensitive also to the killing effects of x rays. The UV sensitivities of the parental and mutant lines however, were similar, as were plating efficiencies and doubling times.

607. Shiomi et al. [S134] compared the gamma-ray induction of 6-TG^R mutations in the L5178Y and the M10 lines and found that in the parental line the frequencies of induced mutations increased steadily with an increase in exposure (25–500 R; 2–3 10^{-7} R^{-1}); in the M10 line however, the frequencies increased in the range from 25–75 R, followed by a sharp decrease thereafter (100–150 R). In the lower exposure range, the

rate of induction per unit exposure in the M10 line was about 4 times that in the parental one. When the induced mutation frequencies were plotted against log survival, the relationship was linear only up to 20% survival in the M10 line (the curves for L5178Y and M10 were superimposable); in the L5178Y cells, a linear relationship was obtained over the whole range down to about 2% survival (see also [T23] and [T33]).

608. Another line isolated by these authors, designated as Q31 (also from L5178Y cells, after nitrosoguanidine treatment) was sensitive to 4-nitro-quinoline-1-oxide (4NQO), i.e., showed no growth in a plate containing 50 ng/ml 4NQO [S82]. Further tests revealed that 10 ng/ml of 4NQO completely inhibited the growth of Q31 cells, but not that of parental cells. Q31 was also found to be more sensitive to the killing effects of UV (D_o of 1.6 J m^{-2} versus 3 J m^{-2}) but did not show any enhanced sensitivity to x-irradiation. Chromosome analysis revealed that the cells of the parental line contained 41 chromosomes while those of Q31, 39 chromosomes.

609. In a subsequent study, Sato and Hieda [S84] compared Q31 and L5178Y cells with respect to the induction of 6-TG^R mutations by UV and caffeine sensitivity. The maximum yield of mutants was obtained after 7 days post-irradiation in L5178Y cells and 14 days in Q31 cells. The mutation frequencies in Q31 are higher after low doses of UV, but show a decline after higher (more than 2 J m^{-2}) doses (while that of L5178Y continues to increase up to 12 J m^{-2}). A plot of the induced mutation frequency as a function of the logarithm of surviving fraction again indicates hypermutability of Q31 cells as compared to the parental strain. Caffeine affected the cell-killing effect of UV in both cell strains to a similar extent, indicating that the defective (repair?) process in Q31 was caffeine-insensitive.

610. Thompson et al. [T32] have reported on the isolation of mutagen-sensitive clones by mutagenizing CHO cells with EMS, UV, MMC and ICR-171. Two of the UV-sensitive clones studied in detail had a D_{37} dose of 1.0 J/m^2 compared to 7.0 J/m^2 for the wild-type cells, and each was shown to have no detectable repair replication following exposure to UV doses up to 26 J/m^2. Although these mutants resemble XP mutants in humans with respect to their repair defect and cross-sensitivity to the carcinogen 4-NQO, one of the two clones is characterized by extreme hypersensitivity to MMC (80-fold, as compared to the wild type). Clones having hypersensitivity to alkylating agents but not UV, were obtained using MMC and EMS. In the latter case, the two clones had significantly increased sensitivity to the killing effects of ^{60}Co gamma rays.

611. Busch et al. [B76] isolated 54 UV-sensitive clones of CHO cells, including two from a parent cell line which is hypersensitive to EMS and is also sensitive to x rays (EMS and ICR-170 were used to mutagenize the cells). Most of the UV-sensitive clones studied thus far appear to be five-fold more sensitive than the original strain, in terms of the slopes of the survival curves. All the seven clones examined for DNA repair competence using a repair replication assay (measurements of repair using alkaline isopycnic gradients) exhibited a DNA repair defect (0–34% of normal) resembling that seen in XP cells. Furthermore, in two of the repair-replication defective clones, there was an approximately nine-fold enhancement of UV mutagenesis (Ouabain resistance, 6-TG^R and 8-azaadenine).

G. SUMMARY AND CONCLUSIONS

612. Further studies on the role of some factors affecting the recovery and type of mutants obtained have been performed. With CHO cells, it was shown that de-amination of 8-azaguanine to 8-azaxanthine by serum under conditions where cell density and expression time were controlled leads to the selection of many mutants which are resistant only to drug concentrations lower than that added to the selecting medium.

613. With synchronized CHO cells, it has been shown that for x-ray-induced cell killing, the sensitive periods of the cell cycle are G_1, G_2, M and early S, whereas for mutation induction (6-TG^R or 8-AG^R) the boundary between G_1 and S shows maximal sensitivity.

614. In CHO cells, 6-^{3}H-thymidine and 5-methyl-^{3}H-thymidine induce 6-TG^R mutants and the dose-response curves are linear. Tritium in the 6 position produces 2–3 times more 6-TG^R mutants than tritium in the 5-methyl position, suggesting that a local effect associated with transmutations at the 6 position in the DNA produces mutations more efficiently than the emitted beta particles.

615. In V-79 cells, the dose-effect relationship for the gamma-ray induction of 6-TG^R or 8-AG^R mutants is non-linear. Fractionation of the dose into two or more fractions leads to an increase in survival and a decrease in mutation frequency (8-AG^R). In V-79 cells and human diploid fibroblasts, accelerated helium, boron or nitrogen ions covering a LET range from 28 to 470 keV/μm produce a dose-dependent increase in the frequency of 6-TG^R mutants. The effectiveness per unit dose for both inactivation and mutation induction increases with increasing LET of the radiation. Aluminium- and carbon-K characteristic ultrasoft x rays are capable of both causing inactivation and inducing 6-TG^R mutants in Chinese hamster (V-79) and human cells. These data also suggest that the sensitive sites for mutation induction and inactivation are smaller than about 7 nm.

616. In mouse lymphoma cells (L5178Y), the induction by gamma rays (high dose rate) of 6-TG^R mutations follows a non-linear kinetics. High dose rate irradiation is more effective than low dose rate irradiation in the induction of these mutations. After a dose of 2 Gy, the mutation frequency continued to decline with a decrease in dose rate (to about one-half of that after high dose rate irradiation) until the dose rate reached about 3.3 10^{-2} Gy min^{-1} below which there was no further reduction. Furthermore, the yields of mutations were the same at both high and low dose rates when the irradiations were carried out at 0°C whereas at 37°C, the yield was less than one-half of that at the higher dose rate.

617. In human diploid fibroblasts, the dose-effect relationship for the induction (by x rays) of 6-TG^R mutations is linear.

618. Analysis of all published data on x- or gamma-ray induction of HG-PRT$^-$ mutations in human and mouse cell strains shows that when the induced mutation frequencies are plotted against log survival, the relationship is linear (with a slope of about 4 10^{-5} mutants per lethal event) suggesting that mutation frequency curves can be predicted from a knowledge of survival curves for each cell type.

619. Studies have been conducted to examine the effects of the combination treatment (PUVA) involving long-wave UV (UVA) and 8-methoxypsoralen (8-MOP). Treatment with 8-methoxypsoralen or UV (UVA) alone was not mutagenic and the combined treatments induced both mutations (6-TG^R) and cell killing. The data suggest a linear relationship between mutant yield and the product of the concentration of 8-methoxypsoralen times the UV (UVA) dose.

620. The autoradiographic method devised by Strauss and Albertini for quantitatively detecting 6-TG^R variants in human peripheral blood lymphocytes is discussed together with the results obtained by these authors with lymphocytes sampled from patients with Lesch-Nyhan syndrome, normal individuals, and individuals who have undergone chemo- or radiotherapy. Evans and Vijayalaxmi have extended the usefulness of the lymphocyte system for detecting HG-PRT- mutations in in vitro studies using 8-azaguanine as the selection agent. X rays and mitomycin-C were the chosen mutagens. With both of these, increases in the yields of 8-AG^R variants with increasing exposures were found. However, while the radiation-induced variants are considered to be mutational events, those induced by MMC are thought to represent cells in which large MMC-guanine adducts have prevented normal transcription of the HG-PRT locus to give functional HG-PRT.

621. In L5178Y mouse lymphoma cells, x rays and UV irradiation produce a linear increase in the frequency of thymidine kinase-deficient mutants with increasing dose. In the same system, unfiltered broad-spectrum radiation emitted by black light, cool white and black light blue, fluorescent lamps and a sunlamp are both toxic and mutagenic when the cells are irradiated in phosphate buffered saline. But their relative mutagenic efficiencies are different.

622. Gamma irradiation is ineffective in producing mutations to ouabain-resistance in Chinese hamster (V-79) cells, but UV irradiation or EMS treatment are effective in this regard. Lack of Oua^R mutation induction by ionizing radiation has also been demonstrated for CHO cells.

623. The effects of fractionated UV irradiation with cycloheximide or caffeine present during the interval between fractions on mutation induction to ouabain resistance have been studied. With cycloheximide present between the dose fractions the effects were different (an increase or a decrease in mutation frequency relative to the unfractionated UV dose) depending on the experimental protocol. Caffeine given as a pre-treatment or between the UV dose fractions always led to an enhancement of the mutation frequency.

624. There is now good evidence that a sizeable proportion of the HG-PRT mutations induced by ionizing radiations (in human and V-79 fibroblasts) is associated with structural changes of the X chromosome. With x rays, this proportion is of the order of 5–25%, whereas with high-LET radiations, it is of the order of 20–60%. Other studies using a CHO hybrid cell line containing a single human chromosome 11 (on which are present genes for cell-surface antigens, a_1, a_2 and a_3 and that for lactic dehydrogenase-A) also provide evidence supporting the thesis that radiation-induced mutations at these loci may be predominantly chromosomal deletions.

625. A number of mutagen-sensitive cell lines have been isolated from cultured mammalian cells in recent years and these are proving to be useful in studies on DNA repair, relationship between DNA repair and mutagenesis, etc.

VII. EVALUATION OF GENETIC RADIATION HAZARDS IN MAN

A. A SUMMARY OF THE MAIN CONCLUSIONS REACHED BY THE COMMITTEE IN ITS 1977 REPORT

626. The 1977 report of the Committee presented the available human and experimental data that were considered suitable in the context of the evaluation of genetic radiation hazards in man; discussed the assumptions and uncertainties involved in making use of these data for such purpose; and gave quantitative estimates of hazards using both the so-called "direct" and the "doubling-dose" methods.

627. With the "direct method", it was pointed out that, with respect to hazards from the induction of mutations, what was desired was an assessment of the risk of induction of mutations causing dominant effects in the progeny with some indication of handicaps and disabilities that they may cause. To do this, the mouse data on the gamma-ray induction of mutations causing dominant effects in the skeleton were used. The reasoning was, and still continues to be, that many of the skeletal abnormalities recovered in the mouse experiments are similar to rare dominants and rare irregularly-inherited dominant conditions in man which together constitute a sizeable proportion of human genetic diseases.

628. The overall estimate of risk arrived at using the data on skeletal mutations with appropriate corrections for low dose, low dose rate irradiation conditions, ease of diagnosis of skeletal defects in humans and severity of effects was 20 10^{-6} per 10^{-2} Gy (or 2000 10^{-6} per Gy) of paternal, low-LET, low dose or low dose rate irradiation. In other words, 2000 individuals per million born will be expected to suffer from one or another serious handicap due to the induction of mutations with dominant effects, per Gy of paternal radiation exposure under the stated conditions. The figure therefore subsumes the effects of mutations which are operationally classified as "dominants" as well as those of "recessives" which have effects in the heterozygous condition.

629. The rate of 20 10^{-6} per 10^{-2} Gy of paternal exposure was arrived at by the Committee by multiplying the estimated rate of induction of skeletal mutations 4 10^{-6} per 10^{-2} Gy (of low-LET, low dose rate irradiation) by a factor of 10 and then dividing the product by a factor of 2. The rationale was set forth as follows: "... Firstly, a perusal of McKusick's latest tabulation of monogenic disorders in man [M17] will reveal that out of the 583 'proved' autosomal dominants, 328 are clinically important; in the latter group, 74 (or roughly 20%) involve one or more parts of the skeleton to a varying extent. However, this figure is undoubtedly a reflection of the ease of diagnosis of such abnormalities by phenotypic inspection and/or radiography. The true figure therefore is likely to be lower and, in the opinion of Carter and McKusick, is of the order of 10%". (This means that only about 10% of

the dominant mutations in man are likely to be associated with skeletal defects. The reciprocal of this, i.e., 100/10, provides the multiplication factor 10 used to convert the rate of induction of skeletal mutations into one applicable to mutations having dominant effects on any of the bodily systems in man.)

630. "Secondly, not all of the skeletal abnormalities of mutational origin studied in the mouse will impose a serious handicap in humans. Selby suggests that this proportion of abnormalities (leading to serious handicaps) may range from 25% to 75%; in Carter's opinion, a figure of 50% may be accepted as a tentative estimate and this has been confirmed in a detailed discussion of the mutants by Selby and McKusick" [U1]. (This is the basis for dividing 10 x 4 10^{-6} by 2.)

631. Similar data on the induction of skeletal mutations in mouse females were not available. The Committee carefully considered the existing evidence from specific locus studies in mouse females, in particular, the data showing that for radiation conditions applicable to man, maturing oocytes manifest a very low level of mutational sensitivity and immature oocytes are virtually insensitive. It was argued that if the mutational sensitivity of human oocytes were similar to that of the mouse, the risk for human females will be low (and very much lower than that for males), but the Committee refrained from giving any quantitative estimate.

632. For computing the risk from the induction of balanced reciprocal translocations (the predominant kind of radiation-induced structural change), the Committee used the limited human and marmoset cytogenetic data obtained in experiments involving acute x irradiation of spermatogonia. Two points deserve mention here: firstly, although, to be on the conservative side, the above data were used, it was noted that the sensitivity of the rhesus monkey (a species more closely related to man than either the marmoset or the mouse) to the radiation induction of reciprocal translocations in their spermatogonia is far lower than that of the marmoset or the mouse; secondly, it was assumed that balanced reciprocal translocations as such are not associated with adverse phenotypic effects of clinical significance and that the risks stem primarily from the unbalanced products generated during meiotic segregation in translocation heterozygotes.

633. Analysis of the cytogenetic data (obtained in experiments involving irradiation of the testes of marmosets and men and screening of the spermatocytes descended from irradiated spermatogonia) permitted an estimate of about 7 $10^{-4}/10^{-2}$ Gy/cell. From this, the rate of heritable translocations was estimated as 1.75 $10^{-4}/10^{-2}$ Gy/gamete (assuming that the rate of recovery in the F_1 will be one-fourth of that in spermatocytes). The rates for low dose x rays, low dose rate x rays and chronic gamma-irradiation were derived by dividing the above figure of 1.75 10^{-4} by 4, 2 and 10, respectively. The rates thus derived (0.44 10^{-4}, 0.88 10^{-4} and 0.18 $10^{-4}/10^{-2}$ Gy/gamete) were used to estimate the proportion of unbalanced zygotes that will result (= twice the above rates; based on the segregational properties of translocation heterozygotes) and the proportion of the unbalanced zygotes that will result in children with multiple congenital anomalies (= 6% of unbalanced zygotes; based on human data; see [U8]). These calculations showed that per 10^{-2} Gy of paternal irradiation, between 2 and 10 per million children born will suffer from multiple congenital anomalies which can be attributed to the induction of reciprocal translocations in the spermatogonia of irradiated males.

634. The Committee stressed the point that the rates of translocation induction used above were based on human and marmoset cytogenetic data with corrections for transmission and expected effects at low doses and dose rates being based on mouse data. It cautioned that "... should it turn out that the rate of induction in human spermatogonia is more similar to that in the rhesus monkey, the estimates may need revision, and consequently the quantitative figures arrived at must be considered provisional at present".

635. There were no data on the rate of translocation induction in human females or in any primate species. The data for mouse females showed that in maturing oocytes exposed to acute x-irradiation, the rate was 0.16 $10^{-4}/10^{-2}$ Gy/gamete (semi-sterility data). The Committee stated that "... although there is no direct evidence on the response of immature oocyte stages to the induction of translocations at low doses and dose rates, the data on specific locus mutations and on X-chromosome losses strongly support the view that the rate for translocations is also likely to be low, but no quantitative estimates can be given".

636. The Committee expressed the view that the risk from the induction of structural aberrations other than reciprocal translocations is likely to be very small since most of them act too early to constitute a real hazard. For chromosomal deficiencies (which are also known to be induced at relatively high frequencies in the mouse after oocyte irradiation) it was stated that "... not enough is known yet about their probable over-all rate of induction or deleterious effects (especially in the heterozygote) to make any estimate of the genetic damage they may cause".

637. The risk from the induction of sex-chromosome losses was considered to be very low after irradiation of males and probably also very low after irradiation of females, these conclusions being based on mouse data. The Committee carefully evaluated the human as well as mouse data on the induction of non-disjunctional effects and concluded that information on this is very inadequate or conflicting and therefore no quantitative estimates could be given.

638. For arriving at estimates of risk using the "doubling-dose method" the Committee made use of the following assumptions and data. The doubling-dose for all genetic effects is probably of the order of 1 Gy and the use of this figure in computations is not likely to underestimate risk. The incidence of autosomal dominant and X-linked diseases in man is 1%; the increase in the frequency of these diseases as a result of radiation exposure will be directly proportional to the mutational rate. Autosomal recessive diseases occur in humans at a frequency of 0.1%; their incidence is only very indirectly related to mutation rate. The incidence of numerical chromosomal anomalies and unbalanced structural anomalies is of the order of 0.4%; the increase in their frequency will be directly proportional to mutation rate. Balanced reciprocal translocations per se may not confer any risk to the carriers; the risk from the induction of such structural rearrangements mainly stems from the unbalanced products generated by these during meiotic segregation. For diseases of complex aetiology, such as irregularly-inherited dominant diseases, multifactorial diseases, and congenital malfor-

mations (together constituting 9%), the mutational component (i.e., the proportion of these diseases that will respond to radiation exposure in a manner similar to that of simple monogenic dominant diseases) is of the order of 5%. Lastly, under continuous radiation exposure (10^{-2} Gy/generation), the population will reach a new equilibrium with respect to the incidence of these diseases; the rate of approach to the equilibrium as well as the incidence values at equilibrium and in the first generation following radiation exposure will be different for the different classes of diseases; thus for instance, the approach to equilibrium will be faster for single-gene dominant diseases, very slow for recessive diseases and somewhat intermediate for diseases of complex aetiology. The first generation incidence following radiation exposure (under conditions of continuous radiation exposure) will be one-fifth of that at equilibrium for single gene dominants and X-linked diseases, nearly the same in the first generation and at equilibrium for chromosomal diseases and one-tenth of that at equilibrium for diseases of complex aetiology.

639. All these considerations permitted an estimate of the total increment expected in the first generation amounting to 63 new cases of genetic diseases per million progeny and 185 cases per million at equilibrium, when the population is continuously exposed to low dose rate, low dose or chronic low-LET irradiation at a rate of 10^{-2} Gy per generation.

B. RELEVANT NEW INFORMATION THAT HAS BECOME AVAILABLE SINCE THE PUBLICATION OF THE 1977 REPORT

640. The new data that have become available since the publication of the 1977 report (and considered in detail in the preceding chapters) can be arbitrarily grouped under at least four categories, with some overlap between them; (i) those that confirm and further document the Committee's earlier conclusions; (ii) those that help to shed light on the validity of assumptions or tentative conclusions (arrived at on the basis of limited data) or controversial view-points; (iii) those that seem relevant in a qualitative sense but which, as yet, cannot be used in a quantitative manner for risk evaluations; and (iv) those which open up potentially useful approaches to hazard evaluations and/or those which may be of use in improving quantitative evaluation of hazards. Some of the most important of these will be summarized in the following paragraphs.

1. Confirmatory data

(a) Human studies

641. The incidence figures for congenital malformations in the Hungarian survey are similar to the estimate made by Trimble and Doughty in the British Columbia survey. The data of Myrianthopoulos and Chung based on an almost complete ascertainment of cases of congenital malformations show that, if anything, their incidence may be even higher. The analysis of the transmissibility of some common congenital malformations summarized by Leck (for all these, see section I.A) serves to illustrate the view expressed by the Committee, namely, that the mutational component of these diseases is probably quite small.

642. The new data from the recent Edinburgh and Japanese surveys on the incidence of chromosomal anomalies in newborns (subsection I.C.1, Table 2) show that, despite the systematic use of banding techniques, the frequencies of different kinds of abnormalities are similar to those reported in a number of earlier surveys. The currently available results from chromosomal studies of children born to survivors of Hiroshima and Nagasaki (subsection I.C.11) show that the frequencies of chromosomal abnormalities are similar to those in controls.

643. Reviews on the incidence of chromosomal anomalies in spontaneous abortions and on aneuploidy (section I.C, Figure 1) document and confirm that:

(a) The overall frequencies of chromosomal anomalies in spontaneous abortions may be as high as 50%;
(b) Spontaneous non-disjunction plays a major role in generating aneuploidy;
(c) Such aneuploidies are frequent among chromosomally abnormal foetuses (sub-section I.C.4) and in newborns (Table 2);
(d) Non-disjunction occurs in the male as well as female germ cells, both in meiosis I and in meiosis II (subsection I.C.7 and Table 4), as suggested by studies on spontaneous abortions and on Down's syndrome;
(e) Evidence for radiation-induced non-disjunction in man continues to be equivocal (Table 8);
(f) Direct studies on aneuploidy in human spermatozoa now appear possible (subsection I.C.10).

644. Many known single-gene traits in humans are associated with neoplasia (section I.D., Table 9). DNA repair studies with human cells (subsection I.E.3) which have been in progress for some years now, have underlined the important role of these processes, particularly with respect to their relationships to cellular response to radiation and other mutagenic agents (subsection I.E.2).

(b) Studies with experimental organisms

645. Further evidence has been obtained in mice for the induction of genetic effects by ^{239}Pu (section II.A). Even low doses from ^{239}Pu alpha rays are capable of causing significant increases in the frequency of translocations (subsection II.B.2). Studies with ^{3}H (given as tritiated water) have shown significant induction of specific locus mutations in both pre- and post-meiotic germ cells of male mice (subsection II.D.1); the mutational spectrum shows no striking disparity from that induced by x rays.

646. The dose-response curve for the induction of specific locus mutations in maturing oocytes of female mice (high dose rate x-irradiation) has now been extended to include the 6 Gy dose point. All the high dose rate data obtained at different doses to maturing oocytes considered together confirm that the dose-response is curvilinear (subsection II.D.2,).

647. Confirmatory evidence for earlier findings that the yield of reciprocal translocations induced in spermatogonia decreases with decreasing dose rate of low-LET radiation has been obtained in a new set of studies (subsection II.B.2; Table 21). Further data on the induction of heritable translocations in female mice are in line with earlier results in showing that the rate in maturing oocytes of females is about one-half of that in

males (subsection II.B.3). The frequency of chromatid interchanges induced in maturing mouse oocytes (scored in metaphase I) is lower by a factor of 10 at low dose rate relative to that at high dose rate (subsection II.B.4).

648. The weight of currently available evidence suggests that, following irradiation of male mice (spermatogonial irradiation), Robertsonian translocations are recovered (if at all) at very low frequencies.

649. A number of studies have further documented the existence of differences in sensitivity for the induction of chromosomal aberrations in male and female mouse germ cell stages (subsections II.B.2 and II.B.4) and of dominant lethals (subsection II.A.1 and Tables 20 and 22). The new data on dominant lethal induction in female guinea pigs, Djungarian and Chinese hamsters (subsection II.A.2) serve to further highlight the existence of species differences in radiosensitivity.

650. A number of studies have been carried out on the induction of aneuploidy by irradiation of male and female mice and female Chinese hamsters (subsection II.C.4). While in mice in some studies the evidence for the radiation-induction of aneuploidy (scored in utero) appears good, in others it is weak; in Chinese hamsters, the evidence is not clear-cut.

651. Completed studies on x-ray-induction of reciprocal translocations in the spermatogonia of rhesus monkeys show that the dose-response is "humped" with a peak around 1 Gy (thus being qualitatively similar to what is known for other mammals studied in this respect) and with a rate of induction (up to doses of 1 Gy) being substantially lower than what has been recorded for other mammalian species (subsection II.B.5; Tables 23 and 24).

652. Studies on the acute x-ray induction of autosomal recessive lethals in maturing oocytes of mice have demonstrated that the rate is nearly the same as that for spermatogonia. Germ cell stages in female foetuses do not appear to be more sensitive to the x-ray induction of autosomal recessive lethals than maturing oocytes in adult females. There is a dose rate effect for the induction of specific locus mutations in oocytes of female mice irradiated shortly before birth, suggesting that the repair capacity of these oocyte stages are not different from that of maturing oocytes in adult females (section II.D).

653. Further data on the relationship between chromosome arm numbers and relative radiosensitivity to the induction of dicentrics in lymphocytes confirm the view expressed in the 1977 report, namely, that chromosome arm number is not a reliable criterion for extrapolation from one species to another with respect to the sensitivity of the chromosomes to the induction of dicentrics (subsection II.F.2).

654. Irradiation of mice or rats at very low dose rates (of the order of 1 10^{-2} to 2 10^{-2} Gy d^{-1}, gamma rays) causes no reduction in spermatogonial stem cell numbers, although at rates $\geq$ 3 10^{-2} Gy d^{-1}, the situation is different (chapter III). Further data from labelling studies of irradiated mouse testis show that the surviving spermatogonial stem cell population is qualitatively the same for that portion of the dose-response curve giving a linear increase in mutation frequency (up to 600 R acute irradiation).

655. Studies on the timing of oocyte maturation in the mouse show that a period of six weeks elapses between the initiation of stage 3b to ovulation. This means that in mutation experiments, conceptions within six weeks after irradiation would utilize oocytes exposed in stages 3b–8 and that litters conceived after six weeks would be derived from stages 1–3a. Since the nuclear morphology of both stages 3a and 3b is similar to one another and also to stage 3 of guinea pig and human oocytes, it would appear that the change in mutational sensitivity of the mouse oocytes occur in a cell stage with "typical" diplotene configuration (chapter IV).

656. Evidence has been obtained that in human fibroblasts and Chinese hamster cells, a significant proportion of x-ray and high-LET radiation-induced HG-PRT mutations is associated with cytologically demonstrable deletions or other aberrations in the region of the HG-PRT locus (section IV.A).

2. Data that shed light on the validity of assumptions, tentative conclusions and controversial view-points

657. The interpretation of the dose-rate effect observed for the induction of specific locus mutations (and thus, of the nature of the mutations induced) in experiments with female mice has been controversial for some time. While W.L. Russell has continued to favour the hypothesis that the mutations themselves are single-track phenomena and other track events are involved in damaging or saturating the repair process at high doses and dose rates, others (Abrahamson et al. Brewen et al.) have preferred an interpretation based on the premise that the mutations are predominantly two-track phenomena. In the discussion of their recent experimental results on dose-effect relationships for specific locus mutations in maturing mouse oocytes, Lyon et al. have supported W.L. Russell's interpretation and have detailed their reasoning for this (subsection II.D.3).

658. The question of whether the genetic radiosensitivity of the immature oocytes of the human female is similar to that of the mouse has been kept under continual review by the Committee (see, for instance, paragraphs 293–298 in the 1977 report). On the basis of all the evidence available the Committee concluded in 1977 that there was no consistent correlation between the induction of genetic effects, cell killing and chromosome morphology in oocytes (in mice, guinea pigs and golden hamsters); that even if one continues to consider the possibility that the human immature arrested oocyte might be mutationally as sensitive as the most sensitive of all oocyte stages in the mouse, for radiation conditions applicable to man the genetic hazard of radiation in the female will still be less than in the male. The new data from studies on the timing of oocyte maturation in the mouse (chapter IV) support the earlier view that nuclear morphology is not a reliable criterion of oocyte sensitivity: the nuclear morphologies of stages 3a and 3b oocytes are similar to one another (and also similar to those of stage 3 human and guinea pig oocytes) and yet, strikingly different in mutational sensitivity.

659. The results of experiments in Drosophila and Escherichia coli have yielded results consistent with one of the main assumptions involved in the use of the "doubling dose" method for risk evaluation, namely, that there is proportionality between spontaneous and induced rates of mutations (subsection II.F.4). However, the consistency in Drosophila exists, so far,

only for induced mutations in spermatozoa, and the consistency in Escherichia coli is dependent on excluding "hot-spots".

660. It may be recalled that in making estimates of increase of dominant and X-linked diseases (using the doubling dose method) under conditions of continuous low-LET radiation exposure at the rate of 10^{-2} Gy/generation, the Committee in its 1977 report assumed that the first generation increment for these diseases will be about one-fifth that at equilibrium. The recent calculations of Childs [C68] show that the increment in the first generation is of the order of 15% of that equilibrium, a figure which is quite similar to the 20% used by the Committee.

3. Data that seem relevant in a qualitative sense

661. The frequencies of chromosome aberrations in lymphocytes of individuals living in an area of high natural radioactivity in Austria have been found to be elevated; this is also true of nuclear dockyard workers in the United Kingdom, of nuclear power plant workers in the Federal Republic of Germany and the United Kingdom, of uranium miners, of workers with internal depositions of plutonium, and of atomic bomb survivors of Hiroshima (section I.F).

662. Studies have been made with rabbits and mice keeping them artificially in huts in areas of high natural radioactivity in France for periods up to 20 months (only four months in the case of mice). In rabbits there was an increase in the frequencies of chromosomal aberrations (lymphocytes) reaching up to about 4% by one year; however, by 20 months, there were practically no aberrations. Male mice kept for four months, showed no translocations in their spermatocytes. But, when such "irradiated" males were mated to unirradiated animals, there were slight increases in litter size, the mean number of offspring sired and the mean number of offspring weaned over a six-month period. Female "irradiated" mice in contrast, under similar conditions showed slight reductions in all of the above indicators (subsection II.F.1).

663. Although it has been known for a long time that certain classical chromosomal syndromes in man are associated with congenital malformations, mental and physical defects, it is only in recent years that studies are beginning to focus attention on the possible clinical significance of other abnormalities such as balanced reciprocal translocations. The currently available data, although not based on random samples, are suggestive of an association between apparently balanced reciprocal translocations (and some other structural rearrangements) and mental and physical defects (subsection I.C.2) and point to the need for further studies (e.g., follow-up of children studied as newborns and who were found to have balanced structural anomalies).

664. In the mouse it has also been shown that some balanced reciprocal translocations can have dominant phenotypic effects on the skeleton (subsection II.D.8).

665. The preliminary results from tests of mutants originally isolated because of the skeletal abnormalities that they caused in the F_1 offspring, show that most of them behave as recessive lethals. Put another way, radiation-induced recessive lethals can have dominant deleterious effects (subsection II.D.8).

666. The utilization of banding techniques to study human chromosomes has, among other things, led to the discovery that partial monosomies and trisomies for practically every chromosome of the human complement are frequent, and are in fact more common than was envisaged a few years ago (subsection I.C.12). The recent discoveries of heritable fragile sites in human chromosomes have exposed another facet of chromosome structural defects (?) whose significance in the context of human pathology remains to be established.

667. Studies of chromosomal evolution in primates using banding techniques have shown that the sequence and types of chromosomal changes in different lines are quite different (subsection II.F.5). However, the questions of whether the predominance of a particular kind of change in the evolutionary history of a given species (for instance, the predominance of pericentric inversions in the line of descent leading to Homo sapiens) puts some constraints on or predispose the species to similar inducible changes or whether the evolutionary history is "irrelevant" in the context of studies on induced aberration remain to be answered.

668. The arguments advanced by Neel in favour of the thesis that the contribution to human disease of mutations technically classified as recessives is currently underestimated, have been considered (section I.A); however, at present, it is difficult to give quantitative estimates.

4. Data useful for quantitative assessment of genetic radiation hazards

669. The only new data that have become available since the publication of the 1977 report and which can be used in the context of quantitative assessment of genetic risks to man are those that derive from experimental studies on the induction of dominant mutations causing cataracts in mice (subsection II.D.8). Further, the data on the induction of reciprocal translocations in the rhesus monkey (subsection II.B.5), although not new, can be used, at least to set an arbitrary lower limit for the risk from the induction of reciprocal translocations.

C. SOME RELEVANT RECENT PUBLICATIONS ON QUANTITATIVE EVALUATION OF GENETIC RADIATION HAZARDS IN MAN

670. In two papers, Selby [S75, S117] has discussed, among other things, the problem of quantitative evaluation of genetic radiation hazards in man and has briefly summarized the risk estimates (including the methods and assumptions used) arrived at by UNSCEAR in its 1977 report and by the BEIR Committee in its report published in 1980 [B77]. The estimates of the latter Committee are discussed later in this section and will not be gone into here.

671. Ehling [E17], Ehling and Kratochvilova [E13] Kratochvilova and Ehling [K23] made a preliminary estimate of genetic risks from the induction of mutations having dominant effects, using the data on cataract mutations in mice obtained in their experiments in which a gamma-ray exposure of 910 R was given to male mice in two equal fractions separated by a 24 h interval (spermatogonial data). As will be recalled (subsection II.D.8), the rate of induction

estimated in this study was 1.3 10^{-6}/gamete/R. This figure was multiplied by 0.85 (to correct for the enhancement effect due to fractionation and based on specific-locus data collected in the same study), by 0.3 (correction factor for dose rate effect), by 1.2 (to correct for DNA content in human cells relative to that in mouse cells) and by 32.4 (to extrapolate from data on dominant cataract mutations to total dominant mutational damage affecting all bodily systems; based on the ratio of dominant cataract mutations to all dominant mutations as estimated from the tabulations of McKusick in 1975 [M17]). The resultant figure was 13 10^{-6}. In other words, following paternal low-LET irradiation, there will be 13 progeny per million born (per R of irradiation) who would be expected to be affected with one or another kind of serious genetic disease of induced mutational origin.

672. In subsequent papers, Ehling [E20] and Ehling et al. [24] extended these calculations to data from studies on the induction of cataract mutations by single acute gamma-ray exposures of 534 R and 600 R. As discussed earlier (Chapter II.D.8), the rates of induction estimated from these data are: 5.5 10^{-7}/gamete/R (534 R) and 4.5 10^{-7}/gamete/R (600 R). These rates were multiplied by 36.8 (the "new" ratio of cataract to all dominant mutations that can be calculated from McKusick's more recent compilation of 1978 [M16]). The resultant figures were: 20 10^{-6}/gamete/R and 17 10^{-6}/gamete/R. In other words, following paternal, low-LET, high dose rate irradiation, 17–20 affected progeny per million per R of exposure will be expected in the F_1. The figures will be one-third of these for low dose rate, low-LET irradiation.

673. In a recent paper, Childs [C68] has made a detailed analysis of published data on birth frequencies, mutation rates and fitness of each of the important dominant and X-linked diseases in humans. For dominant diseases, the author made use of the list compiled by Carter [C49, C50] with minor modifications. The frequency of rare dominant diseases was estimated based on the frequency of diseases given by Trimble and Doughty [T1]. For X-linked diseases, the source was the list compiled by Stevenson and Kerr [S124] and selected data from Trimble and Doughty.

674. From his analysis, Childs estimated that these diseases (dominant and X-linked) affect about 0.6% of liveborn individuals of which 16% or 0.1% of livebirths carry a newly-arisen mutation. Assuming that the population is exposed to low-LET irradiation at a rate of 10^{-2} Gy/generation and that the doubling dose is 1 Gy, he estimated that at equilibrium, there would be about 61 extra cases per million livebirths of serious genetic disease; the expected increase in the first generation following the radiation exposure would be 15% or 9 cases per million. The increase in the first two generations would be 24% of that at equilibrium and a 50% increase would occur by the ninth generation. For dominant diseases alone, the increase would be 14% in the first, 23% by the second and 50% by the tenth. For X-linked diseases alone, the increase in the first generation is 25%, and in the first two generations, 50%. (As X-linked diseases have a birth frequency of only 4% of that of dominant diseases, the combined increase is only slightly higher than for dominant diseases alone.)

675. Childs considers that the estimates arrived at above may be maximum estimates for two reasons. Firstly, Neel et al. [N24] calculated that the minimum doubling dose, based on mortality data of the children of atomic bomb survivors of Hiroshima and Nagasaki, and mutation induction in mice at low dose rates, should be 1.38 Gy for males and more than 10 Gy for females, i.e., a harmonic mean of about 2.4 Gy. Secondly, some of the dominant disorders included in the analysis (the two common disorders hypercholesterolaemia and otosclerosis account for 50% of the birth frequency of dominant disorders) are likely to be maintained by selection pressure alone and would therefore not change in frequency with a change in mutation rate [N25].[19] Childs concludes that the "overall dominant genetic risks from ionizing radiation may have been overestimated by UNSCEAR (1977) by a factor of at least 6". Thus, using a doubling dose of 2.4 Gy and excluding the disorders mentioned above and X-linked ones, the expected extra number of defective children would be 3 per million births and 12 per million births at equilibrium.

676. Other papers of interest are those of Neel, Schull and Otake [N21], Schull, Otake and Neel [S130] and Schull et al. [S131], the last of which is the most recent. In these papers, the authors presented an analysis of all the currently available genetic data obtained from continuing studies of the Hiroshima and Nagasaki populations. The data pertain to untoward pregnancy outcomes,[20] survival through childhood, incidence of sex-chromosomal aneuploids and incidence of biochemical variants. In all the calculations, an RBE of 5 for neutrons has been assumed. As Schull, Otake and Neel [S130] point out "in no instance is there a statistically significant effect of parental exposure. But for all indicators, the observed effect is in the direction suggested by the hypothesis that genetic damage resulted from the exposure". Doubling dose estimates have been made only for the first three of the indicator traits since the data on biochemical variants are considered too preliminary to provide a meaningful estimate for this end-point.

677. The gametic doubling dose estimates presented [S131] are the following: untoward pregnancy outcomes: 0.69 Sv (standard deviation, 0.93); survival through childhood: 1.35 Sv (standard deviation, 3.88); sex-chromosomal aneuploids: 5.35 Sv (standard deviation, 24.31). The weighted average of the estimates is 1.39 Sv with a standard deviation of approximately 1.56. The authors [S130] consider that this estimate should be multiplied by a factor of 3 to convert it into a relevant estimate for low doses and dose rates.

678. The Committee examined the data and the analysis presented and concluded that in view of the lack of statistically significant effects and high standard deviations associated with the doubling dose estimates, it would be premature to use these for genetic risk assessments at the present time.

679. *Genetic risk assessments for radiological protection purposes.* Oftedal and Searle [O18] have summarized the conclusions of a Task Group set up by ICRP (hereafter to be referred to as Task Group) to make a quantitative risk assessment and to express the risks in terms comparable to those for somatic risks. Most of the main conclusions reached by the Task Group are similar to those of UNSCEAR in its 1977 report. This is to be

[19] It should be noted that the paper referred to by Childs gives no evidence in support of this belief, which must be considered speculative at present.

[20] An untoward pregnancy outcome is one that terminated in a child who had a major congenital defect, was stillborn, or died in the neonatal period.

expected in view of the fact that the basic data and several of the assumptions used are similar in both cases. To facilitate easy reference the summary table of the Task Group is reproduced below as Table 40.

680. UNSCEAR used both the direct and the doubling dose method for the computation of risks. The Task Group, however, used the doubling dose method (except for reciprocal translocations to be discussed later) because "(i) it allows the risk to be expressed in terms of basic human hereditary damage and (ii) if an overall genetic doubling dose is accepted, it allows an overall genetic risk assessment to be made even in the absence of direct experimental evidence on certain categories of hereditary defect".

681. In the UNSCEAR 1977 report, the risks (calculated using the doubling dose method) are expressed as a certain number of cases of serious genetic disease per million progeny following low-LET, low dose or dose rate irradiation of a population (assumed to be stable in size) at a rate of 10^{-2} Gy/generation. The Task Group has expressed the risks, instead, as a certain number of cases per million man-rem (which is another way of expressing them, allowing for the possibility of exposure to different kinds of irradiations with different RBEs and LETs).

682. The doubling dose used by UNSCEAR is 1 Gy (low-LET irradiation) and that by the Task Group 100 rem; with this method, the Committee computed the expected increments for the different categories of genetic disease as a certain number of cases in the first generation and at equilibrium. The Task Group gave in addition, figures for the second generation as well.

683. For simple dominants and X-linked diseases, the expected increments in the first generation and at equilibrium computed by the Committee and by the Task Group are the same (namely 20 per 10^6 in the first generation and 100 per 10^6 at equilibrium).

684. For diseases of complex aetiology (incidence figure of 9% or 90 000 per 10^6), the Committee assumed that the mutational component is of the order of 5%, which is another way of saying that the incidence of only a small fraction of these diseases (5% of 90 000 per 10^6 = 4500 per 10^6) will respond in direct proportion to mutation pressure (just like the simple dominants and X-linked ones) while with the bulk of these, radiation would not produce any increase in their incidence rates. Thus with a doubling dose of 1 Gy, and under radiation exposure at the rate of 10^{-2} Gy/generation, the expected increase at equilibrium will be 45 cases per 10^6 individuals born (i.e., 4500 × 1/100 = 45). The Committee made the further assumption (based on the BEIR Report [B60]) that one-tenth of these cases (or about 5) will be expressed in the first generation.

685. The Task Group split up the category of diseases of complex aetiology into dominants of incomplete penetrance and multifactorial diseases maintained by mutation and multifactorial disease not maintained by mutation and stated that "these two categories of genetic damage are very difficult to study and their birth frequency in the population cannot be determined with any degree of assurance." That is, they did not use the incidence figure of 9% (for both categories together) arrived at in the British Columbia Survey. Consequently, the expected increments after radiation exposure were arrived at in a way different from the one used by the Committee described above. The Task Group "... felt that the number of extra cases at equilibrium after a parental dose of 1 million man rem could be taken as the sum of the equilibrium values of the categories (unbalanced translocations, aneuploid conditions and simple dominants), that is 100 + 30 + 30 = 160 of which 10% would become manifest in the first generation after a single exposure..." (see Table 40). For the second category described above the expected increment was given as zero. Thus, one of the main discrepancies between the conclusions of the Committee (1977 report) and of the Task Group (45 cases per 10^6 versus 160 cases per 10^6) stems from the different assumption and the way of calculating the effects of irradiation on the category of diseases with complex aetiology.

686. Regarding diseases with a recessive form of inheritance, the Committee in its 1977 report expressed the opinion that the effect of low level irradiation on the incidence of these diseases in the first generation will be "relatively slight" while at equilibrium (which will be attained after hundreds of generations) there will be a slight increase..

687. The Task Group used the same lines of reasoning as those used by the Committee in its 1977 report as will be clear from the following statements: "... The probability of a newly induced recessive mutation pairing up with a previously existing mutant allele at the same locus, so that the deleterious condition is expressed in the first generation after exposure, is regarded as negligibly low. In general, homozygous effects of induced recessives will be spread over hundreds of generations, with a very slow attainment of equilibrium ... for the above reasons, and in the context of radiation protection, it was thought that the true recessives would probably not contribute significantly to the extra mutation load following low level radiation exposure...".

688. The Task Group however mentioned that "... the evaluation of recessive mutational effects is very difficult and, not surprisingly, members of the Task Group were not unanimous in their views on this subject ... Two corresponding members have stated that the risk from 'nominal' recessive disorders, although largely concealed for many generations, may be a far graver problem than all other hazards combined, especially if these so-called recessives have significant effects in the heterozygotes. However, in the present state of our knowledge, this aspect of the risk problem is extremely difficult to quantify...".

689. Turning now to chromosomal diseases, the Committee in its 1977 report used an incidence figure of 0.4% (sex-chromosomal and autosomal trisomies, XO, mosaics and unbalanced structural aberrations) and estimated that with a doubling dose of 1 Gy and radiation at the rate of 10^{-2} Gy/generation, there will be about 40 cases of affected individuals per million; since the reproductive fitness of these individuals will be zero, there will be no accumulation over generations and thus the effects seen in any given generation will be essentially those of new chromosomal changes of the above kinds.

690. For the Task Group, the starting point, i.e., the incidence figure for these diseases was 0.5% (the overall frequency of sex-chromosomal and autosomal trisomies and the XO); this figure was multiplied by a factor of 0.6 to take into account the possibility that the frequency of transmission (to the gamete) of aneuploid

conditions may be lower after treatment of spermatogonia than of oocytes, as has been found in experimental studies with mice. It was stated that "... since all these aneuploids will be manifest in the first generation and will not reproduce, the expected frequency of extra cases for a doubling dose of 100 rem will be 0.005 × 0.6 × 0.01 per rem which is a risk of 30 per million in the offspring of a person receiving 1 rem".

691. In the 1977 report, the risk of producing unbalanced gametes leading to congenitally malformed children (stemming from the induction of balanced reciprocal translocations in males) was estimated using the combined marmoset and human cytogenetic data as 2 to 10 per million per rad. The risk for the irradiation of females was considered to be low, but no quantitative estimates were given.

692. The Task Group however, used the same data base (marmoset and human data) and gave an estimate for only low dose rate x-irradiation, i.e., a reduction factor of 0.5 was used noting "that the human x ray doses were below 100 rad". The rate so obtained was doubled to take into account irradiation of males and females. The rationale for this procedure was set forth as follows: "Heritable translocations can be induced in female mice after x-irradiation of dictyate oocytes. Although mutation rates are similar to those after spermatogonial irradiation, it seems probable from the results of specific locus experiments that the effect of lowering the dose rate will be more pronounced in oocytes than in spermatogonia. On the other hand, because translocations induced in oocytes would be in the form of chromatid exchange, a gamete from an affected oocyte would be six times more likely to have an unbalanced form than a balanced one [S135]. It seems reasonable to regard these opposing factors as cancelling each other out. Therefore, the risks from translocation induction in female germ cells have been taken to be similar to those in male ones." It will thus be clear that the nearly two-fold higher risk estimated by the Task Group derives from the assumption of equal sensitivity of males and females, one which was not used by the Committee.

693. *The BEIR Committee's assessments.* To facilitate discussion, the summary table from the above Committee's 1980 report [B77] is given below (Table 41).

694. Two methods have been used. The first is the indirect relative-mutation-risk method used by the BEIR Committee in its 1972 report (and what in UNSCEAR reports is referred to as the doubling dose method) and the second, the direct method for estimating total phenotypic damage induced in a single generation. With the first method, the estimates are expressed in terms of risk per rem of added exposure.

695. The BEIR Committee adopted a range for the relative mutation risk of 0.02 to 0.004 per rem (doubling dose, 50–250 rem). As is pointed out "this is based mainly on our best substantiated estimate of the doubling dose, namely, 114 R for mouse spermatogonia (for x- and gamma-radiation, the Roentgen, R, and the rem are virtually equal). We approximately halve and double this to get our range of 50–250 R, which we believe overlaps the true value. Further reason for thinking that this range is broad enough comes from the estimates of 100–200 R obtained when data from both sexes are combined ... The few human data suggest that humans are not notably more sensitive, and are probably less sensitive than mice".

696. For autosomal dominant and X-linked traits, the range of 40–200 (Table 41) under the heading "equilibrium" has been arrived at by multiplying the current incidence figure of 10 000 (per million) by the relative mutation risk range of 0.02–0.004 mentioned in the preceding paragraph. Although no corresponding figure for the first generation is given (see Table 41), it is pointed out that "... if we were to use the BEIR I method of estimating first generation expression from equilibrium estimates, then a mean persistence of 5 generations would imply first-generation expression in the range of ... 8–40 per million liveborn per rem of parental exposure".

697. For irregularly inherited diseases, the BEIR Committee assumed that the mutational component of these diseases is in the range of 5–50% (the same as that used in their 1972 report). When the current incidence (9%) is multiplied by this range as well as by the relative risk range, the range of 20–900 given in Table 41 is obtained. Again, the BEIR Committee did not give the increment in the first generation. However, it was stated that "... these mutants would be expected to persist for longer periods than would the simple, autosomal dominants. BEIR I assumed a mean persistence of 10 generations, which would lead to an expectation of a first generation expression of about one-tenth the equilibrium expression".

698. For autosomal recessives, the conclusions of the BEIR Committee (see Table 41) are essentially the same as they reached in their 1972 report (this was also discussed in the 1977 report of UNSCEAR).

699. Turning now to the range of 5–65 cases per million per rem given in Table 41, this represents the direct estimate of the total phenotypic damage in the first generation. The skeletal data obtained by Selby and Selby and by Ehling in mouse studies were used for this purpose and this was also the case with the estimate of UNSCEAR. The estimate of UNSCEAR was however 20 cases per million per 10^{-2} Gy of paternal irradiation. The reasons for the difference in the quantitative estimates are the following.

700. First, to convert the rate of induction of skeletal mutations in mice to an overall rate involving all bodily systems in humans, the UNSCEAR used a multiplication factor of 10 (i.e., $4\ 10^{-6} \times 10 = 40\ 10^{-6}$). This was divided by a factor of 2 to exclude mutations whose effects are slight; the BEIR Committee on the other hand, used a range of 5–15 to make the first conversion and used a range of 0.25 to 0.75 to make the second conversion. In its view, these ranges reflect the uncertainties involved. These operations (i.e., $4\ 10^{-6} \times 5 \times 0.25$ and $4\ 10^{-6} \times 15 \times 0.75$) give a range of 5–45. In other words, following paternal low-LET, low dose rate irradiation at a rate of 1 rem per generation, the expected number of individuals (in the generation following the exposure) who will suffer from the effects of serious genetic diseases of induced mutational origin will be in the range of 5–45 per million livebirths.

701. Second, to take into account the effects of irradiation of females, the BEIR Committee multiplied the upper limit of 45 given above by 1.44 (the UNSCEAR 1977 report assumed that the risk for irradiated human females will be negligible and did not give any quantitative estimate). The rationale for this multiplication

was set forth as follows: "The mutational response of resting oocytes in mice is negligible, compared with that of spermatogonia, and mature and maturing oocytes in mice have a mutation rate no greater than 0.44 times that found in spermatogonia. We do not know which of these two classes of oocytes would have a mutational response more similar to that of arrested oocytes in women. To incorporate this range of uncertainty into our risk estimate for the combined effect of irradiation of both sexes, we have simply kept the lower limit of our estimate the same as it was (assuming a negligible mutation frequency in resting oocytes) and multiplied the upper limit by 1.44 (assuming the maximal estimate of the mutation frequency in mature and maturing oocytes). This gives an estimate of 5–65 induced serious disorders per million liveborn as the first generation expression, after exposure of the entire population to 1 rem per generation."

702. For estimating the risk from the induction of reciprocal translocations, the UNSCEAR in its 1977 report used the marmoset and human cytogenetic data as the basis and arrived at an estimate of between 2 and 10 congenitally malformed children per million births per 10^{-2} Gy of low-LET irradiation of males. Briefly, the calculations were the following: $7\ 10^{-4}$ (rate of translocation induction; spermatocyte data) × 0.25 (multiplication factor to get the rate for heritable translocations in the progeny) × 0.1 or 0.5 (multiplication factors to account for dose-rate effect after chronic gamma and low dose rate x rays, respectively) × 2 (multiplication factor to estimate the rate of production of unbalanced products of reciprocal translocations) × 6% (the proportion of unbalanced products that was assumed to give rise to viable, but congenitally malformed progeny). The risk for the irradiation of human females was considered to be small, but no quantitative estimate was given.

703. For the BEIR Committee's calculations of risks for irradiated males, the starting point was the same cytogenetic data as those used by UNSCEAR. The estimate of risks (see Table 41) was also nearly the same, but the method of calculations was different. Some of the salient aspects of the calculations and the rationale behind them can be summarized as follows.

704. In mice, the ratio of the observed incidence of partial sterility to that calculated on the basis of the incidence of multivalents in primary spermatocytes was about 1:2 for 300 R and higher exposures, but was 1:1 at 150 R, for reasons yet unknown. To take into account the above uncertainty, the BEIR Committee assumed an overall ratio of 1:1.5. Thus from the rate of $7.7\ 10^{-4}$ per R (spermatocyte data; note that the UNSCEAR used a figure of $7\ 10^{-4}$) the "rate of potentially transmissible rearrangements in spermatocytes" was estimated as $4.7\ 10^{-4}$/rem (i.e., two-thirds of $7.7\ 10^{-4}$; the UNSCEAR's calculations imply a ratio of 1:1).

705. To convert the above figure into one that will be applicable at low total doses or at low dose rates, the BEIR Committee used a reduction factor of 2. This figure was arrived at by assuming a quadratic model for translocation induction in mouse spermatogonia, applying it to the published mouse data of Searle et al. ([S125]; 600 R; different dose rates), estimating the contribution of the linear and quadratic components to the total yield at an exposure of 100 R (because the human and marmoset data pertain to exposures of 100 R and below) and thus computing the expected dose-rate effect. The resultant rate was $2.3\ 10^{-4}$ per rem.

706. From the above rate and assuming that on the average, alternate segregations occur in 45% of the spermatocytes and that half of the recoveries carry the translocation, the BEIR Committee computed that the probability of transmitting a newly-induced translocation to an offspring will be $5.2\ 10^{-5}$ per rem (i.e., $2.3\ 10^{-4} \times 0.45 \times 0.50$). It follows that "the combined expectation for all adjacent segregations" would be 55% of $2.3\ 10^{-4}$ or $1.3\ 10^{-4}$.[21] Assuming further that "no more than 5% of all translocations are capable of producing viable aneuploids", the probability of generating this was estimated as 5% of $1.3\ 10^{-4}$ or $6.5\ 10^{-6}$ per rem.

707. The BEIR Committee stated "... however, we would expect only one of the four kinds of aneuploid segregation products to be capable of giving rise to viable zygotes. Taking into account that this might not always be one of the less frequent products, dividing by 4 to accommodate the one-out-of-four expectation gives the figure of $1.6\ 10^{-6}$. Using the order-of-magnitude range of uncertainty ... gives the range $0.5\ 10^{-6}$ to $5\ 10^{-6}$ per rem".[22]

708. For estimating risks for irradiated females, the BEIR Committee made the same assumption as that used in their 1972 report, namely, that the rate of induction of reciprocal translocations in females may be the same as that in males. "Thus, the expected frequency of viable aneuploids for both sexes is assumed to range from $1\ 10^{-6}$ to $10\ 10^{-6}$ per rem." The BEIR Committee also used "an alternative and independent approach based on litter-size reduction observed after acute irradiation of mouse germ cells" and pointed out that "the upper limit of $10\ 10^{-6}$ for both sexes combined may be an overestimate, and that the true value could indeed be near to zero".

709. In conclusion therefore, it can be stated that there is no major disagreement between the quantitative values presented in the 1977 UNSCEAR report and in the 1980 BEIR report, although some of the methods used are not the same.

D. CURRENT RISK ASSESSMENTS OF THE COMMITTEE

1. Direct method

(a) Mutational damage

710. As mentioned earlier, in its 1977 report, the Committee estimated genetic risks using a direct and a doubling dose method. With the former (and using the data on the induction of skeletal mutations in male mice as a basis), it was estimated that the risk from the induction of mutations (which will be expressed in the first generation progeny as serious genetic diseases, handicaps and disabilities) is of the order of 2000 cases per million births per Gy of paternal, low-LET, low dose or low dose rate irradiation. The Committee considers that the above estimate is still valid.

[21] Alternate and adjacent-1 segregations have the same meiotic consequences in translocations, providing there is chiasma formation in at least one of the interstitial segments, which is normally the case (see [S126]). In the absence of adjacent-2 segregation therefore, one-quarter of the sperm produced by spermatocytes heterozygous for a translocation will carry the translocation in balanced form. This is indeed a maximum figure, as stated in the BEIR report.

[22] See however Dutrillaux et al. [D26].

711. An independent estimate of risk from the induction of mutations in males can be arrived at using the data on the induction of dominant cataract mutations in male mice following spermatogonial irradiation. These data discussed in subsection II.D.8 permit estimates of 12.7 10^{-7}/R/gamete (fractionated gamma irradiation; 455 + 455 R, 24 h interval) and 5.0 10^{-7}/R/gamete (average estimate based on the data from the two single gamma-ray exposure experiments involving 534 R and 600 R, respectively). These rates however, need first to be converted into those that will reflect the response under low dose, low dose rate irradiation conditions in the mouse, and, secondly, to be transformed into quantities that will express the risk in humans. The performance of these operations rests on the validity of the following two assumptions. Firstly, that the quantitative changes in response of the dominant cataract mutations and of recessive specific locus mutations in mice to changes in dose rate and dose fractionation procedures are similar (and its corollary, that, if the rate under one set of radiation conditions is known, those for other radiation conditions desired can be estimated using the specific locus data). Secondly, that since in man, about 2.7% (20/736) of all known and proven dominant mutations are associated with one or another form of cataract [M61], the reciprocal of this (i.e., 100/2.7 = 36.8) can be used in the context of estimating the overall genetic risk from the induction of mutational damage [E20].

712. The relevant calculations are the following:

(a) Expected rate of induction of cataract mutations at low doses or low dose-rates of low-LET irradiation:

(i) From the data in exposure fractionation study:

$$\frac{12.6\ 10^{-7}}{1.2 \times 3} = 3.5\ 10^{-7}$$

(the factor 1.2 comes from the enhancement effect observed due to fractionation, in concurrent specific locus studies; the factor 3 is the dose rate reduction factor);

(ii) From the data on single exposures:

$$\frac{5\ 10^{-7}}{3} = 1.67\ 10^{-7}$$

(the factor 3 is the same as in (i) above).

The average of these two estimates (weighted by the number of mutants in the fractionation and single exposure series) is 2.6 10^{-7}.

(b) Overall risk from the induction of dominant mutations causing serious effects in the first generation progeny:

$$2.6\ 10^{-7} \times 36.8 \simeq 10\ 10^{-6}$$

(the factor 36.8 is the same as that mentioned in the preceding paragraph). In other words, about 10 individuals per million born will be affected by one or another kind of clinically important serious genetic disease (of induced mutational origin) per 10^{-2} Gy of paternal, low dose rate or low dose, low-LET irradiation (or 1000 individuals affected per million born per Gy of irradiation under the stated conditions). It is worth pointing out that in these calculations, the multiplication factor 2 and the division factor 2 used in similar computations with the skeletal mutations to take into account ease of diagnosis and severity of effects, respectively (see Section VII.A), have not been employed.

713. It is clear that the above estimate of 1000 cases per million per Gy of paternal irradiation is similar to that derived using the data on the induction of dominant skeletal mutations in mice. The finding that the estimates derived from two different sets of mouse data and using different correction factors are similar strengthens the earlier conclusions of the Committee. However, it bears reiterating here that all these estimates involve a number of assumptions and that these estimates merely reflect the current status of knowledge and may be subject to revision at some future date.

714. Since there are no experimental data on the induction of either skeletal or cataract mutations in female mice, it is not possible to use a similar approach to estimate the risk associated with the irradiation of human females. However, the probable magnitude of risk to the latter can be derived in a very indirect manner by comparing the specific locus mutation rate estimates for spermatogonia and mature (and maturing) oocytes after low-level low-LET irradiation. As the Committee stated in its 1977 report "... the four rates for low-level irradiation of mature and maturing oocytes estimated by Russell are only 0.17, 0.27, 0.33 and 0.44 times as effective, and only in the highest of these is the induced rate in oocytes significantly above the control rate. Thus the ratio of effectiveness to the spermatogonial mutation rate could be zero".

715. If, for the sake of argument, it is assumed that these ratios will hold also for the induction of mutations having dominant effects; and if it is accepted that the mutational response of the human oocytes will be more similar to that of mature and maturing mouse oocytes for low-level irradiation; then the risk from irradiation of human females can be estimated to be in the range from 0 to 0.44 of that from irradiation of males. In other words, irradiation of human females may entail a risk of producing between 0 and 9 affected children per million births per 10^{-2} Gy or between 0 and 900 affected children per 10^{6} births per Gy of low-LET low level radiation,

716. It should be stressed that the computation of this estimate is not meant to suggest that a new risk from irradiation of females has been uncovered, but rather, to take into account the possibility that the mutational sensitivity of the immature human oocyte may not be as low as that of the immature mouse oocyte. Thus the earlier conclusion of the Committee is still valid, namely that: "... even in the event that the human immature arrested oocyte does not respond like the mouse arrested oocyte, but more like the most sensitive stages in the mouse, it seems likely that the genetic hazard of radiation in the female will still be less than in the male". This applies to low dose or low dose rate low-LET irradiation.

717. As discussed in chapter I of this Annex, the thesis that the impact of spontaneous mutations in man that are classified as recessives and which are null mutations in a molecular sense (i.e., those which cause an absence or near-absence of enzyme activity) on human health may be currently underestimated remains speculative. Nonetheless the Committee takes note of this point, but wishes to point out that at present there is no way to translate this concern into meaningful figures. It believes that the risk from the induction of mutations having dominant effects in the progeny far outweighs that from the induction of recessive mutations per se.

718. Turning now to possible risks from the induction of minor (polygenic) mutations, the UNSCEAR 1972 report [U8] stated the difficulties involved in making a risk estimate for this kind of mutations as follows: "... Experiments with Drosophila show that mutation resulting in minor deleterious effects grossly outnumber those with severe effects. The calculations ... do not take into account this class of mutations which lead to minor disability and disease. Because of the greater frequency of occurrence of these mutations, their total effect in terms of genetic burden to the population could be greater than that of a smaller number of relatively more serious conditions... There is, however, no way at present to assess their contribution to the genetic burden of man". In the 1977 report, the above general conclusion was implied (although not explicitly stated) and no risk estimates for this class of mutations were made. The situation has not changed in the meantime and therefore, the Committee does not see a need to alter the above point of view. (For recent reviews on the effects of spontaneously-arising and radiation-induced polygenic mutations on population fitness in Drosophila, see [S127, M68].)

719. In its 1972 and 1980 reports, the BEIR Committee expressed a similar opinion. The 1972 report stated the situation as follows: "... Perhaps the major reservation that we have about our estimates is the failure to take adequately into account mutations that have very mild effects ... this is the most frequent class of mutations in Drosophila and because they persist longer in the population than those with more drastic effects, each mutant affects a correspondingly larger number of persons... Perhaps the human counterparts of these mutations, in addition to causing a slight reduction in life expectancy, are responsible for greater susceptibility to disease, impaired physical or mental vigor, or a slight malformation of some organ ... Despite a concern for this effect, we shall not attempt to estimate it quantitatively... At least in Drosophila, the evidence is now good that this class of mutations is relatively less frequent among radiation-induced mutations than among spontaneous mutations... The empirical experiments on mice argue that such genetic mutations are not making any substantial impact on mouse populations for up to 45 generations of continuous radiation, far longer than we are able to consider in any meaningful way for the human population".

(b) Chromosomal damage

720. As was discussed earlier, the Committee made use of the limited human and marmoset cytogenetic data to give estimates of risk from the induction of reciprocal translocations in males in its 1977 report. The risk was estimated as 2 to 10 cases of congenitally malformed children per million births per 10^{-2} Gy (or 200 to 1000 such cases per million births per Gy) of low level, low-LET irradiation and the risk was assumed to stem primarily from the unbalanced products generated by radiation-induced balanced reciprocal translocations (see Section VII. C for a recapitulation of the procedure used in the calculations).

721. Studies on rhesus monkey spermatogonia using improved techniques have yielded far lower rates of translocations than those previously reported for human and marmoset spermatogonia. Since there is no a priori reason to assume that human spermatogonial sensitivity is similar to those of the marmoset and since the possibility exists that human spermatogonia may manifest a pattern similar to that of the rhesus monkey, one can use the rhesus monkey data to define a probable lower limit of risk; this procedure will not materially alter the Committee's earlier assessments as long as it is assumed that the sensitivity of human spermatogonia may lie anywhere between the limits defined by those of rhesus monkey and marmoset.

722. If this line of reasoning is accepted, then correction factors similar to those used in the 1977 report can be used to arrive at an estimate of risk as follows (all rates are per 10^{-2} Gy):

(a)	Rate of induction in rhesus monkey spermatogonia; cytogenetic data	0.86	10^{-4}
(b)	Rate of induction that relates to recoverable translocations in the F_1 progeny [divide (a) by 4]	0.215	10^{-4}
(c)	Rate after low dose rate x rays [divide (b) by 2] based on mouse cytogenetic observations	0.1075	10^{-4}
(d)	Rate after chronic gamma-irradiation [divide (b) by 10] based on mouse cytogenetic observations	0.022	10^{-4}
(e)	Expected rate of unbalanced products: [multiply (c) and (d) by 2]: for (c)	0.215	10^{-4}
	for (d)	0.043	10^{-4}
(f)	Expected frequency of congenitally malformed children in the F_1 assuming that about 6% of unbalanced products [item (e) above] contribute to this:		
	low dose rate x rays	1.3	10^{-6}
	chronic gamma irradiation	~0.3	10^{-6}.

Thus, on the basis of the rhesus monkey data, one can estimate that the risk of producing congenitally malformed children (as a consequence of the induction of balanced reciprocal translocations in the fathers) is between 0.3 per 10^6 and 1.3 per 10^6 per 10^{-2} Gy (or between 30 and 130 per 10^6 per Gy) of paternal low level irradiation. Taking into account all the primate data, it can be estimated that there will be between about 30 and 1000 cases of abnormal children per million progeny per Gy of paternal low level irradiation, stemming from the unbalanced products of radiation-induced balanced reciprocal translocations.

723. Although the risk estimated above is based entirely on unbalanced products of balanced reciprocal translocations, the Committee takes note of the observations in humans (chapter I) and in mice (subsection II.D.8) that some balanced reciprocal translocations are associated with dominant phenotypic effects. The risk from these is not, however, ignored: it forms part of the total risk estimated for mutational events with dominant effects. Thus, some of the dominant skeletal mutations are associated with, and probably caused by, balanced reciprocal translocations. The basis for dominant effects of balanced reciprocal translocations has not been elucidated, although at least two formal possibilities can be envisaged: loss of chromosome material at the site of chromosome breakage, perhaps too small to be detected, and position effect. In humans, the documented cases of position effects involve only the X chromosome [D16, T26] and are associated with abnormal phenotypes. In mice, in addition, there is evidence that position effects can also be generated in the case of autosome-autosome translocations.

724. The rate of translocation induction in human females is not known and there are no marmoset or rhesus monkey data. In its 1977 report, the Committee

stated that "... the data for mouse females show that in maturing oocytes exposed to acute x-irradiation, the rate is 0.16 10^{-4}/gamete/rad ... although there is no direct evidence on the response of the immature oocytes stages to the induction of translocations at low doses and dose rates, the data on specific locus mutations and on X-chromosome losses strongly support the view that the rate for translocations is also likely to be low, but no quantitative estimate can be given".

725. It is now possible to make further arguments (necessarily indirect) and calculations to show that the above statement is probably correct for low dose rate gamma irradiation. One can start with either of the following two assumptions: for radiation conditions applicable to humans, the human immature oocyte will respond in a manner similar to the mature and maturing mouse oocyte, and the immature human oocytes will respond in a manner similar to that of the immature mouse oocytes. In the latter case, the risk is negligible or zero. The following discussion focuses on the consequences if the first assumption is correct.

726. In mice, as discussed earlier, maturing and mature oocytes are only one-half as sensitive as spermatogonia to the induction of heritable translocations. There is a pronounced dose-rate effect (subsection II.B.4) for the induction of chromatid interchanges in maturing oocytes. If these findings are applicable to humans, marmosets and rhesus monkeys, the following two rates of heritable translocation induction can be computed for high dose rate low-LET irradiation (all rates per 10^{-2} Gy): 0.875 10^{-4} (marmoset and human data base; $0.5 \times 0.25 \times 7 \times 10^{-4}$) and 0.108 10^{-4} (rhesus monkey data base; $0.5 \times 0.25 \times 0.86 \times 10^{-4}$). At low dose rates, these rates will be an order of magnitude lower (i.e., 0.0875 10^{-4} and 0.0108 10^{-4}).

727. Since heritable translocations recovered from irradiated oocytes are induced as chromatid interchanges, a gamete from an affected oocyte would be six times more likely to have an unbalanced form of the translocation than a balanced one (see references [S128, S135]). In other words, the rates for unbalanced products will be six times those quoted above (i.e., 0.5275 10^{-4} per 10^{-2} Gy and 0.0648 10^{-4} per 10^{-2} Gy). Assuming as before that about 6% of the unbalanced products will result in congenitally malformed children, it can be estimated that there will be 3 children per million who will be affected per 10^{-2} Gy (or 300 per million per Gy) (marmoset + human data base) or 4 affected children per 10 million births per 10^{-2} Gy (or 40 per million per Gy) (rhesus monkey data base) of maternal, low-LET, low level irradiation. In either case, it is clear that the risks are low for irradiated human females. It is worth reiterating here that if the sensitivity of the human immature oocytes is similar to that of immature mouse oocytes, the risk will be close to zero.

728. With respect to structural aberrations other than reciprocal translocations, the Committee's earlier view that the risk from their induction is probably small (since most of such changes may act too early to constitute a real hazard in liveborns) is still valid. It is known that deficiencies are induced and no doubt some of these will contribute to dominant effects. The risk for these, like that for balanced reciprocal translocations, is included in the scoring of mutational events with dominant effects. Likewise, the Committee's earlier conclusion (based on mouse data) that the risk from the induction of sex-chromosome losses in males is very low or nil is still valid. For chronic gamma irradiation of maturing oocytes of mouse females, L.B. Russell [R30] has estimated (from the data of W.L. Russell and colleagues) an induction rate of 5 10^{-6}/R; for irradiation of immature oocytes, the induction rate is zero. These findings would suggest that if the human oocytes respond like those of the mouse, the risk is probably no higher than 5 10^{-6}/R (or about 500 10^{-6}/Gy) for irradiation of females. Similarly, the Committee's earlier conclusion that the risk from the induction of non-disjunction (leading to viable trisomies) is small, although it cannot be quantified at present, still stands.

729. The "expected rates" of induction of different kinds of genetic damage (derived from the relevant data discussed in this section) are summarized in Tables 42 and 43.

2. Doubling dose method

730. The estimates of risk arrived at by the Committee using the doubling dose method are given in Table 44. They are essentially the same as those given in its 1977 report, except for three changes: (a) the current estimates are based on an assumed exposure of 1 Gy/generation (instead of an assumed exposure of 10^{-2} Gy/generation, as was the case in the 1977 report) of low dose rate, low-LET irradiation; (b) on the basis of the calculations of Childs [C68] for dominant and X-linked diseases, discussed earlier, the Committee has now assumed that the first generation increment of these diseases is 15% of that at equilibrium, instead of the 20% figure assumed in the 1977 report; and (c) the Committee has refrained from applying the doubling dose of 1 Gy to the overall incidence of chromosomal diseases in order to estimate the increment which would be expected to result from irradiation. Instead, it has applied the doubling dose only to the structural component of these diseases, for the reasons discussed below.

731. Chromosomal diseases are divided into two very distinct components, namely, those based on structural and those based on numerical changes. Structural changes in the form of reciprocal translocations were included in the mutational end-points from which an overall doubling dose of 1 Gy for low dose, low-LET irradiation was calculated. Therefore, it seems appropriate to apply the same value to the structural anomalies in Table 44. However, data on trisomies which result from the process of non-disjunction rather than chromosome breakage, were not used in doubling dose calculations and the results of more recent experiments do not permit a doubling dose for this category to be estimated with any confidence. No experiments have been carried out under chronic exposures and no clear-cut dose-response relationship has been obtained under acute exposures. Moreover, there are complicating factors like maternal age which lead to considerable heterogeneity of response. Therefore, no attempt has been made to estimate the likely effect of 1 Gy/generation on the incidence of numerical anomalies. This effect is likely to be very small.

732. For the purpose of doubling dose calculations, the incidence of diseases stemming from structural aberrations of chromosomes has been derived from the figures for structural aneuploids given in Table 2 of this Annex. However, aneuploid Robertsonian translocations have been omitted because of the evidence that these are not induced by radiation (see text); the

"others" category has also been omitted because they are mainly mosaics and therefore probably result from events in early development rather than in either parent. For the same reasons, mosaics have also been omitted from calculations of the incidence of numerical anomalies.

733. Other data and assumptions that are now used to derive risk estimates are the same as those used in the 1977 report. Among these are the following: the use of a doubling dose of 1 Gy to estimate risks at low doses of low dose rate, low-LET irradiation; the assumption of the same incidence figures for the different classes of genetic diseases as those used earlier (1% dominant and X-linked diseases); 0.25% recessive diseases, including those maintained by heterozygous advantage, but this inclusion does not affect the risk estimate; 0.34% chromosomal diseases and 9% diseases of complex aetiology; the assumption that under conditions of continuous exposure to low level low-LET irradiation, the incidence of diseases in the population will reach a new equilibrium with an elevated incidence rate; and the assumption that the equilibrium frequency, the rate of approach to equilibrium and the expected effects in the first generation will be dependent on the kind of disease under consideration.

734. It should be noted that the genetic risk estimates given in Tables 43 and 44 refer to gonadal radiation exposures before or during the reproductive period, i.e., all the dose is genetically significant. When dealing with population exposures, it is sufficient to assume for the purposes of calculation that the child expectancy per parent is 1.0 until the mean age at conception and zero thereafter. Thus, if the mean age at conception is 30 years, then the genetically significant dose will be that received by the gonadal germ cells up to the age of 30. If the mean life expectancy in the population is 70 years, then the genetically significant dose will be 3/7 of the mean lifetime gonadal dose.

3. Index of harm, genetic detriment and the impact of genetic disease

(a) Introduction

735. The quantitative figures of risk arrived at earlier (Tables 43 and 44) refer to expected numbers of cases of "serious genetic disease" due to radiation-induced mutations and chromosome aberrations in the progeny of those exposed to irradiation. The term "serious genetic disease" used in this context connotes ill-health, handicap or disability of genetic origin which can set in at any time from birth onwards; it does not, however, discriminate between the impact of these diseases on the individual, family, society or health-care facilities, to mention only a few. As Newcombe has stressed [N5], "... such numbers are poor indicators of harm if one lacks a satisfactory measure of the spectrum of severities among the various individuals affected by the hereditary conditions". For instance, no one doubts that Huntington's chorea and Down's syndrome are serious genetic diseases, but yet they are different: Huntington's chorea is a disease in which there is a gradual but very serious degeneration of the central nervous system with onset during the third to fifth decades of life. Down's syndrome children suffer from a multiplicity of problems from birth onwards.

736. What is obviously needed are some objective and quantifiable indices of severity such as years of life lost due to the disease, the relative durations of hospitalization or medical care needed, etc., which can, at least in principle, be used to "weight" the different diseases to arrive at an overall estimate of genetic detriment. Only on the basis of such an estimate (or a group of estimates, depending on the criteria used) can one make meaningful comparisons between, and realistic appraisals of (i) the impact of diseases of different genetic aetiologies and (ii) the relative contribution of somatic and genetic effects to human ill-health. This premise is valid for both spontaneously-occurring and induced effects.

737. These considerations would suggest that, in the context of comparing genetic and somatic effects of radiation, equating the number of cases of induced genetic disease per unit amount of radiation with the number of cancer deaths (and then adding the two together as a measure of total harm or detriment) is neither wholly satisfactory nor entirely adequate. An example will make this point clear: if a fatal induced cancer involves, say, 10–12 years of loss of life and if the average age at death from what are classified as major genetic defects were at age 15 (i.e., with about 60 years of loss of life expectation), there would immediately be a factor of 4 or 5 greater average detriment for each major genetic defect than for each fatal cancer, as judged by only life loss, and apart from the difference in disability during life.

(b) Indices of harm

738. A recent ICRP document [I6] considered in detail the problems involved in developing indices of harm from the standpoint of recommending appropriate limits for any occupational or other exposure to radiation and the assessment of the safety of an occupation involving such an exposure and comparing it with the safety of other occupations. In that document, both the limitations and utility of certain criteria such as fatality and mean loss of life, various occupational injuries and their severity (expressed for instance as the total number of working days lost) were dealt with and compared with similar consequences of somatic and genetic effects of radiation exposures. It suggested that the index of time lost (an integrated measure taking into account all these criteria) from a full and normal working life (expressed as man-years per year per 1000 employed) is a possible approach, despite a number of limitations.

(c) Genetic detriment

739. The reasons why, in spite of its importance, the problem of developing adequate measures of genetic detriment has been largely neglected thus far, have been succintly stated by Trimble and Smith [T2] and can be summarized as follows. It is difficult to define parameters that could be considered valid measures of overall burden; it is equally difficult to amass large volumes of objective data covering the whole life span of both diseased and normal individuals, and such research is still generally thought to be scientifically unrewarding. Notwithstanding these difficulties, a few attempts have been made to develop an index of harm for genetic diseases. Although all these attempts concern spontaneously-occurring genetic diseases, the remainder of this section will be devoted to a discussion of these, if only to illustrate the methodology that could

eventually be used to assess the genetic effects of radiation.

740. Several tangible criteria have been used to assess and quantify the actual burdens imposed by genetic diseases on the individual, the society and public health facilities. These include mortality (and consequent reduction in life expectancy), number of days of hospitalization, frequency of hospital readmission, etc. These do not include however entities such as the reduction in the quality of life for the carrier of a given genetic disease nor does it include the anguish experienced by the parents of a child with a genetic defect. There is no doubt that these are important, but they do not readily lend themselves to quantification.

(i) *The use of years of life lost as an index of genetic detriment*

741. As has been emphasized by the ICRP document [16] and by Jones [J13, J14], a life-shortening genetic disease is not necessarily a cause of death in the sense one uses the word in the context of death due to an automobile accident or drowning. Genetic conditions may shorten one's life by altering one's risk of mortality over a considerable period of time. Unlike a cause of death which acts at the time of death only, a genetic condition is a risk-altering state that may act from birth onwards. A person with a genetic disease is born into a different life table with different risks of death than other people.

742. Years of life lost can be defined as the number of years of life that would eventually be gained if the cause or condition under study were somehow eliminated [J13, J14]. Jones [J13] has stressed the point that "... it occasionally happens that an investigator calculates the years of life lost by taking the difference between the age at death and life expectancy at birth ... this procedure is incorrect". For instance, an individual of age x has already survived many risks of death and can expect to live to an appreciably riper age than he could have as a newborn. It is thus clear that for a proper estimation of years of life lost, one should take into account the age and sex-specific mortality rates of individuals with and without the condition considered.

743. Jones [J13, J14] has illustrated the use of years of life lost (YLL) index for genetic diseases with respect to Down's syndrome (DS) which manifests itself at birth and Huntington's disease (HD), one with a delayed onset. For Down's syndrome the procedure is as follows: consider the average age at death for a person with DS, $\bar{y}_{DS}$, and the expectation of life at birth for everyone else, $\mathring{e}_0'$. If Down's syndrome were eliminated, then everyone who would have lived $\bar{y}_{DS}$, years now lives $\mathring{e}_0'$ years. Hence for each person, the gain in years of life equals $(\mathring{e}_0' - \bar{y}_{DS})$. If I_{DS} is the incidence of Down's syndrome per 100 000 born, then years of life lost through Down's syndrome is

$$YLL_{DS} = I_{DS}(\mathring{e}_0' - \bar{y}_{DS}) \text{ years per 100 000 liveborn} \quad (1)$$

I_{DS} and $\bar{y}_{DS}$ can be determined from reports on Down's syndrome and $\mathring{e}_0'$ can be inferred from the same information and published life expectancy figures. It is not, however, the same as published life expectancy at birth, $\mathring{e}_0$, because the published figures include the deaths of persons with Down's syndrome, whereas $\mathring{e}_0$ does not. The two figures are related according to the equation:

$$\mathring{e}_0' = \frac{100\,000\,\mathring{e}_0 - I_{DS}\,y_{DS}}{100\,000 - I_{DS}} \quad (2)$$

Substituting in equation (1) gives

$$YLL_{DS} = I_{DS}(\mathring{e}_0' - \bar{y}_{DS}) + \frac{I_{DS}^2(\mathring{e}_0' - \bar{y}_{DS})}{100\,000 - I_{DS}} \quad (3)$$

744. The data and assumptions used are the following: the incidence figure for Down's syndrome at birth estimated by Carter et al. [C48] of 1 in 660 in England is a reliable one and can be considered applicable for the United States; although the sex distribution at birth appears slightly to favour the males, with complete ascertainment at birth, the female and male neonates with Down's syndrome would be of equal numbers; and the data from two large studies of mortality, one an American and the other a Danish, can be used; in the first, Fabia et al. [F20] have presented sex-specific life tables up to 10 years of age, based on all Down's syndrome children born alive in Massachusetts from 1950 through 1966 (a total of 2421 cases). In the second, Oster et al. [O19] have presented similar tables from 5 to 80 years of age for all the Down's syndrome cases (526 cases) born in a certain area of Denmark in 1949.

745. From these data, Jones calculated that the average age at death for Down's syndrome males is 35.7 years and for females, 35.5 years. In 1970, the life expectancy at birth in the general United States population was 67.1 years for males and 74.8 for females [N19]. Applying equation (2), he arrived at a YLL_{DS} figure of 5364.2 years per 100 000 persons born alive, or a little more than 53.5 years for every 1000 livebirths.

746. With diseases such as Huntington's chorea, the situation is somewhat different. In these cases, having the genotype (but not the disease) is usually not a risk-altering state. Since the onset is often gradual, fixing a point in time in the natural history of the disease with delayed onset (where the risks to a patient's life first differ from the risks for other people) is difficult. It can conservatively be assumed that until onset as conventionally defined for that disease, the person's life is subject to the same forces of decrement as others. Account must also be taken of the fact that many people with the genotype for the disease never develop it because they die before the onset. In a disease with delayed onset, the incidence at birth of the underlying genotype is always higher than lifetime incidence, i.e., the number of persons relative to (say) 100 000 born who will develop the disease at some time in their lives. In calculating years of life lost, it is the latter number (lifetime incidence) which is important, since under the assumption used, the lives of people who die before onset have not been shortened by the genetic disease for which they are at risk [J13].

747. Jones [J13] has shown that lifetime incidence, although rarely reported in the literature as such, can be estimated from the relationship

$$I_g = \frac{B_g}{\bar{s}_g} \quad (4)$$

where I_g represents lifetime incidence per 100 000 born; B_g is the number of persons in the life-table population affected at a given time; and $\bar{s}_g$ is the average duration of disease g. In other words, incidence = prevalence ÷ duration. He has also shown that once I_g is determined,

the remainder of the calculations is essentially the same as for a disease which manifests itself at birth (e.g., Down's syndrome considered earlier). The equation is

$$YLL_g = \sum_{x \geq 0} (p_x l_g)(\mathring{e}_x - \bar{s}_{g,x}) = \frac{B_g}{\bar{s}_g}(\mathring{e} - \bar{s}_g)$$

years per 100 000 born (5)

where p_x is the proportion of l_g with onset at age x; and $\bar{s}_{g,x}$ is the expected duration of illness for a person with onset at age x.

748. The data used by Jones are those published by Reed and Chandler [R63] for Michigan for which the prevalence was estimated by Reed and Chandler as 4.1 per 100 000; to obtain this figure, these authors determined the number of choreics living in the Lower Peninsular of Michigan on April 1, 1940 and divided this number by the total Lower Peninsular population on that day. Jones however based his calculations on the national 1970 life-table population which contained more choreics per 100 000 than reported by Reed and Chandler. Weighting the age-specific prevalences from the Michigan study according to the 1970 age-distribution yielded an overall prevalence in the 1970 life-table population of 4.8 choreics per 100 000. The 1970 life-table population numbered 7 085 472 persons, and the total number of choreics in the study population was 338.

749. In the Reed and Chandler study, the average duration of illness was essentially the same for both sexes: 15.85 years. Using equation (4), the number of men and women per 50 000 born who became choreic at some time in their lives can be estimated as 169/15.85 = 10.7 persons; for both sexes together, the lifetime incidence is 21.3 persons per 100 000. Examination of the age distribution at onset revealed that the average life expectancy at onset was 36.1 years for males and 41.2 years for females. Using equation (5)

$$YLL_{HD} = l_g(\mathring{e} - \bar{s}_g) = 10.7\,(36.1 - 15.85) =$$
$$= 216.7 \text{ years}$$

for every 50 000 males and 10.7 (41.2 – 15.85) = 271.2 years for every 50 000 female births. For both sexes together, a little less than 5 years of life are lost due to HD for every 1000 persons born.

750. A comparison of the above figure with that obtained for Down's syndrome will reveal that the effect is about an order of magnitude higher for the latter when the criterion of life loss is used. In other words, the amount of genetic detriment associated with Down's syndrome is much higher than that with Huntington's disease, partly owing to the seven times higher incidence of Down's syndrome. It bears reiterating that the detriment measured here pertains to life loss only and does not include the personal or family hardship and the trauma associated with having a genetic disease.

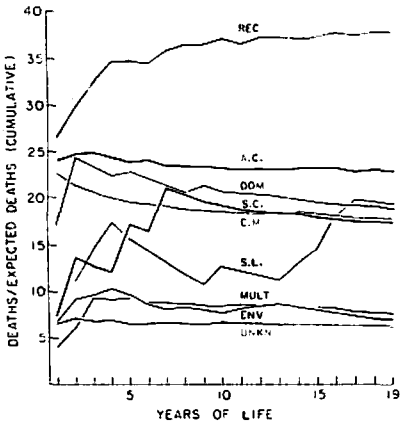
(ii) *Does a given kind of genetic disease lead more frequently to early mortality? The results of the British Columbia study*

751. Thus far, the most extensive and perhaps the most illuminating studies, from the standpoint of the assessment of the relative impacts of different classes of spontaneously-occurring genetic diseases, are those by Trimble and Smith [T2] and by Newcombe [N5]. Both these represent an extension of the earlier work by Trimble and Doughty [T1] on the incidence of genetic disease in the Canadian province of British Columbia with a current population of over two million people. Using automated record linkage, ill-health records of various kinds have been linked to the records of all births (approximately 800 000). Trimble and Smith estimate that nearly 90% of all potentially linkable pairs of ill-health and birth records were successfully brought together and linked. The specific examples, to be discussed below, were obtained using the health histories of 835 774 children who were born in the province between 1946 and 1970, including the histories for 370 children with known single-gene dominant disorders, 559 with identified recessive diseases, 928 with chromosomal diseases (of which 43 were with sex-chromosomal diseases and the remainder with autosomal disorders, primarily Down's syndrome) and 14 460 with irregularly inherited congenital malformations.

752. One of the questions asked was whether a given kind of disease leads more frequently to early mortality. As Table 45 shows, within the first year of life, approximately 2.5% of all liveborn children die from one cause or another; this value is about 4 times higher for children with dominant or recessive diseases and about 5 times higher for children born with irregularly inherited conditions; the overall risk of childhood death drops after the first year of life to about 2 per 1000 livebirths in the second year of life, 1 per 1000 in the third and to nearly half this figure for the fourth and fifth years; for children with genetic diseases, while the absolute risk of mortality decreases, the relative risks do not; children with dominant disorders appear to have as great, if not greater, relative risk of death in the second through fifth years of life compared to the same risk for infant mortality; for surviving children with recessive diseases, there is an almost 20-fold increased risk of death in the second year and this relative risk becomes greater during the third to fifth years of life; children with congenital malformations, however, appear to have a fairly constant, 4- to 6-fold higher risk of dying at all ages up to five years, when compared to all livebirths; and by ages 4 and 5, children with single-gene disorders, especially those with recessive diseases, appear to have even greater absolute risks of dying compared to children born with irregularly inherited disorders.

753. Figure III (taken from the paper of Newcombe [N5]) compares the age-specific cumulative mortality among cases in different categories of genetic diseases over the first nineteen years of life; mortality is expressed as a factor by which it exceeds the expected numbers of deaths based on all births in the same years. It can be readily seen, with this criterion, that recessive diseases are associated with the highest severity; that diseases classified under the headings "multifactorial", "environmentally caused" and "unknown aetiology" are associated with the least severity; and that the remaining classes fall in between.

754. As Newcombe [N5] cautions, these different degrees of severity apply, however, only to the cases that actually got into the different registries and are clearly not applicable to those manifestations that were too mild to be registered as handicapping conditions. Thus for instance, whereas the registration of Down's syndrome in the British Columbia registries can be considered complete, the same is not true of other



Legend: REC: recessive diseases; AC: autosomal chromosome disorders; DOM: dominant; SC: sex-chromosomal diseases; CM: congenital malformations; SL: sex-linked gene disorders; MULT: multifactorial disorders excluding congenital malformations; ENV: environmental; UNKN: unknown aetiology

Figure III. Age-specific cumulative mortality among cases of chromosomal and non-chromosomal disorders and other handicapping conditions [N5]

chromosomal anomalies. Newcombe has estimated that about two-thirds of the total cases of chromosomal anomalies are not registered in the above registries. The exclusions, however, are of the less severe traits. In assessing the public health impact of these diseases, one should clearly not take data on degrees of severity as derived from cases that have attracted special attention and then assume that these severities are typical of the total number of cases as derived from the surveys that have aimed at complete ascertainment.

755. While mortality is a useful measure of severity and data on this are more readily obtainable, one should not over-emphasize its importance. For instance, for chromosomal diseases, mortality per se is perhaps one of the least useful indicators of severity and this would be particularly true of Down's syndrome which may result in prolonged stays in institutions from an early age. In such circumstances the burden to society is perhaps inversely related to mortality. The same is true of several single gene diseases which have a late onset in life and of sex-chromosomal anomalies which tend to be mild and to escape notice until after puberty.

(iii) *Overall estimates of lost life and impaired life for spontaneously-arising genetic diseases*

756. Recently, Carter [C51, C69] has provided some rough estimates (Tables 46–49) of the average disability caused and the average length of life lost by the more common genetically determined diseases in a developed country. Carter did not give similar estimates for irregularly-inherited diseases, but the Committee has made some crude estimates for these diseases (see Table 50) taking into account the list of Trimble and Doughty [T1], but wishes to caution that there may be considerable errors in these estimates. In considering the information presented for single-gene dominants, X-linked recessives and autosomal recessives (Tables 46–49), the following points made by Carter are worthy of note.

757. The estimates of birth frequency (equivalent to the life-time incidence figures used by Jones [J13, J14]) given in the above tables are mostly those given in review articles by Carter [C49, C50]. They are derived from the prevalence estimates by multiplying the latter by the average duration of life in the population (assumed to be 70 years) divided by the average duration of clinical illness. The birth frequency estimates are underestimates, since these do not include those who die from other causes before the disease becomes clinically manifest. However, in developed countries, this will usually be a small proportion of the whole, and in them, the genetic disorder cannot be said to have caused lost years of life. Three chronic dominant neurological disorders have been added to those quoted in Carter [C50]. Estimates of their prevalence are variable [S129] but they are not uncommon disorders in neurological practice.

758. The estimates of age of onset, duration of clinical illness and age at death are reasonably well established, though in debilitating disorders, where intercurrent infection is the usual final cause of death, modern antibiotics are substantially prolonging life. The estimates of average degrees of disability are inevitably somewhat arbitrary and subjective. The rough guide has been limitation of working capacity in adult life and/or, in childhood, educability. The life-long disability of congenital blindness is somewhat different from a slowly progressive disorder such as dominant cerebellar ataxia, which at first causes little disability but, towards the end, is totally incapacitating; or from neurofibromatosis, which causes little disability in some patients but severe disability in others. While all estimates are approximate, they are perhaps useful for comparison with similar estimates for radiation-induced neoplasms.

759. An examination of the summary Table 50 will reveal that, depending on the index of detriment used, the ranking of severities varies (columns 4 and 5 in Table 50). Thus in terms of years of impaired life, the rank order is: chromosomal diseases > X-linked diseases > recessive diseases > dominants > irregularly inherited. If years of life lost is taken as the index of detriment, then the rank order becomes: recessive diseases > irregularly inherited diseases > X-linked diseases > chromosomal diseases > dominants. The ranking for the degree of impairment is: recessive diseases > chromosomal diseases > X-linked diseases > dominant diseases. Finally, for impaired life weighted for degree of impairment the rank order is: recessive diseases > chromosomal diseases > X-linked diseases > dominants. The finding that dominant diseases as a whole rank lower than others is not unexpected; nearly one-half of all dominant diseases included in the calculations have a late onset (giving unimpaired life durations of 30 years or more) whereas a sizeable proportion of diseases belonging to the other categories have an onset in childhood.

760. The last two columns in Table 50 provide some rough idea of the social impact in terms of impaired or lost life per 10^6 births. As can be seen, the rankings are now different. On the whole, spontaneously-arising genetic diseases account for about 2 300 000 years of impaired life per 10^6 births and about 3 000 000 years of life loss per 10^6 births (the assumed average life expectancy at birth for the general population is 70 years or 70 10^6 per 10^6 births).

(iv) *Utilization of hospital services as an index of genetic detriment*

761. A number of investigators have used utilization of hospital services as a rough measure of the degree of the detriment associated with genetic diseases (e.g., [C5, D17, H2, P32, S85]). In these studies, medical charts of the patients were examined for given periods, the patients subdivided into different categories and data on the number of admissions, length of hospitalization (and in some cases, costs), etc., were collated. Since the diagnostic criteria varied in the different studies, precise comparisons are not possible. The study of Hall et al. [H2] is illustrative of the principal aspects and will be discussed below.

762. This study pertains to cases admitted to the Children's Orthopaedic Hospital and Medical Centre (COHMC) in Seattle area. 4115 medical charts were examined and the patients were assigned to one of five categories which were:

(a) Clearly genetic disorders;
(b) Multifactorial/polygenic conditions;
(c) Development anomalies;
(d) Familial disorders;
(e) Non-genetic disorders.

Each patient was assigned to only one category, irrespective of the number of admissions. The results of the analyses showed that:

(i) Of all admissions, 4.5% had clearly genetic disorders (0.6% chromosomal, 1.2% autosomal dominant, 2.2% autosomal recessive, 0.5% X-linked recessives), 22.1% had multifactorial/polygenic conditions, 13.6% developmental anomalies, 13.2% familial disorders and 46.6% non-genetic disorders;
(ii) Patients with clearly genetic disorders (category a) had an average of 5.3 admissions as compared to 1.3 for patients with non-genetic conditions;
(iii) Of "genetic" patients (category a), 12.8% had more than 20 admissions as compared to only 1.2% for all patients studied;
(iv) The length of hospitalization for "genetic" patients was 3.4 days as compared to 2.5 days for non-genetic patients;
(v) In terms of general costs, the "genetic" patients (and their families) incurred more expenses than others.

763. The frequency of genetic diseases among hospital admissions in the above study is compared with similar data from some other studies in Tables 51 and 52. It can be seen that the results are roughly similar, except for some of the entries in the last row. Penchaszadeh [P32] points out that this difference is due to several factors among which the most important is the persistent burden of environmental infectious and nutritional diseases in the paediatric age population in Venezuela.

764. In the British Columbia study of Trimble and Smith [T2] mentioned earlier, data on the utilization of hospital services by individuals with different genetic conditions were also collected. These are summarized in Tables 53 and 54. Excluded from the Tables are hospitalizations due to common childhood disorders such as respiratory and infective diseases. It can be seen that: for 1000 livebirths, there are some 200 hospital admissions in the first year of life, dropping to about one-third of this figure by the second year and to about one-fifth during the fifth year of life; that children with dominant or recessive diseases or congenital malformations are, on the average, admitted to hospitals 5–7 times more often up to age 1, with the relative risk gradually increasing with age, except for those with congenital malformations; that with respect to hospital stays, considering all livebirths, there are over 200 days of hospitalization per 100 children during the first year of life and this figure decreases to about one-fifth by age 5; that children with dominant diseases account for 9–13 times as much in-patient hospital usage per capita during the first year of life and this value increases drastically for those who survive this period; that for children with recessive disorders, the amount of hospital usage per affected child is 12–24 times greater than for all livebirths, and these children have average lengths of stay per admission per affected child of 13–19 days during the first year of life; and that children with congenital malformations spend consistently slightly less time, on average, in hospital than those with either dominant or recessive diseases, but they have a 7–11 times greater use of in-patient services per capita than normal children. It is worth pointing out that these figures are qualitatively similar to those discussed in paragraph 762.

(d) Genetic detriment for radiation-induced genetic diseases

765. In principle, it is possible to use one or more of the indices discussed in the preceding paragraphs to compute the amount of detriment that is likely to result from the estimated induction of genetic diseases by radiation. It hardly needs to be stressed however that such an attempt is beset with considerable uncertainties, as will be outlined below.

766. Firstly, for those diseases for which a proportionality between spontaneous and induction rates was assumed (i.e., single-gene dominants, X-linked diseases and a small proportion of diseases of complex aetiology), it is necessary to make the additional assumption that the spectrum of detriment for "induced" diseases will be similar to that for spontaneous ones. For instance, for dominant diseases, the numerical estimates of risk given in Tables 43 and 44 subsume diseases with early as well as late onset. Whereas for spontaneously-arising diseases one has sufficient knowledge of the degrees of severity, this cannot be said to be true for "induced" ones. The reason for this is that the quantitative estimates of risks from the induction of mutations having dominant effects are based on rates of induction estimated from animal experiments and consequently are subject to the limitations inherent in the extrapolation procedure employed.

767. Secondly, spontaneously-arising autosomal recessive diseases are associated with a considerable degree of detriment (see Table 50). Our risk estimates for radiation exposure however, do not include recessive diseases per se, since their incidence is not expected to increase appreciably in the foreseeable future as a result of radiation exposure.

768. Thirdly, the major component of spontaneously-arising chromosomal diseases is constituted by numerical anomalies. However, as discussed earlier, it has not been possible to provide an estimate for the radiation-induction of numerical anomalies and the risk has been assumed to stem primarily from the unbalanced products of induced balanced reciprocal translocations.

769. Finally, for the class of diseases which is numerically most frequent among spontaneously-arising diseases, namely, the irregularly-inherited ones, it is difficult to make the kind of estimates (in terms of impaired life, life loss, etc.,) which Carter has made for other classes. The figures for those given in columns 3–7 of Table 50 are no more than crude guesses and may be associated with considerable errors. This limitation doubtless applies also to estimates of detriment associated with radiation-induced irregularly-inherited diseases.

770. In spite of these problems and difficulties, the Committee considers it worthwhile to attempt some estimates of detriment for radiation-induced genetic diseases, if only to illustrate a possible method and to gain some rough idea of the impact of these relative to that for spontaneously-arising ones. Such estimates are given in Table 55. It is worth reiterating that the numerical values are only approximate and must be viewed in the light of the number of reservations mentioned earlier.

771. It may be noted that the numerical figures given in column 2 of Table 55 (induced cases per 10^6 births) are those from Table 44, but the dominant and X-linked categories are shown separately. Furthermore, following Childs [C68], the first generation incidence for dominant and X-linked diseases is assumed to be 14% and 25%, respectively, of the equilibrium incidence. For chromosomal and irregularly inherited diseases, the figures given in column 2 are the same as those given in Table 44. For impaired life and life loss, the figures used are the same as those given in Table 50, except that for chromosomal diseases, the figures given in Table 49 for autosomal structural aneuploidy are employed.

772. The general conclusions to be drawn from Table 55 can be stated as follows: if a population is exposed to low dose rate, low-LET irradiation at a rate of 1 Gy per generation, the expected increment in genetic disease is of the order of about 2000 cases per 10^6 births in the first generation; this frequency is about one-seventh of that at equilibrium. These diseases are likely to cause about 50 000 years of impaired life per 10^6 births and an equal amount of life loss per 10^6 births in the first generation. At equilibrium, the figures are about 6 to 7 times higher. A comparison of these figures with the magnitude of detriment associated with spontaneously-arising genetic diseases (Table 50) will show that the former are relatively small for the stated radiation conditions. The Committee wishes to stress again that these figures (Tables 50 and 55) are crude, but may be useful in the comparison of detriment associated with spontaneously-arising and radiation-induced cancers.

E. SUMMARY AND CONCLUSIONS

773. In its 1977 report, the Committee made use of both the "direct" and "doubling dose" methods to obtain quantitative estimates of genetic radiation hazards in humans. The main conclusions were the following.

774. Using the direct method, the Committee estimated that following low-LET, low dose rate irradiation of males, there will be about 20 cases of affected progeny per million births per 10^{-2} Gy who will suffer from the effects of induced mutations having dominant effects. The data on the induction of dominant skeletal mutations in mice were used to make this estimate. For structural aberrations of chromosomes—predominantly reciprocal translocations—the risk was estimated to lie between 2 and 10 per million livebirths per 10^{-2} Gy under similar radiation conditions. The cytogenetic data on radiation-induction of reciprocal translocations in marmoset and human males were used for this purpose.

775. The risk for irradiation of human females, both from the induction of mutations having dominant effects and from the induction of reciprocal translocations was considered low, but no quantitative estimates were given.

776. The risk from the induction of sex-chromosome losses in either sex was also considered low, for the radiation conditions applicable to humans.

777. The risk estimate arrived at using the doubling dose method was that, under conditions of continuous radiation exposure to low-LET, low dose rate irradiation at a rate of 10^{-2} Gy/generation, the additional number of cases of genetic disease will be about 63 per million births in the first generation and about three times this frequency at equilibrium (over and above the 105 200 per million births occurring spontaneously). The doubling dose assumed was 1 Gy.

778. Since the publication of the 1977 report, new data have become available. Among these are those which confirm and further document the Committee's earlier conclusions; those that help to shed light on the validity of the assumptions and tentative conclusions (arrived at on the basis of limited data) or controversial view-points: those that are relevant in a qualitative sense, but which as yet cannot be used in quantitative risk assessments; and those that are of relevance for quantitative risk assessments. These have been briefly reviewed in this chapter. The new data pertain to the induction of dominant cataract mutations in mice and to the induction of reciprocal translocations in the rhesus monkey. Use was made of these data (in addition to those that were used in the UNSCEAR 1977 report) in quantitative hazard evaluations.

779. New publications on quantitative estimation of genetic hazards in humans (those of individual authors and of scientific bodies) have appeared since the UNSCEAR 1977 report. Brief summaries of the main conclusions reached in these are given, in addition to some detailed discussions on the similarities and differences between the conclusions reached by the UNSCEAR in 1977, an ICRP Task Group and the BEIR Committee in its 1980 report. It is pointed out that the conclusions reached by all three scientific bodies are similar and where differences exist, they stem from the different assumptions used (the basic data for all three are the same).

780. The Committee's current estimates of genetic hazards have also been made using the direct and doubling dose methods. With the former method, the risk from the induction of mutations having dominant effects in the progeny has now been estimated to lie in the range of 1000 – 2000 cases of affected individuals per million born per Gy of low-LET, low dose rate

irradiation of males. For the irradiation of females, the rough estimate of risk under similar conditions is 0–900 cases per million births. The lower limit of this estimate assumes that the mutational sensitivity of the human immature oocytes will be similar to that of mouse immature oocytes whereas the upper estimate assumes that the human oocyte will respond in a manner similar to that of maturing mouse oocytes under conditions of chronic low-LET irradiation.

781. The risk from the induction of reciprocal translocations has now been estimated to lie in the region of about 30 to 1000 cases of affected individuals per million births per Gy of low-LET, low dose rate irradiation of males; for irradiation of females, the very indirectly estimated risks are lower (range of 0–300 cases of affected individuals per 10^6 births).

782. As in the 1977 report, the Committee has used a doubling dose of 1 Gy to estimate risks using the doubling dose method (the argument that the doubling dose is likely to be higher than 1 Gy was considered, but it was decided to keep the figure of 1 Gy for this Annex until more data on this aspect accumulates). The quantitative estimates of risk arrived at in this Annex are slightly different from those arrived at in the 1977 report. It is now estimated that under conditions of continuous irradiation at a rate of one Gy per generation (low-LET, low dose rate), the expected total increment in the frequency of genetic diseases is about 2000 cases per million births in the first generation (instead an estimated 6300 cases per million) and about 15 000 cases of affected individuals per million births at equilibrium (instead of 18 000 cases per million). The reasoning for this change has been: recent calculations indicate that for dominant and X-linked diseases, the first generation increment is 15% of that at equilibrium (thus lowering the number of cases from 2000 per million to 1000 per million); the conclusion of the Committee (arrived at on the basis of all available evidence) that the assumption of a doubling dose of 1 Gy for all chromosomal disorders (most of which are numerical anomalies of chromosomes) rests on particularly uncertain grounds; the Committee's current assessments relate only to the structural component of chromosomal disorders; the risk from the induction of numerical anomalies is considered to be very small.

783. In this Annex, the Committee has reviewed data that bear on severity or detriment associated with genetic diseases and has also made a first attempt to give some crude estimates of genetic detriment based on a number of assumptions, for spontaneously-arising and radiation-induced genetic diseases. Under the assumption that the average life expectancy at birth is 70 years (and thus, for a million liveborn, 70 10^6 years), it has been estimated that overall, spontaneously-arising genetic diseases cause about 2 300 000 years of impaired life per million livebirths and about 3 000 000 years of life loss per million livebirths. For a population exposed to low-LET low dose rate irradiation at a rate of one Gy per generation, the additional cases of genetic disease induced, would cause about 50 000 years of impaired life per million livebirths and an approximately equal amount of life loss per million livebirths in the first generation following the radiation exposure. At equilibrium, the comparable figures are, 340 000 years of impaired life per million livebirths and about 286 000 years of life loss per million livebirths. The Committee wishes to reiterate that these estimates are very crude ones, but are illustrative of at least one method to estimate genetic detriment.

VIII. SUGGESTIONS FOR FUTURE RESEARCH

784. In this Annex, the progress that has been made in mammalian and human genetics, cytogenetics, somatic cell genetics and in other areas pertinent to the evaluation of genetic radiation hazards in man has been reviewed, and revised estimates of genetic risks have been presented. The Committee feels that, in order to increase our precision in risk assessment, more research effort along the following lines will be useful (the order in which these are listed do not reflect the order of importance).

(a) Human studies

Continuation of surveys on hereditary diseases in human populations and correlation of clinical data and chromosomal defects; studies on the contribution of mutations to irregularly-inherited disorders; continuation of studies on genetic disorders such as ataxia telangiectasia in which the cells derived from patients suffering from the disorders show enhanced sensitivity to damage induced by radiation and by other mutagens, using all possible approaches and comparisons.

(b) Studies with mammals and other higher eukaryotes

Continuation of studies on the nature of radiation-induced dominant and recessive mutations at defined gene loci; studies on the induction of mutations in germ cells and somatic cells at low doses and low dose rates; studies on factors modifying radiation-induced genetic damage and on mutational assay systems in somatic cells; studies on the possible influence of genetic background on the induced frequency of dominant mutations in higher eukaryotes.

(c) Studies at the chromosomal level

Studies on the induction of reciprocal translocations (including primates and human testis material when possible) using cytogenetic techniques, especially at low dose rates and low doses of radiation; studies on the induction of structural aberrations in mammalian oocytes; studies on factors influencing the induction and recovery of chromosome aberrations in germ cells and somatic cells in suitable mammalian systems.

(d) Biochemical studies using suitable prokaryotic and eukaryotic systems

On: the relationships between DNA damage, its repair and the origin of mutations and chromosome aberrations; mechanisms of constitutive and induced DNA repair by physical and chemical agents and their relevance for mutagenesis; mechanisms of regulation of DNA repair and of genetic recombination (possible role of hormones and growth factors) and their role in differentiation and carcinogenesis; DNA repair during gametogenesis; relationship of DNA lesions to changes in DNA sequences.

(e) Research on biological dosimeters to monitor radiation exposures

New approaches on the use of chromosomes as biological dosimeters; development of biochemical and immunological techniques for monitoring changes in DNA sequences and their application to estimate cumulative doses arising from exposure to physical and chemical agents.

Table 1

Recurrence risks of common malformations
[L2, C6, W3]

Type of malformation	Prevalence at birth (%)	
	In sibs of index patients	In offspring of index patients
Anencephaly, spina bifida	5	4
Malformations of heart and great vessels (same type in index patients and relatives)	2-3 according to type	2-4 according to type
Cleft lip (± cleft palate)	4	3
Infantile hypertrophic pyloric stenosis		
Male index patients	5	4
Female index patients	7	13
'Non-postural' talipes equinovarus	3	-
Dislocation of hip(s) in patients not screened at birth		
Male index patients	6	5
Female index patients	2	2

Table 2

Incidence of chromosomal abnormalities in newborn infants
[B1, B20, H3, L1, M53, U1, W2]

Survey centre [a/]	Number of infants			Sex-chromosome anomalies						Autosomal anomalies												Total	Frequency (%)
				Males			Females			Numerical (trisomics)				Structural (euploid)				Structural (aneuploid)						
														Robertsonian		Reciprocal T and insertional	Inversions	Robertsonian	Reciprocal T	Deletions	Supernumerary			
	Male	Female	Total	47, XYY	47, XXY	Oth. [b/]	45, X	47, XXX	Oth. [b/]	+D	+E	+G	Oth. [b/]	D/D	D/G							Oth. [b/]		
1	493	437	930 [c/]	2	1	-	-	-	-	-	-	-	-	-	-	1	1	-	-	-	-	-	5	0.54
2	1066	1015	2081	4	1	-	-	-	-	-	-	2	-	1	-	-	-	1	-	1	-	-	10	0.48
3	7176	6763	13939	4	6	2	-	5	2	1	3	14	-	12	1	11	1	-	1	-	-	3	66	0.47
4	5761	5387	11148	3	6	9	1	7	3	1	1	16	-	15	2	15	1	-	6 [d/]	1	6 [e/]	-	93	0.83
5	7849	3831	11680	10	9	5	-	5 [f/]	2	-	2	17	1	6	4	10	2	1	-	-	1	3	78	0.67
6	2072	1921	3993	4	5	1	-	3 [f/]	-	-	1	3	-	3	-	5 [g/]	2	-	-	-	2	-	29	0.73
7	13751	-	13751	11	9	12	-	-	-	-	-	19	-	5	3	12	4	2	-	2	5	-	84	0.61
8	2184	2182	4353 [h/]	3	4	-	1	3	-	1	1	3	-	2	1	3	-	-	-	-	-	-	22	0.51
9	1303	1197	2500 [h/]	-	1	6	-	-	-	-	-	4	2	-	1	3	1	-	-	1	-	-	19	0.76 [i/]
10	1393	1233	2626	2	-	2	-	1	3	-	-	3	-	4	2	-	-	1	-	-	-	-	18	0.69 [i/]
Total																								
	43048	23966	67014	43	42	37	2	24	10	3	8	81	3	48	14	60	12	5	7	5	14	6	424	0.63
				158 (0.24 %)						95 (0.14 %)				134 (0.2 %)				37 (0.06 %)						

a/ Survey centres: 1: Hamilton, Canada; 2: London, Canada; 3: Winnipeg, Canada; 4: Arhus, Denmark; 5:Edinburgh I, United Kingdom; 6: Edinburgh II, United Kingdom; 7: Boston, United States; 8: New Haven, United States; 9: Moscow, USSR; 10: Kanagawa, Japan.

b/ Most of these are mosaics.

c/ Included 1 twin-pair and 1 triplet.

d/ Unbalanced Y-autosome translocation.

e/ Supernumerary small metacentric chromosomes including two mosaics.

f/ Also had inversion.

g/ One Y-autosome translocation.

h/ These 2500 infants are a random sample of 10237 infants born during the study period (1969-1972) and included 15 twin-pairs, 29 newborn infants with various congenital malformations, 5 stillborn and 13 delivered prematurely [B1].

i/ The authors observed 7 infants with a pericentric inversion of chromosome 9 and 1 with a pericentric inversion of the Y, but for some reason, did not include these in their tabulations.

NOTE: Data on heritable fragile sites are not included in this Table.

Table 3

A comparison of the frequencies of chromosome abnormalities in newborn and in 7- and 8-year old children

(based on Table 2 and reference [P1])

Type	Newborn surveys N = 67014	7 and 8-year old N = 4342
Sex-chromosomal abnormalities a/	0.24 % (158) b/	0.23 % (10)
Autosomal trisomics	0.14 % (95) c/	0.04 % (2) d/
Autosomal structural rearrangements	0.20 % (134)	0.21 % (9)

a/ Includes sex-chromosomal aneuploids, mosaics, deletions, inversions, etc.
b/ Number of chromosome anomalies given in parenthesis.
c/ 81 out of 95 were + G (trisomy-21).
d/ Both the autosomal trisomics were + G (trisomy-21).

Table 4

Non-disjunctional origin of the extra chromosome in autosomal trisomies studies in spontaneous abortions [J15]

There were 49 informative cases in 124 cases examined.

Origin				Chromosome						Total	
Male I	Male II	Female I	Female II	13	14	15	16	21	22		
+							2			2	8 %
	+			1			1			2	
+	+									0	
		+		3	1	2	12	4	11	33	92 %
			+				1	1		2	
		+	+	1		2	1	3	3	10	
				5	1	4	17	8	14	49	

Table 5

Mutation rate estimates for balanced structural rearrangements
[J16]

Population	Number examined	Number abnormal	Robertsonian translocations D/D de novo	D/D Familial Pat.	D/D Familial Mat.	D/D Familial ?	Robertsonian translocations D/G de novo	D/G Familial Pat.	D/G Familial Mat.	D/G Familial ?	Reciprocal translocations de novo	Reciprocal translocations Familial Pat.	Reciprocal translocations Familial Mat.	Reciprocal translocations Familial ?	Inversions de novo	Inversions Familial Pat.	Inversions Familial Mat.	Inversions Familial ?	Total de novo	Total Familial Pat.	Total Familial Mat.	Total Familial ?
Spontaneous abortions	5726	16	0	1	3	0	0	0	0	1	4	1	4	0	0	1	0	1	4	3	7	2
Live births	59452	113	2	12	15	12	2	6	3	0	13	16	14	9	1	3	4	1	18	37	36	22
Percentage:																						
Spontaneous abortions				0.070				0.017				0.157				0.035				0.279		
Live births				0.069				0.018				0.087				0.015				0.190		
Gametic mutations rate:																						
Spontaneous abortions				0				?				$3.49\ 10^{-4}$				?				$3.99\ 10^{-4}$		
Live births				$0.24\ 10^{-4}$				$0.16\ 10^{-4}$				$1.31\ 10^{-4}$				$0.09\ 10^{-4}$				$1.88\ 10^{-4}$		
All recognized conceptions				$0.20\ 10^{-4}$				$0.16\ 10^{-4}$				$1.63\ 10^{-4}$				$0.09\ 10^{-4}$				$2.20\ 10^{-4}$		

Table 6

Mutation rate estimates for unbalanced Robertsonian translocations
[J16]

Population	Number examined	Number abnormal	D/D de novo	D/D Familial Pat.	D/D Familial Mat.	D/D Familial ?	D/G de novo	D/G Familial Pat.	D/G Familial Mat.	D/G Familial ?	G/G de novo	G/G Familial Pat.	G/G Familial Mat.	G/G Familial ?	Total de novo	Total Familial Pat.	Total Familial Mat.	Total Familial ?
Spontaneous abortions	5726	46	15	1	11[a/]	6	4	0	4[a/]	2	1	0	0	2	20	1	15	10
Live births	59452	4	1	0	1	1	0	0	0	0	1	0	0	0	2	0	0	1
Percentage:																		
Spontaneous abortions				0.576				0.175				0.052				0.803		
Live births				0.005				0				0.002				0.007		
Gametic mutation rate:																		
Spontaneous abortions				$16.00\ 10^{-4}$				$4.37\ 10^{-4}$				$2.60\ 10^{-4}$				$22.32\ 10^{-4}$		
Live births				$0.13\ 10^{-4}$				0				$0.10\ 10^{-4}$				$0.23\ 10^{-4}$		
All recognized conceptions				$2.51\ 10^{-4}$				$0.66\ 10^{-4}$				$0.48\ 10^{-4}$				$3.54\ 10^{-4}$		

a/ Includes two sibs.

Table 7

Mutation rate estimates for unbalanced structural rearrangements (non-Robertsonian types) [J16]

Population	Number examined	Number abnormal	Stable structurally abnormal chromosomes				Rings				Supernumerary				Total			
			de novo	Familial Pat.	Mat.	?	de novo	Familial Pat.	Mat.	?	de novo	Familial Pat.	Mat.	?	de novo	Familial Pat.	Mat.	?
Spontaneous abortions	5726	42	15	8[a/]	6	10	1	0	0	2	0	0	0	0	16	8	6	12
Live births	59452	18	3	1	1	2	0	0	0	0	2	1	5	3	5	2	6	5
Percentage:																		
Spontaneous abortions				0.681				0.052				0				0.733		
Live births				0.012				0				0.018				0.030		
Gametic mutation rate:																		
Spontaneous abortions				$17.60\ 10^{-4}$				$2.6\ 10^{-4}$				0				$19.53\ 10^{-4}$		
Live births				$0.36\ 10^{-4}$				0				$0.23\ 10^{-4}$				$0.58\ 10^{-4}$		
All recognized conceptions				$2.95\ 10^{-4}$				$0.39\ 10^{-4}$				$0.20\ 10^{-4}$				$3.42\ 10^{-4}$		

a/ Includes three sibs.

Table 8

Radiation and Down's syndrome: epidemiological studies [S6]

Country	Study type	Cases	Outcome	Ref.
Canada				
1961	Retrospective	81 DSM a/	Significant increase in DS[b/] incidence in exposed mothers (abdominal exposures or fluoroscopy)	[U4]
1968	Prospective	861 M	Significant increase in DS in exposed mothers	[U5]
Denmark				
1970	Retrospective	?	No significant radiation effect.	[V3]
Japan				
1962	Prospective	15034 M[c/]	Frequency of DS in the progeny of exposed mothers was less than half of the controls; not significant;	[S18]
United Kingdom				
Scotland, 1959	Retrospective	117 DSP[d/]	No significant radiation effect.	[L6]
England, 1961	Retrospective	51 DSM	Non-significant increase of DS in controls.	[C9]
N.Ireland,1962	Retrospective	197 DSM	No significant radiation effect.	[S17]
England, 1970	Prospective	630 M	No significant radiation effect.	[S20]
England, 1972	Retrospective	465 DSP	Significant increase in DS in exposed mothers who had received radiation 10 years or more before the conception of the cases.	[A5]
United States				
1965	Retrospective	216 DSP	Significant increase in DS in exposed mothers.	[S19]
1969	Retrospective	61 DSM	No significant radiation effect.	[M14]
1977 e/	Retrospective	128 DSP	No significant radiation effect.	[C8]

a/ DSM: mothers of Down's syndrome cases.
b/ DS: Down's syndrome.
c/ M: Mothers.
d/ DSP: Parents of Down's syndrome cases.
e/ A follow-up of the 1965 survey above [S19].

Table 9

Specific chromosomal defects in some cancers
(from [M20, R12] and other sources)

Disorder	Main chromosomal anomalies	Comments and reference
Chronic myeloid leukaemia	Ph^1-chromosome: t(9;22)(q34;q11) i(17q)	Present in over 90 % of patients in chronic phase in blast phase [R12, D9]
Chronic lymphocytic leukaemia	t(14q-;14q+)	[M32, W25]
Acute non-lymphatic leukaemia	+8; -7; t(8q-; 21q+); t(15q+;17q-); t(9q+;22q-)	Anomalies in 50 % of the cases; [D9] [P35]
Burkitt lymphoma a/		
- African type	t(8q-;14q+)	Lymphoma usually associated with Epstein-Barr-virus (EBV) [Z4, Z12]
- American type	t(8q-;14q+)	Not usually associated with EBV
Non-Burkitt lymphoma	14q+	[M61]
Hodgkin's lymphoma a/	14q+	[R18]
Lymphoblastic leukaemia	6q-; +8; t(4;11)(q13;q22)	[O20, P35, D20]
Lymphocytic lymphoma a/	14q+	[R18]
Multiple myeloma	14q+	[W14]
Plasma cell leukaemia	14q+	[W14]
Meningiomas	-22; -8; -9; -X; -Y	[M31, M30, Z5, Z6]
Seminomas a/	Long submetacentric marker chromosome	[M28]
Aniridia-Wilms' tumour - gonadoblastoma association	del(11p13)	[F26, F27, R66]
Retinoblastoma	del(13q14)	[Y3]
Chronic lymphocytic leukaemia in ataxia telangiectasia	t(14q-;14q+)	[M32]

a/ Based on 1-2 cases only.

Table 10

Sensitivity of cells from patients with inherited disorders to the lethal and chromosome-breaking effects of mutagens
(from [A11] and other sources)

Cells	UV	AAF	Ionizing radiation	Cross-linkers	MMS	EMS	MNNG	NQO	References
XP	SS	SS	N	N	N	N	N	S	[C25, L14, M34, T12]
XP variant	N / S	N	N	N	N	N			[A12, C25, L14, M35]
AT	N	N	SS	S or N	S or N	N	S		[H33, L13, L14, P38, T7]
FA	N		S / N	SS		N / S		S / N	[F8, F9, L14, S104]
BS	S / N		N		N	S			[A28, G19, K13]
Cockayne's syndrome	SS	N / S	N		N	S / N			[A28, S45, W15, M37]

AAF: acetylaminofluorene
MMS: methylmethane sulphonate
EMS: ethylmethane sulphonate
Cross-linkers: mitomycin C, psoralen + UV light; nitrogen mustard
MNNG: N-methyl-N'nitro-N-nitroguanidine
NQO: 4-nitroquinoline oxide

S = sensitive
SS = very sensitive
N = normal
N / S = conflicting results.

Table 11

Sensitivity of cells from patients with inherited disorders to the chromosome-breaking and SCE-inducing effects of mutagens (from [A11] and other sources)

Cells	UV	AAF	Ionizing radiation	Cross-linkers	MMS	EMS	MNNG	NQO	References
				Chromosome breakage effects					
XP	S				N		N	SS	[M36, S43]
AT			SS						[N12,T8,T9]
FA	S		N	SS	N	[N/S	N	N	[A14, H34, S44]
BS	N		N			SS			[E15, K13, K12]
				SCE-induction					
XP	S					[N/S		S	[H34, W17, P15]
AT			N	N					[G20]
FA				less than N					[L16]
BS						S			[K13]
Cockayne's syndrome	S								[M36, S45]

MMS: methylmethane sulphonate
EMS: ethylmethane sulphonate
Cross-linkers: mitomycin C, psoralen + UV light; nitrogen mustard
MNNG: N-methyl-N'nitro-N-nitroguanidine
NQO: 4-nitroquinoline oxide

S = sensitive
SS = very sensitive
N = normal
[N/S = conflicting results.

Table 12

Some characteristic properties of XP complementation groups (based on [C61, L12, R10, S107, S108, T29])

Group	Clinical features: Cutaneous	Clinical features: Neurological	DMF a/	UDS b/	Endo-sites c/	Photolase d/
A	+	+	9.6	0-5	0	36
B	+	+	-	3-7	0-5	0
C	+	-	4.8	10-15	10	16
D	+	+	9.9	25-50	10	8
E	+	-	1.4	40-60	60-70	49
F	+	-	-	10	60	?
G	+	+/-	-	10-15	0	?
Variant	+	-	1.6	60-100	100	20

a/ Average dose modifying factors (UV), ratios of D_0 values for normal to mutant, from survival curves.
b/ Percentage of normal cell UDS in autoradiographs.
c/ Loss of endonuclease sensitive sites 0-16 hours post UV-irradiation, relative to normal cells, in per cent.
d/ Per cent of normal.

Table 13

Damaging agents or products for which XP (Xeroderma pigmentosum) cells are repair-proficient or repair-deficient a/ (from [S42])

Proficient	Deficient
Ionizing radiation	UV
strand breaks	dimers
anoxic	protein DNA links
4-NQO (minor compound)	strand breaks
NO-carbaryl	Ionizing radiation
NO-methyl guanidine	anoxic
MNNG	4-NQO
MMS	AAF damage
MNU	ICR-170
EMS	Aflatoxin
N-7 alkylguanine	K-region epoxides
Proflavin + light	Br benzanthracene
Propane sultone	Br_2 Me benzanthracene
Mitomycin C	EMS
	O-6 alkyl guanine
	Psoralen + light
	Chlorpromazine + light
	CCNU
	HNO_2
	Decarbomyl mitomycin C

a/ Cells are categorized on the basis of survival, host-cell reactivation, or chromosomal, or biochemical, or biophysical measures of repair (a listing in both categories means that there are several products of an agent or that all cell lines are not the same).
For abbreviations, see Table 10.

Table 14

DNA repair properties of AT fibroblast strains [P37]

DNA-damaging agent	Repair hallmark	Strain a/ exr⁻	Strain a/ exr⁺	References
Hypoxic γ rays	DNA repair replication	D b/	P b/	[P17, P18]
	Unscheduled DNA synthesis	D	P	[P36]
	M. luteus endonuclease-sensitive site removal	D	P	[P17, P36]
	Single-strand break rejoining: velocity sedimentation	P	P	[P17, P36]
Oxic γ rays	Thymine glycol removal:			
	in cells	P	P	[C62]
	by cell extracts	P	P	[R71]
	Single-strand break rejoining:			
	velocity sedimentation	P	P	[T7]
	alkaline elution	P	P	[F28]
	endonuclease S_1	P	P	[S109]
	Double-strand break rejoining:			
	velocity sedimentation	P	P	[L17]
	unscheduled DNA synthesis	D	D	[V6]
Bleomycin	Single- and double-strand break rejoining: velocity sedimentation	P	P	[F28, L44]
4NQO	Alkali-labile lesion removal	D,P	D	[S112]
MNNG	DNA repair replication	D	P	[S110]
MMS	DNA repair replication	P	P	[S110]
Far-UV light	UV endonuclease-sensitive site removal	P	P	[P17, A29]
	DNA repair replication	P	P	[S110, P17]
	Unscheduled DNA synthesis	P	P	[P37, A29]
	Post-replication repair	P	P	[L13]
N-acetoxy AAF	DNA adduct removal	P		[A19]
	DNA repair replication	P	P	[A29]

a/ exr^-: deficient and exr^+ proficient in DNA repair replication induced by hypoxic gamma rays;
exr^- strains: AT1BE, AT2BE, AT3B1, AT81CTO, AT194CTO;
exr^+ strains: AT3BE, AT4B1, AT5B1, AT7B1.
b/ D: deficient; P: proficient; no entry: not tested.

Table 15

Frequency of aberrant cells by dose in 23 heavily exposed atomic bomb survivors of Hiroshima
[S52]

Dose group (Gy)	Mean	Number of cases	Number of cells analysed	Number of aberrant cells	
				O (%) a/	G (%) a/
1.00-1.99	157.8	8	295	68 (23.1)	78 (26.4)
2.00-2.99	258.2	6	257	80 (31.1)	92 (35.8)
3.00-3.99	331.7	3	137	52 (39.0)	63 (46.0)
4.00-4.99	405.7	3	85	25 (29.4)	29 (34.1)
5.00+	710.7	3	122	68 (55.7)	80 (65.6)
Total exposure	311.1	23	896	239 (32.7)	342 (38.2)

a/ O is ordinary stain, G is banding stain.

Table 16

Post-implantation foetal survival data for different mating periods after injection of plutonium-239
[G23]

Experiment number	Mating period (weeks after injection)	Exposure level (MBq/kg)					
		0		0.19		0.37	
		IMP	LE/IMP a/	IMP	LE/IMP a/	IMP	LE/IMP a/
1	20-31	727	0.9574	-	-	744	0.9449
2	12-15	409	0.9560	-	-	415	0.9349
	22-33	926	0.9600	-	-	981	0.9378
	43-48	464	0.9547	-	-	501	0.9441
3	11-15	626	0.9473	595	0.9412	626	0.9281
	21-25	582	0.9691	612	0.9346	576	0.9167
	31-35	505	0.9485	588	0.9303	488	0.9078
	41-45	605	0.9570	573	0.9564	540	0.9333

a/ IMP: total number of uterine implants;
LE: total number of live implants.

Table 17

Post-implantation foetal survival data for different mating periods after irradiation of continuous whole-body external cobalt-60 gamma-irradiation

(All matings were within the 0-35 day post-irradiation interval)
[G23]

Expt. number	Mating period (weeks from start of experiment)	Exposure level								
		Control			3.36×10^{-2} Gy d^{-1}			5.98×10^{-2} Gy d^{-1}		
		IMP	LE/IMP	Dose a/	IMP	LE/IMP	Dose a/	IMP	LE/IMP	Dose a/
1	28,30,32,34	267	0.9588	0	290	0.9379	0.59	246	0.9268	1.05
	14-17,24,26	274	0.9453	0	321	0.9377	0.94	320	0.8875	1.67
2	10-13	533	0.9568	0	526	0.9297	1.06	513	0.8577	1.89
	10-23	402	0.9527	0	460	0.8870	1.06	453	0.8389	1.89
3	9	689	0.9419	0	583	0.9108	1.06	681	0.8737	1.89
	21	579	0.9482	0	473	0.9027	1.06	442	0.8801	1.89
	32	566	0.9576	0	455	0.8791	1.06	291	0.8900	1.89

a/ Mid-line tissue absorbed dose in Gy accumulated over 5-week period prior to mating and adjusted for radiation-free periods.

Table 18

Dominant lethal mutation rates, per gamete per 10^{-2} Gy, based upon post-implantation foetal survival [G23]

Radiation quality	Cell stage exposed	Mutation rate (x 10^4)		
		Single exposure	Weekly exposure	Continuous exposure
^{60}Co γ rays	Postmeiotic a/	10 ± 1.1	11 ± 0.9, 10.1 ± 0.63 d/	5 ± 0.6
	Premeiotic b/	1.1 ± 0.2	0.35 ± 0.06	0.14 ± 0.07, 0.22 ± 0.06 d/
Neutrons	Postmeiotic a/	54 ± 4.0	88 ± 21, 54 ± 2.2 d/	-
	Premeiotic b/	3.9 ± 0.9	2.6 ± 0.6, 2.7 ± 0.54 d/	-
^{239}Pu α-particles	All stages c/	-	-	64 ± 11

a/ Rates based upon total dose delivered up to 5 weeks prior to mating and adjusted for radiation-free period;
b/ Rates based upon total dose accumulated prior to mating;
c/ Rate based upon total dose delivered over a 4-week period;
d/ Rates based upon pooling of all data in both sets within the brace.

Table 19

Relative biological effectiveness ratios for exposure to ^{239}Pu alpha particles (α), weekly fission neutron irradiation (n_f), or continuous cobalt-60 gamma-irradiation (γ_c) [G23]

Genetic end point	Response coefficient (x 10^4 10^{-2} Gy) a/			Ratio		
	α	n_f	γ_c	α/γ_c	n_f/γ_c	α/n_f
Dominant lethals						
Postmeiotic stages	64.0	54.0	5.0	13.0 ± 3.0	11.0	1.2
Premeiotic stages	-	2.6	0.14	-	19.0	-
Translocations	≤6.8 b/	6.8	0.18	≤38.0 ± 5.0	38.0	≤1.0
Fragments	93.0	-	2.8	33.0 ± 5.0	-	-
Abnormal sperm	2.7	1.1	0.11	25.0 ± 8.0	10.0	2.5
Testis weight loss	3600	2300	380	9.5 ± 4.0	6.1	1.6

a/ Frequency per gamete or cell per 10^{-2} Gy, except testis weight loss as mg per 10^{-2} Gy.
b/ Assumes that initial portion of dose-response curve corresponds to that seen following weekly neutron irradiation.

Table 20

Frequencies of dominant lethals (DLM) expressed at various stages of mouse embryo development in vitro at various times after irradiation of males (4.5 Gy) [G28]

Germ cell stage irradiated	Day after irradiation of males	Fraction arrested before morula stage		Frequency of DLM a/	Fraction arrested before blastocyst stage		Frequency of DLM b/	Fraction arrested before trophoblast outgrowth stage		Frequency of DLM c/
		Experimental	Control	Per cent	Experimental	Control	Per cent	Experimental	Control	Per cent
Sperm	0	99/590	33/219	5	82/491	9/491	14	95/409	33/177	5
	4	214/956	73/608	13	40/742	89/535	12	237/702	37/446	28
	7	142/966	69/479	0	127/824	83/410	-6	164/697	13/327	20
Spermatid	11	148/709	78/377	0	132/561	65/209	2	115/429	25/234	18
	14	244/731	29/286	26	93/487	16/257	14	145/394	25/241	29
	18	397/971	73/542	32	210/574	51/469	29	154/364	35/418	37
	21	279/867	111/576	22	155/588	41/465	19	132/433	49/424	21
Spermatocyte	24	170/441	94/580	26	57/271	22/486	17	58/214	33/464	22
	28	75/239	76/574	21	35/164	83/498	6	19/129	22/415	9
	35	52/297	83/686	7	60/245	59/603	16	7/185	51/544	-6
Spermatogonia	49 d/	40/264	81/641	3	36/224	99/560	2	23/188	54/461	-1

a/ Per cent of DLM = $[1 - (\frac{1 - \text{fraction arrested at early cleavage stage, experimental}}{1 - \text{fraction arrested at early cleavage stage, control}})] \times 100$.

b/ Per cent of DLM = $[1 - (\frac{1 - \text{fraction arrested at late morula stage, experimental}}{1 - \text{fraction arrested at late morula stage, control}})] \times 100$.

c/ Per cent of DLM = $[1 - \frac{1 - \text{fraction arrested at late blastocyst stage, experimental}}{1 - \text{fraction arrested at late blastocyst stage, control}})] \times 100$.

d/ Data from day 42 are not included because fewer than fifty 2-cell experimental embryos were produced.

Table 21

Frequency of reciprocal translocations induced per R of gamma-irradiation for different dose rates [B26]

Exposure rate ($R\ min^{-1}$)	Translocations/R a/	Goodness of fit
0.0012	$1.3\ 10^{-5}$	$P > 0.30$
0.0035	$1.5\ 10^{-5}$	$P < 0.05$
0.012	$2.1\ 10^{-5}$	$P > 0.30$
0.105	$4.0\ 10^{-5}$	$P > 0.40$
1.0	$6.7\ 10^{-5}$	$P > 0.05$ c/
100.0	$2.0\ 10^{-4}$ b/	$P > 0.01$ c/

a/ Presented as the linear coefficient "b" of the dose-response curve, $Y = bD$, where Y is the yield and "D" the dose.

b/ These data were for x-irradiation and so the translocation yield per R was multiplied by 0.8 to account for the relative biological effectiveness of gamma rays relative to x rays.

c/ This P value is not very informative, because for comparative purposes the data were fitted to a linear curve, although it is known that there is a significant two-track component.

Table 22

Frequency of chromatid aberrations observed in metaphase-1 mouse oocytes at various intervals following x-irradiation [B32]

Interval (days)	0 R			50 R			100 R			200 R			300 R		
	Number of cells	D a/	X b/	Number of cells	D a/	X b/	Number of cells	D a/	X b/	Number of cells	D a/	X b/	Number of cells	D a/	X b/
1.5	500	1	0	150	0	1	225	3	2	150	5	3	160	9	4
3.5				125	1	1	150	2	1	175	10	5	170	12	16
5.5				160	1	1	170	4	4	225	10	8	128	16	17
7.5				150	1	1	175	5	4	143	8	7	169	25	35
9.5				125	2	1	200	5	6	125	15	13	200	52	71
13.5 to 14.5				150	2	2	265	11	11	350	31	46	361	99	145
17.5				166	2	2	200	9	9	125	17	17	153	51	39
21.5				125	2	2	188	13	10	162	17	17	200	48	44
24.5				100	2	0	125	5	4	92	15	11	125	39	34
28.5				75	1	1	-	-	-	-	-	-	-	-	-

a/ D = deletions.
b/ X = interchanges.

Table 23

Frequencies of reciprocal translocations induced in the spermatogonia of rhesus monkeys [B35, B36]

Dose (Gy)	Number of monkeys	Number of testes	Number of cells scored	Translocations (%)
0	15	16	1500	0
0.5	6	10	2750	0.36
1.0	7	11	4650	0.86
2.0	7	9	3350	0.99
3.0	4	4	1475	0.68

Table 24

A comparison of the slope of the linear regression "b" estimated for the monkey with those estimated for other species for the induction of reciprocal translocations in spermatogonia a/ [B36]

Animal	b 10^4 ± sd 10^4	P	Ref.
Monkey	0.86 ± 0.04	-	[B36]
Mouse	1.92 ± 0.22	< 0.01	[L24]
	2.90 ± 0.34	< 0.01	[E9]
	2.51 ± 0.20	< 0.01	[M43]
	1.53 ± 0.17	< 0.01	[W20]
	1.29 ± 0.02	< 0.01	[B37]
	1.96 ± 0.18	< 0.01	[P25]
Rabbit	1.48 ± 0.13	< 0.01	[L25]
Guinea pig	0.91 ± 0.10	> 0.05	[L25]
Marmoset	7.44 ± 0.95	< 0.01	[B38]
Man	3.40 ± 0.72	< 0.01	[B38]

a/ The linear regression coefficients were estimated for all the animals using the data given by the different authors at doses to those giving peak yields of translocations.

Table 25

Incidence of spontaneous aneuploidy (n-1 and n+1) and polyploidy in early embryos of various mammalian species (after [C52])

Species	Embryonic stage	Number studied	n-1	n+1	Poly-ploid	Aneu-ploid (%)	Poly-ploid (%)	Ref.
Mouse	1-cell	616	a/	a/	12	-	1.9	[M45]
		516	3	3	a/	1.2	-	[M45]
		338	3	-	5	0.9	1.5	[D15]
	1-2 cell	193	-	1	8	0.5	4.1	[K20]
Chinese hamster	4-8 cell	226	1	1	5	0.9	2.2	[B43]
Sheep	2-8 cell	89	-	4	-	4.5	-	[L46]
Rabbit	5.5 day	463	-	4	8	0.9	1.7	[F29]
Pig	10 day	88	-	-	7	-	8.0	[M64]
Cow	12-16 day	12	-	-	-	-	-	[M65]
Mouse	8-11 day	607	-	3	6	0.5	1.0	[F17]
	9-10 day	561	-	2	1	0.4	0.2	[C35]
Rat	11 day	410	-	-	3	-	0.7	[B70]

a/ Not studied.

Table 26

Incidence of "spontaneous" non-disjunction in oogenesis from several rodents a/ (after [H40])

Species	Aneuploidy assessed in	Number of oocytes or embryos analysed	Number hyperploid	Incidence of aneuploidy (%) (hyperploid x 2)	Reference
Mouse	oocytes	5853	28	0.96	[B71,H41,H57, M66,R26,R73, R74,S115,U10]
	pronuclei	2902	24	1.65	[M45]
Hamster Chinese	oocytes	455	0	0	[H39, H43]
	4-8 cell embryos	226	1	0.89 b/	[B43]
Syrian	oocytes	455	1	0.44	[B72, H43]
Djungarian	oocytes	197	0	0	c/

a/ The data are put together, although different methods have been used (in vivo/in vitro maturation, hormone induced ovulation, spontaneous ovulation, different strains, etc.) for the different groups.
b/ One embryo affected by a monosomy was reported by the authors.
c/ Hansmann and Probeck, unpublished.

Table 27

Mutation frequency at 7 specific loci in offspring of male mice injected with tritiated water [R31]

Cell stage exposed to radiation	Experi-ment	Injected amount (MBq/gm of body weight)	Number of offspring	Number of mutations	Estimated weighted mean dose to germ cells (Gy)
Post-spermatogonial	1-1	28	515	1	
		18	3327	4	4.30
	1-2	18	4101	6	
Spermatogonial a/	1-3	28	2408	3	
		18	18218	13 b/	6.15
	2	18	11481	7 b/	

a/ A negligible portion (< 1 %) of the dose was received in post-spermatogonial stages.
b/ The number includes both mutants of a cluster of two in the offspring of one male in this experiment.

Table 28

Distribution of ^{3}H-induced mutations in mice according to locus and viability of homozygote
[R31]

Cell stage exposed to radiation	Result of viability test	Number of mutations at specified locus							
		a	b	c	p	d	se	s	Total
Post-spermatogonial	Viable		1	1			1		3
	Sublethal a/				1				1
	Lethal b/	1	1		1				3
	Sterile c/		1			1		1	3
	Untested							1	1
	Total	1	3	1	2	1	1	2	11
Spermatogonial	Viable		3	4	2	1			10
	Sublethal					2		1	3
	Lethal		2		2			1	5
	Untested				1			2	3
	Total		5	4	5	3		4	21

a/ Defined here as lethal after perinatal period and before breeding age;
b/ Lethal before birth or perinatally;
c/ Mutants themselves were sterile and, therefore, could not be tested.

Table 29

Specific locus mutations after irradiation of maturing mouse oocytes
[L32]

Dose (Gy)	Number of mutants	Total progeny	Mutation rate per locus per 10^{-2} Gy x 10^{7}
0 a/	2, 3 or 8	204639	-
2 b/	3	10379	-
2 (new data)	4	8488	-
2 (total)	7	18867	2.65
4	7	7501	3.33
6	26	9875	6.27

a/ Reference [R38].
b/ Reference [L31].

Table 30

Distribution of major classes of c-locus mutations induced in the mouse
[R42]

Germ-cell stage irradiated	Type of radiation	Number of mutations	Type of mutation (%)		
			Viable	Subvital	Lethal a/
Spontaneous b/		18 c/	94.1	5.9	0
Spermatogonia	x or gamma	51	66.7	2.0	31.4
	neutrons	15	60.0	6.7	33.3
Postgonial	x or gamma	5	40.0	0	60.0
	neutrons	3	33.3	0	66.7
Oocytes	x or gamma	7	57.1	14.3	28.6
	neutrons	9	22.2	0	77.8

a/ Includes prenatal and neonatal lethals.
b/ Control group, plus mosaic mutants from all groups.
c/ One of these not tested for homozygous viability.

Table 31a

Gamma-ray induction of dominant cataract mutations in male mice [E24]

(For comparisons, the numbers of recessive specific locus mutations recovered in the same experiments are given in the last column)

Exposure (R)	Germ-cell stage treated	Number of F_1 offspring	Number of cataract mutants	Frequency per gamete ($\times 10^5$)	Rate per gamete per R ($\times 10^6$)	Number of specific locus mutations
0 a/	-	8174	0	-	-	2
455+455 b/	Spermatogonia	5231	6	114.7	1.26	9
534	Spermatogonia	10212	3	29.4	0.55	7
600	Spermatogonia	11095	3	27.0	0.45	14
455+455 b/	Post-spermatogonial stages	272	1	367.6	4.04	2
534	Post-spermatogonial stages	1721	1	58.1	1.09	3
600	Post-spermatogonial stages	865	1	115.6	1.93	3

a/ For specific locus mutations, the historical control currently stands at 6 mutations in 103 218.

b/ Fractionated irradiation separated by a 24-h interval.

Table 31b

Features of radiation-induced dominant cataract mutations in mice [E20, E24, K23]

Mutant	Provisional gene symbol	Manifestation	Penetrance	Expressivity	Fertility
		Exposure group 455+455 R			
Male 001 a/	Vlm	Vacuolisation of the whole lens, microphthalmia, iris adhesion, bilateral	complete	constant	normal
Female 160	Iac	Iris anomaly with cataract, long teeth, bilateral	complete	variable	normal
Female 116	Nzc	Nuclear and zonular cataract, bilateral	complete	constant	normal
Female 165	Nuc	Nuclear cataract, bilateral	complete	constant	reduced
Female 132	Apyc	Anterior pyramidal cataract with corneolenticular attachment and remnants of the pupillary membrane, uni- and bilateral	incomplete	variable	normal
Male 143	Apoc	Anterior polar cataract, posterior synechiae, uni- and bilateral	complete	variable	reduced
Female 206	Acc	Anterior capsular cataract, posterior synechiae, uni- and bilateral	incomplete	variable	normal
		Exposure group 534 R			
Male 284 a/	Alm	Anterior lenticonus, microphthalmia, white spotting on the belly, bilateral	complete	constant	reduced
Male 257	Mci	Microphthalmia with cataract of the left lens			sterile
Male 236	Idc	Iris dysplasia with cataract, spotting on the belly, bilateral	complete	constant	normal
Male 223	Anc	Anisocoria, ovoid pupils, occasionally with cataract, uni- and bilateral	incomplete	variable	normal
		Exposure group 600 R			
336 a/		Anterior polar cataract	-	-	sterile
340		Nuclear and posterior suture cataract	incomplete	constant	normal
341		Anterior polar cataract, pupillary membrane	incomplete	constant	males normal females reduced
395		Anterior polar cataract, corneal lens attachment, microphthalmy	complete	constant	normal

a/ Derived from post-spermatogonial irradiation.

Table 32

Incidence of congenital anomalies in the offspring of male or female mice exposed to 0.36-5.04 Gy of x irradiation [N23]

Living foetuses on day 19				Offspring surviving more than 7 days			
Incidence	(%)	P	Details a/	Incidence	(%)	P	Details a/
			Male parents irradiated				
45/2041	(2.2)	< 0.001	8 CP, 5 T, 13 D, 14 OE, 4 Ex, 1 Hy, 1 Ga.	20/2314	(0.9)	< 0.05	3 T, 7 D, 3 OE, 6 TA, 1 A.
			Female parents irradiated				
25/942	(2.7)	< 0.001	8 CP, 3 T, 4 D, 10 OE, 2 Ex, 1 Ga.	29/1750	(1.7)	< 0.01	10 T, 16 D, 1 Lu, 1 Li, 1 A.
			Controls				
4/1026	(0.4)		1 D, 1 OE, 1 Ex, 1 PD.	1/809	(0.1)		1 T.

a/ CP, cleft palate; T, tail anomalies (kinky and/or short); D, dwarf (less than 75 % of body weight of untreated groups); OE, open eyelid; Ex, exencephalus; Hy, hydrocephalus; Ga, gastroschisis; TA, testicular atrophy, Lu, lung anomaly (mislobulation); Li, liver anomaly (mislobulation); A, atresia hymenalis.

Table 33

Some internal emitters of interest for the genetic risk [S76]

Radionuclide	Half-life	Mode of decay	Mean track length (μm)	Remarks
^{3}H	12 a	β	1	Possible transmutation effect when in DNA
^{14}C	5730 a	β	42	As above
^{32}P	14 d	β	1900	As above; skeletal effects
^{137}Cs	30 a	β,γ	380	All tissues irradiated
^{226}Ra	1600 a	α	40	Main dose to skeleton
^{239}Pu	24390 a	α	40	Main dose to skeleton, liver
^{241}Am	458 a	α	40	As above

Table 34

Some genetic results with radioactive isotopes in mammals [S76]

Radio-nuclide	Activity	End point	Result	Ref.
		1. Beta-emitters in rodents		
^{3}H	~ 10-15 MBq per gram	Specific locus mutations (male mice)	Significant induction in pre- and post-meiotic cells	[R31]
^{3}H	~ 110 MBq ml water	Dominant lethals (mice, both sexes	Significant induction in both sexes	[C38]
^{32}P	~ 0.2-1 MBq per mouse	Dominant lethals (female mice)	Significant increase	[K25]
^{89}Sr	~ 0.035 MBq per gram	Dominant lethals (male rats)	Evidence for induction in premeiotic cells	[B47]
^{90}Sr	~ 0.93 MBq per mouse	F_1 translocations (male mice)	Evidence for induction in post-meiotic cells	[R52]
^{90}Sr	~ 0.75 MBq per mouse	Dominant lethals (male mice)	No significant effect in post-meiotic cells	[F19]
^{131}I	0.0075-0.026 MBq per mouse	Dominant lethals (male mice)	Significant increases (post-meiotic cells)	[R53]
^{131}I	0.13 MBq per gram	Dominant lethals (male rats)	Evidence for induction in post-meiotic cells	[B47]
^{14}C	0.55 MBq per gram	Dominant lethals (male mice)	Significant increase	[S133]
^{14}C	1.24 MBq per gram	Translocations in spermatogonia	Significant increase	[S133]
^{14}C	2.50 MBq per gram	Translocations in spermatogonia	Significant increase	[S133]
		2. Alpha-emitters in male mice		
^{239}Pu	0.37 MBq/kg	Translocations	Significant increase	[B44]
^{239}Pu	0.0018-0.018 MBq per mouse	Dominant lethals, semi-sterility	Extra intra-uterine death, also in F_1	[L33]
^{239}Pu	~ 0.15 MBq/kg	Dominant lethals fragments, translocations	RBE about 23 (relative gamma rays)	[S53]
^{239}Pu	0.37 MBq/kg	Specific locus mutations	Significant increase	[R37]
^{239}Pu	0.18-0.37 MBq/kg	Dominant lethals, fragments, translocations	RBE estimates from 13-40 (relative to gamma rays)	[G23]

Note: For routes of administration and other details, see the cited references.

Table 35

Mean number of A_s spermatogonia scored per mouse 120 and 207 h after x-irradiation [O10]

Treatment	Experiment 1				Experiment 2	
	x rays only		[^{3}H]dThd + x rays a/		x rays only	[^{3}H]dThd + x rays b/
	120 h	207 h	120 h	207 h	120 h	207 h
Control	147.5±3.25 c/	147.5±3.25	133.25±5.16	133.25±5.16	118.25±4.29	105.21±3.36
100 R					98.25±7.53	84.25±6.61
300 R	39.5±2.40	69 ±1.58	24 ±2.20	65.5 ±5.95	60.5 ±3.01	48.75±3.97
500 R	16.5±1.71	33.5±2.02	13.75±1.65	25.5 ±3.43	27.75±3.59	21.0 ±0.58
600 R	13.7±1.89	23.7±2.81	12.25±0.85	16.75±2.10	15.25±1.44	10.5 ±2.02
1000R	5.2±1.03	2.0±0.58	2.75±0.85	1.25±0.75	3.75±0.95	0.75±0.25
500+500R d/	5.0±1.08	5.0±0.82	8.5 ±1.55	2.0 ±0.63	2.75±0.63	0.75±0.25

a/ 0.46 MBq [^{3}H]dThd 1 h before x rays.
b/ 3 injections of 0.46 MBq [^{3}H]dThd at 9 h intervals, x rays 24 h after last injection.
c/ Standard error of the mean.
d/ 24 h between fractions.

Table 36

Frequency of labeled A_s spermatogonia 207 and 414 h after acute x-ray exposure
[010]

Treatment	Experiment 1 0.46 MBq [^{3}H]dThd a/		Experiment 2 3 x 0.46 MBq [^{3}H]dThd b/			
	207 h		207 h		414 h	
	Number of cells	% labelled	Number of cells	% labelled	Number of cells	% labelled
Control	800	21.0	1000	29.20	1600	22.81
100 R			800	29.00	800	33.75 c/
300 R	800	6.0	800	24.25	800	33.25 c/
500 R	800	2.9	200	27.50 d/	800	39.88 c/
600 R	800	2.6	800	26.25	800	36.50 c/
1000 R	228	6.6	166	10.24 e/	800	15.25 e/
500+500 R	226	2.2	216	47.22 c/	800	35.50 c/

a/ 1 injection of 0.46 MBq [^{3}H]dThd 1 h before irradiation.
b/ 3 injections of 0.46 MBq [^{3}H]dThd given 9 h apart. Irradiation 24 h after last injection.
c/ Significantly above control.
d/ Based on only one mouse.
e/ Significantly below control.

Table 37

A comparison of cell survival, mutation frequency and percentage of labelled A_s spermatogonia after x-irradiation of the male mouse
[010]

Exposure (R)	6 x 0.46 MBq ^{3}H-thymidine 24 h before irradiation (% labelled cells) a/		3 x 0.46 MBq ^{3}H-thymidine 24 h before irradiation (% labelled cells)		Cell survival (% of control)		Mutations per locus per R 10^5 b/
	207 h	414h	207 h	414 h	Minimum c/	207 h interval	
0	7.8	0.7	29.2	22.8			0.75
100	15.6	1.6	29.0	33.8 d/		80.0	
300			24.3	33.8 d/	18.0	46.3	8.72
500	16.3	1.7	27.5	39.9 d/	10.3	20.0	
600			26.3	36.5 d/	9.2	10.0	13.29
1000	2.4	0.2	10.2 c/	15.3 e/	0.9	0.7	9.28
500+500, 24 h apart	39.1	3.1	47.2	35.5 d/	1.5	0.7	49.91

a/ From references [011, 013].
b/ From reference [R58].
c/ These values are calculated from Table 35: the first three entries correspond to 120 h and the last two to 207 h.
d/ Significantly above control, 5 % level.
e/ Significantly below control, 5 % level.

Table 38

X-ray exposures (R) required to kill all ovarian oocytes in different mammalian species
[B50]

Species	Primordial follicles[a]		"Growing" and graafian follicles
	Juvenile	Adult	
Mouse[b]	15 (7)	50 (10-15)	2200
Rat	100	315 (100)	4400
Guinea pig		15000 (500)	
Pig	(500)	(>500)	
Cow	(900)	(>900)	
Monkey	2000?	7000 (5000)	~ 5000
Human[c]		5000? (2000)?	

Note: The data available are not matched for species differences in the rate of oocyte development. This is important, since, for example, if survival of oocytes in the rat has been recorded after a somewhat longer survival time interval, a much lower exposure would have given a 100 % killing.

a/ Figures in parentheses are LD_{50} exposures.

b/ Varies with age, strain and radiation procedure.

c/ Depends on authority and on fractionated doses to women under 35 years.

Table 39

Frequency of occurrence of different subclasses of a_1^- clones in mutagenesis experiments with the CHO hybrid cell line
[W28]

Markers lost	Untreated controls		x rays		MNNG	
	Number	Per cent	Number	Per cent	Number	Per cent
Only a_1	13	16	1	2	8	28
a_1 and up to two others	44	56	30	64	19	65
All four	22	28	16	34	2	7
	79	100	47	100	29	100

Table 40

Estimate of the number of cases of serious genetic ill health in offspring (excluding abortions) from parents irradiated with one million man-rem in a population of constant size, arrived at by the ICRP Task Group
[O18]

Category of genetic effect	Equilibrium[a]	1 + 2 generation
Unbalanced translocations; risk of malformed liveborn	30	23 + 6 = 29
Trisomics and XO	30	30 + 0 = 30
Simple dominants and sex-linked mutations	100	20 + 16 = 36
Dominants of incomplete penetrance and multifactorial disease maintained by mutation	160	16 + 14 = 30
Multifactorial disease not maintained by mutation	0	0
Recessive disease	b/	b/
Total	320	89 + 36 = 125

a/ Over all generations following the generation exposed.

b/ No estimate given.

Table 41

Estimates of genetic effects of an average population exposure of 1 rem per 30-year generation arrived at by the BEIR Committee in its 1980 report [B77]

Type of genetic disorder a/	Current incidence per million liveborn offspring	Effect of 1 rem per generation per million liveborn offspring	
		First generation b/	Equilibrium c/
Autosomal dominant, X-linked	10000	5-65 d/	40-200
Irregularly inherited	90000		20-900 e/
Recessive	1100	Very few; effects in heterozygotes accounted for in top row	Very slow increase
Chromosomal aberrations f/	6000	Fewer than 10 g/	Increases only slightly

a/ Includes disorder and traits that cause serious handicap at some time during lifetime.
b/ Estimates directly from measured phenotypic damage or from observed cytogenetic effects.
c/ Estimates by the relative-mutation-risk method.
d/ No first generation estimate available for X-linked disorders; the expectation is that it would be relatively small.
N:B. A typographical error in the BEIR report is corrected here.
e/ Some estimates have been rounded off to eliminate impression of considerable precision.
f/ Includes only aberrations expressed as congenital malformations, resulting from unbalanced segregation products of translocations and from numerical aberration.
g/ Majority of the Subcommittee feels that it is considerably closer to zero, but one member feels that it could be as much as 20.

Table 42

Expected rates of induction per Gy of various kinds of genetic damage in humans at low dose rates of low-LET irradiation

Kind of damage	Based on	Rate per 10^6 gametes following irradiation of	
		Spermatogonia	Oocytes
1. Mutations having dominant effects	A. Dominant skeletal mutations in mice	400 a/	0-180 b/
	B. Dominant cataract mutations in mice	35 c/ 16.7 c/	0-15 b/
2. Balanced reciprocal translocations (RT)	A. RT in marmoset and humans	1750-8750 d/	0-875 e/
	B. RT in rhesus monkey	220-1080 d/	0-110 e/
3. Unbalanced products of item (2) above	Item A of (2) above	3500-17500 f/	0-5250 g/
	Item B of (2) above	440-2160 h/	0-660 g/
4. X-chromosome loss	X-chromosome loss in mice	negligible	0-500 h/

a/ Same estimate as that presented in the 1977 report.
b/ Estimated from the spermatogonial data using the assumptions that the immature human oocytes will be mutationally insensitive, i.e., similar to the mouse immature oocytes, or will have a mutational sensitivity which is 0.44 times that of spermatogonia; see text for details.
c/ The figure of 35 10^{-6} is that derived from fractionation experiments and the figure of 16.7 1^{-6} from the two single exposure experiments.
d/ The lower rate is for chronic gamma irradiation and the higher one is for low dose rate x rays; based or cytogenetic results.
e/ Under chronic gamma irradiation conditions; the upper limits of 880 or 100 10^{-6} are derived from the spermatogonial estimate for heritable reciprocal translocations assuming that the oocytes will be one-half as sensitive; the lower limit of zero is based on the assumption that the oocytes will be practically insensitive to the induction of translocations.
f/ Assumed to be twice that of balanced RT.
g/ Assumed to be six times that of balanced RT.
h/ Based on results obtained with chronic gamma irradiation of maturing oocytes; see text for details.

Table 43

Risk of induction of genetic damage in humans per Gy at low dose rates of low-LET irradiation according to the direct method

(See Table 44 for risk estimates using the doubling dose method)

Risk from the induction of	Expected frequency (per 10^6) of genetically abnormal children in the first generation after irradiation of	
	Males	Females
Mutations having dominant effects a/	~ 1000 - ~ 2000 b/	0 - ~ 900 c/
Unbalanced products of translocations	~ 30 - ~ 1000 d/	0 - ~ 300 e/

a/ Includes the risk from the induction of dominant mutations, as well as recessive mutations, deletions and balanced reciprocal translocations with dominant effects.

b/ The lower limit of ~ 1000 is derived from the data on cataract mutations and the upper limit of ~ 2000 per 10^6 is derived from data on skeletal mutations and is the same as the one arrived at in the 1977 report. A multiplication factor of 2 has been used in the skeletal estimate but not in the cataract one; this factor is an attempt to allow for the likelihood that many dominant mutations (especially those affecting systems other than the skeleton) remain to be detected. A correction factor of 0.5 to allow for skeletal mutations which are not clinically significant is not required for the cataract estimate. See text for further details.

c/ The lower limit of zero is based on the assumption that the mutational sensitivity of human immature oocytes is similar to that of mouse immature oocytes; the upper limit of 900 10^{-6} is based on the assumption that the sensitivity of human oocytes is similar to that of mature and maturing mouse oocytes and that the latter is 0.44 times that of spermatogonia. See text for further details.

d/ The lower limit of ~ 30 10^{-6} is based on rhesus monkey cytogenetic data; the upper limit of ~ 1000 10^{-6} is based on combined marmoset and human cytogenetic data.

e/ The lower limit of zero is based on the assumption that the sensitivity of human immature oocytes to the induction of heritable reciprocal translocations will be similar to that of mouse immature oocytes with respect to the induction of chromosome aberration phenomena; the upper limit of ~ 300 10^{-6} is based on the assumptions that the sensitivity of the human immature oocytes to the induction of translocations will be one-half of that of human and marmoset spermatogonia (based on results with mice on heritable translocations), that the frequency of unbalanced products will be six times that of recoverable balanced reciprocal translocations and that 6 % of the unbalanced products will result in congenitally-malformed children. See text for further details.

Table 44

Estimated effect of 1 Gy per generation of low dose or low dose rate, low-LET irradiation on a population of one million liveborn according to the doubling dose method

Assumed doubling dose: 1 Gy

(See Table 43 for risk estimates using the direct method)

Disease classification a/	Current incidence b/	Effect of 1 Gy per generation	
		First generation c/	Equilibrium
Autosomal dominant and X-linked diseases	10000 d/	1500	10000
Recessive diseases	2500 e/	slight	slow increase
Chromosomal diseases			
Structural	400 f/	240	400
Numerical	3000 g/	probably very small	probably very small
Congenital anomalies, anomalies expressed later and constitutional and degenerative diseases	90000 h/	450	4500 i/
Total	105900	2190	14900

a/ Follows that given in the BEIR report [B60], except that chromosomal diseases are divided into those with a structural and those with a numerical basis.

b/ Based on the results of the British Columbia survey and other studies. For details, see [U1] and Table 2 of the present Annex.

c/ The first generation incidence is assumed to be about 15 % of the equilibrium incidence for autosomal dominant and X-linked diseases (see text for details), about 3/5 of the equilibrium incidence for structural anomalies and about 10 % of the equilibrium incidence for diseases of complex inheritance.

d/ Includes diseases with both early and late onset.

e/ Also includes diseases maintained by heterozygous advantage.

f/ Based on the pooled values of Table 2 but excluding euploid structural rearrangements, Robertsonian translocations and "others" (mainly mosaics). See text for details.

g/ Excluding mosaics; see text.

h/ Includes an unknown proportion of numerical (other than Down's syndrome) and structural chromosomal anomalies.

i/ Based on the assumption of a 5 % mutational component; see [U1] for details.

Table 45

Mortality to the age of 5 years for selected kinds of childhood hereditary disorders [T2]

Disorder	Deaths per 1000 living affected a/				
	Age (years)				
	1	2	3	4	5
All livebirths	23.6	1.8	1.0	0.7	0.6
Dominants	98.0 (x4) c/	19.4 (x11)	4.2 (x4)	4.7 b/ (x7)	
Recessives	98.5 (x4)	35.0 (x19)	32.6 (x33)	27.0 (x39)	13.1 (x22)
Congenital malformations	130.0 (x5)	11.2 (x6)	5.6 (x6)	3.0 (x4)	3.3 (x5)

a/ All rates, in this and later tables, are based on individuals who have survived to at least the beginning of the age being considered and only for those data which cover the relevant age groups.

b/ Pooled estimate because of very small numbers of deaths at these ages.

c/ Numbers in parentheses, in this and later tables, are the approximate increases in risk compared to the same risk for all livebirths (e.g., 4 = 98.0/23.6).

Table 46

Estimates of load from monogenic dominant disorders
[C51, C69]

Condition	Birth frequency per 10^4	Average years of: Unimpaired life	Average years of: Impaired life and degree of impairment	Lost life years	Cause of death
Familial hypercholesterolaemia	20	55	10 (50 %)	5	Coronary thrombosis
Deafness - congenital (dominant)	1	0	70 (30 %)	0	none
- adult onset	10	30	40 (20 %)	0	none
Polycystic kidney	8	30	10 (50 %)	30	Renal failure
Huntington's chorea	5	45	15 (50 %)	10	Cerebral degeneration and infection
Multiple exostosis	0.5	15	50 (20 %)	5	Cancer
Neurofibromatosis	4	20	30 (50 %)	20	Cancer
Retinoblastoma (untreated) (dominant)	0.3	2	1 (50 %)	67	Cancer
Myotonic dystrophy	2	40	10 (50 %)	20	Dementia and infection
Congenital spherocytosis	2	10	30 (10 %)	30	Haemolytic crisis
Blindness, early onset (dominant)	1	10	60 (50 %)	0	none
Tuberose sclerosis	1	5	45 (80 %)	20	Dementia and infection
Multiple polyposis	1	30	5 (50 %)	35	Cancer
Osteogenesis imperfecta	0.4	2	63 (40 %)	5	Infection
Marfan syndrome	0.4	30	20 (30 %)	20	Aortic aneurysm
Peroneal muscular atrophy (dominant)	2	10	60 (20 %)	0	none
Spastic paraplegia (dominant)	0.5	20	50 (30 %)	0	Infection
Cerebellar ataxia (dominant)	0.5	35	25 (50 %)	10	Infection

Table 47

Estimates of load from autosomal recessive disorders
[C51, C69]

Condition	Birth frequency per 10^4	Average years of: Unimpaired life	Average years of: Impaired life and degree of impairment	Lost life years	Cause of death
Cystic fibrosis (untreated)	5	2	8 (50 %)	60	Lung infection
Phenylketonuria	1	0	40 (95 %)	30	Infection
Neurogenic muscle atrophy	1	1	4 (90 %)	65	Paralysis and infection
Adrenal hyperplasia	1	0	60 (30 %)	10	Electrolyte loss
Congenital deafness (recessive)	2	0	70 (50 %)	0	none
Early onset blindness (recessive)	1	5	65 (50 %)	0	none
Non-specific mental retardation (recessive)	5	0	50 (90 %)	20	Infection

Table 48

Estimates of load from X-linked recessive disorders
[C51, C69]

Condition	Birth frequency per 10^4 males	Average years of: Unimpaired life	Average years of: Impaired life and degree of impairment	Lost life years	Cause of death
Muscular dystrophy (Duchenne type)	2	4	16 (60 %)	50	Debility and intercurrent infection
Haemophilia A	1	0	50 (20 %)	20	Haemorrhage
X-linked ichthyosis	1	0	70 (15 %)	0	none
X-linked forms of mental retardation	1	0	50 (80 %)	20	Intercurrent infection

Table 49

Estimates of load from some selected chromosomal disorders
[C51, C69]

Condition	Birth frequency per 10^4	Average years of: Unimpaired life	Average years of: Impaired life and degree of impairment	Lost life years	Cause of death
Down's syndrome	12	0	35 (95 %)	35	Associated malformation or infection
Edward's syndrome	1	0	1 (100%)	69	"
Autosomal structural aneuploidy	5	0	20 (95 %)	50	"
XXX	5	5	65 (30 %)	0	none
XXY	5	5	65 (30 %)	0	none
XYY	5	5	65 (20 %)	0	none

Table 50

A comparison of the estimates of load from different kinds of spontaneously-arising genetic disease
[C51]

Disease category	Frequency per 10^6 births (A)	Average years of: Unimpaired life (B)	Average years of: Impaired life (C)	Average years of: Lost life (D)	Years impaired per 10^6 births (A x C)	Years lost per 10^6 births (A x D)
Autosomal dominant	9000	33	25 (33%) a/	13	225000	117000
X-linked (males only)	1000	1.5	40 (39%) a/	28	20000 b/	14000 b/
Recessive	2500	1	35 (80%) a/	32	87500	80000
Chromosomal	4000	2	44 (55%) a/	24	176000	96000
Irregularly inherited c/	90000	20	20 (?) a/	30	1,800000	2,700000
Total	106500				2,308500	3,007000

a/ Degree of impairment.
b/ Birth frequency is halved to take into account both sexes.
c/ Crude assessments by the Committee.

Table 51

Frequency of genetic disease among paediatric hospital admissions (per cent of total admissions) [H2, P32]

Number studied	Disease category						Ref.
	Chromosomal	Single gene	Multifactorial	Developmental anomalies	Familial	Heterogeneous, non-genetic or unknown	
9352	0.7	6.4	31.5		8.2	53.2	[C5]
1089	0.4	6.9	3.9 → 22.8 ← 18.9		6.9	63.0	[S85]
200	0	5.0	16.5 → 53.0 ← 36.5		16.5	25.5	[D17]
4115	0.6	3.9	22.1 → 35.7 ← 13.6		13.2	46.6	[H2]
6161	0.7	3.1	3.3 → 3.4 ← 0.1			92.7	[P32]

Note: The studies mentioned above were carried out in hospitals in Baltimore [C5], Montreal [S85], Boston [D17], Seattle [H2] and Caracas [P32].

Table 52

Frequency of single-gene diseases among paediatric admissions (per cent of total admissions) [H2, P32]

Autosomal dominant	Autosomal recessive	X-linked recessive	Ref.
1.3	4.2	1.3	[C5]
2.1	2.1	2.7	[S85]
1.0	3.5	0.5	[D17]
1.2	2.2	0.5	[H2]
0.3	2.5	0.4	[P32]

Table 53

Numbers of selected hospital admissions (per 1000 living affected) for certain kinds of childhood hereditary disorders [T2]

Age	1	2	3	4	5
All livebirths	201	70	49	44	42
Dominants	1104 (x5)	527 (x7)	371 (x8)	302 (x7)	382 (x9)
Recessives	1384 (x7)	571 (x8)	470 (x10)	443 (x10)	287 (x7)
Congenital malformations	1051 (x5)	420 (x6)	275 (x6)	256 (x6)	281 (x7)

Table 54

Numbers of days hospital stay per 100 affected children with certain kinds of hereditary disorders [T2]

Age	1	2	3	4	5
All livebirths	229	63	38	33	30
Dominants	2022 (x9)	803 (x13)	473 (x12)	424 (x13)	981 (x33)
Recessives	2685 (x12)	804 (x13)	603 (x16)	799 (x24)	378 (x13)
Congenital malformations	1500 (x7)	569 (x9)	307 (x8)	291 (x9)	331 (x11)

Table 55

Approximate estimates of detriment resulting from the induction of genetic damage in a population exposed to low dose, low dose rate, low-LET irradiation at a rate of 1 Gy per generation

Condition	Induced number of cases per 10^6 births (A^+)	Average years of life		Years impaired per 10^6 births	Years lost per 10^6 births
		Impaired (C)	Lost (D)	($A^+ \times C$)	($A^+ \times D$)
		FIRST GENERATION			
Autosomal dominant	1400	25	13	35000	18200
X-linked (both sexes)	125	40	28	5000	3500
Chromosomal a/	240	20	50	4800	12000
Irregularly inherited	450	20	30	9000	13500
Total	2215			53800	47200
		EQUILIBRIUM			
Autosomal dominant	9000	25	13	225000	117000
X-linked (both sexes)	500	40	28	20000	14000
Chromosomal a/	400	20	50	8000	20000
Irregularly inherited	4500	20	30	90000	135000
Total	14400			343000	286000

a/ Only unbalanced products of induced reciprocal translocations resulting in livebirths considered.

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ANNEX J

Non-stochastic effects of irradiation

CONTENTS

Introduction

1. The main purpose of this Annex is to review damage to normal tissues caused by ionizing radiation. Only the so-called "non-stochastic" effects are considered, i.e., those resulting from changes taking place in large numbers of cells. In its publication 26 the ICRP suggests that "non-stochastic effects are those for which the severity of an effect varies with the dose and for which a threshold may therefore occur" [I1]. In contrast, "stochastic" effects are those for which the probability (rather than the severity) of an effect occurring is a function of dose. In this Annex effects such as the induction of cancer, hereditary defects, teratogenesis and life shortening are specifically excluded.

2. This Annex will therefore review radiation effects on normal tissues, in animals and in man, in order to determine the threshold dose levels for non-stochastic effects. It should be pointed out immediately that the threshold will depend entirely on the end-point adopted and on the sensitivity of the measuring technique. For example, functional changes in some tissues may only be detected after several tens of Gy, whereas structural abnormalities may be detected after much smaller doses by using an electron microscope. The concept of threshold dose presents difficulties throughout the discussion. Consideration is given to radiation quality, dose rate, fractionation and the volume of tissue irradiated. In general, permanent rather than transient biochemical changes have been emphasized.

3. Another important parameter is the time at which a radiation response occurs. In gut, microscopic changes can easily be detected using histological techniques after hours or a few days, in skin after a week and in liver the reaction may take months or years to develop. These differences result in part from the different cellular proliferation characteristics of the cells involved, to which some attention is paid. However, other basic factors (e.g., genetic, hormonal, nervous) are certainly involved in the time of onset of late radiation injury.

4. The precise way in which ionizing radiation causes cells to lose their reproductive integrity is not understood. There is, however, good evidence pointing to the most sensitive sites being in the region of the cell nucleus rather than in the cytoplasm. A considerable body of circumstantial evidence suggests that some part of the chromosome is the primary target [H6], especially the DNA molecule [H64], but there is also evidence implying that effects on membranes are involved in the primary damage [A26]. The two possibilities are not mutually exclusive. However, detailed discussion of fundamental radiobiology is beyond the scope of this report.

5. The topic of this Annex is extremely wide. By no means have all aspects been considered, but an attempt is made to be interpretive rather than to simply compile available data. The basic premise is that the non-stochastic response of a tissue depends on the level of cell killing (which is in itself a stochastic process). Therefore the first chapter is devoted to basic concepts of cell survival, to the factors influencing tissue response to fractionation or continuous irradiation and to the empirical formulae proposed to estimate the doses producing the same level of injury under different treatment schedules. The second chapter is a discussion of radiation effects on individual animal tissues. The third is a review of data obtained on humans, mostly derived from radiotherapy results but including also a small number of radiation accident reports. The effects of radiation quality are discussed in chapter IV with most emphasis on fast neutrons. A review of the effects of radionuclides introduced into the body is given in chapter V. Chapter VI is a brief review of studies of radiation damage to the vascular system.

6. Experiments and clinical findings have resulted from irradiations with photons of differing energies. Sometimes these have been specified in the original reports, but often they have not. Also, doses in early reports have been quoted in roentgen (R). However, differences in effects due to different photon energies are considered to be negligible. Moreover, in view of the uncertainties in estimating the dose in most of the early work, it is reasonable to assume that 1 Gy is not significantly different from 100 R.

I. BASIC CONCEPTS OF RADIATION EFFECTS ON CELLS AND TISSUES

A. CHARACTERISTICS OF CELL SURVIVAL

7. The relationship between the dose of radiation and the reduction in cell surviving fraction is a cell survival curve. Knowledge of survival curves is basic to an understanding of "non-stochastic" effects, and their shape is an indication of how cells will respond to many small dose fractions or to continuous exposures. Cell survival is defined as the capacity of the cell to undergo sustained proliferation, a survivor being able to produce a "clone" or a "colony". Cell survival may be measured in vivo or in vitro.

8. The effects of radiation are dependent on the stage of a cell in its mitotic cycle. Basically there is a specific period, designated S, during which DNA is synthesized (in proliferating cells). There is a period between mitosis M and S, which is known as G_1; the interval between S and the next mitosis is known as G_2. Almost the first observable effect of radiation on cells both in vivo and in vitro is that they are temporarily prevented from entering mitosis. This is often referred to as the G_2 block or mitotic delay [E1]. For cells in vitro 10 Gy seems to produce a delay of approximately one cell cycle in duration. Denekamp [D1] analysed both in situ and in vitro results covering a wide range of cycle times and found a similar result for cells in situ, namely, that in general 10–15 Gy causes a delay of approximately 1 cell cycle duration.

9. After irradiation, cell death for most cell types occurs when the cell attempts to divide. Death does not always occur at the first division. After low doses of radiation cells may complete 1, 2 or even 3 divisions before failing. In some cases, however, cells die in interphase, the most notable example being the lymphocyte. Schematic examples of survival curves for mammalian cells irradiated with low-LET radiation are shown in Figure I. No systematic differences have been demonstrated between such curves derived from animal or from human cells. For low-LET radiations, such as x rays, gamma rays or electrons, survival curves may be continuously bending, i.e., effectiveness of the radiation

may increase with increasing dose, or they may become exponential at large doses, with slope defined as $-\frac{1}{D_o}$. D_o (the mean inactivation dose) is the dose required to reduce the surviving fraction by a factor of e on an exponential curve.

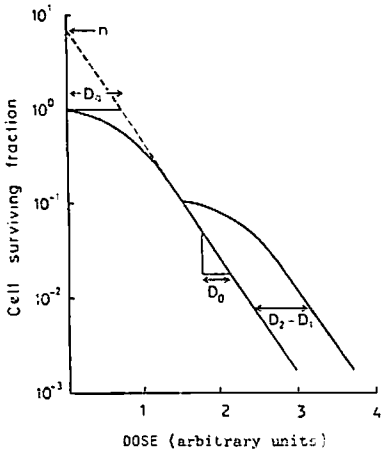

Figure I. Diagrammatic representation of a single- and split-dose cell survival curve. The "shoulder" region is characterized by the extrapolation number n or the quasi-threshold dose D_q. D_o is the dose to reduce survival to 37% on the exponential part of the curve. The parameters are related by: $\log_e n = D_q/D_o$

10. At lower doses the radiation is less effective and there is a shoulder region. Exponential curves may be extrapolated to determine n or D_q, as shown in Figure I. The sizes of these parameters indicate the capacity of the cells to accumulate sublethal damage [E2, F1]. With low-LET radiation and for cells in vitro n normally varies from 1 to 20 for the majority of cell types. With high-LET radiation, (e.g., neutron or alpha particles) n and D_q are both smaller, indicating less capacity for accumulation of sublethal damage. D_o is also generally less for high-LET radiation. Sublethal damage can normally be repaired in a few hours. This is of great importance in interpreting dose fractionation and low dose rate effects.

11. Survival curves have been measured for cells in situ as well as in vitro. The former has been achieved for cells of bone marrow, small intestine, stomach, colon, testis, cartilage, skin, as well as for a range of experimental tumours. In general the values of n and D_q are greater for tissues in vivo than for cells in vitro. This is also true when D_2-D_1 is measured, where D_1 and D_2 are the single dose and dose in two fractions, respectively, to produce the same level of tissue damage. Since D_2-D_1 is analogous to D_q from the cell survival curve, this means that the cells in organized tissue have a greater capacity to recover from sublethal damage than cells in vitro.

12. An example of evidence that the gross tissue response reflects that of its constituent cells is obtained from a comparison of the LD_{50} in 4 days (gut damage [Q1]) with cell survival by counting the number of surviving crypts [W1]. It was seen that for a variety of different types of treatment, different dose rate and LET, the reduction in the proportion of surviving cells resulting in 50% death of the mice was the same for all treatments [H1].

13. Various models for describing the shapes of cell survival curves have been proposed [I4, S33]. The simplest is the single exponential model, fitted by

$$S(D) = e^{-kD}$$

where S(D) is the surviving fraction after dose D, and

$$k = 1/D_o$$

A population of cells may consist of 2 or more subpopulations, each following an exponential curve. In this case

$$S(D) = a\,e^{-k_aD} + b\,e^{-k_bD} + \ldots$$

where a, b, etc. are fractions of the total population. This model describes a curve with a series of exponential slopes, the initial slope depending on the most sensitive cells and their proportions [S76]. The multitarget single-hit model is described by

$$S(D) = 1 - (1 - e^{-k_nD})^n$$

where k_n is the sensitivity of each of n targets, each of which must be hit to kill a cell. This curve has zero initial slope, a finding which is not supported by the majority of recent data. A model incorporating a finite initial slope is the modified multi-target single-hit curve, is given by

$$S(D) = e^{-k_1D}[1 - (1 - e^{-k_nD})^n]$$

where $dS/dD = -k_1$ for $D \to 0$. Thus the initial slope is given by $-k_1$. The final slope of the curve is given by $-k_o$, where $k_o = k_1 + k_n$. This model describes a curve with a finite initial slope, consistent with many experimental findings. A continuously bending survival curve, which has often been adequately used to describe survival curve data is:

$$S(D) = \exp - (\alpha D + \beta D^2)$$

where α and β are constants. This model also has a finite initial slope but continues to bend, the rate of the change in slope depending on the values of α and β.

14. It is possible to construct curves with almost any shape, but is normally not possible to distinguish experimentally between the more realistic models. Nevertheless knowledge of cell survival characteristics at low dose levels is extremely important in order to extrapolate data from single doses to many dose fractions or to continuous irradiation.

15. Cell sensitivity to ionizing radiation depends on the phase of the cell generation cycle. This phenomenon has been widely investigated, mainly in vitro. In general, cells exhibit a bimodal response during the cell cycle, in which a peak of resistance appears early in G_1 and another late in S. The greatest sensitivity occurs at mitosis (and G_2) and at the G_1-S border. In cell lines with a short G_1 the peak in G_1 may not be evident, but the general features are the same [S1]. The response of a normal synchronous cell population will thus reflect the different responses of cells in different stages of sensitivity.

16. There are, however, variations from one cell line to another [S1]. Cell cycle times vary from a few hours (e.g., intestinal mucosa) to many weeks or even months in some tissues (e.g., lung or kidney). These very long

cycle times are due to extended G_1 periods, the other phases differing less markedly from those in more rapidly dividing tissues. With high-LET radiations, e.g., fast neutrons, the fluctuation in sensitivity through the cell cycle is qualitatively similar to that for photons. However, the extent of the fluctuations is much less with high-LET radiation [W2, M1].

B. RESPONSE TO FRACTIONATED IRRADIATION

17. When radiation is split into two or more dose fractions the total dose required to produce a given level of damage is altered. This is due to a number of factors [W3]: repair of sublethal damage; repair of potentially lethal damage; other slower repair processes; repopulation of surviving cells; reassortment of cells in their mitotic cycle; and reoxygenation of hypoxic cells. These factors have been shown to occur to a different extent in different tissues, so that the effect of dose fractionation is tissue dependent.

1. Repair of sublethal damage

18. Cells are capable of absorbing energy which results in sublethal damage and only with increasing dose is this converted to lethal damage. Thus survival curves may be exponential at large dose levels but usually have a pronounced shoulder in the low dose region. This region of relatively inefficient killing is due to the accumulation of sublethal damage. Sublethal injury may be repaired in a few hours and repair is manifest by a return of the shoulder region (D_2-D_1 or D_q) for the second treatment (Figure 1 [E2]). Thus, repair of sublethal damage is the operational definition of repair between two radiation doses. Accumulation of and recovery from sublethal damage are smaller for cells in vitro than for the cells of many tissues in situ, possibly owing to the greater intercellular contact between cells in solid tissues. When cells have been grown as multicell spheroids in which they are in contact through desmosome-like junctions, the capacity of those cells to accumulate and repair sublethal damage is also markedly increased [D2]. The extent of repair of sublethal damage is very large in some tissues, e.g., intestine, skin, lung but much less in others, e.g., the haemopoietic system. It may be measured as the difference between the single dose or two fractions which produce the same level of injury. i.e., D_2-D_1. Values for some tissues are given in Table 1.

19. As the number of fractions is increased and the dose per fraction decreased, the proportion of dose that is effective in killing cells, relative to that which is used in accumulating sublethal damage is decreased. For very small doses per fraction, only about one-third of the dose is effective in some tissues. This means that in these tissues, to produce the same reaction in an extended fractionation regime as in a single treatment, three times more dose must be given.

2. Repair of potentially lethal damage

20. The technique by which cells are cultured after irradiation will affect the radiation response. It is possible to decrease radiation sensitivity by various means, including delaying plating [P3, H5]. This type of repair has been called "repair of potentially lethal damage" (PLD). It is operationally defined as the repair which takes place after irradiation, depending on the environmental conditions and usually tested by stimulating cells into division. There is a tendency for cells to exhibit repair of PLD when they are grown into crowded conditions so that their number is no longer increasing. They then develop the capability of repairing radiation damage before being called upon to divide. In general this causes an increase in D_o of the cell survival curve. The phenomenon has been shown to occur in tumours [S2] but techniques are not yet available for demonstrating repair of PLD in normal tissues. There is, however, no reason why the phenomenon should not occur in normal tissues and it may play an important role in determining tissue radiation response. Repair of PLD is normally complete within a few hours. Repair of chromatid aberrations in testes and bone marrow has also been observed with a similar time course [B40].

3. Slow repair

21. Various types of slow repair have been identified. Van den Brenk et al. [V2] and Reinhold and Buisman [R3] investigated the response of capillary endothelium to irradiation. The technique used by both groups was to stimulate cell proliferation in these otherwise slowly dividing tissues at various times after treatment. By this means these authors observed a repair process with a half-time of about one week, analogous to repair of potentially lethal damage, but taking much longer. Curtis [C1], using chromosome abnormalities as the end-point for damage to mouse liver, also observed a very slow removal of damage, manifest by a steady disappearance of the abnormalities. This type of repair may also be analogous to a slow repair of PLD, although McKay et al. [M50] believe that there is no repair of chromosome damage in liver of Chinese hamsters. In mouse lung there appear to be two phases of repair of sublethal damage as measured by an increasing D_2-D_1 with time between two fractions, the second phase taking about 100 times longer than the first [F17]. This second phase of slow repair is thought not to result from cellular proliferation [C31].

4. Repopulation

22. Following irradiation cells undergo a period of mitotic delay, after which there may be renewed proliferation. Tissue damage is repaired in this way, often rendering radiation decreasingly effective as the period of protraction of the dose is increased. It is known, at least in some tissues (e.g., skin and intestine) that cell proliferation after irradiation is stimulated by homeostatic control in response to the presence of dying cells or to products of cell lysis. Two techniques have been used to estimate compensatory cell proliferation. Where cell survival can be estimated by a clonal assay (intestine), the survival ratio with various intervals between dose fractions can be measured. Where clonal assays are not available and only gross tissue response can be assessed, repopulation is measured in terms of the increase in D_2-D_1 as doses are separated beyond the time during which sublethal damage is repaired. However, it is difficult with these techniques to distinguish between repopulation and slow intracellular repair processes. Long-term changes in proliferation resulting from irradiation have been reviewed by Beer [B78].

5. Reassortment

23. Since, as described earlier, cell sensitivity varies with the mitotic cycle, a dose of radiation will preferentially kill the sensitive cells, leaving mostly those in the resistant phases as survivors. After irradiation the remaining resistant cells are at first delayed and then move towards the more sensitive phase. Thus a second dose will be more effective if given some time after the first treatment than if given immediately afterwards. This process is in competition with the repair processes, all of which render the population less sensitive with time after a first irradiation. In addition mitotic delay is not constant for cells at all stages of the cell cycle and the net effect of irradiation is to cause a temporary accumulation of cells in the G_2 phase. This process adds to the partial synchrony of the population caused by preferentially killing the sensitive cells. All these processes combined cause a tissue to express a pattern of sensitivity to a second treatment with peaks and troughs, at times depending on the kinetics of the various phenomena. The effect of reassortment becomes extremely complicated with many fractions or with irradiation at low dose rates and cannot be predicted with any certainty.

6. Reoxygenation

24. It is well known that hypoxic cells are more resistant to low-LET radiation than are well oxygenated cells. The factor by which the dose must be increased to produce the same level of damage in hypoxic as compared to well oxygenated conditions is normally 2.5–3. Most experimental tumours and some normal tissues have been shown to contain hypoxic cells, e.g., mature cartilage. Radiation will sterilize selectively the well oxygenated cells. It may also cause a reduction in respiration and after removal of the dead cells and shrinkage of the tissue, all surviving cells will have a greater proximity to blood vessels. Therefore after irradiation many of the surviving hypoxic cells become better oxygenated, a process which has been termed reoxygenation [T2]. This is extremely important for tumours. However, in most normal tissues, a majority of cells are well oxygenated and if there is any reoxygenation these tissues will, in a protracted regime of irradiation, respond as if all their cells were well oxygenated. It is therefore unlikely that hypoxia and reoxygenation are important mechanisms in most normal tissues.

C. IRRADIATION AT LOW DOSE RATE

25. It is clear from the above considerations that dose rate is a very important parameter. This is especially true for low-LET radiation. As the dose rate is reduced and the time of irradiation is therefore extended, the overall effectiveness is reduced. This is due to two separate processes: (a) during the exposure there will be repair of sublethal damage occurring; (b) if the dose rate is low enough cellular repopulation can occur. Both of these repair processes cause the radiation to be less effective. Changes in the distribution of cells along their mitotic cycle may also be a contributing factor. The subject has often been reviewed, e.g., by Rajewsky et al. [R37] and by Hall [H6].

26. The effect of repair of sublethal damage on sensitivity may be dealt with by considering low dose rate as if it were many small fractions. This was the approach taken by Lajtha and Oliver [L1] who assumed that sublethal damage would be repaired with a half time of 1.5 hours. If many small fractions are given, the survival curve becomes shallower and the extrapolation number is reduced, as illustrated in Figure II. As the dose rate is reduced and treatment time protracted a greater proportion of the dose is inflicted as sublethal damage and is repaired. Ultimately a point is reached where effectively all the sublethal damage is repaired and there can be no further effect of decreasing the dose rate based on sublethal damage. The limiting slope is shown by the upper solid line in Figure II. The magnitude of this dose rate effect will depend on the inherent ability of the cells to repair sublethal damage. This is a very large effect for many, but not all organized tissues. In general the effect occurs between dose rates of about $2\ 10^{-3}$ – 1 Gy min^{-1}. Outside of these rates there is little or no further effect attributable to recovery from sublethal damage.

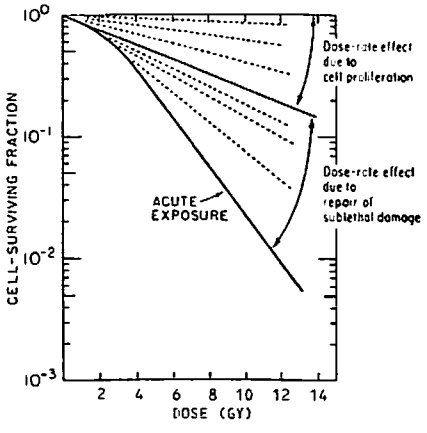

Figure II. Illustration of the dose rate effect due (a) to repair of sublethal damage and (b) to cell proliferation [H6]

27. In addition to repair of sublethal damage, in rapidly dividing tissues there may be an effect of proliferation during exposure if the dose rate is sufficiently low and if exposure time is long compared with the normal length of the cells' mitotic cycle. Cell death will then be balanced by cell proliferation causing a further reduction in biological effect as the dose rate is progressively reduced. There may also be a proliferative stimulation of cells not in the division cycle.

28. The dose rate at which the cell death rate cannot be balanced by the birth rate is critical, since that is the dose rate above which the tissue will gradually be destroyed. The critical dose rate is very tissue dependent. For the rat intestine it is about 4 Gy per day [Q2]. The figure is high because of the high proliferative capacity of the intestinal mucosa. For the bone marrow the threshold is about 0.5–1 Gy per day for the erythropoietic system in mice and rats [B1]. White cell and platelet levels in rats are maintained at 0.5 Gy per day [L2] and a steady state of granulocyte precursors develops. However, it was also shown in the rat that 0.5 Gy per day caused a reduction in the level of lymphoid cells in bone marrow, thymus, spleen and in the blood. In mice, and particularly in the rabbit and guinea pig, it was suggested that the threshold steady state dose was lower than 0.5 Gy per day [B41]. Testis has a far greater intrinsic sensitivity. Only if the dose rate is below a few hundredth of Gy per day [B2] can rats and mice maintain reproduction for 10 generations or more.

Obviously the repair potential for developing sperm cells is extremely limited.

29. Little is known of the effects of low levels of continuous irradiation on non-stochastic effects in slowly proliferating tissues. It may be expected that critical dose rates will be much lower than for rapidly proliferating tissues, which seem readily able to compensate for the damage.

D. RESIDUAL INJURY

30. The extrapolation from single doses to treatments extending over years, i.e., over a significant proportion of the recipient's life time, is very difficult to make in the present state of knowledge. Some information may be obtained from the data on fractionation, but this is not generally available for more than 30 fractions and for treatment times longer than a few weeks. These data do not answer the questions about long term recovery potential which are related to the complete repair of parenchymal cell damage through proliferation; to the role of slow repair in this capacity; to the presence and extent of irreparable damage, for example, to the vascular system, as mentioned in section II.A. and discussed further in chapter VI.

31. Experiments in which a "priming" treatment (a single dose or a series of doses) is followed some time later by a test treatment can be of help in answering some of these questions. The priming treatment is normally below tolerance and the "residual" damage at a given time is estimated by the response of the tissue to a further test treatment. The results of Denekamp [D3] and of Brown and Probert [B3] in mice, show that by about 6 months after the priming treatment the tissue responsible for the early skin damage has almost totally repaired and only about 10% of the priming dose is "remembered" [D5, F5]. This early reaction is the result of killing of the basal epidermal cells, so clearly their repopulation can restore the tissue to near normal. The same is true for the rapidly proliferating mucosal epithelium of the intestine. Human skin can also almost fully recover, as assessed by early reactions [H7].

32. Brown and Probert [B3] also investigated the end-point of late deformity in the mouse foot. In their experiments 35–40% of the priming dose appears to be "remembered" if assayed for late foot deformity. It was suggested that different components of the limb were responsible for late reactions and that for these there was less repair. The accuracy of the Ellis formula for partial tolerance (see section I.F.) with time after treatment was tested in the same set of experiments and found to give a fairly close prediction of the results from 1 to 10 months after the priming treatment.

33. Hendry et al. [H8] investigated residual injury using necrosis of the mouse tail as the end-point. The results were consistent with those for early skin damage in that the residual injury in the tail was 10% of the first treatment after 6 weeks. However, if a further "priming" treatment was given, the residual injury was increased to 35%, at which level it remained for repeated "priming" treatments, each separated by 6 weeks [H9].

34. Thus it appears that rapidly proliferating systems can almost fully repair a radiation injury, whereas tissues responsible for late injury have a reduced repair potential and would, therefore, be expected to accumulate more damage during protracted irradiation. The relationship, if any, between the early and late reactions has been the subject of much debate and is still not resolved [D5, B3, F5, F6, P4, D6, R35].

35. Residual injury has also been investigated after neutron irradiation. Hendry et al. [H8], using necrosis of the mouse tail, observed that the residual injury was greater after a treatment with neutrons than after x rays. A similar set of experiments was performed on mouse foot skin by Field et al. [F7]. In this case both the early and late reactions were assessed after test doses given 6 months after the priming irradiations. In general, residual injury after neutron irradiation was greater than after x rays. Skin reaction increased with increasing priming dose, but was not dependent on whether this was x rays or neutrons. Residual injury, manifest as late deformity after x ray priming doses, was only slightly greater than for early reactions, but the residual injury measured for the same end-point after neutron priming doses was larger.

36. An interpretation of these observations is that recovery from tissue damage leading to late reactions is at least partly due to slow repair and that this is absent with neutrons and possibly other high-LET radiations. Thus the RBE for late damage might be expected to increase for protracted irradiations if there were less long-term recovery after neutrons than after photons. Such an observation was made from a skin experiment in which the RBE measured for short overall treatment times was compared with treatment over 6 months. The RBE for the latter was about 30% higher [F9]. However, it is not known whether or not this concept may have general validity.

E. MODIFIERS OF RADIATION RESPONSE

37. Perhaps the most important modifier of the response to radiation is oxygen. Its absence protects cells and tissues by a dose factor of 2.5–3 in comparison with fully oxygenated cells and tissues. The fact that some normal tissues may be partially hypoxic and thereby protected to some extent has already been discussed (section I.B.6). Drugs which are vasoconstrictors may also protect tissue by causing hypoxia. Some drugs are radiation protectors, e.g., the sulphydryl compounds such as cysteamine, 2-β-aminoethylthiouronium (AET) and the compound WR2721. Other drugs are radiation sensitizers, e.g., many of the anti-cancer agents including the antibiotics, some alkylating agents, sulphydryl-binding agents and antimetabolites. The halogenated pyrimidines such as BUdR and IUdR are also sensitizers. A rather special group of drugs essentially sensitize only hypoxic cells. The best known are the nitro-imidazoles and these may be useful in connection with radiotherapy of cancer. Heat also sensitizes to radiation with temperatures in excess of 41°C, and sensitizing factors of 3 or 4 have been reported. These factors will be important for patients undergoing radiotherapy, although it seems rather unlikely that the response of whole human populations to irradiation would be significantly affected by any of these modifying factors. Many of these factors are considered in detail in Annex L; reviews are also to be found in [R50 and P59].

F. ISOEFFECT FORMULAE

38. Data relating the total dose, number of fractions and overall treatment time for a given degree of normal tissue damage are all derived from radiotherapy results or animal studies aimed at providing useful information for the radiotherapist. Isoeffect formulae to fit these data have been suggested. Whether or not these formulae are accurate over the therapy range of treatment times and number of fractions is the subject of much debate. It is even more dubious whether these relationships may be extrapolated beyond the therapy range, but they can certainly be useful in giving an indication of the dose required to produce a given level of damage in long protracted irradiations.

39. In 1918 [K2] the results of experiments on human skin indicated that radiation was less effective if given in many fractions. Regaud and Ferraux [R4] confirmed this observation on skin and also indicated an improved therapeutic ratio by fractionation. The subject was further studied in the 1930s, [e.g., R5 and M2]; and it became standard radiotherapy practice to treat in many fractions. A classic paper appeared in 1944, by Strandqvist [S3]. He constructed isoeffect curves for the cure of skin cancer and for various levels of damage to skin, i.e., erythema, dry desquamation, moist desquamation and necrosis. The total required dose was plotted against the overall treatment time, both on logarithmic scale. The topic was further considered by Cohen [C2] who also published data for skin damage and for tumours. Skin damage was taken from McComb and Quimby [M2] and Reisner [R5] for erythema and from Paterson [P5], Jolles and Mitchell [J1] and Ellis [E3] for tolerance.

40. It was initially thought that the number of fractions was less important than the overall treatment time. However, this view was changed in the 1960s as the meaning of repair of sublethal damage became clearer [F10]. Ellis [E4], on the basis of Cohen's earlier publication suggested separating the factors for overall treatment time T (days) and number of fractions N giving the empirical formula

$$\text{total dose} = (\text{NSD})\, N^{0.24}\, T^{0.11}$$

where NSD is known as the nominal standard dose; its "units" are designated as the ret. The NSD is a "constant" referring to the maximum single dose which a particular normal tissue can tolerate in radiotherapy. It will depend, therefore, to some small degree on the judgement of the physician. It is not considered reasonable to extrapolate the Ellis NSD formula to less than $N = 4$ or $T = 5$ and it is questionable whether or not the formula holds for very large values of N and T. In addition, the exponents of N and T will vary, to some extent, from tissue to tissue. The formula was, however, based on human data.

41. The main limitation of the concept of NSD is that the formula is applicable only at the level of normal tissue "tolerance". Various modifications have been made to make it possible to apply the formula to levels of injury lower than tolerance. One of these is the concept of "partial tolerance" (PT)

$$PT = \text{NSD}\, N/N_{TOL}$$

where N_{TOL} is the number of fractions to give full tolerance and N is the number actually given. By this means PT becomes an additive quantity, unlike NSD. For convenience in radiotherapy Orton and Ellis [O1] introduced TDF (time dose factor) which is proportional to partial tolerance, but is independent of specific values of NSD.

$$TDF_f = N\,(d\ 100)^{1.538}\,(T/N)^{-0.169}\ 10^{-3}$$

where d is the dose per fraction in Gy.

42. An alternative generalization of the NSD formula is that of the Cumulative Radiation Effect (CRE) [K3] where

$$CRE_f = \left(\frac{T}{N}\right)^{-0.11} d\, N^{0.65}$$

where N is the number of fractions given and T is the overall time for those fractions including the first and last treatment days. CRE is applicable at less than tolerance, as is the case for TDF. Like NSD, CRE is also based on human data. Differences between CRE and TDF have been discussed by Turresson and Notter [T28].

43. Both CRE and TDF have been generalized for low dose rate continuous irradiation, such as implant brachytherapy [K48, O14]. Thus $CRE_c = k'\ r\ T^{0.71}$ where r is the dose per day, T is the overall treatment time in days, and k' is a normalizing constant between CRE_f and CRE_c or $TDF_c = k''\ (r\ 100)^{1.35}\ T\ 10^{-3}$ the symbols having the same meanings as for CRE_c.

44. Recently these models have been subjected to critical testing both clinically and experimentally on pig skin by Turesson and Notter [T28, T29, T30]. Attention was focussed on CRE. In the clinical study there was good agreement between CRE_f and acute skin reactions for a variety of treatment schedules with different fractionation and overall treatment times. The agreement with late reactions was less good. The same was true for the experimental study with significant differences between prediction and observation with small numbers of large dose fractions. A modified CRE formula was thus proposed [T28] where

$$CRE = L(d)\left(\frac{T}{N}\right)^{-0.11} d\, N^{0.65}$$

where L(d) is a correction factor for reactions following doses per fraction of size d. For early reactions $L(d) = 1$. This is also the case for late reactions with $d = 2$ Gy. For $d = 10$ Gy, L(d) rises to 1.18. Turesson and Notter [T28] also compared the predictions of both CRE_c and TDF_c for low dose rate continuous irradiation at two dose rates (1.20 and 0.54 Gy h^{-1}). It was observed that the normalization constant k was significantly different from the proposed values and that the irradiation was more damaging than implied by these formulae. Turesson and Notter proposed revision in the values of k' in CRE from 0.80 to 0.57 and in k'' in TDF from 2.02 to 1.57. The modifications proposed to both TDF and CRE require further experimentation.

45. The N factor is related to the number of dose fractions, and is thought to be primarily influenced by repair of sublethal damage. As this is usually complete in a few hours it is theoretically possible to give several fractions per day without changing the N factor. Extensive repair of sublethal damage will normally be consistent with a large N factor, i.e., a large sparing of fractionation and vice versa. Techniques are not yet available to determine repair of potentially lethal damage in normal tissues in situ, but if it occurs, it also will cause the N factor to be increased.

46. The T factor is more difficult to explain. In rapidly proliferating tissues it is probably due to cellular repopulation, in which case a power function, such as $T^{0.11}$ is unlikely to be universally applicable. In slowly proliferating tissues T may be due to "slow repair" for which a power function would be more appropriate. McKenzie [M75] attempted to derive the CRE formula from a cellular survival model with Gompertzian repopulation. The agreement obtained with the N factor was good, but T could not be explained by this model.

G. CELL PROLIFERATION AND ITS RELATIONSHIP TO THE TIME OF EXPRESSION OF RADIATION INJURY

47. Cell proliferation is important for two reasons. Firstly, it is related to the time of death of cells in tissue and thus to the time after irradiation when damage becomes apparent. Secondly, it is a mechanism by which a tissue is restored to near-normal after irradiation. In addition, radiation can perturb the cell proliferation kinetics of a population, and as the cell kinetics can influence the response of the cell population to any further dose of radiation, these mutual interactions are of importance in the response of tissues to single doses and fractionated irradiation. Changes may take place many years after irradiation, such as cell death which has been reported after treatment of the breast region of female babies for haemangiomas [F44, K36].

48. Most adult normal tissues show no net growth under normal circumstances but an exact balance of cell production and cell loss. This may result from very slow production and slow loss as in lung or kidney, or from more rapid production and loss as in most epithelial tissues. The cell production is determined by the cell cycle time (intermitotic time T_c) and the fraction of cells in the proliferation cycle (i.e., the growth fraction or GF). The cell loss may be by migration (as occurs in the villus of the intestine) or by differentiation and death (as for blood cells formed in the marrow).

49. In the last two decades, experimental techniques have been developed to investigate the proliferation rates of cell populations both in vitro and in vivo. These include labelling studies with radioactive precursors of DNA, based on the work of Howard and Pelc [H10]. The cell cycle time and the growth kinetics of a wide variety of tissues, both normal and malignant, have since been studied, in undisturbed growth and also after injury by various agents, including radiation. Because of the difficulties in measuring per cent labelled mitoses curves in populations which are not in steady state of growth, continuous labelling by repeated injections of tritiated thymidine (^{3}HTdR) has also proved to be a useful technique [D7, H63]. More recently techniques of cytofluorometry have been introduced. In addition, some tissues have been studied after radiation injury by comparing the doses needed to inflict a given level of injury if two dose fractions are separated by a varying interval of time (Table 1).

50. In the response of any cell population to a dose of radiation, there is initially a delay in the progress of cells around the cell cycle (mitotic delay), which is dependent on the radiation dose administered, the stage of the cycle and the cell cycle time. The cells accumulate in the premitotic G_2 phase and are blocked from entry into mitosis for some time. The radiation damage is then expressed in dividing cells as a loss of their proliferative capacity. Most cells die at one of the mitoses subsequent to the radiation-induced mitotic delay. At high doses (10–20 Gy) cells die at the first post-irradiation division, but after smaller doses (i.e., a few Gy) many or most cells die at a second or third division. There are a few exceptions to radiation death occurring at mitosis, e.g., lymphocytes and germ cells, which can die during interphase without any attempt to divide. For most somatic cells, however, the expression of radiation damage is delayed until mitosis is attempted. After 10 Gy this may occur within 12 hours in the intestine, within 4–5 days in skin, and presumably not for many weeks in tissues with very long turnover times such as liver, lung and kidney [D1]. Since most tissues consist of a variety of cells with different proliferation rates, the expression of radiation damage is likely to occur at different times in the different cell compartments and be further complicated by various feedback processes.

51. Organ functions may be impaired either when the majority of cells have died or else when a critical subpopulation has started to express its damage. For this reason it has been suggested that radiation damage in many organs may have a common pathway of expression in the form of endothelial cell death. Endothelial cells are generally thought to have a very long turnover time of 2–4 months as measured by simple tritiated thymidine uptake studies [T3]; however, it seems likely that this may result from a very small proportion of the cells ($\sim$ 1%) cycling with a cell cycle time of about 20 hours [H4, K4]. The role of vascular damage will be discussed more extensively in chapter VI.

H. NORMAL TISSUE KINETICS: CHANGES AFTER IRRADIATION

52. In normal tissues there is a finely balanced homeostatic mechanism, such that a significant drop in cell numbers below the normal level is compensated by an increased rate of cell production. This increased production may occur in different ways, e.g., from a shortening of the cell cycle time, as in the small intestine and skin [D7, L3, H11], or by an extra division in the amplification process of cell production, as in the bone marrow or in the small intestine [L4, L5]. Recognition of cell depletion and compensatory proliferation may take place in most normal tissues.

53. Accelerated proliferation in response to injury can be very rapid when the injury results in immediate cell destruction such as from mechanical trauma, incision or burns caused by caustic chemicals. Shortly after such injuries to skin (within 6–48 hours) a wave of DNA synthesis and cells in mitosis are observed near the site of cell death.

54. The compensation appears to occur when cell depletion has been recognized, and since the expression of radiation damage is usually delayed until a subsequent mitosis, the compensatory proliferation after radiation injury is also delayed. In skin, for example, the proliferation kinetics do not alter for at least one week after either a single dose or the beginning of a course of repeated doses that will each kill a substantial

proportion of the cells [D3, D7, H11, D8]. Thus a course of radiation therapy, as usually administered over a period of 4–7 weeks, will not induce proliferation until the second and third weeks as more and more cell depletion is recognized. More rapidly dividing tissues, such as intestine, will respond earlier [W5, L6, C3] but more slowly dividing tissues such as lung, liver, kidney, muscle, nervous tissue and vascular and connective tissue, are not likely to commence compensatory proliferation in response to cell death until a long time after irradiation [D5]. This has recently been demonstrated in mouse bladder epithelium [S4].

55. The cell cycle time varies enormously in different normal tissues. It is well known for several rapidly dividing tissues but little detailed information is available for the very slowly dividing tissues [D36].

56. The relationship between tissue kinetics and radiation response is of great importance. Recently Michailowski [M70] has suggested a refinement to the accepted concepts, on the basis that tissues fall into two categories, i.e., types H and F. In type H (hierarchical) there exists a defined stem cell compartment, differentiating into histologically distinguishable functioning cells. Radiation-induced tissue damage will result from inadequacy of the mature cell compartment which depends on the life span of the functional cells. A similar model has been the accepted view for many years. In type F (flexible) all cells are thought to be capable of proliferation and specific tissue functions. In these tissues radiation will lead to a dose-dependent loss of functional cells through their mitotic death, both following exposure and during the next phase of compensatory proliferation, resulting in accelerated expression of the radiation damage ("avalanche"). Consequently the more severe damage following larger doses of radiation is seen earlier than milder reactions produced with smaller doses. Likely examples of type H tissue include the epidermis and the intestinal epithelium. Type F tissues would include the dermis, endothelium, liver parenchyma. Late reactions in type F tissues can therefore never be totally excluded and may be precipitated by some unrelated trauma, such as infection or mechanical injury. Similar phenomena are well known in radiotherapy.

I. SUMMARY

57. Radiation-induced tissue injury of a "non-stochastic" nature is likely to have its origin in the sterilization of a large proportion of the critical cells of that tissue, although these cells may be a small proportion of the total cells. The consequent injury results from the natural loss of post-mitotic cells which are not replaced or loss of cells which are stimulated into division. The characteristics of cell survival are of great importance in this context, particularly at low doses, in gaining an understanding of the response of tissues to fractionated or continuous irradiation. Various processes of repair and repopulation will increase the threshold level of dose when irradiation is given over a long period or when a second period of irradiation is encountered some time after an earlier exposure. Attempts to express these parameters have been made in terms of iso-effect formulae. The timing of tissue injury depends on the cells' natural proliferation characteristics and also on kinetic changes characteristic of the tissue which result from the irradiation itself.

II. EFFECTS OF EXTERNAL IRRADIATION ON TISSUES OF EXPERIMENTAL ANIMALS

58. Animal tissues often closely resemble those in man and respond to irradiation in a similar way. It is therefore of value to consider data on animals. These have frequently been irradiated with a wide range of doses, both in single treatments and in many different fractionated regimes. From examination of the non-stochastic response of different animal species, cautious extrapolation to man seems justified and at least will increase confidence in the extrapolation of data directly derived from the human [F11].

59. It was recognized long ago that most cells die from radiation damage only when they attempt to divide. The rate of proliferation is therefore an important determinant of the timing of response to irradiation. Rapidly proliferating tissues exhibit early responses to irradiation and also reach a peak of injury sooner than the more slowly proliferating tissues. Rapidly proliferating tissues are also capable of considerable repair of damage due to cellular repopulation, which may be important during fractionation or low-dose-rate irradiation. This is in contrast to slowly proliferating tissues which are less able to repair damage during irradiation through repopulation.

60. The tolerance of normal tissues to irradiation is organ specific. It also varies with the volume which is irradiated, bigger effects occurring in bigger volumes. Experiments on some organs are limited to specific regions as in grid therapy [B52], but there is little information available on this topic.

A. SKIN

61. The earliest evidence of the damaging effects of ionizing radiation on tissues came from skin reactions observed after radiotherapy [S5, M3]. The accessibility of the skin for observation has subsequently resulted in its being the most studied and documented normal tissue regarding its response to radiation. Several important principles may be illustrated by reference to results of skin damage.

62. After irradiation of the skin there are a variety of observable changes [R1]. There may be several waves of erythema leading to dry desquamation and depilation. Healing may still occur. For larger doses there may be moist desquamation and permanent pigmentation. Blood vessel and connective tissue damage can lead to ulceration and necrosis with no epithelialization possible. Repair from moderate doses often takes place from the wound edges and therefore large irradiated areas produce greater reactions and are slower to heal. Damaged tissue may be replaced by fibrosis in man, pig and goat, but not normally in the skin of rodents.

63. The relationship between kinetic parameters and radiation response can readily be demonstrated in skin. Mouse skin has a cell cycle of 4–5 days for most of the cells of the basal layer and a transit time of 10–15 days through the superficial 2–3 layers of differentiating cells [H11]. Mitotic activity in mouse skin is totally depressed 2–4 days after 5 Gy [K45]. Desquamation occurs after 20–30 Gy for moderately large areas, at 15–20 days, in agreement with the transit time through the differentiating layers [H11, F11, F12]. Skin which has been stimulated before irradiation, e.g., by plucking, develops a reaction earlier, and skin with more super-

ficial layers (pig or man) reacts later. Large doses cause considerable mitotic delay, followed by extensive cell death in the basal layer, but the rate of progression of cells into the more superficial layers is unchanged, at least for several days [E6]. Eventually the lack of cell production results in significant lack of basal layer cells and this may be the signal for more rapid compensatory proliferation [F11]. The proliferative response is thus delayed by 1–2 weeks after single large doses of about 20 Gy or after starting multiple small doses of a few Gy. After surgical or mechanical wounding, however, a deficit is recognized immediately and proliferation is faster within 24 hours [R48, F11].

64. The level of cell depletion affects the rate of compensatory proliferation and in skin the cell cycle time can shorten from its normal value of 4–5 days, down to 2 days after moderate damage, or to 18–24 hours after severe depletion [W4, D7, D8]. This delayed compensatory response is unusual. The only other form of injury producing a delayed response is that of a deep thermal burn involving the dermis [W9]. After the initial lag, compensatory proliferation will commence during a course of daily radiation fractions and presumably continuous irradiation and in mice can be sufficiently effective to heal the radiation-induced desquamation even though daily irradiation at over 10 Gy per week is continuing [F13]. Mucosal or epithelial healing is also sometimes observed during prolonged clinical radiotherapy.

1. Single doses

65. Skin damage has been assessed in animals by estimating the early or late changes on arbitrary scoring scales or by measuring the survival of individual cells in the basal layer of the epidermis. Pig skin has been used in radiobiological studies by several groups. It has many features in common with man, i.e. colour, the presence of relatively few hair follicles, sweat glands and a layer of subcutaneous fat. The gross response of pig skin qualitatively resembles that of man. The quantitative study of pig skin was pioneered by Fowler and his colleagues [F10]. They irradiated a number of rectangular fields on the flank. The very early erythema was not scored but the next two waves of erythema and desquamation were. Long-term damage was assessed by the degree of induration, which is taken as a measure of fibrosis, but more recent studies have improved on this late end-point [B4, W10]. To establish dose-effect relationships average reactions were taken over various time periods and these values related to the dose. An example is shown in Figure III. The smallest single dose found to produce an observable effect was about 10 Gy.

66. Non-uniform exposures of pig skin have been reviewed by Wells et al. [W38] and Osanov et al. [O13]. It was not possible to produce visible damage with 0.7 MeV beta rays to fields less than 10^{-2} cm^2 with doses up to 100 Gy, due to sparing by repopulation of hair follicle cells. With increasing energies of beta rays less dose was required to produce visible damage. The basal layer was clearly seen as being the critical cell component. Thus a 1 cm^2 field of 15 Gy to the basal layer was approximately the minimum dose which produced a visible injury.

67. Rodent skin reactions have been assessed by several workers, e.g., [F2, F12, B5, L7]. In mice, feet show a wave of damage starting at 7 days after irradiation, peaking at about 20 days and healing, according to the dose, by 30–50 days. Rat feet show a distinct wave of damage, at higher dose levels, which is not seen in mice. The feet of both rats and mice and the ears of mice ultimately become deformed after large doses and the deformity is permanent. In rodents the minimum single dose to produce a visible reaction is at least 10 Gy.

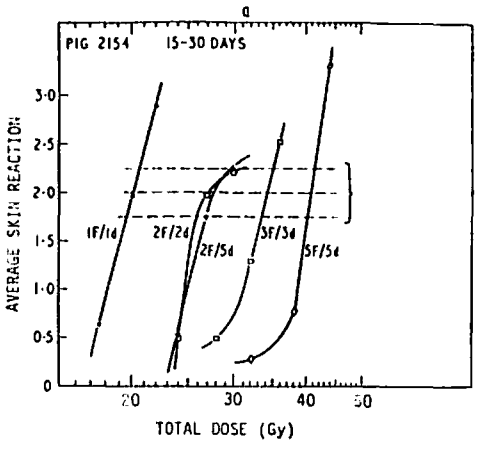

Figure III. Dose-effect curves for pig skin irradiated with x rays, obtained from the average reaction between 15 and 30 days after irradiation. A score of approximately 0.5 indicates the threshold erythema. The number of fractions given and overall treatment time are indicated in the figure [F1]

68. Both in animals and in humans the correlation between early and late radiation reactions is a matter of controversy. The early reactions of erythema and desquamation are due primarily to damage to the basal layer of the epithelium whilst late damage is more complex, probably involving damage to endothelial cells and increased blood vessel permeability. However, little is known for certain about the processes leading to later damage. A good correlation between early and late damage has been seen by some authors [F5, F6, D6], but others have observed late injury developing many years after irradiation without corresponding early reaction [W10, A2]. More recently [F7], mice feet were irradiated with graded doses of x rays (or fast neutrons) given once per week for 25 weeks. The threshold for production of an erythema was 3 Gy per week, but even after 10 Gy per week for 25 weeks the reaction faded when irradiation ceased. No late damage was observed with 10 Gy per week to a total dose of 250 Gy. The result was similar with neutrons up to 12.5 Gy.

69. A method for estimating survival curves for mouse skin cells was developed by Withers [W4]. The technique used was to isolate a defined area by heavily irradiating a moat around it. The small test areas were then given a series of graded test doses and the dose which allowed one or more nodules to grow in the test area was determined. A nodule was assumed to have grown from a single cell. The usable dose range was extended by varying the test area but practical considerations limited the applicable dose range to between 8 and 25 Gy. The survival curve obtained had D_0 = 1.35 Gy, similar to many values obtained in vitro. From split dose experiments the D_2-D_1 was about 3.5 Gy, and the extrapolation number n was found to be about 12. Similar experiments by Emery et al. [E7] gave a value of D_2-D_1 of 5.7 Gy but a similar value of D_0 to that found by Withers [W11]. By comparing the survival curves

with the dose effect curves for skin reaction it can be found that 15 Gy leaves only one cell per mm^2 surviving and produces a very mild skin reaction indeed. After a few days the skin cell doubling time is reduced to about 22–36 hours [E7, W11]. Presumably this rapid repopulation is sufficient to prevent a severe reaction following this degree of cell killing.

70. If a sufficient area of skin is irradiated, death of the animal can result. LD_{50} values, calculated at 30 days for this end-point have been measured in rats. Values in the range of 44–50 Gy for external irradiation with ^{90}Sr beta rays, and 17–30 Gy for x rays have been quoted [A38, A39, S36].

2. Fractionation effects

71. When the dose to the skin is fractionated, more radiation is required to produce a given level of injury. Fractionation experiments have been performed by varying the number of fractions, but keeping the overall treatment time constant to determine the N factor; or by keeping the number of fractions constant to determine T (see section I.F.).

72. Experiments to determine N have been based on an experimental design of Dutreix et al. [D9]. These authors aimed at estimating repair between small doses. If a single dose D_1 is split into two fractions at total dose D_2 to give the same effect, then D_2-D_1 is the additional dose required by splitting the treatment, as discussed earlier. If each of N fractions is split into two fractions to a total dose D_2N given in the same overall time as D_N in N fractions, then the additional dose per fraction is given by

$$D_r = \frac{D_{2N} - D_N}{N}$$

The experiments of Dutreix et al. [D9] indicated that D_r became zero when the dose per fraction was 3 Gy or less. This means that fractionating to doses smaller than 3 Gy resulted in no further sparing effect. These results, however, were subject to considerable statistical uncertainty. Results of some similar animal experiments [F15] are summarized in Figure IV. It is seen that D_1 becomes small, but does not approach zero at 3 Gy per fraction and possibly not until the dose per fraction is zero. However, it is extremely difficult to resolve the situation at doses less than 2–4 Gy, although this is the important region for extrapolation to many small fractions.

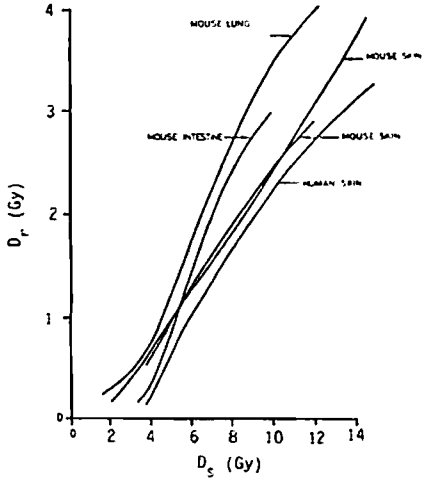

Figure IV. A plot of the additional dose per fraction, D_r, against the dose per fraction, D_s, for various tissues [F15]

73. An alternative approach which may be made from similar experiments is to derive the ratio of the initial to final slope of the survival curve, in order to make the extrapolation from a single dose to an infinite number of fractions, excluding the effects of repopulation. The initial slope determines the effect of giving an infinite number of fractions. The method of analysis is given by Field et al. [F13] who derived a slope ratio of 1:5 or 1:6 [F13, F15]. This value may be compared with 1:3 from Dutreix et al. [D9].

74. Douglas and Fowler [D10] extended mouse skin experiments to 64 fractions. All treatments were given in a total time of 8 days with the advantage that repopulation could be considered negligible during this period [D8]. Their techniques also avoided the use of anaesthesia. The results indicated that there was additional recovery down to the smallest doses given ($D_s \simeq 1.9$ Gy) in agreement with Field et al. [F13] but contradicting Dutreix et al. [D9]. From the results Douglas and Fowler [D10] derived a slope ratio of 1:5.5. They also favoured a survival curve with the form

$$S = \exp - (\alpha D + \beta D^2)$$

75. Denekamp and Harris [D11] measured the slope ratio in a different way. They gave mice feet a series of daily small "priming" doses of 1.5, 2.5 and 3.5 Gy, respectively, and measured the size of a single large test dose required to produce a given reaction. The results were subject to a moderate degree of scatter, but most of the derived values were in the range of 1: 4 to 1: 7. The results were found to be inconsistent with the multi-target single-hit curve, which was also the conclusion of Field et al. [F13]. The results of such experiments may also be compared with the Ellis formula. The value derived for N between 4 and 30 fractions varied between 0.24 and 0.33 [F13, D12] but there are indications that the curve relating log total dose to log number of fractions becomes flatter above 30 fractions [D10].

76. The T factor in a rapidly proliferating tissue, such as the skin, is primarily due to cellular repopulation between fractions. Vascular autoradiographic studies have been made of the proliferation of irradiated areas of skin and mucosa. The results generally showed a reduction in cycle time both in the irradiated zone and in the border region, indicating healing [H11, D13, B6, Y1]. After a long time (up to 1 year) the skin appeared thinner and the cycle time was slightly elongated [Y1, L8].

77. An alternative method of measuring proliferation after irradiation is by estimating D_2-D_1, D_2 being the dose given in two fractions and D_1 the equivalent single dose. When two treatments are separated by up to 1 day the change in D_2 is primarily due to sublethal damage. Beyond 1 day an extra dose is required to counteract repopulation. Since the D_o value for the skin epidermal cells is known to be approximately 1.35 Gy [W4, E7], D_2-D_1 may be interpreted in terms of doubling time. Various estimates of the doubling times in skin have been obtained in this way (Table 2). Several authors have estimated a value equivalent to 0.3 Gy/day [D3, F10, C4]. This value corresponds to a doubling time of

about 3–4 days in experiments covering a wide range of dose per fraction and intervals between doses from 1 to 5 weeks. Higher dose increments and therefore shorter doubling times have been estimated by Comas [C5] and by Fowler et al. [F16]. Both Withers [W4] and Emery et al. [E7] used the Withers cloning technique to estimate the repopulation rate. However, this type of experiment requires the hair to be plucked before irradiation, which may initiate a slightly faster rate of proliferation. The doubling times estimated in this way were 1–3 days. From human skin, Dutreix et al. [D14] estimated a cell doubling time of 1–1.5 days from the rate of growth into irradiated areas.

78. Repopulation during and after multifraction experiments has been measured using a radiobiological [D8] and a labelling technique [D7] in order to estimate the extent and timing of stimulated repopulation after irradiation. Daily fractions of 3 Gy of x rays were given on 4, 9 or 14 occasions. After 4 fractions there seemed to be little proliferation as judged from the skin reaction experiments and the labelling studies indicated an extended period of division delay, lasting for approximately 5 days after the last fraction. There was a small reduction in doubling time after 9 days but after 14 days proliferation was very rapid with a doubling time of less than 1 day. This more rapid proliferation returned to normal in the second week after the end of the fractionated treatment.

79. In conclusion, skin has an enormous capacity to repair radiation damage so that very large doses must be given, if the treatment is in many fractions, in order to produce erythema threshold changes (Table 3). However, microscopic changes in the finger ridges of monkeys have been observed with fractionated doses of about 10 Gy [G32]. The two main types of repair are recovery from sublethal damage and repopulation. The former is characterized by the N factor in the Ellis formula, which is in the region of $N^{0.3}$. Alternatively it may be described by the slope ratio, which on average is about 1:5. Thus on the basis of repair of sublethal damage alone the single dose may be increased by 5 times if given over a very long period. The other repair process is repopulation of surviving cells. When injury is manifest, proliferation increases until the population is restored to normal or near normal. Observations on mice and on radiotherapy patients substantiate this view.

B. GASTROINTESTINAL TRACT

1. Oesophagus

80. The histological changes observed in irradiated oesophagus are similar in the mouse and rat [P1, J2, K5]. More than 20 Gy in a single treatment produce mitotic death of the cells in the basal layer of the oesophageal epithelium. This is first seen at about 3 days after irradiation using a dose which kills about 20% of mice by 8 days. Hornsey and Field [H2] observed that this dose caused almost complete loss of the basal layer. Between one and two weeks after irradiation the pattern is more mixed with recovery occurring by repopulation in competition with further denudation. If the degree of damage to the basal layer is sufficiently severe the keratinized layers will not be replaced as they are lost, the underlying tissues will be exposed and radiation ulcers will result. Death occurs usually between the second and third weeks. After a reduction in food intake, animals become inactive, they suddenly lose weight and die. The probable cause of death is dehydration. Round-cell inflammatory infiltration in the submucosa and muscularis are possibly contributing factors [P1]. Mice which do not die appear to recover totally by repopulation of the basal layer. After 4 weeks surviving animals appear normal. The syndrome in mouse may be similar to the acute oesophagitis seen in patients during thoracic irradiation. However, late effects occur in patients, such as telangiectasia and fibrosis, which are only observed in animals after high doses, i.e., greater than 30 Gy in a single treatment, which is well beyond the LD_{50} for pulmonary damage.

81. The LD_{50} endpoint for damage to the oesophagus was developed by Phillips and Margolis [P2]. It was found that in anaesthetized mice the oesophagus is protected from radiation by hypoxia [P1, H2]. Whether or not the oesophagus of man is radiobiologically hypoxic is not known. In fractionated or low dose rate irradiation the tissue would, in any case, be expected to reoxygenate, so the oxygenated values of LD_{50} will be more applicable.

82. The results of Phillips and Ross [P1] and of Hornsey and Field [H2] on 3 mouse strains are in good agreement regarding the LD_{50}, as single dose values are close to 30 Gy. If the single doses are corrected for hypoxia, 20 Gy may be appropriate for the fully oxygenated oesophagus. An LD_{50} of 20 Gy has been measured for rats after irradiation of the thorax only, animals dying between 16 and 30 days [A19].

83. The repair capacity of the oesophageal epithelium is very large, values of D_2-D_1 between 5.5 and 8.5 Gy having been reported [H2, P1]. These values might be even larger if the single doses were not affected by hypoxia. The slope of the isoeffect curve is about 0.4. It incorporates both N and T in this case as the available data do not allow separation of the factors. Proliferation of the basal cells is rapid with a cycle time of about two days [L9]. However, Phillips and Ross showed a very small effect of increasing the temporal separation of two doses of x rays, for which there is no obvious explanation.

84. In summary, the reaction of the oesophagus is unlikely to be a limiting factor with thoracic irradiation, either for single or fractionated treatments. Oesophageal cells have a considerable ability to recover from sublethal damage and the cellular proliferation is high so that the tissue is able to withstand high levels of single and fractionated irradiations. Animals without signs of oesophageal reaction may die later from pulmonary damage.

2. Abdominal organs

85. Total body acute exposure of 10 Gy or more results in the gastrointestinal syndrome with death occurring between 3 and 10 days later, depending on species [M74]. The characteristic symptoms are nausea, vomiting and diarrhoea, leading to dehydration, electrolyte imbalance, loss of weight and infection. These symptoms are attributable to the depopulation of the intestinal epithelial lining. Loss of the cells in the crypts of Lieberkühn will lead to denudation of the villi owing to lack of replacement when the cells are naturally worn off. A close relationship between cell survival and the probability of death has been established by Hornsey [H1] who found that the

relationship was unaffected by either dose rate or radiation quality. A detailed review of gastrointestinal response to irradiation is given by Maisin et al. [M43].

86. Any whole-body radiation dose large enough to cause death from gastrointestinal syndrome is larger than that required to cause death at a later time from damage to the haemopoietic system [H3, B7]. Typical LD_{50} values at 5–8 days for six species range from 8 to 15 Gy [B7]. If the intestine is irradiated in isolation, the doses must be increased and the animals survive longer. If less than the whole intestine is irradiated the LD_{50} is further increased. Values of 13.2, 18.6 and 17.7 Gy were obtained in rats for treatment of the whole abdomen, front region or back region only [Z5]. It has been found that the small intestine is the most sensitive part of the gastrointestinal tract [B7]. Apart from lethality studies, there have been experiments using absorption changes, protein and fluid loss, electrolyte balance and changes in the incorporation of DNA precursors [B77, G42, M74, S72, T25, V19].

87. Withers and Elkind [W1, W5] developed two methods of estimating cell survival in irradiated small intestine by scoring either macrocolonies (visible to the naked eye) or microcolonies (visible in histological sections). From these studies a D_o of 1.3 Gy and D_2-D_1 of 4–5 Gy were derived. The value of D_o is similar to that from many other cells and tissues. The value of D_2-D_1 is similar to that derived from LD_{50} experiments and is also similar to values from other organized tissues (see Table 1). The large value of D_2-D_1 obtained indicates that the intestine has a very large capacity for accumulation and repair of sublethal damage. Withers [W12] presented results from which a slope ratio for jejunal crypt cells of about 3 may be derived.

88. Vatistas and Hornsey [V3] measured dose-effect relationships for the leakage of molecules of plasma protein size into the intestine. Radioactive PVP was used and the activity in the faeces was measured. Doses greater than 2 Gy of x rays produced increased leakage. The effect is not due to damage to the intestinal epithelium but to increased blood vessel permeability.

89. A recent quantitative method of assessing changes in the gut due to irradiation is the measurement of the absorptive surface [M5]. This is done from histological preparations. A minimum value is seen at about 3 days after irradiation and the technique can detect single doses of 3 Gy or greater.

90. With fractionated or low dose rate treatments the major repair component in the intestine is compensatory cellular proliferation. The natural cell cycle time in intestine is short, and it has a very high capacity for rapid proliferation. For example, the cycle time may be shortened to about 7 hours [L3].

91. Sato et al. [S32] observed numbers of cells in crypts and villi of mice where the trunks only had received 10 Gy x rays. The results confirmed the high degree of compensatory feedback and proliferation in the crypts. The timing of onset of this compensation varies with normal cell cycle time and tissue structure, being fastest in the jejunum and somewhat slower in stomach and colon (for a review see [D1]).

92. The potential for compensatory proliferation makes the intestine relatively unresponsive to fractionated or low dose rate treatments. Studies on rats [Q2, L10, W13] indicate that irradiation at 4 Gy per day produces an initial depopulation of the crypt cells, after which a new equilibrium develops. The cell number remains constant but their rate of proliferation is much increased. The animals appear to withstand this daily dose.

93. Maisin et al. [M6] studied the response of mice given 2 Gy daily to the abdomen. The animals survived this treatment up to the maximum total dose given, which was 60 Gy in 6 weeks. Compensation took the form of a reduced cell cycle time and an increase in the size of the stem cell compartment. The villi were, however, reduced to about 70% of normal and the number of cells per villus to about 60% of normal. The animals could not tolerate 3.5 Gy given daily.

94. In contrast to small intestine, far less is known about the responses of stomach or large bowel to irradiation. Changes in the characteristics of gastric emptying have been detected with single doses as small as 0.5 Gy [T27], but these changes are transient. Absorption changes [O15] and effects on gastric acid and bioelectric potentials were noted above 1.3 Gy [V20]. Gastric mucosa has typical survival curve characteristics [C32]. New methods to assess large bowel response are just becoming available [H65].

95. In conclusion, it is clear that the gut can withstand very large daily doses of radiation. All the studies mentioned have concentrated on the early forms of radiation injury but other major problems may arise later and very little information exists on late damage to the intestine. Quantitation of fibrosis and of changes in bowel habits are being attempted in several laboratories but no dose-response curves have yet been published.

C. CARTILAGE AND BONE

96. A growing long bone consists of an ossified shaft, the diaphysis, having metaphyses with an epiphysial growth cartilage at each end. The effect of irradiation is to reduce the growth potential, by sterilizing the stem cells in the epiphyses. The result is that the bone becomes permanently stunted. The phenomenon is therefore especially important in the young where growth is most active.

97. Kember [K6] developed a technique for estimating cell survival parameters for cells of growing cartilage in the tibia of young rats. He derived a D_o value of 1.65 Gy and an extrapolation number of 6 [K1]. Although the technique did not allow very precise measurements, these values of D_o and n were similar to those obtained for other types of cell.

98. Stunting of growth of bones has been investigated by various workers. Early measurements by Bisgard and Hunt [B8] indicated that in rabbits more than 3 Gy was required to cause measurable stunting. In a review of the older literature, Wells [W14] quoted values between 1 and 5 Gy for the threshold doses to cause stunting in various animals. In his own experiments on mouse tibia, Wells [W14] found a threshold of about 2 Gy and a 10% reduction caused by 4 Gy. On average 1% stunting was caused by 0.33 Gy.

99. Dixon [D15] performed similar experiments on the tails of 7-day old rats. The technique used allowed very accurate results and no threshold was observed. In these experiments 1% stunting was caused by approxi-

mately 0.2 Gy. By varying the oxygen concentration breathed by the rats, Dixon [D15] concluded that the epiphyseal stem cells were uniformly slightly hypoxic; the sensitivity was increased by about 10% when pure oxygen was breathed.

100. The effects of dose fractionation were examined by Dixon [D5] on rats. Considerable dose sparing due to recovery from sublethal damage was observed. D_2-D_1 increased with increasing dose to a maximum value of about 4 Gy. Kember [K1] using the clonal assay, obtained a value for D_2-D_1 of 3.5 Gy. These values are similar to those found with other tissues (Table 1).

101. In summary, growing cartilage appears to be one of the more sensitive tissues. The threshold dose for causing permanent stunting of bone growth is small or perhaps non-existent. The rate of stunting per Gy in growing rodents may be 3–5%.

D. HEART

102. The response of the heart to ionizing radiation has been the subject of few investigations, but there is little doubt of its radiation resistance. After moderate doses only histological techniques have revealed changes. Kurohara and Casarett [K5] noted degenerative changes in the rat myocardium after 24 Gy in a single treatment. At 28 days there was a loss of striation and granularity in the cytoplasm of myocardial cells. Fajardo and Steward [F35] showed identical pathology in rabbit and man: 20 Gy caused death of 4% of rabbits between 70 and 150 days after irradiation from injury to the pericardium or myocardium and often with congestive heart failure. The histological results indicate that the primary damage is to the capillary endothelium often leading to loss of capillary function. Insufficient microcirculation leads to fibrosis.

E. LUNG

103. The lung is a highly differentiated and complex tissue in which the capacity for cellular proliferation and hence restoration of the normal structure is poor. Therefore this tissue cannot easily restore function after large parenchymal losses. On the other hand, the respiratory system has a large reserve capacity which can compensate for losses in functioning parenchyma so that even after loss of an entire lung the other is usually adequate for respiratory requirements. It may thus be expected that pulmonary function is an insensitive index by which to measure the effects of irradiation up to doses which become life threatening. As a result, dose-effect relationships based on physiological changes tend to assume "all or none" threshold characteristics.

104. The pathological changes in irradiated lung have been described by various authors [K5, J3, P6, V4, M7, A20]. Changes tend to be patchy and are dose-dependent although not strongly. They occur in three phases. Microscopically, little effect is seen in the first days after irradiation, after which and for the first month or so, damage to the epithelial cells of the alveoli may appear, associated with fibrin-rich exudation. After low doses, although they may be sufficiently large to cause late changes, these early sequelae are very slight or even totally absent. Between 3 weeks and lasting for several months radiation pneumonitis is seen; it is characterized by fibrin-rich membranes lining the alveoli together with desquamative and consolidative changes and cellular infiltration. The walls of the alveoli become thickened. Late changes include further thickening of the reticulum and condensation resulting in atelectasis, fibrosis and loss of respiratory function.

105. The epithelium of the air passages, the hyaline cartilage and muscle appear to be relatively resistant and are not considered to be limiting components in the radiation response of the respiratory organs. However, other factors which tend to complicate the pathologic picture are: obstruction to air passages; infections and inflammatory reactions; capillary permeability changes; and haematologic changes.

106. The most important constituent of lung connective tissue is collagen [C28]. This has been often studied as a measure of lung fibrosis, both microscopically and biochemically [K46, C29, D50, G40, L11]. However, if the hemithorax of mice is irradiated, changes in relative collagen content occur much later than the time of death when both lungs are irradiated [K46, L11]. The indications are therefore that the pulmonary syndrome in mice leading to death as described above, results primarily from pneumonitis and its complications and not from fibrosis. Changes in elastin [F53] have also been reported.

107. Physiological studies have been performed on dogs, rats and mice by various authors [M8, S6, T4, T5, T6]. With doses greater than 10 Gy in a single dose or 30 Gy fractionated over 8 weeks there was a decrease in the diffusion of carbon monoxide, suggesting an alveolocapillary block and consistent with the histologically observed thickening of the alveolar walls. After doses of this magnitude or greater, a reduction in a variety of lung function parameters followed.

108. In general it appears that the time course of radiation-induced changes in lung is relatively independent of species. In all species the latent period for the onset of acute radiation pneumonitis is 1 to 3 months, similar to that in man. Also the doses required to cause measurable changes in physiology are similar to or greater than doses to kill animals from pulmonary insufficiency, i.e., greater than 10 Gy in a single treatment.

109. Following irradiation with single doses of x rays of approximately 12 Gy or higher (or equivalent fractionated doses) animals die from acute pneumonitis between about 3 and 7 months after irradiation. After lower doses, surviving animals may develop long-term changes leading to pulmonary fibrosis [T31]. Radiopneumonitis is thought to result primarily from direct effects on parenchymal cells with secondary damage to the vascular connective tissue. Fibrosis is thought to be a consequence primarily of damage to capillaries with secondary effects on the parenchyma [A20, K5, P6, M7]. Van den Brenk [V4] suggested that the primary target cells are the type II alveolar cells which produce surfactant, a lipoprotein preventing adhesion and collapse of the alveoli on expiration. A reduction in surfactant would lead to an unbalance of osmotic and hydrostatic pressures resulting in accumulation of fluids in the alveoli, a characteristic of radiation pneumonitis which however could also result from damage to blood vessels. Various studies of the function of type II cells have been made. Total lung lipids, total phospholipids, lipid turnover and surface tension have all been measured, but the results do not yield a clear picture [S69, G40, P38, P39, P40, M76, G41].

110. Perhaps the most sensitive end-point for assessing damage to lung in experimental animals is the probability of survival late after irradiation. Phillips and Margolis [P2] observed that mice die from lung damage from about 80 days after irradiation and that no further deaths occur beyond 160 days. They estimated the LD_{50} at 160 days for a variety of treatment regimes with x rays. The mice died with obvious signs of respiratory failure, the lungs were wet, indicating vascular leakage. This was also indicated by isotope studies [H52]. Bacterial infections were rare and the main damage was to the alveoli. Field et al. [F17] reported very similar results to those of Wara et al. [W15]. They may be summarized as follows: the LD_{50} in mice is 12–14 Gy, depending on the strain. There is a marked effect of fractionation of x rays, such that data are fitted by $N^{0.39}$ up to 8 fractions and $N^{0.25}$ from 8 to 32 fractions (Figure V). Repair of sublethal damage

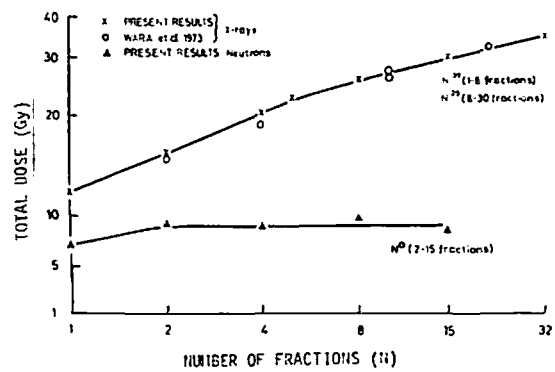

Figure V. Isoeffect curves of total dose versus number of fractions for lung LD_{50}. The upper curve is for x rays and the lower curve for neutrons. All data are corrected for an overall effective treatment time of 1 day [F17]

between two fractions occurs in a few hours as is the case for other cells and tissues [F3]. If lung damage is examined by the method of Dutreix et al. [D9], it is seen that repair of sublethal damage is considerable, perhaps greater than for other tissues. When the slope ratio is calculated for lung the ratio is very similar to values derived for skin with a ratio of 1 : 7 [F15].

111. With a constant number of fractions and a variable time between them, the T factor for lung may be derived. Two experimental series [W15, F12] showed that $T^{0.07}$ was a good fit to the data. This is smaller than that for skin owing to lack of repopulation in lung. Field and Hornsey [F8] showed that for neutrons there was no further effect of extending the treatment time beyond an hour, i.e., after repair of sublethal damage. Since repopulation is thought to be similar after x rays and fast neutrons, a slow repair process was suggested as the explanation for the x-ray result which is absent after neutrons. Repopulation between fractions has been excluded as the explanation by labelling experiments [C31] leaving slow repair as the explanation for the T factor.

112. In summary, lung is a highly complex organ comprising more than 40 cell types. The pathological changes following irradiation have been described, but the primary target or targets remain uncertain. Damage to type II cells or vascular damage are considered generally to account for the changes in elastic properties, pneumonitis and fibrosis that occur. Lung is a relatively sensitive tissue, probably because it lacks the rapid proliferative ability. However, lung has a large capacity for repair of sublethal damage which enables it to tolerate a high level of fractionated or presumably continuous irradiation.

F. LIVER

113. The liver performs a variety of essential functions. Its cells are normally not actively dividing and, therefore, radiation damage caused by moderate doses can only be demonstrated late after irradiation. As a result there has been a long debate as to whether liver is a radioresistant organ or not (see [L31] for details of post irradiation changes). Irradiation of the whole liver in laboratory animals is exceptionally difficult without causing severe damage to other more rapidly proliferating organs such as the intestine, irradiation of which can lead to early death. The liver has a very large reserve capacity and is able to maintain apparently normal function despite a large part of it having been damaged. In addition, the hepatocytes have an extraordinary capacity for regeneration. Should part of the liver be injured these cells will rapidly proliferate to maintain hepatic function.

114. The literature contains few animal experiments on liver and most of these are confined to studies of repopulation and regeneration. Results obtained also appear to be highly variable (see review [L12]) and it has been suggested that this is due to variations in the state of liver cells at the time of irradiation or subsequently. Any liver disturbance which elicits a proliferation response may seriously increase the reaction to irradiation, and most experiments have been performed in this way.

115. A technique for measuring liver damage was devised by Weinbren et al. [W16] in which latent damage was unmasked by stimulating the liver into division either by surgical removal of part of the organ or by using damaging chemicals, e.g., carbon tetrachloride. These experiments involved irradiation of two-thirds of the liver of rats (on exteriorization) to 50 Gy in a single dose. Major changes were not noticed unless partial hepatectomy was subsequently performed. Kinzie et al. [K7] reported fairly minor changes in rat liver after single doses of 15 Gy and Dettmer et al. [D16] showed very slight changes after total liver irradiation with 10 Gy but severe after 25 Gy. De Mignard et al. [D17] measured only a transient change in rats after 6 Gy, which had returned to normal by 6 weeks. Damage to the microsomal drug metabolizing enzyme system in the rat has been observed, but only after high doses of 7.5 Gy given daily. [Y3, N12]. Verga and Cali [V5] irradiated rats with 0.5 Gy per day for a total of 33 Gy before an abnormality was observed, i.e. hypertrophia of Kupfer cells. When 3 Gy per day for a total of 60 Gy was given to rats there was no reduction in the effect of detoxification.

116. Thus, liver is a slowly proliferating organ, but its cells can be stimulated into division by injury (including that from radiation) and thereby unmask latent radiation damage. Single doses of x rays of more than 10 Gy are needed for demonstrable permanent changes and this dose may be increased by a factor of 3–6 by extended fractionation.

G. URINARY SYSTEM

117. Under normal circumstances there is little cell proliferation and except for large radiation doses the effects of irradiation occur late. These late effects include proteinuria, hypertension and reduction in kidney function. It is possible to measure various aspects of kidney function, e.g., glomerular filtration rate (GFR), effective renal plasma flow (ERPF) and tubular resorption rate (TM_{PAH}).

118. Human and animal kidneys show similar histopathological changes resulting from irradiation. These changes are reported to occur to varying degrees and at varying times but can be summarized as degeneration, necrosis or atrophy of the tubular epithelium; increased interstitial connective tissue; thickening of basement membranes; hyalinization of connective tissue; replacement fibrosis; degeneration necrosis; swelling or proliferation of endothelial cells; intimal vascular thickening; thickening of vessel walls and narrowing of lumina; degeneration, necrosis, or atrophy and scarring of glomeruli. Similar changes were described after irradiation of dog kidney by fast protons [F36]. A detailed review of the kidney pathology after irradiation has been made by Mostofi and Berdjis [M9].

119. It is by no means clear whether vascular or parenchymal damage in kidney is the more important. However, it is known that blood vessels become more sensitive to irradiation in conditions of hypertension [A3]. Animal experiments on kidneys have in general led to wide differences in interpretation. There is no consensus on the degree, extent or time of onset and progression of specific changes and considerable disagreement has resulted in interpreting the histological findings [M9].

120. The dog has been used by various experimenters. In some cases whole-body irradiation has been given, sometimes only the kidneys or one kidney has been treated and sometimes one kidney is removed and the other irradiated. Doses of 20 Gy or less cause profound changes. Mendelsohn and Caceres [M10] performed unilateral nephrectomy, allowed 15 weeks for compensatory hypertrophy of the remaining kidney and irradiated over 13 days. Kidney function tests indicated that tubular function was the most sensitive index but the authors suggested that the ultimate effect was through vascular damage.

121. Pospisil and Zaruba [P7] and Zaruba [Z1] measured kidney changes after whole body irradiation and found some with 6 Gy, but concluded that they were through indirect effect rather than direct damage to the kidney. Maier and Casarett [M11] irradiated dogs with a range of doses from 5 Gy. Physiological changes were measured during a 6 months period after irradiation. It was found that 5 Gy produced very little change but 10 Gy produced morphological and functional modifications at 6 months. In the neonate 3.3 Gy did produce changes in renal function later in life [L32].

122. In pigs, Hopewell and Berry [H12] measured physiological changes and observed thresholds for reduced function after approximately 10 Gy in a single dose or 40 Gy in 30 fractions in 6 weeks.

123. Rabbit kidney may be rather radioresistant [M9] but Caldwell et al. [C7] reported LD_{50} values at 6 months of 18 Gy in a single dose or 57 Gy in 24 fractions.

124. Effects in rats have been studied by Bennet et al. [B10] and Lamson et al. [L13] who observed hypertension with doses as low as 5 Gy. Hypertension was observed even if only one kidney was irradiated [W17]. Berdjis [B11] observed nephrosclerosis 1 year after 9 Gy to rat kidneys which was reduced but not eliminated if the rats had been given 5 Gy whole-body irradiation. Kärcher and Schulz [K8] observed functional and enzymatic changes if both kidneys were given 10 Gy, which were reversible if only 1 kidney was irradiated. Chauser et al. [C8] measured ERPF and collagen deposition at 18 weeks after irradiation of 1 kidney only in rat; 10 Gy had no effect on function and caused a very small increase in collagen; 20 Gy caused renal failure between 16 and 18 weeks, but the rats appeared normal.

125. Many authors irradiated mice over the whole body and estimated kidney changes. These occur at fairly low doses of about 5 Gy, but as stated previously, may not be direct effects on the kidney [B12, G1, C9]. Irradiation of only the kidneys by Glatstein [G2] demonstrated a threshold dose for impairment of renal blood flow of less than 10 Gy. Phillips and Ross [P8] estimated the LD_{50} to be 13 Gy at 16 months by unilateral nephrectomy and irradiation after hypertrophy of the remaining kidney. The threshold dose to cause death in these experiments was about 8 Gy. Donaldson et al. [D18] measured the inhibition of compensatory renal growth after unilateral nephrectomy in weaning mice. In this case the threshold for a permanent effect was 10–15 Gy. Geraci et al. [G3] measured decrease in kidney weight at 6 months and observed a threshold of about 10 Gy x rays and 7 Gy neutrons. Dogs irradiated with two doses of 3.5 Gy of fast protons and kept alive by shielding part of the bone marrow, showed a variety of changes after 6 months, including a decrease in secretory activity, proteinurea, hypertony and blood changes [N10]. Threshold doses from single dose experiments are summarized in Table 4.

126. Fractionation experiments have been performed on mouse kidney by Phillips and Ross [P8] and by Glatstein [G4] and on pigs by Hopewell and Wiernik [H13]. All series showed a marked reduction in the effect of irradiation with increasing fractionation. Recovery from sublethal damage was perhaps even greater than with skin but less than for lung [P8]. In general the Ellis formula provides a reasonable description of the fractionation effects on kidney.

127. The late foetal or neonatal kidney has been shown to be more sensitive than in the adult. For example, mice irradiated at birth showed far more intercapillary glomerulosclerosis than if irradiated at 12, 23 or 53 days of age [G1]. Guttman showed that 4.5 Gy given to mice at birth caused significant changes in the glomeruli followed by deposition of collagen. Phemester et al. [P29] observed beagle dogs which had received 2.7–4.4 Gy either at 55 days in utero or at 2 days old. The animals subsequently died with chronic renal failure.

128. Very few studies on the response of the urinary bladder to irradiation have been performed. However, recently a functional assay for damage to the mouse bladder has been developed [S73] and it has shown that beyond 5 months after single doses of irradiation the threshold for detectable changes is 15 Gy. Damage was to the epithelium with a loss of the specialized polyploid surface cells. Fibroses became apparent after one year. Compensatory proliferation occurred only when loss of function became apparent [S74].

129. In conclusion, a wide range of physiological measurements and histological changes have been reported for kidney. Data for threshold doses are relatively consistent between experimenters and for different species and are in the range 5–12 Gy. With extended fractionation these threshold doses would be increased by a factor of at least 3. Kidney is considerably more sensitive around the time of birth.

H. CENTRAL NERVOUS SYSTEM

130. Effects of radiation on the nervous system were comprehensively reviewed by the Committee in 1969 [U4]. The main findings were that the central nervous system is very sensitive whilst developing. Transient functional and behavioural changes can occur in animals with doses greater than 0.5 Gy and in some cases ionizing radiation can be detected at levels of a few tens of mGy, but there is no evidence of permanent injury at these dose levels. It was noted that workers exposed for many years within the recommended limits did not develop any consequence of note. This topic was reviewed by Maisin [M71]. It was pointed out [U4] that for permanent injury the nervous system of the adult was less sensitive than some other tissues and organs. During the subsequent years no new data have significantly altered these views. Additional information has been obtained, particularly on the role of the vascular system in the pathogenesis of radiation-induced neurological syndromes, although its exact role remains unclear since the vascular changes occurred more than one year after irradiation [R49].

1. Spinal cord

131. Irradiation of the spinal cord in animals and in man may result in myelopathy whose probability and time of onset are dose dependent. In some cases the time of onset both in rats and mice has been found to be inversely related to the dose of irradiation [C10, G5]. However, other experimenters observed after about 100 days acute ataxia and paralysis the probability of which was dose dependent [W6, V6]. In these experiments only a short segment of the cord was irradiated.

132. At the dose levels required to produce such late paralysis after irradiation of the cervical cord, necrosis was restricted to the white matter, but small haemorrhages were observed scattered throughout both the grey and white matter.

133. Using rats, White and Hornsey [W6] found that no paralysis occurred with single doses of less than 20 Gy. Van der Kogel [V7], also using rats, found that doses above 17 Gy caused paralysis. In these experiments paralysis occurring within 6 months was attributed to necrosis of white matter, i.e., neurological damage, whereas vascular injury appeared to cause later paralysis at 12–18 months at slightly lower dose levels. In mice, Geraci et al. [G5] observed a threshold of about 12.5 Gy x rays and Goffinet et al. [G6] observed only a small effect with the lowest dose used of 20 Gy.

134. The effects of dose fractionation on the spinal cord were carefully investigated by van der Kogel [V8] and by White and Hornsey [W6] on rats and by Geraci et al. [G7] and Goffinet et al. [G6] on mice. In all cases the dose to provide myelitis increased more rapidly with increasing the number of fractions than for most other tissue end-points, showing that the spinal cord has a relatively large capacity for accumulation and repair of sublethal damage. In both rat experiments the effect of varying the time between fractions was tested. There was initially no effect on LD_{50} of increasing the time separation, until 8–16 weeks [V1] or about 5 weeks [W6]. Both studies suggest that there is no slow repair in the spinal cord, but delayed repopulation. The repopulation gave a time factor of about $T^{0.03}$ and the dose fractionation an N factor of approximately $N^{0.4}$.

135. Goffinet et al. [G6] also tested the effects of irradiating different lengths of cord. They found that the tolerance for a single dose was reduced by about 20% when the irradiated length of mouse cord was increased from 6 mm to 12 mm.

2. Brain

136. Neuro-physiological methods to enable detection of effects of irradiation to the brain [L14] indicate that in some respects it is radiation sensitive. For example, Minamisawa et al. measured changes in evoked potentials recorded from the visual cortex of rabbits on photic stimulation and showed that this function gradually decreased over the lifetime of the animal after single doses of 1–3 Gy or 3–30 Gy fractionated [M44, M45, M72]. However, in general the organ was considered to be fairly radiation resistant. Doses greater than about 20 Gy are required to produce morphological changes and the latent period is shorter with increasing dose [Z2].

137. Russell, Wilson and Tansley [R6] investigated the response of rabbit brain. They estimated the minimal single dose to produce delayed necrosis to be between 20 and 24 Gy. Hopewell and Wright [H14] measured the latent period between irradiation and death in rats. In normal animals irradiated with 10 Gy to the head there was no weight loss, no neurological symptoms and their life span was not different from controls. However, 20 Gy did cause weight loss and the life span was reduced. Histologically there were three types of change: the earliest changes were in the subependymal plate, a region of mitotically active cells found around the anterior of the lateral ventricles; large areas of necrosis were observed later, mainly in the white matter; vascular lesions in particular hyaline thickening, fibrinoid necrosis of vessel walls and microaneurysms occurred still later.

138. The cells of the subependymal plate are the stem cells for neuroglia of the white substance [L15]. After irradiation with photons the number of these cells is depressed but recovers for doses of 10 Gy or less. With 15 Gy of photons there is total destruction of the subependymal layer [C11]. Even 5.5 Gy cause a persistent change in the glial cell balance [R52]. With fast neutrons there appears to be no recovery after doses as small as 1 Gy [C11].

139. Irradiation of rabbits with 1.5 Gy produced a decrease in intracranial pressure, while 10 Gy caused a transient increase in intracranial pressure persisting for 2 days [L26, L27].

140. An increasing amount of data supports the view that structural damage to neurones can occur after relatively low doses [A21, V14]. Fast protons (50–645 MeV) [K33] and gamma rays in the range 1–6 Gy produced degeneration in the rat brain cortex between

1 and 12 months after irradiation, leading to neural destruction. At 12 months after 2–4 Gy, 25–40% of the external granular layer of rat brain cortex was irreversibly altered. These degenerative changes were increasing with an increasing period of observation after irradiation, indicating that the nervous tissue cannot simply be regarded as radioresistant.

I. ENDOCRINE ORGANS

1. Thyroid

141. The parenchymal cells of the thyroid are not normally actively dividing and therefore do not exhibit early radiation-induced mitotic cell death. After doses of 50–100 Gy from ^{131}I interphase death occurs, detectable during the second week after irradiation [W43]. At later times there is no further radiation-induced cell death. However there is progressive atrophy of the parenchyma resulting in hypothyroidism [W44], due to prolonged impairment of cellular reproductive capacity, as demonstrated by reduced response to goitrogenic stimulation. Early radionecrosis of the gland, which is the result of damage to the fine vasculature, may appear but requires massive doses, well in excess of those which produce late changes resulting from damage to the epithelial cells. The pathogenesis of the thyroid changes associated with the development of hypothyroidism appears to involve primarily patchy degeneration and fibrosis of the fine vasculature and interfollicular stroma and secondarily degeneration of the follicular epithelium. In some of the less affected regions there may be hyperplastic reactions resulting in atrophic nodular structures containing little colloid [R1].

142. The time of onset of the late hypothyroidism is dose related, occurring earlier with larger doses. Using adult dogs, Michaelson et al. [M12] showed radiation-induced primary hypothyroidism occurring 3–4 years later with a threshold of about 10 Gy in a single dose. At these times the animals showed signs of thyroid malfunction, such as decreased activity, coarsening hair, increasing obesity and reduced body temperature. The uptake of ^{131}I by the thyroid was also reduced. The authors suggested that this radiation-induced chronic thyroiditis may involve an autoimmune mechanism through leakage of thyroglobulin and microsomal material, both of which have been shown to be antigenic.

143. Techniques to estimate epithelial cell survival have been developed. These are based on the fact that application of a goitrogenic stimulus, e.g., methylthiouracil, prevents hormone iodination and leads to a reduction in blood hormone level. As a result thyrotropic hormone level (TSH) is raised and the thyroid gland increases its weight by 3–5 times over a period of about a month. This weight increase is reduced by irradiation. With a single dose of 10 Gy the response is reduced by about 50% [M13]. Clearly the thyroid has a large reserve capacity. Not only can it tolerate a considerable loss of material, but it will also produce relatively more T_3 hormone at the expense of T_4, the former being by far more effective.

144. A transplantation technique was recently developed to assess thyroid cell survival. Irradiation was performed either in situ or in vitro after preparation of a cell suspension. In both cases the parameters of cell survival were found to be within the range for most mammalian cell types, although the D_0 of 19 Gy was rather higher than usually observed, indicating that thyroid cells could be rather more resistant than most [C22].

145. The thyroid is, in conclusion, a non-proliferating tissue in which radiation effects occur after many years. 10 Gy x rays in a single external treatment is required to cause signs of malfunction or a 50% reduction in epithelial cells.

2. Pituitary

146. In the adult the pituitary is regarded as a radioresistant organ. Its suppression results in a fall of gonadotrophin and in reduced function of other endocrine organs such as the thyroid and the adrenals [S34]. However, a fall in growth hormone may result from damage to the hypothalamus, as has been reported after radiotherapy, particularly in children [K52]. In the adult animal, very large doses of approximately 300 Gy are required to ablate the pituitary [R1]. In immature animals the organ is far more sensitive, for example, whole-body irradiation of 1 Gy caused weight loss in squirrels and 6 Gy caused stunting of growth in 2-day old rats [M46].

3. Adrenals

147. Evaluation of the response of the adrenals to irradiation is complicated. The adrenal responds to the stress from irradiation by an increase in weight and hormone production. It is therefore difficult to assess direct effects on the gland. As with the pituitary, the organ is resistant in the adult, but in immature animals it appears to be more sensitive. Six Gy to calves caused significant hypertrophy [R31] and 4 Gy to young rats prevented weight gain [W39]. Older animals are more resistant, although 9 Gy to rats caused medullary venous thrombosis and atrophy of the gland. In all the above experiments the animals died from intestinal injury a few days after irradiation and therefore the effects on the adrenals may not have been permanent, as was shown in experiments in which rats lived longer [S34]. Permanent changes to the adrenals require doses of 20 to 30 Gy [E18].

J. GONADS

1. Testis

148. Irradiation of the testes produces sterility, which may be permanent or temporary depending on the dose levels and dose rates employed. An understanding of the effects of irradiation on the testis requires a knowledge of the development of mature sperm from the testicular stem cells. The accepted model for this process is that described by Oakberg [O2, O3, O4] which has recently been re-examined by Meistrich et al. [M14]. The basic stem cell is an undifferentiated type A spermatogonium designated A_{is} which has an LD_{50} of 2–3 Gy [O5, E8, M42] and cycle times ranging from 2–9 days [O4, H15]. The developing spermatogonium is most sensitive when it is in the differentiated stages A_1 to B. There also exists an intermediate stage, designated A_{al}, with intermediate sensitivity between the stem cells A_{is} and the differentiated spermatogonia. Progression of differentiation continues through spermatocytes, spermatids to spermatozoa, the resistance to irradiation

increasing with further differentiation. The full cycle takes about 6 weeks in a mouse and about 10 weeks in man. Biochemical changes due to irradiation with x rays or protons have been investigated [S38, F37]. The topic has recently been reviewed by Kondratenko [K32].

149. From this description, it is clear that small doses will induce temporary sterility by killing the sensitive differentiating spermatogonia. Larger doses may also deplete the type A_{al} spermatogonia without inducing permanent sterility, since the stem cells are more resistant. If the stem cell compartment is seriously depleted, it will be initially restored by cell proliferation, after which it will begin to differentiate and ultimately produce sperm. About 20% of the normal spermatozoa count is required for conception.

150. Radiation doses to induce sterility have been measured by various workers. In mice, the Russells [R7, R8] observed recovery after single doses of 6 Gy and later after 10 Gy, but mutations were produced in the survivors. In rats, Shaver [S7, S8] measured single threshold doses of 5 Gy in adult and 3 Gy in immature animals. Erickson observed a threshold of about 4 Gy in the rat [E19]. In rabbits, single doses greater than 9.5 Gy were required [C12] and in bulls 8 Gy produced only reversible injury and not permanent sterility. With dogs, Casarett and Eddy [C13] demonstrated that even after 20 Gy some recovery occurred. In man single doses of about 5 Gy would appear to be around the threshold level [L16].

151. The response of the testis to fractionated and low dose rate radiation is different from most other tissues. The evidence suggests that there is no "dose sparing" by protracting the treatment as is normally the case but fractionated treatments may actually be more effective for a given total dose. Brown et al. [B13] reported that continuous irradiation at 0.02 Gy/day to rats and mice allowed reproduction for at least 10 generations although there was some evidence of life shortening [D19]. At dose rates slightly greater than 0.02 Gy/day, sterilization ultimately resulted. However, Stadler and Gowen [S9, S10] reported maintenance of the germ line in mice irradiated for 11 successive generations with daily doses of up to 0.03 Gy/day. A total dose of 15 Gy was accumulated without causing reduction in reproductivity or a change in the sex ratio. Oakberg and Clark [O6, O7, O8] reported a threshold of about 0.13 Gy/day in mice. Total doses accumulated at 0.014 Gy/day to 3 Gy caused the spermatogonial population to reach a new equilibrium ratio of 80% of the control.

152. Casarett and Eddy [C13] compared the effects of single and fractionated irradiation of testis in dogs using whole-body irradiation. Treatment at 0.03 Gy/day to a total of 3.75 Gy caused a greater degree of irreversible depression in sperm production than did a single exposure of 3.75 Gy. When 4.75 Gy was given at 0.03 Gy/day, all dogs became permanently aspermic. With life-long irradiation, 0.0012 Gy/day causes no deleterious effects, but 0.006 Gy/day ultimately caused permanent aspermia and sterility if total doses greater than 10 Gy were given. It is possible that recruitment of cells from an otherwise resting and resistant population into a more sensitive phase may be primarily responsible for this unusual and important effect of dose fractionation.

153. Fedorova and colleagues [F39, F40] irradiated dogs for 6 years at varying dose rates. There was no effect on sperm production below 0.0017 Gy/day, but 0.0034 Gy/day to a total of 7.5 Gy led to oligospermia. Giving 0.0017 Gy per day plus a single treatment of 0.42 Gy three times per year caused a still greater effect and after 2.5 years the ability for fertilization was lost, although recovery took place.

154. The hormonal secretory function of the testis is far more resistant to irradiation than spermatogenesis since 0.25–0.5 Gy/day to a total of 50–100 Gy in 25 weeks causes no reduction in secretory function [R32].

155. In summary, irradiation of the testes causes temporary sterility and with larger doses sterility may become permanent. The testis is unlike other normal tissues in that repair of sublethal damage does not occur. Moreover, fractionated or continuous irradiation renders the tissue more rather than less sensitive. In mice continuous life-long irradiation between 0.02 and 0.13 Gy/day is reported to cause permanent sterility. In dogs, the figure is lower, 0.006 Gy/day being sufficient but 0.0012 Gy/day insufficient to cause sterility.

2. Ovary

156. The most sensitive and critical component in the female reproductive system is the germ cell. In the ovary all cells in the oogonial stages progress to the oocytes in the embryo. Soon after birth all oocytes are in the resting phase with no further cell division and in the adult there are no stem cells but a finite number of follicles. These have been graded into categories related to their degree of maturity. In some species, e.g., mice, rats and rabbits, the primordial oocyte is more radiosensitive than the later stages of oocyte maturation [O7]. Such differences in sensitivity with stage of development have not, however, been observed in guinea pig, pig or cattle [E9, E10] or the trend in sensitivity is reversed, as in the monkey [B14].

157. There are great interspecies differences in the sensitivity of the ovary to irradiation. In mice 0.1 Gy in a single treatment was sufficient to destroy 50% of the primordial follicles [O9] and 1 Gy produced permanent sterility [R9]. Rat ovary is less sensitive, about 0.7 Gy being required to destroy 50% of the primordial follicles [M15], and more than 8 Gy to produce sterility [K9]. In monkey, the oocyte is little affected by 10 Gy [B14] and the minimum sterilizing dose is about 20 Gy [B15]. With the marmoset, more than 6 Gy is required to kill half the oocytes [L16]. Erickson has shown that the doses to kill half the oocytes in pigs and cows are 5 and 9 Gy, respectively. Single doses of 4 Gy or two doses of 3 Gy each, separated by 55 days, had little effect on the germ cell or follicular count, no effect in the production of ovarian abnormalities, and no change in fertility or quality of offspring [E11]. These differences in radiation sensitivity of ovarian follicles between species are discussed in chapter V of Annex I. They may simply reflect the existence of a sensitive stage, which may or may not be irradiated during the development of these species.

158. Andersen and Rosenblatt [A4] studied fertility after single or fractionated irradiation of female beagles. A single dose of 3 Gy had no noticeable effect, but 7.5 Gy given at 0.5 Gy per week caused total sterilization. Many authors [B2, S9, S10, G8, G9] reported maintenance of the germ line in mice given continuous irradiation for 11 successive generations with daily doses of less than 0.03 Gy. Mice accumulated 15 Gy at

these low dose rates, apparently without harm and with normal reproductivity and sex ratio, although at 0.02 Gy/day there was a progressive reduction in litter size [B2].

159. The developing oocyte is more sensitive. Afollicular ovaries and sterilization were produced by fractionated irradiations of 0.1 Gy/day to a total of 2 Gy in 2–4 day old dogs and 2.7 Gy in foetal monkeys [A5, A6]. In another experiment [A7], doses of 0.115 Gy given twice weekly to a total of 2 Gy severely damaged the ovaries of eight out of nine foetal bonnet monkeys and reduced follicle counts to less than 25% of normal, without causing damage to any other organ.

160. In conclusion, although there are considerable differences in sensitivity between species, the adult ovary is generally more resistant than the testis because the oogonial stages have progressed to the more resistant oocyte by the time of birth. However, the ovaries in foetal animals are severely damaged by much lower doses than those required to cause serious changes to the adult ovary. Fractionated treatments to a total of 2 Gy cause severe damage to the developing ovary in dog and monkey.

K. THE EYE

161. The eye is generally considered to be one of the more sensitive organs to irradiation. Damage to any part of the eye may occur, but for long term effects the most sensitive structure is thought to be the lens. Here, clinically significant progressive or irreversible changes can occur well into maturity, by radiation doses which evoke only transient reactions in other ocular structures, such as the cornea and conjunctiva.

162. Detectable changes in the normally transparent lens may vary from tiny flecks to almost complete opacification resulting in total blindness. Cataracts are most usually associated with old age or with abnormal metabolic disorder, chronic ocular infection, or trauma. The lens consists largely of fibre cells and is covered with an epithelium anteriorly. Dividing cells are limited to the anterior equatorial region, and the progeny of these dividing cells migrate posteriorly and then centrally to form the lens fibres. Cell division continues throughout life, and so the lens may be regarded as a self-renewing tissue. However, it is a cellular system that has no blood supply and no mechanism for cell removal. If dividing cells are injured by radiation, the resulting abnormal fibres are not removed from the lens but migrate toward the posterior pole and, because they are not translucent, they constitute the beginning of a cataract.

163. Many of the cells in the central portion of the lens are capable of proliferation but are in the resting stage G_0 [G10]. These cells may be stimulated into division, for example by injury. According to Bateman and Berdjic [B16], cataractogenesis can proceed either by germinal zone epithelial damage or by metabolic deficit of cortical fibres. They suggest that the former predominates at low radiation doses and the latter at higher doses.

164. Work on establishing the threshold doses in animals seems to fall into two groups. In all animals, including man, there is a finite probability of developing lens opacities during a life-time. In some laboratory animals this probability is very high. The threshold dose in these cases is defined as the dose to significantly increase the probability of opacification. The values obtained are very low indeed, ranging from a few hundredths of Gy depending on the type of damage [e.g., B16, U2].

165. In other animals, including man, the natural probability is very low. It was shown by Focht et al. [F18] that in this case increasing the dose causes a reduction in the latent period. In this type of response the threshold is much higher, for example, single doses of 5 Gy in mice at 1 year [R10], more than 3 Gy in rabbits at 4 years, and 5 Gy in rats at 2 years [U2].

166. Protons ranging from 25–645 MeV produced qualitatively similar effects to photons, at the same dose levels, independent of proton energy. The inverse relationship between dose and latent period was confirmed and it was shown that the probability of causing opacities decreased with decreasing dose rate or by giving the treatment in 2 fractions [K30, K31].

167. As with many other tissues, damage to the lens is reduced by protraction of irradiation. In experiments to test the time-dose relationships, mice were irradiated with 14 different schedules and followed for cataractous changes [S11]. The effects of number of fractions and overall treatment time were not separated and the slope of the "Strandqvist" isoeffect formula was calculated as 0.3. An analysis of earlier work [K10], also on mice, gave a similar figure. However, Merriam and Focht [M16] derived a factor of 0.17 from studies on rat and on man which represents a more pessimistic view of the sparing by fractionation.

168. It could be concluded that a minimum of 3–5 Gy are required to produce significant opacities in animals which are normally not prone to cataract development, as is the case for man. But in animals who are especially prone, very much lower doses increase the incidence. More dose is required when fractionated, but the dose sparing may be rather less than in other tissues.

L. HAEMATOPOIETIC TISSUES

169. Changes in all the elements of the haemopoietic tissues are observed after fairly low doses of radiation from the circulating blood cells, to bone marrow, spleen, thymus and lymph nodes (see [P10] and [M51] for reviews). These tissues have been extensively studied, partly because some elements are very radiosensitive and partly because relatively easy quantitative end-points are available.

170. Changes in peripheral blood counts have been well documented in both man and experimental animals (Figure VI). A differential count is considered to be a useful biological dosimeter in man but is too variable from animal to animal to be a good quantitative assay in rodents. In man, if the lymphocyte count falls below 1200 within 24–48 hours, the prognosis is serious and if it falls below 300, the patient is almost certain to die [D21, G30, A22].

171. Early experimental studies were mainly on organ weight loss and cellularity. After 4 Gy in mice there is a measurable weight loss in spleen, lymph nodes and thymus. The organs reach a minimum weight at 2–4 days, but are restored to normal at 2 weeks [B17]. In the bone marrow cell depletion is maximal at 3–4 days [B17] but later haemorrhage masks the hypocellularity

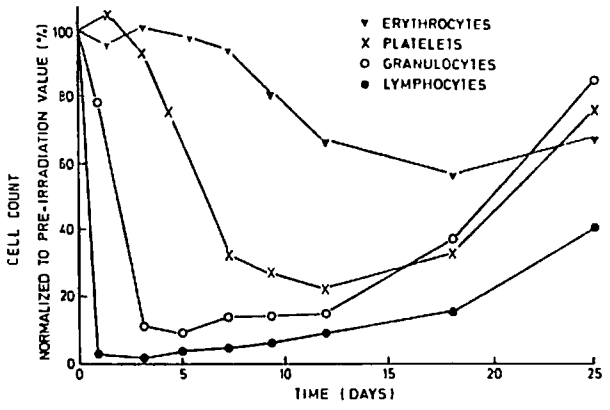

Figure VI. Peripheral blood counts of rats following 5 Gy whole-body radiation [D21]

[F19, N1]. Temporary changes in weight of these organs may be caused by very small doses, and as little as 0.4 Gy can be detected [K11, M17]. Changes in the bone marrow architecture (in excess of 20 Gy) cause permanent hypocellularity of the bone marrow, probably due to fibrosis [K12, K13, F19, S70].

172. Much effort has been directed towards the study of lethality from whole-body irradiation at 20–30 days caused by bone marrow depletion and resultant haemorrhage (from lack of platelets) and infection (from lack of lymphocytes and phagocytic cells). Table 5 shows some lethality results for a range of animal species. There appears to be a tendency towards lower LD_{50} values (higher radiosensitivity) in the larger species (Figure VII), but this may be partly a result of infestations with intestinal parasites [H6].

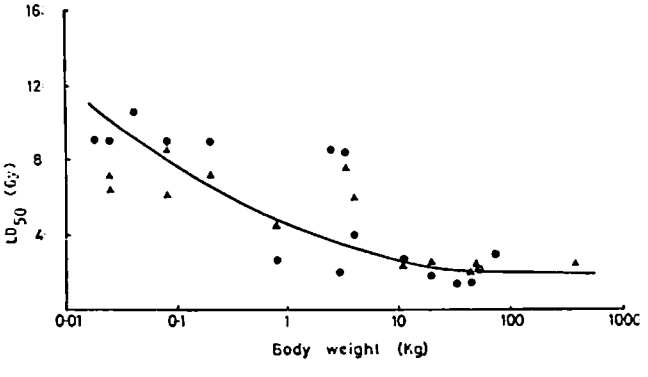

Figure VII. LD_{50} for bone marrow depletion as a function of animal weight [H6, B7]

173. If partial body irradiation is performed the LD_{50} increases. In rats the LD_{50} at 30 days was 11.5, 15.3 and 16 Gy for irradiation of the whole abdomen, front region and back region respectively [Z5]. LD_{50} was also shown to be related to the average area of individual endothelial cells from the aorta of different species [S37]. In mice it was 7.7, 14.7, 11.6 or 18.0 for irradiation of whole body, head, trunk or lower body, respectively [S71]. When mice were given 5 Gy of x rays either whole body or to the lower body, trunk or head only, the changes in leukocyte or platelet count were essentially similar. Loss of cells was greater, however, after whole-body than partial-body treatment [K47].

174. Among the more quantitative assays are those which test for the pluripotential stem cell, from which all blood cells are believed to derive. This cell is unidentifiable on morphological criteria, although the suggestion has been made that it resembles a small lymphocyte [Y2]. Survival of haemopoietic stem cells has been studied by a variety of tests. These include quantitative transplantation of bone marrow cells into lethally irradiated hosts with the subsequent assay of host survival [M18, S12], spleen colonies in the host for the estimation of colony-forming units (CFU) [T7, M19, B19], cell culture techniques [S35] or incorporation of ^{59}Fe to test for erythropoiesis [C14, H16]. Other tests include the response to exogenous erythroprotein in polycythaemic mice [J4], to endogenous erythroprotein in fasted and re-fed mice [P11], or scoring of granulocytes [H17]. Comparisons of functional assays of haemopoietic stem cells have been made [H54].

175. Belousova [B43] estimated the sensitivities of certain cells of the haemopoietic organs: 1–2 days after 4 Gy, depletion of lymphoid organs is at a maximum and 2 days after 7 Gy the same is true for bone marrow. All these studies indicate that the haemopoietic "stem cell" is a rather radiosensitive cell [S40, S41] with a D_o of 0.6–1.1 Gy and an extrapolation number of 1.2–2.7. A correction for various technical differences and for radiation quality brings most of the D_o estimates into the narrow range of 0.65–0.7 Gy [L18]. The bone marrow stem cell is therefore more sensitive than most other cell types.

176. If irradiation is not administered to the whole body, stem cells can migrate from unirradiated bone marrow and repopulate the irradiated areas [H63, R11, N2, S42, P27].

177. Fractionation studies have shown that the bone marrow has a rather small capacity to repair sublethal damage, consistent with the low values of extrapolation number (1.2–2.7) [T1]. Mole [M20] has even demonstrated an increased sensitivity with fractionation, which he attributes to recruitment of resting cells into the cell cycle.

178. When continuous irradiation is used there appears to be no sparing effect over the first 10–20 days [J5] with 2.4 Gy given as a single dose in 5 minutes or at 0.01 Gy/hour over 10 days, giving a similar reduction of CFU's to 40% of normal. However, a steady state of repopulation is then established, so that 38 Gy given over 160 days also depletes the CFU's to about 40% of normal. Fedotova [F42] observed mice given 0.025 Gy/hour showing a progressive reduction in stem cells up to 80 Gy. A similar but smaller reduction was found with 0.054 Gy/hour up to 60 Gy [M47, M48]. These experiments show that dose rate is of greater importance than the total dose, and this is due to compensatory proliferation.

179. Studies by Porteous and Lajtha [P12] at approximately 0.5 Gy/day showed a fall in CFU's to 10% by 20 days, with a rise by day 30 in spite of continued irradiation. The work of Lamerton and his colleagues [B1, L5] established that the erythropoietic system in rodents could tolerate continuous irradiation at 0.8–1 Gy/day. Other blood components are rather more sensitive but could tolerate 0.5 Gy/day [B1, L5, M49].

180. Differences in bone marrow response have been noted with different species. It was shown by Belousova that for mice irradiated at 0.5 Gy/day, after two weeks the level of bone marrow lymphoid cells sharply decreased. This was also the case for spleen and thymus. Granulocytes also decreased and after a total

of 40 Gy the number of erythroid cells also decreased. In rabbits and guinea pigs the same dose rate led to the development of a subacute form of radiation sickness with death occurring due to bone marrow failure at 45 Gy with rabbits and 20 Gy with guinea pigs [B43].

181. Very few late effects have been observed, apart from those reported after doses of 20–100 Gy given locally to a single limb [K12, K13] which are the result of local fibrosis. Late damage has been observed in the erythroid precursors in the rat bone marrow after 1.7 Gy, with an exponential return to normal, the half-life being 30 weeks [G11]. After doses higher than 40 Gy marrow undergoes delayed or lasting aplasia due to damage to the stroma. Recovery can only be effected by transplantation of healthy marrow into the marrow cavity [W44].

182. In summary, cells of the haemopoietic tissues, and in particular lymphocytes and bone marrow stem cells, appear to be very radiosensitive but they have a remarkable regenerative capacity and can show complete recovery, if the animal survives the initial cellular depopulation.

M. IMMUNE SYSTEM

183. An important effect of irradiation is impairment of the immune response. This may result in a decreased resistance to pathogens, development of auto-immune disorders and possibly increased probability of neoplasia. It is beyond the scope of this Annex to discuss changes in the immune response in detail. The topic was reviewed in the UNSCEAR 1972 report [U5], in which it was concluded that decreased resistance to immune challenge resulted from irradiation with more than approximately 2 Gy of photon irradiation, although short-term changes can be detected at lower doses. The radiosensitivity of immunologically competent cells have been reviewed by Anderson and Warner [A25] who concentrated on early changes, and more recently by Doria [D41] who points out the lack of knowledge to account satisfactorily for the changes in the immune system following irradiation. This is particularly true since the introduction of the network theory of the immune system [J25, U6]. Bazin [B80] has recently reviewed the effects of irradiation on subsequent infection, with emphasis on the gastrointestinal tract. A range of late changes in the immune system have been studied by Sado et al. [S47] on mice. They were unable to detect any significant effects up to 4.5 Gy x rays although all the immunological indices used showed changes at early times. Sado [S48] noted the paucity of studies of late effects, but also pointed out that in general few late changes have been observed in animals or humans surviving whole-body irradiation.

N. SUMMARY

184. The time at which radiation damage is maximal depends on the normal and post-irradiation proliferation kinetics of each tissue. Rapidly proliferating tissues such as the bone marrow exhibit the damage soon after treatment. Slowly proliferating tissues such as the connective and the vascular do not show serious changes until months or years after irradiation. With acute single exposures the bone marrow is a most critical tissue. For animals of similar size to man the LD_{50} is 2–3 Gy and there is no evidence that the human response would be very different. However, the bone marrow, as many other tissues, is capable of considerable repopulation between dose fractions or during low dose rate continuous irradiation. Observations on mice indicate that daily treatment with 5% of the LD_{50} dose can be tolerated for extended periods. Extrapolating to large animals, this would be 0.1 Gy/day. At this continuous dose level, the tissue likely to be the most affected is the testis or, in young females, the ovary. Continuous exposure to 0.006 Gy/day sterilized male dogs but 0.0012 Gy/day had no effect. Mouse testis is rather more resistant, 0.02 Gy/day being the lowest figure reported to cause permanent sterility. The pituitary is sensitive in the very young, 1 Gy causing weight loss in the squirrel. Doses of 2–5 Gy cause lens opacities if given in a single treatment, but more than 10 Gy are needed if the treatment is fractionated. Other tissues are more resistant and have significant repair capabilities so that they are able to tolerate still larger doses if fractionated or given continuously. Table 6 summarizes approximate values for threshold doses in experimental animals.

III. EFFECTS OF IONIZING RADIATION ON MAN

185. The effects of ionizing radiation on human tissues were first noticed by the early radiation pioneers. The first publication was in the "German Medical Weekly" in 1896 by a victim, an engineer, less than 6 months after Roentgen's discovery. A year or two later the dose required to produce dermatitis was being used to check the output of x-ray tubes. The early workers were unaware of the need for radiation protection and at least 336 fatalities were attributed to radiation exposure. Of these, 251 died as a result of skin cancer and 56 of blood dyscrasias, e.g., anaemia and leukaemia [H18]. When the importance of radiation protection was realized, the incidence of deliberate whole body exposure in humans fell sharply and most of the later information has been obtained from atomic bomb survivors, accidents with portable radiation sources, accidents in atomic energy establishments and patients treated with total-body irradiation. In some of these groups, treatments with pharmacological agents could alter the picture of radiation-induced changes.

186. Three different phases of injury are distinguishable in man as in other mammals. These are both dose and time related. After very high doses, damage to the central nervous system occurs which can be lethal within two days. After lower whole-body doses, death from gastrointestinal damage can occur between 1–2 weeks. Still lower doses may allow recovery from the gastrointestinal damage but death may result later from damage to various tissues, mainly to the bone marrow. A summary of the symptoms and injuries from Hiroshima and Nagasaki casualties is given in Table 7 [O16].

187. For whole-body exposure the threshold dose appears to be between 1 and 2 Gy for clinical symptoms. The LD_{50} is uncertain but probably within the range of 3 to 5 Gy [L17, B18]. If the exposure is only to a part of the body, the reactions may be much reduced. This is due to the regenerative capacity of stem cells from shielded areas (bone marrow) such that the level of dysfunction before repopulation is not sufficiently severe to cause death (e.g., by dehydration in the gastrointestinal syndrome). Partial-body exposure has been considered by Gregoriev and others who, on a

model basis, demonstrated that the dose may be increased as much as a factor of 5 to produce a given effect, depending on the dose distribution [G31, D37, D38].

188. Since the present document deals with localized exposure, it will consider only the results derived from radiotherapy. In radiotherapy of cancer normal tissues are unavoidably included in the treatment volume and it is the damaging effects on these tissues that limits the dose which can be tolerated. For each cancer site, a tolerance dose for a limited volume of normal tissue has been established empirically from years of practice. This dose is usually defined as the dose that will produce a small but detectable incidence of serious complications resulting from the radiation effect on the normal tissue. Each clinician has a slightly different level of morbidity that he considers acceptable, but often 5% of serious complications is considered reasonable. It should be emphasized that this tolerance dose is not the same as a threshold dose because it is concerned with serious long-term complications which may significantly alter the quality or duration of the patient's life. Transient early damage, or detectable but non-life-threatening damage are not normally considered to be dose limiting in radiotherapy. Threshold doses for a range of tissues are likely to be in the same hierarchy of sensitivity as serious complications although at lower dose levels.

189. Defining a threshold dose depends on the method of assaying the damage. Some tissues can withstand a high degree of cell depletion with no gross change; an example is the skin, for which the dose to produce signs of desquamation is equivalent to cell survival of about 0.1% on the basis of cell survival estimates (see paragraph 69). With a surviving fraction between 10% and 1% there is no gross visible damage, although changes are detectable histologically. The severity of damage that can be tolerated in a tissue or organ depends on a number of factors including: the level of cell depletion that causes tissue malfunctions; the time of expression of damage; the repair and recovery capacity of the tissue; the volume included in the field; the total dose administered; and the overall time and number of fractions into which the dose is subdivided.

190. Much clinical practice involves daily fractionation on 5 days per week with approximately 2 Gy per day, i.e., 10 Gy per week. In the following paragraphs this will be referred to as conventional fractionation treatment. In some cases the dose given will be converted to the Nominal Standard Dose (ret) according to the Ellis formula (see section I.F).

191. Nowadays, most treatments are given with supervoltage radiation, e.g., from a 4–20 MeV linear accelerator or from ^{60}Co source, both of which deposit their maximum dose several millimetres below the body surface, resulting in sparing of the skin. Treatments prior to 1950 utilized lower energy machines which deposited the maximum dose at the skin surface. Treatment planning has also progressed so that each daily fraction may be administered as 3–6 subfractions through different portals in order to maximize dose in the tumour and spread dose to the normal tissues.

192. In 1906, Bergonié and Tribondeau proposed their "law" relating radiosensitivity to the proliferation activity. Tissues with a high mitotic index showed a high "radiosensitivity" (i.e., severe early damage) whereas those with a low mitotic index showed a low "radiosensitivity" (i.e., little early damage or delayed expression of damage). Since radiation damage is mainly expressed at mitosis this concept of tissue sensitivity relates more to time of expression than to the dose that will cause a particular level of cell survival or a particular level of tissue dysfunction (see paragraph 59).

193. Rubin and Casarett [R1] have assessed their own clinical experiences and performed a major review of the literature. Their findings are summarized in Table 8 and Figure VIII, where the injury scored at 5 years and the threshold doses suggested as likely to give 1–5% or 25–50% complications is shown as an example. The amount of tissue included in the beam is also given. These data are also plotted in Figure VIII in order of increasing radiation resistance both in terms of actual dose administered, normally as 10 Gy per week at 2 Gy per day, and in terms of the Nominal Standard Dose in ret [E4].

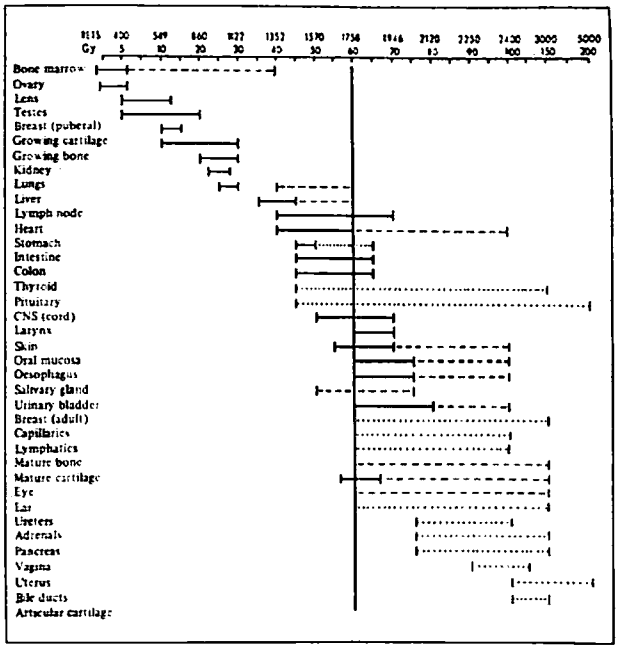

Figure VIII. Acceptable doses in radiotherapy. Both the total doses (conventional radiotherapy treatment) and doses in ret are given. The definition of "acceptable" is the personal view of the authors [R1]

194. Table 8 shows that there is a wide variation of acceptable doses from one tissue to another, the acceptable dose in radiotherapy being that for which side effects are reversible. This may result from a difference in inherent cellular radiosensitivity or may depend on critical levels of survival for limited subpopulations of cells. Some tissues react because of a primary response of the parenchymal cells, e.g., testis and ovary. Other tissues react by a delayed depletion of parenchymal cells, which may either be a late primary response to radiation or a secondary response to vascular damage resulting in a loss of nutrient supply. A third form of tissue failure results from radiation-induced fibrosis. The threshold doses are below the 1–5% acceptable doses. Both Figure VIII and Table 8 are summaries of the personal views of the authors [R1] and the doses quoted would vary somewhat if compiled by other radiotherapists, although for the purposes of this Annex the differences may not be considered large. Specific normal tissues are discussed in more detail below.

A. SKIN AND MUCOSA

195. Because the skin and the buccal mucosa are so readily accessible and because the early radiation sources delivered their maximum dose at the surface, these tissues have been more widely studied than any others in the body. Most of the clinical concepts of fractionation were originally based on clinical observations of skin reactions.

196. The threshold dose for the production of skin erythema is 6–8 Gy in a single treatment for fields greater than about 5 cm^2. This dose may cause a transient reaction a day or two after exposure with blood vessel congestion and subcutaneous oedema but without gross effect on the epidermis. The initial erythema may increase during the first week, but will fade after about 10 days. It is followed by the main erythematous reaction which reaches a maximum after about 2 weeks and lasts from 20 to 30 days. This reaction does involve the dermis and may, for larger doses, be followed by dry or moist desquamation or even necrosis. There may be several waves of reaction. With fractionated radiation the tolerance dose for the skin is considered to be 6–7 Gy/30F/6w (per 30 fractions given in 6 weeks).

197. The early phase of desquamation has usually healed by the end of a 6-week course of therapy by compensatory regeneration of the basal layer which is initiated when the skin function begins to fail. This compensation can even produce new cells more rapidly than they are being killed so that healing may occur before radiotherapy treatment is ended.

198. Late injury to the skin appears to result from damage to the tissue elements in the dermis, rather than the epidermis. It occurs at months to years after irradiation and can take several forms. Deep fibrosis and contraction of irradiated areas occurs with an increased deposition of collagen in a thick mat-like network. Progressive occlusion of blood vessels is seen, which may gradually lead to an undernourished atrophic epithelium with a greatly increased susceptibility to any external trauma. Cold, heat, friction or bruising can then lead to reversible or irreversible breakdown of tissue, in the worst instances resulting in ulceration and necrosis. Other late changes are depigmentation, depilation and telangiectasia. The term poikilodermia is also used to describe atrophy, telangiectasia and dislocation of pigment.

199. The degree of skin reaction and the tolerance dose are known to be influenced by a number of biological variables, including the age of the patient, the hormonal status, and the anatomical location [R1]. These factors may produce their effects as a result of differences in the thickness of the epidermis in different regions, the degree of friction to which it is normally exposed and thence the underlying cell proliferation kinetics. Anoxia of the skin is known to give radioprotection, whether it results from local pressure or from anaemia [R1]. Skin which has been recently grafted is more radiosensitive than normal but a successful graft gradually returns towards the sensitivity of undisturbed skin [R1].

200. The tolerance dose differs for different skin appendages, as was recognized by Borek [B20]. Detectable changes can be seen after 3–5 Gy to hair follicles when temporary depilation results and histological changes have been reported after 1–2 Gy [R1]. However, these are temporary or reversible changes of no serious consequence. It is common practice in radiotherapy for skin to receive 50–60 Gy in 30F over 6 weeks without severe consequences [F54]. However, in a study of functional changes in the skin of occupationally exposed workers, using capillary microscopic techniques, Leny et al. [L33] showed microscopic alterations of the capillaries without changes in the structure of the dermis after 10–30 Gy exposure during 8–25 years. Small fields have also been irradiated in experimental clinical studies of human skin prior to using neutrons in radiotherapy [M4, K29]. Dose-response curves for human skin are shown in Figure IX. The threshold single dose for x rays is about 7 Gy [J17].

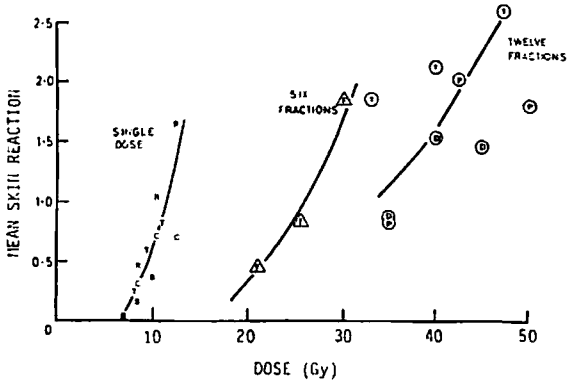

Figure IX. Dose-effect curves for human skin irradiated with x rays, obtained from average reaction between 5 and 80 days after treatment. A score of 1 represents a faint erythema. Each symbol represents a patient [F14]

201. The volume of tissue irradiated is critical, the damage being greater for greater areas or volumes. Cohen [C2] has reviewed this subject and suggests that the isoeffect dose is proportional to L^{-3}, where L is the average diameter of the irradiated field. Penetration of the radiation is also of great importance. For β rays, which do not penetrate through all the layers of the skin, less injury is produced with better recovery than for more penetrating radiation [O13]. This result has been confirmed by analysis of data resulting from occupational exposure [B44].

202. The relationships between total dose, number of fractions and total treatment time were considered in section I.F. These were mainly derived from data on skin and subcutaneous connective tissues, but the extrapolation to very large numbers of fractions over very long times is still the subject of some argument.

B. GASTROINTESTINAL TRACT

203. Damage to the intestinal tract leads to many acute and chronic symptoms ranging from diarrhoea and dyspepsia to ulcer, strictures and obstructions which can be life-threatening. There are, however, fairly wide variations in the radiosensitivity of the different parts of the gastrointestinal tract, the stomach, small intestine and colon being the most sensitive [F54].

204. The stomach will tolerate doses up to 40 Gy with conventional radiotherapy fractionation. Beyond this, the risk of ulceration or perforation increases rapidly with dose. This was discovered in a tragic series of treatments at the Walter Reed Hospital 40 years ago [A8, H19] where about one-quarter of 61 patients receiving 45–54 Gy developed ulcers, some with perforation.

205. The small intestine is also a radiosensitive organ commonly showing acute mucosal reactions after 30 Gy given in 3–4 weeks. These reactions are however reversible even after doses of 40 Gy. Higher doses than this will lead to chronic damage in the form of obstructions, constrictions and adhesions, unless a rest period is introduced during therapy to allow repopulation to take place. The incidence of intestinal complications is much higher after surgery if adhesions are already present, because these prevent the mobility of the intestine, which usually spares any region from accumulating the total dose. Gastrointestinal complications are much reduced by protracting the irradiation procedure [N13].

206. The colon has a similar or slightly lower radiosensitivity but because it is not mobile it is more likely to be exposed to the full dose. Early damage resulting in diarrhoea occurs at 1–2 months but this is not a good predictor of late damage due to fibrosis and vascular injury [R12].

207. The rectum is considerably more resistant than other portions of the gastrointestinal tract, although epithelial denudation causes transient symptoms after 30–40 Gy of fractionated treatments [R12]. The oesophagus is also a more radioresistant portion of the gastrointestinal tract and can withstand doses of 60 Gy. After higher doses fibrosis causes stricture which can lead to painful or even disastrous obstructions. After much lower doses of 20–30 Gy fractionated over 2–3 weeks, epithelial denudation leads to clinical symptoms of burning and dysphagia, but these are transient and recovery is rapid.

C. BONE AND CARTILAGE

208. Growing bone and cartilage are known to be much more sensitive to radiation than are these same tissues in the adult. A considerable body of data exists from children treated for abdominal tumours or for tumours of the limbs. In both situations growing cartilage and bones exposed to radiation show a dose-dependent retardation or even cessation of growth. Such growth disturbances were recognized in the 1930s [D22, S13] and 1940s [S14]. There are many descriptions of deformity of the spine caused by unequal irradiation of the vertebrae so that one side of each vertebral body grows more than the other, resulting in scoliosis. Varying degrees of radiologic change are observed in the vertebrae, depending upon the dose and the age of the child [N3]. Ten Gy (given in 6 daily doses/week) produced mild radiographic changes in a young patient, whilst 12–20 Gy produced moderate to severe changes in most of the children aged 0–6 years at irradiation. The younger the child, the more severe the degree of growth deformity. When fractionation results [T8] are transformed to NSD value it is found that the approximate threshold for producing detectable changes varies with age, being about 300 ret between 0 and 1 year, 800 ret at 1–2 years, and 1000 ret beyond 2 years.

209. Similar conclusions were drawn from 44 children treated with megavoltage radiation, using conventional fractionation, compared with 15 000 normal unirradiated children [P13]. Changes in both the sitting and standing heights were observed. In children treated with less than 25 Gy, there were differences, but very slight. Those treated with more than 35 Gy showed greater differences. The maximum depression of growth was seen in children whose bones were in active growth at the time of irradiation, i.e., up to the age of 6 years and during puberty (see also [G33, R36]).

210. Mature cartilage is known to be much more resistant to radiation damage and the doses to produce necrosis are high. For example, it has been noted that the elastic cartilage of the pinna will tolerate 60–65 Gy in 6–8 weeks of daily fractions. The tolerance levels for hyaline cartilage are similar. Laryngeal cartilage will tolerate 65–70 Gy over 2–8 weeks or more than 70 Gy in a more prolonged pattern of dosage over 10–12 weeks [B21]. With shorter overall treatment times there can be a marked increase in the incidence of necrosis as reported by Fletcher and Klein [F20] when they increased their dose from 48.5 to 55 Gy given in 20 fractions over 4 weeks.

211. In bone, the dose to produce necrosis is difficult to determine because the absorbed dose is dependent on the mineral content and changes markedly with the energy of the incident radiation [S15]. For 50 keV photons the local absorption in bone is 5 times that in water, at 200–5000 keV it is similar to that in water, and at higher energy it again becomes greater than water. Thus the doses quoted to produce osteonecrosis in the old literature may be in error by a significant amount, depending on the circumstances [P14]. At the higher energies used in modern radiotherapy bone necrosis is rare.

212. In general adult bone is considered to be fairly radioresistant, but it becomes susceptible to trauma and infection after irradiation and has a poor regenerative capacity. Osteonecrosis of the mandible occurs after irradiation of buccal tumours, but this is almost always associated with a break in the overlying mucosa, allowing infection to commence. Radionecrosis may occur between 2 months and 15 years after therapy [S16]: it is related to oral hygiene and precipitating trauma to a greater extent than to dose or fractionation scheme. A dose of 65 Gy given in 6–8 weeks does not normally lead to osteonecrosis, but may give a greater predisposition to fracture. This is site-dependent and is more common in the weight-bearing head of the femur than, for example, in the ribs [P14]. Another effect of radiation on bone is to delay the healing process of callus formation after fracture, and this is worse in adults [R13].

D. HEART

213. For many years the heart has been considered to be a radiation-resistant organ and only isolated examples of radiation-induced carditis had appeared in the literature. This was in part due to the limitation on thoracic irradiation resulting from the much greater sensitivity of the lungs. However, by the mid-1960s a large number of patients had survived more than 1 year after mantle irradiation for Hodgkin's disease and 25 cases of radiation-induced heart diseases were noted [S17]. This finding was subsequently confirmed by a more comprehensive study [S18, P19]. The changes observed in the heart all involve fibrosis, and may occur to varying degrees. Pericardial effusions may lead to clinical symptoms. After higher doses constrictive disease is seen, which may necessitate surgery, or may result in death. In general the pericardium is a more sensitive tissue than the myocardium, although transient early effects on the heart muscle have been noted. The dose-response curve is very steep, with a

threshold of 1350 ret. The dose to produce 5% mild complications is 1500 ret, and for 50% is 1650 ret. Stewart and Fajardo [S18] stress the high incidence of complications and severe damage after retreatment of patients suffering from Hodgkin's disease to a total dose in excess of 60 Gy.

214. If a smaller volume of heart is irradiated the same type of changes are observed, with diffuse fibrosis in the treated volume, but the tolerance dose for 5% mild complications is increased to 1850 ret [S18]. Other changes have been observed, e.g., in the electrophysiological patterns [T9] as reviewed by Berdjis [B22], but most of these have not been as carefully quantified in relation to dose as in the studies by Stewart and colleagues [S18].

E. LUNG

215. The lung is the most sensitive organ in the thorax. Although there is a large functional reserve in the pulmonary system, there is little capacity for regeneration and reformation of the elaborate structure after widespread cell depletion. A large literature exists on radiation responses in human lungs [V4]. In general, radiotherapists try to avoid including large lung volumes in a radiation field because the threshold dose for tolerance is low. Phillips and Margolis [P2] have estimated tolerance to be 900 ret for 5% complications and 1040 ret for 50% complication. A dose of 700 ret to the whole lung caused no measurable changes [C30]. The dose-response curve is however very steep [P2]. With total-body irradiation for treatment of leukaemia or aplastic anaemia, where reconstitution of bone marrow is performed, lung becomes the critical organ [T26]. Normally, single whole-body irradiation is given, lasting several hours, for which the accepted tolerance is in the region of 8 Gy. With non-uniform irradiation such as with ^{131}I for treatment of thyroid metastases in the lung, fibrosis has not been observed, in contrast with the effects of large fields of external irradiation.

216. Radiation pneumonitis may occur soon after irradiation, followed weeks to months later by radiation fibrosis. The reaction is complex, involving cell death, desquamation of epithelial cells, exudation into the alveolar space, thickening of the alveolar walls and finally collagenous changes, possibly with calcification or ossification [V4]. After irradiation of the chest wall in patients with cancer of the breast, pleural effusion leading to fibrosis has been reported [R1].

217. The main change discernible in irradiated patients is radiological evidence of fibrosis [T10, W20, D23]. This is evident after irradiation of large or small fields and is apparent even in the absence of any measurable functional impairment. Fibrosis is thought to be the end-result of a failed attempt to regenerate the complex units of normal alveoli. High doses to small fields may also lead to lung fibrosis [D39]. Functional changes that have been observed include reduced vital capacity and a reduced maximum exhalation volume. The volume irradiated is extremely important. Localized severe fibrosis can be well tolerated provided there is a considerable volume of unirradiated tissue.

218. There is much debate about the primary cause of radiation pneumonitis. Some authors postulate that the primary target is the endothelial cell and that this leads on to the occlusion of vessels, oedema and fibrosis [P2, P6]. Others favour the damage to the surfactant-producing alveolar epithelial cell, depletion of which would result in increased surface tension, fluid loss across the alveolar wall, haemorrhage and eventually fibrosis [V4].

F. LIVER

219. The liver, which was once considered to be a radioresistant organ is now known to tolerate doses of 40–50 Gy in 30 days to only part of the organ [K14]. The threshold for measurable effects to the whole liver seems to be 30 Gy conventionally fractionated [K14, I2, J6, K15]. The changes observed are both dose and time related [I2].

220. In the early literature, very few irradiated specimens had been studied. Lacassagne [L12] quotes only 30 livers at autopsy and about 12 studied by biopsy in which changes after external irradiation had been looked for. Most of the specimens were obtained within weeks to months after irradiation and showed lesions characteristic of non-specific venous occlusive changes. Endothelial cell sloughing, fibrosis and sclerosis are usually seen later. The most critical element in the liver appears to be the small central vein in each lobule. After irradiation of the whole abdomen for cancer of the ovary when the "strip technique" was used, liver necrosis was reported, increasing with increasing dose per fraction [D51].

G. URINARY SYSTEM

221. The urinary system, comprising kidney, ureter, bladder and urethra, shows a wide range of radiosensitivities. The kidney is the most sensitive element, the bladder has an intermediate sensitivity and the ureters are more resistant, although they seldom have their full length irradiated. For irradiation of abdominal tumours, kidney change is frequently a limiting factor and the kidneys are often shielded or the irradiation field shaped to avoid their exposure if possible. The kidney is a complex organ and a variety of functional disturbances are observed, including acute or chronic nephritis, hypertension and proteinuria [M21]. Stenosis of the ureters is a frequent complication of irradiation of the pelvis [F54].

222. Acute nephritis occurs within 6–12 months and can be lethal, or may lead to chronic nephritis. Some patients develop chronic nephritis without an early acute phase. The pathology of early nephritis is complex with glomerular, tubular and capsular changes. Chronic nephritis is characterized by sclerosis and fibrosis. Hypertension usually accompanies these changes. It appears earlier after higher doses, and depends upon the proportion of kidney that has been irradiated.

223. Less severe damage can be detected as changes in renal function. A fractionated dose of 20–24 Gy in 3–4 weeks usually produces between 10% and 60% reduction in renal plasma flow, with a reduction in glomerular filtration rate. The tolerance dose for the kidney is therefore normally set at about 23 Gy/5 weeks. Higher doses may be given if radioprotection is achieved by vasoconstriction with epinephrine. As with animals, renal injury is more severe in the young human. Urinary examination of children who were in utero during the atomic explosions at Hiroshima and

Nagasaki revealed proteinurea which was not found in adults [F43].

224. The bladder will tolerate 55–60 Gy given in 20 fractions over 4 weeks [M22]. It is usually exposed to a high dose when cervical cancer is treated with combined external beam and radium implants. The damage observed ranges from erythema to fibrosis, ulceration and contraction. A minor symptom is the frequency of urination but severe oedema of the ureteral orifices can lead to back-pressure on the kidneys resulting in hydronephrosis which may be fatal. Little information is available on the effects of radiation on the normal prostate. Late effects may include obstruction, incontinence, and, most frequently, impotence.

H. CENTRAL NERVOUS SYSTEM

225. The central nervous system was in early times regarded as a radio-resistant tissue. It has, however, negligible capacity for repopulation and there is now much evidence from physiological experiments and radiotherapy experience for it no longer to be regarded as resistant [L14, G24, G25, G26, B42, G44]. The lesions generally observed are consistent with the primary damage being to the vascular system and death or paralysis may result at times varying between 3 months and 9 years, although mostly between 1 and 3 years. Occasionally, an acute demyelinating process has been observed [R14, L19] after moderately high doses (in excess of approximately 60 Gy given in fractionated treatments), which may be transient or lethal. For a recent review see [G44].

226. It is believed that relatively few large fractions, or just excessively large total doses are the cause of most of the 57 cases of radiation-induced brain necroses that have been found in a review of the world literature [K16]. In this review only 1 case of dementia was reported [W21] although this symptom has been seen with higher frequency after fast neutron irradiations [C21]. This effect of size and number of fractions is observed also in the spinal cord and has been confirmed by animal studies (see paragraph 134) [G6, G7, V8, W6].

227. The tolerance dose for the whole brain is thought to be about 55 Gy fractionated over 5–6 weeks. An extra 10 Gy is sometimes given to a small area containing a tumour. For small parts of the brain 65 Gy fractionated over 6.5 weeks is considered safe. If these doses are exceeded, brain necrosis may result [K16, G27]. The threshold for morphological changes is approximately 40 Gy when fractionated [D40]. A recent review of the subject has been made by Franke and Lierse [F45].

228. For the spinal cord the tolerance doses are lower than for brain. The estimates of a safe dose for cervical, thoracic and lumbar cord vary from 35 Gy in 4 weeks [P16] to 50 Gy in 5 weeks [K16, P17]. The dorsal cord appears to tolerate a dose of 45 Gy in 4.5 weeks [K16]. Transient radiation myelopathy occurring 3–4 months after therapeutic irradiation (in the range of 26 Gy over 29 days to 56 Gy over 70 days) has been reported. This is described as similar to the perception of an electric shock when the spine is flexed [J23]. It is important that injury to the cord is inversely related to the length of cord irradiated [P18].

229. Months or years after irradiation (local or whole-body), diffuse demyelination and encephalitis may result [G26, B42, G25, G28]. After irradiation of the head with single doses mostly between 3 and 12 Gy (but up to a maximum of 30 Gy) acute radiation was followed between 3 and 10 years later with small degrees of demyelination and changes in brain circulation [G25, G27, G30]. In one individual who accidentally received 30 Gy to the head, brain necrosis had developed by 3 years [G30]. Thirty to 50 Gy given in fractionated radiotherapy at 2 Gy per fraction or single treatments between 3 and 10 Gy caused profound functional disturbances of the CNS, resulting in, for example, impairment of memory and weakness [G30, G28]. Functional changes after radiotherapy to the cranial axis region in children with medulloblastoma have been reported. Survivors for more than five years developed changes in character, impairment of memory and learning ability and even dementia and idiocy resulted if the age at exposure was less than 1.5 years. Severity of impairment was related to age at irradiation. Children with acute lymphatic leukaemia irradiated with 24 Gy over two weeks to the CNS developed loss of memory [B83].

I. GONADS

230. The ovary is a highly radiosensitive organ. It contains a limited number of germ cells which cannot be replaced if they are depleted. A loss of all the ova (approximately 400 000 in an adult human) results in total sterility. Table 9 shows some of the published observations on doses causing sterilization in women. Single doses of 1.7–6.4 Gy have been shown to cause temporary sterility, with higher doses required to produce the same effect when fractionated. Permanent sterility results from 3.2–10 Gy in a single dose, or higher fractionated doses. Doses in the range of 5.6 Gy almost invariably produce permanent sterility. Doll and Smith [D20] reviewed over 2000 women treated for menorrhagia by irradiation. A value of about 6 Gy given in 2–4 fractions was referred as the dose to ablate the human primordial oocyte population.

231. The radiosensitivity of the ovary depends on the degree of maturity [M24] being more resistant in young women, although the differences with age are hard to estimate [A24]. This is unlike other species of animal. Also, in women, unlike in rodents, the ova seem more resistant than the bone marrow.

232. Very small doses of radiation were used in the 1920s to 1940s to treat infertility. A treatment of three times 0.5–0.75 Gy in 3 weeks to the ovary was reported to increase the fertility of many women treated for amenorrhoea, resulting in normal pregnancies, normal children and normal grandchildren [K17]. There seems to be little or no evidence of an increase in malformed offspring resulting from conception after irradiation of the ovary or testis [L16].

233. The testis is also a sensitive organ, as indicated in Table 10. Doses as low as 0.1 to 0.15 Gy have been recorded as causing temporary sterility, although > 2 Gy and possibly about 6 Gy are needed to produce permanent aspermia. Type B spermatogonia seem to be exceptionally sensitive, with D_0 being about 0.2 Gy. The seminiferous epithelium in man requires many years before recovery of the spermatogonial series may be completed [L16]. Japanese fishermen exposed to fallout received doses of gamma rays estimated at about 1.4 to

6 Gy over 14 days, corresponding to approximately 0.7–3 Gy given as single doses. Their sperm counts were severely depressed, but began to increase by 2 years after exposure and most of these men produced healthy children [K51].

234. The testis is unusual in that fractionated treatment may be more effective than single doses, e.g., 20 doses of 0.25 Gy each cause a more rapid depletion and a slower recovery than after a single dose of 5 Gy [L16, H21]. This is attributed to the stimulation of relatively resistant type A spermatogonia into the much more sensitive type B compartment.

J. THE EYE

235. The eye was recognized as being vulnerable almost as soon as x rays were produced. It was also soon realized that the different components of the eye had different sensitivities, and that the lens was especially sensitive when uniformly irradiated. However, the threshold is greatly increased by non-uniform irradiation [B81]. Although epithelial tissues around the eye seem to have a sensitivity similar to that of skin, the human lens responds to doses of ~ 2 Gy in a single treatment, or ~ 4 Gy when fractionated, resulting in the formation of cataract [M25]. Table 11 indicates the sensitivity of different parts of the human eye.

236. The extent of cataract formation, as well as the incidence, is dose dependent. Higher doses yield more progressive cataracts with greater loss of vision. The latent period varies from 0.5 to 35 years, with an average of 2–3 years, although this latency is also dose dependent [F18]. Minimum stationary opacities have been observed after single doses of 1–2 Gy, but with 5 Gy more serious progressive cataracts occur. A single dose of 7.5 Gy causes some degree of cataract formation, with a probability of occurrence of 100%. The lens is spared by fractionation with the slope of Strandqvist curve perhaps slightly less than that for skin. Ten Gy over 3–12 weeks was shown to give 75% incidence of cataract and 14 Gy over the same period leads to 100% incidence [H25].

237. Occupational exposure during 10 or 20 years has also been shown to affect the eye. At between 0.5 and 2 Gy the optical density and staining properties of the lens were increased. For doses between 1.5 and 4 Gy the frequency of senile cataract was significantly increased together with changes in the vascular system [L28, L29]. With mixed gamma and neutron irradiation, doses of 0.7–1 Gy produced changes [L29]. Recent reviews [C23, B53, B35] suggest that the threshold for cataract for occupational exposure or lengthy fractionation is in the range of 6–14 Gy.

K. HAEMATOPOIETIC SYSTEM

238. The haematopoietic system is one of the more sensitive tissues in the body. Responses can be seen after 0.5–1 Gy of radiation, whether it is given as a single exposure [B7] or as a series of small fractions [T11]. The bone marrow is the source for most circulating cells, the lymphocytes, granulocytes, erythrocytes and platelets. The response of the peripheral elements depends upon their normal turnover time, except that the lymphocytes respond very rapidly. These cells are unusual in that they are generally believed to be differentiated end-cells yet are extremely radiosensitive, with a D_0 of 0.2–0.3 Gy [T11] and undergo interphase rather than mitotic death. There are also thought to be subpopulations of lymphocytes with different sensitivities [E20, S75]. A depletion of the lymphocytes is seen within hours after irradiation, whereas the fall in platelets and granulocytes is delayed for several days and the fall in erythrocytes occurs slowly, over weeks [B7]. The differential and total blood counts bear some relationship to dose received but the response of the lymphocytes is sufficiently dose dependent for it to be a useful dosimeter in some circumstances. The time at which the peripheral elements return to normal depends upon the level of dose and hence on depletion of the bone marrow. After higher doses, the rate of repopulation appears to be greater than after low doses which cause little depletion [B7].

239. Mitotic abnormalities are observed in the bone marrow cells from about a few hours to two weeks after irradiation [F21, P28] but no prolonged systematic study has been performed at much later times. In the bone marrow of Japanese fishermen exposed to radioactive fallout in 1954, chromosome aberrations of the stable type were found 15–25 years after exposure [K51].

240. If the depression in peripheral blood cells is too severe the patient may die from infection (due to loss of granulocytes) or haemorrhage (due to loss of platelets). The timing of death from the haemopoietic syndrome in man (at 3–6 weeks after exposure) coincides with the period of maximum depletion in these peripheral elements. In other species the maximum depletion and the "haemopoietic death" also coincide but usually occur at 10–30 days. The reason for this species difference in timing is not understood [B7]. The influence of radiation on the reticulo-endothelial phagocytes of the spleen and liver in maintaining the bloodstream free of bacteria is important, and the ability to resist infection may be reduced by doses smaller than those required to cause death [M26].

241. Long-term changes resulting from irradiation of bone marrow also occur. Evidence comes from three sources: local radiotherapy, systemic irradiation and atomic bomb survivors. Reduction in numbers of white cells was found up to 7 years after radiotherapy of mammary glands and adjacent tissues with doses of 50–150 Gy over 1–3 months [D39]. After localized irradiation at rather higher doses than can be tolerated by the whole body, long-term changes in the irradiated bone marrow have been observed, although the reserve capacity of the untreated bone marrow will maintain the peripheral blood count at a normal level. Local changes have been observed up to 3 years after fractionated treatments of 20–65 Gy delivered locally, and up to 18 months after 40–45 Gy to the sternum [S19]. Baisogolov and Pavlov [B50] investigated 45 cancer patients between 1 and 36 months after local radiotherapy. Persistence of bone marrow aplasia was dose-dependent with a threshold of 30 ± 5 Gy. Hirashima et al. [H68] showed that after local radiotherapy for uterine cancer to a total dose of 60 Gy in 1 month, the functional activity of T-lymphocytes was significantly impaired immediately and at one year after therapy, but had returned to normal by two years. In an analysis of nine patients who received non-uniform irradiation of bone marrow between 2 and 5 Gy, Sudovora et al. have shown that recovery is governed by the repopulation of individual areas,

indicating an absence of migration of human haematopoietic stem cells [S78]. In A-bomb survivors decreased white blood cell counts have been observed for up to 15 years, accompanied by changes in the bone marrow [W23]. Extra-corporeal irradiation of human blood for treatment of leukaemia has shown that red blood cells and platelets are very radiation resistant but lymphocytes are sensitive [C15].

242. Thus the effect of small doses of radiation to the haemopoietic tissues may produce a profound response, but unless the total bone marrow stem cells are depressed below a critical level, the numbers of peripheral blood cells will recover and the patient will survive. After acute, accidental exposure the LD_{50} for man is between 3 and 5 Gy [L17] but maintenance in sterile chambers, antibiotics and careful medical support, including transfusions and bone marrow transplants, have enabled accident victims to survive higher doses.

IV. EFFECTS OF RADIATION QUALITY

A. BIOPHYSICAL ASPECTS

243. Energy is deposited by radiation as discrete "events", with about 50–100 eV of energy absorbed per event [I10]. According to target theory only one or few such events are required to elicit a biological response, such as cell death. The quality of a radiation determines the biological response, the quality of two radiations being deemed the same if the biological effect per unit dose is the same. The quality of a radiation is thought to be primarily determined by the microscopic distribution of energy along the tracks of the particles. In the case of photons and neutrons these are secondary tracks, photons producing secondary electrons and neutrons secondary protons and other nuclei.

244. Specification of radiation quality is difficult. The most used parameter is Linear Energy Transfer (LET) where L_∞ = total stopping power of a particle in tissue. The width of the track core is often specified, e.g., L_{200} specifies energy transferred per unit length of track to electrons having initial energies of 200 eV or less. Electrons with greater range will be considered as producing separate tracks (δ rays) [I5].

245. The Relative Biological Effectiveness (RBE) is defined as the dose of a reference radiation (usually of low-LET x rays) divided by the dose of the radiation in question to produce a given level of damage. If the RBE is referred to ^{60}Co gamma rays or high-energy x rays, it is approximately 10–20% greater than if the reference radiation is 250-kVp x rays. However, this difference could be greater at very low doses [B82]. RBE is a relevant parameter only if the damage is qualitatively identical in the two cases. This is normally the case, but two examples of differences in response to photons and neutrons are the gut architecture [H29] and the disappearance of cells of the subependymal plate in the brain [C11].

246. It is known from experiments on cells, using the track segment technique, in which particles of a specific energy traverse a cell, that RBE increases with increasing LET to a maximum value and then decreases. For a neutron beam there is a spectrum of secondary charged particles and a mean LET may be calculated. This may be a "dose mean" or a "track length mean". However, for a number of reasons which have been discussed in detail by Bewley [B25] and Rossi [R17], LET, although a useful parameter for describing radiation quality, is by no means fully adequate [I5].

247. An alternative method of specifying radiation quality is based on the lineal energy, y, (the energy deposited in an event, divided by the mean chord length of the volume in which it occurs) and z (the energy deposited by one or more events, divided by the mass of the volume in which it occurs) as recommended by the ICRU [I3]. Spectra of y and z may be measured using small proportional counters filled with approximately tissue equivalent gas [R17] but as yet neither the experimental techniques nor biological knowledge are adequate to predict biological effects.

B. BASIC DIFFERENCES IN RESPONSE TO PHOTONS AND HIGH-LET IRRADIATIONS

1. Oxygen effect

248. With few exceptions throughout radiobiology, cells and tissues are more sensitive when irradiated in the presence of oxygen than in its absence. With increasing LET there is a constant decrease in the oxygen enhancement ratio (OER = ratio of doses with and without oxygen to produce a given level of damage) such that with mammalian cells the OER becomes 1 at a LET of about 180 keV/μm [B26]. Over a very wide range of neutron energies up to 50 MeV or probably greater, the OER is significantly reduced relative to photons, but to an approximately constant value, independent of energy, of about 1.5–1.8 [H22]. With lower energy neutrons (e.g., fission neutrons) the OER is rather less, between 1 and 1.5 [B27]. These values compare with 2.5–3.0 for photon irradiations. As a neutron beam penetrates into tissue, the OER is hardly altered [M27, B28, N5, B29].

2. Repair as a function of radiation quality

249. Differences in biological effectiveness of beams of varying quality are markedly affected by differences in the ability of the tissue to undergo the various repair processes. It is also important to establish whether or not the gross biological response of a tissue is similar after different qualities of radiation. If not, the concept of RBE is inapplicable.

250. *Repopulation* (see Section I.B.). It is necessary to establish whether or not repopulation is the same after comparable doses of x rays or fast neutrons for two reasons. One is that an analysis of RBE depends on there not being a difference and the second is to obtain knowledge of the effect of repopulation as a mode of repair during a protracted course of high-LET radiation. In general, it appears that there are no important differences in repopulation after x rays or fast neutrons [B30, B31, C16, D24, D25, F2, F14, F22, F23, F24, F25, H23, W24].

251. *Sublethal damage* (see Section I.B). With increasing LET the shoulder of a cell survival curve becomes reduced and repair between fractions is less. This difference is illustrated schematically for x rays and neutrons in Figure X. A major effect of this difference between neutrons and x rays is that the RBE is dose dependent, increasing with decreasing dose or dose per fraction. With fractionated irradiations, the RBE will primarily depend on the dose per fraction,

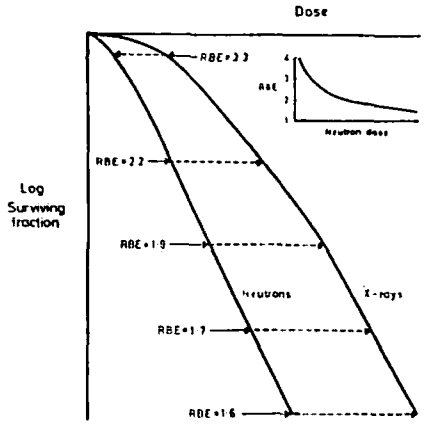

Figure X. Hypothetical survival curves for x rays and neutrons illustrating the smaller shoulder on the high-LET curve and the consequent increase in RBE with decreasing dose per fraction [F26]

providing any repopulation between fractions is indeed the same after the two types of radiation. Since the dose per fraction depends on the number of fractions, the RBE will also, but secondarily, depend on the fraction number. Tissues exhibit a considerable degree of sparing due to recovery from sublethal damage, usually far more than for cells in vitro. Therefore, at low doses per fraction, the RBE for tissues may have high values.

252. These RBE considerations were first tested in vivo using pig skin. It was shown that the RBE increased with increasing number of fractions (due to the decreasing dose per fraction [Figure X]). It was suggested that this increase in RBE might explain the severe reactions observed by Stone [S20] in an early trial of neutron therapy, since the original dose calculations were based on information from single treatments and various fractionated regimes were used in the clinical trial [F27, S21].

253. Recovery from sublethal damage may occur later for neutrons than for photons. There are some results consistent with this observation [F26, B32] but others which are not [H24, G16] and the question is not yet fully resolved.

254. *Potentially lethal damage (PLD)* (see Section I.B.).Whereas sublethal damage occurs during an interval between two dose fractions and manifests itself by repeating the shoulder region of the cell survival curve normally without a change in D_0, PLD does not require a second dose but only time before allowing further cell division to occur and is normally manifest by an increase in D_0. It appears that PLD is much reduced or absent after neutrons [H25, G16, S2].

255. *Slow repair* (see Section I.B.) It was shown [F8] that when two doses of x rays were given to mouse lung, there was an increase in LD_{50} due to pulmonary damage with increasing separation of the two treatments. During the first few hours after the initial dose this increase in LD_{50} is attributed to repair of sublethal damage between the two fractions, but the further increase was slow repair. In similar experiments with neutrons the initial repair of sublethal damage was observed (although, as expected, much reduced) but no further slow repair was observed. This phenomenon is thought not to be due to cell repopulation [C31]. It has also been shown by Curtis [C1] that there is a disappearance of chromosome aberrations in liver irradiated with x rays, but not with neutrons, which may also be a manifestation of slow repair.

256. The indications are therefore that with x-irradiation slow repair may occur in slowly dividing tissues, but is absent after neutrons. This has two consequences:

(a) The RBE for slowly dividing tissues would increase with increasing overall treatment time. Such an increase has been observed for skin damage with fractionation over 6 months compared with the same number of fractions in shorter time intervals [F9];
(b) There would be a greater degree of residual injury after neutrons than after x rays because of long term repair occurring after x-ray damage but not after neutron damage. Some evidence along these lines has been reported [D5, H8, F7].

257. As slow repair occurs after x rays then long fractionated regimes should spare slowly proliferating tissues which are presumed to be those involved in late radiation reactions. Such sparing of tissue damage would not occur with neutrons, so that the RBE would be higher for late than for early damage. This is a controversial issue and is not fully resolved at present.

C. RBE AS A FUNCTION OF NEUTRON ENERGY

258. In recent years a variety of neutron sources have been used for radiobiological experiments relevant to radiotherapy. These neutrons are generally in the range 6–50 MeV. In contrast, most work on lower energy neutrons was done earlier when the dosimetry was even less certain than it is today.

259. Hall et al. [H35] presented RBE as a function of the mean neutron energy for various in vitro and plant systems and showed that RBE was maximal at about 400 kV (Figure XI). In general, the RBE at 400 kV was 4 times that at 10 MeV. This result is in broad agreement with predictions based on the theory of dual radiation action [K20]. Fission neutrons would therefore have about twice the RBE of fast neutrons [D26, D28, S24].

260. With normal tissues, most comparisons of RBE with different energy neutrons have been obtained for jejunal crypt survival. Hendry and Greene [H36] have shown that the RBE of uncollimated monoenergetic neutrons (14 MeV d-T) is much smaller than for collimated beams [B36, H37] indicating that the dose from scattering material contributes an important element to neutron dose, at least with intestinal damage. RBE comparisons on both gut (clonal assay) and skin (average skin reactions) have been made for a variety of beams. The preliminary results are summarized in Figure XII [F29]. In this case neutrons were produced by deuterons of a given energy onto a beryllium target. The neutrons produced have a spectrum of energies, the mean being about 40% of the deuteron energy. It is clear that the RBE decreases with increasing energy and for neutrons of Ed = 16 MeV(Be)[1] it is 30–40% greater than for Ed = 50 MeV(Be).

[1] Ed = deuteron energy; e.g., 16 MeV(Be) = 16 MeV deuterons onto a beryllium target.

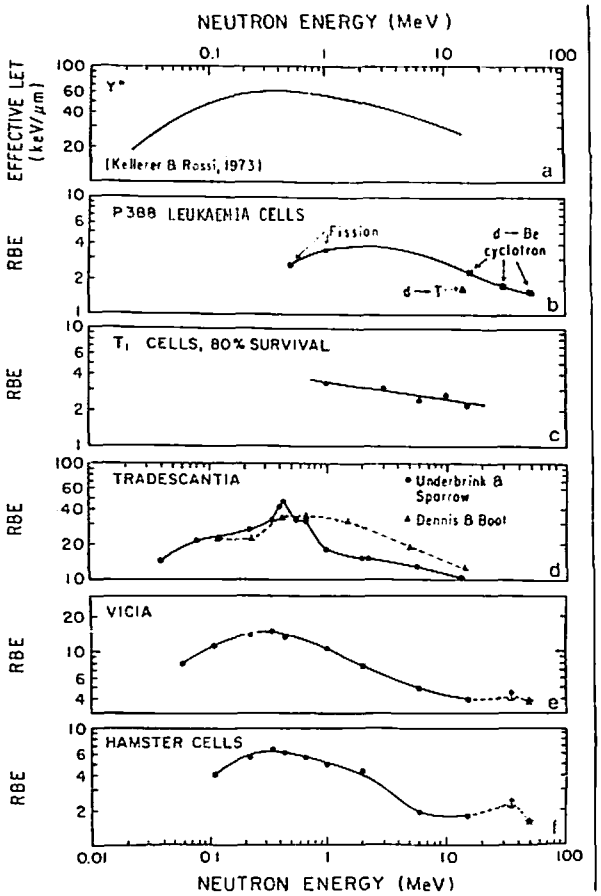

Figure XI. RBE as a function of neutron energy for plant and mammalian cells in culture. The top panel is a theoretical curve. The peak RBE at 0.3–0.4 MeV is clearly illustrated and it is a factor of 3 or 4 greater than the RBE for neutrons of energies in excess of about 10 MeV. The photon dose ranges were 2–12 Gy for the mammalian cells, 0.5–6 Gy for Vicia faba and 0.1–4 Gy for Tradescantia [H35]

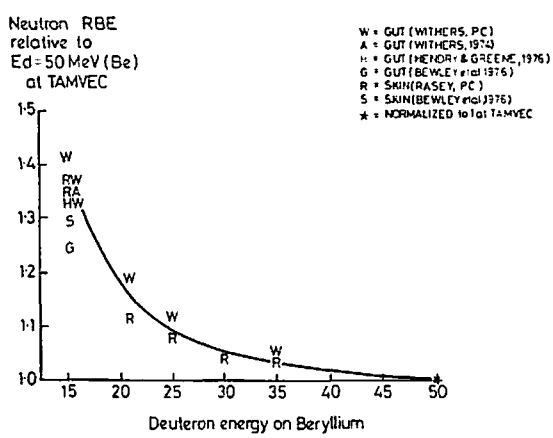

Figure XII. RBE for skin and intestine, as a function of neutron energies in the therapeutic range, i. e., mean energies from about 7 MeV upwards [F29]

D. NEUTRON FRACTIONATION

261. The two major factors governing the effects of fractionation of dose in radiotherapy are the number of fractions N and the overall treatment time T In the Ellis formula (section I.F.). Values for the exponents of N and T for damage to subcutaneous connective tissues are 0.24 and 0.11, respectively, for x rays. It is now clear from animal work that the exponents for N and T vary from tissue to tissue [A10, H28, H66, H67, W6, V1].

262. For clinical usage the Ellis formula has been adjusted, based on isoeffect curves for early skin damage, i.e. [F30]

$$TD = NSD_N N^{0.04} T^{0.11}$$

In the case of skin, the T factor is probably due to repopulation and was therefore specifically chosen to be the same for x rays and neutrons. The exponent of N is less because sublethal damage is less for neutrons. The formula was used successfully in the Neutron Therapy Clinic at Hammersmith Hospital when the routine neutron fractionation regime had to be altered.

263. Exponents of N and T for tissue damage, when measured for both x rays and neutrons, are given in Table 12. They are seen to vary from tissue to tissue but the factor for both N and T is small after high-LET radiation, indicating little or no sparing by fractionation. Small T factors indicate the lack of time-related repair after neutrons in slowly proliferating tissues. Small N factors may be a reflection of the highest LET component of the neutron dose playing the dominant role at low doses per fraction. Support for this interpretation is given by the reduction in OER observed with increase in fractionation of neutron dose [H33]. Domination of the low dose region of the neutron survival curve by the highest LET component of the beam implies that the initial region of a neutron survival curve would be exponential and with higher doses would bend downwards [H34, G20]. This would lead to the requirement for increasing the dose of neutrons to produce a given level of damage only on changing from a single dose to two or three fractions (i.e., on the bending part of the curve) without further increase with increasing number of fraction, as is seen to be the case with most tissues.

E. NEUTRON RBE FOR NORMAL TISSUES

264. There are two ways of examining the non-stochastic effects of neutrons. One is the direct examination of tissue response to the high-LET radiation; this is clearly the most desirable, but the information on it is rather limited. The second method is to study the RBE for various tissues, as a function of dose level. This is a less direct approach, but if RBE considerations can be generalized, as seems to be the case, then by using RBE as the conversion factor much of the available low-LET information can be extrapolated to neutrons or other high-LET radiation.

265. The relationship between RBE and dose/fraction for damage to a variety of normal tissues was analysed by Field [F28] who showed, as predicted from survival curves, that the RBE was high at low doses per fraction and decreased as the dose per fraction increased. The curve drawn through this data was used by Sheline et al. [S21] to calculate the appropriate RBE values and thus equivalent doses of x rays in a reassessment of Stone's first neutron therapy trial.

266. With the accumulation of more data it became apparent that the RBE was different for different tissues [H26]. This has been particularly clearly demonstrated with the Ed = 16 MeV(Be) beam from the Hammersmith cyclotron giving neutrons with a mean energy of about 7.5 MeV. More data exist from this beam than from any other. There are variations in RBE between different tissues of almost a factor of 2 (Figure XIII). Variation in RBE for normal tissue has also been

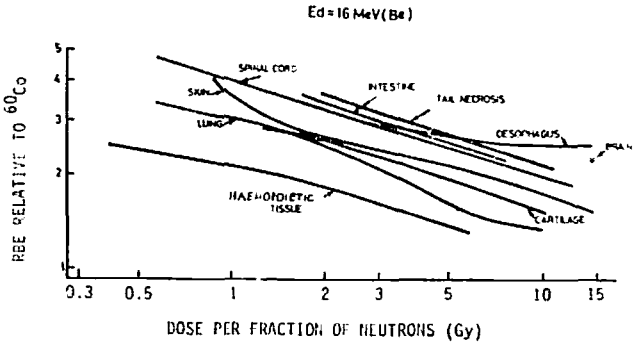

Figure XIII. RBE versus dose per fraction for neutrons produced by bombarding beryllium with 16 MeV deuterons. In all cases there is an increase in RBE with decreasing doses per fraction but there is an overall factor of about 2 in the range of tissues investigated

shown for other neutron beams [F29]. Differences in RBE have been mainly associated with differences in the degree of repair of sublethal damage [B33, H27] but slow repair may also play a role with some tissues.

1. Skin

267. More data are available for skin than for other tissues. The RBE for damage to skin of mouse, pig, rat, and man is shown in Figure XIV. The curve applies to damage leading to erythema, desquamation and regenerating clones of cells in the four species. The fact that the results from experimental animals and man fall on the same curve indicates that it is reasonable, at least for skin, to extrapolate results from animals to man. As predicted by theory [K20] over most of the dose range the RBE increases with decreasing dose, and the same is true for irradiation at low dose rates, for example, by ^{252}Cf [K29]. At the highest dose levels the RBE tends to increase with increasing dose, and this is due to hypoxia in the skin which will only be important with the largest doses. The above reactions observed in skin are primarily the result of damage to the basal epithelial layer. However, some observations on late damage (deformity in mice feet) also fall on the main curve in Figure XIV. This type of late damage has been shown to have a well-defined threshold which is higher than that for the production of an early reaction (as in the case with photons), after which there is a rapid increase in effect with increasing dose.

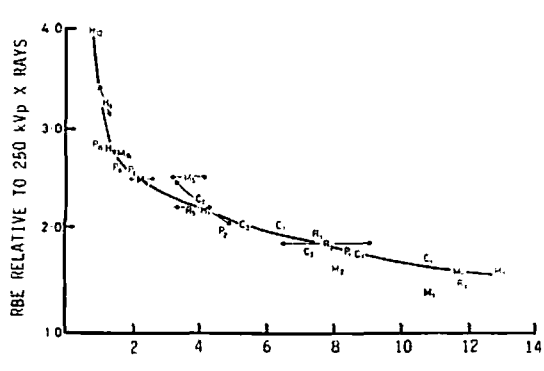

Figure XIV. RBE versus dose per fraction for the skin of four species. H, human; P, pig; R, rat; M and C, mouse. The subscripts indicate the number of fractions used. It is clear that the important factor is the dose per fraction, not the number of fractions

268. The relationship between early and late reactions was found to be similar for various treatments, both single and fractionated, photons or neutrons. It is, however, doubtful whether the late deformities seen in rodents are relevant to the human problem. In rodents these early and late reactions may stem from a common cause [F5, D6]. Rodent skin is very thin compared with that in larger animals and man and does not respond by producing extensive late subcutaneous fibrosis as is occasionally seen in patients following radiotherapy. Rodents may not therefore be suitable animals in which to study late skin damage relevant to that which occurs in man, despite the close correspondence with the early reactions.

269. In studies on pig skin, Withers et al. [W25] found, in a 6-week course of treatment, that gamma rays given twice weekly produced a worse late response than 5 times weekly, for the same early response. With neutrons (Ed = 50 MeV(BE)) they found no increase in sparing of late damage with an increase in neutron fractionation from twice weekly to four fractions weekly and both neutron regimes gave a more severe late response for a given early response than either of the gamma ray regimes. However, the authors suggest that this was probably associated with the increased absorption of neutrons in the subcutaneous fat. Human skin was irradiated with x rays and fast neutrons to establish RBE values for a neutron cancer trial [F14]. The results are quoted in Table 13.

270. Hendry et al. [H28] investigated necrosis in mouse tails. Necrosis seems to arise from an unhealed ulceration and closely follows the acute skin response. The RBE values both for skin damage and necrosis in tails are higher than those observed for other acute endpoints in skin [A10]. However, the tail acts as a temperature-regulating organ, and there is evidence of hypoxia in its skin which affects the sensitivity even at 16 fractions of 2–3 Gy x rays [H24]. This might increase the dose required to produce an effect and also be responsible for the high RBE values observed.

271. Retreatment of rodent skin a long time after a primary treatment with x rays or neutrons has shown more residual damage remaining after neutrons compared with x rays [H8, F7]. This implies that the skin tolerance dose for either x rays or neutrons (and possibly for other trauma) will be less after previous neutron treatment than after x rays.

272. In summary, the RBE for single doses of neutrons for production of skin damage is 1.5–2 and will depend on the neutron energy. The effect of fractionation with neutrons is much less than with x rays, and beyond two fractions the main contributing factor will be repopulation. A summary of threshold doses is given in Table 13.

2. Gastrointestinal system

273. RBE values for oesophageal damage in mice are rather higher than for most other tissues [H27, P20, G18]. The damage is primarily to the basal epithelial cells [P2, K5] which are of ectodermal origin, and one might therefore expect RBE values similar to those of skin rather than intestine. The histology of the mouse oesophagus is also similar to skin. However, hypoxia has been shown to influence the oesophageal sensitivity in anaesthetized mice, at least at high doses per fraction [H2]. Minimum single doses of neutrons required to

cause oesophageal death of mice are at least 8 Gy in a single treatment and 20 Gy in 10 fractions in 11 days [H2, P1].

274. RBE values for acute intestinal damage have only been derived for mice. In general the values obtained are slightly higher than those for skin (Figure XI) and this may be due to the greater reduction in sublethal damage compared with other tissues. For example, the fraction of recovery from sublethal damage after neutrons of 7.5 MeV mean energy compared with that after x rays was 0.2 for gut damage compared with 0.4–0.6 for skin damage [F23]. The minimum single dose of this energy neutrons to produce either a reduction in crypt count or animal death was close to 4 Gy in a single treatment.

275. When two fractions of neutron are given, there is a small degree of repair of sublethal damage. However, when the fraction number is increased above two, there is no further sparing of neutron dose [W2]. There will, however, be sparing due to cellular repopulation, just as with x rays.

276. The homeostatic control in the small intestine is such that although there may be rapid regeneration of stem cells in the crypt, the numbers of cells differentiating may be considerably depleted by cell death in fractionated regimes in therapy. This can be seen in a "stunting" of villus height [M5] which is first noted after doses greater than 1 Gy neutrons or in a change of the surface architecture seen with the scanning electron microscope [H29]. Differences in response for a given level of crypt loss were seen using these techniques for x rays and neutrons with single doses and these differences may be exacerbated with fractionation. The architectural changes may be more relevant in the case of long fractionation regimes but results are not yet availabile.

277. Late damage leading to fibrosis and narrowing of the lumen or adhesions and ulceration may occur. Geraci et al. [G17], following irradiation of a 4-cm segment of the ileum, have taken death within 6–90 days as a measure of such late intestinal complications which occur at higher doses than that for the early syndrome. These workers have suggested that the RBE is also greater than for acute intestinal damage but data from which conclusions may be drawn with any certainty are inadequate.

278. There is, in conclusion, no further effect of increasing the number of neutron fractions above 2, i.e., the exponent for N is zero, in contrast to the effects of x rays. There will, however, be considerable sparing during protracted irradiation by cellular repopulation. Single doses of neutrons greater than 4 Gy can cause a reduction in the number of crypts leading to animal death. Doses greater than 1 Gy cause architectural changes in the intestine.

3. Cartilage

279. The RBE for fast neutrons has been measured for growing cartilage, using two different methods. Kember [K19] counted surviving clones in the cartilage of 6-week old rats and obtained RBE values slightly higher than by the method of Dixon [D4, D27] who quantified stunting of growth in 7-day old rats. The average value for these measurements was similar to the RBE obtained for skin at the same level of dose per fraction. The results of Dixon [D27] indicate no threshold for neutron-induced stunting in the young rat. It was found that 1% stunting was caused by 0.13 Gy of fast neutrons. Kember [K19] measured a D_o for neutrons of approximately 0.8 Gy which is similar to that obtained in other tissues.

280. It has been suggested that cartilage in adults might contain a large fraction of hypoxic cells because the tissue is relatively avascular. Experiments by Dixon [D4] who varied the oxygen concentration in the air breathed by young rats showed that all the cells were slightly protected from x irradiation by hypoxia, but that the effect was insufficient to cause a large increase in RBE. Kember [K1] was unable to improve the oxygenation of the cartilage in young rats by the animals breathing hyperbaric oxygen. Whether these results may be extrapolated to man is not clear.

4. Lung

281. The RBE for lung damage to mice is lower than for skin and most other tissues, with the exception of the bone marrow (see subsection IV.E.5) although the differences are not great. Unlike skin but similar to intestine, there is no further sparing of damage by fractionation of neutrons beyond splitting the dose [F17]. This is in contrast to x irradiation, from which the sparing of damage to lung continues to increase with fractionation [H30]. This difference may be due to slow repair, which is important in lung (and possibly in other tissues which have a slow cell turnover) and which does not occur after neutrons [F8].

5. Nervous system

282. *Spinal cord.* The spinal cord shows considerable capacity to repair sublethal damage after x irradiation. The D_2-D_1 values for x rays are large ($\sim$ 9 Gy) and the slope of the isoeffect curve from 1–30 fractions is $\sim$ 0.4 [W6, V8]. Using 15 MeV D-T neutrons, van der Kogel and Barendsen [V6] have shown little recovery from sublethal damage after neutrons and the isoeffect curve is flat between 5 and 23 fractions. The RBE values obtained were similar to those for other normal tissues with this beam. Geraci et al. [G5], using neutrons with a mean energy of $\sim$ 8 MeV (Ed = 22 MeV(BE)) also obtained RBE values in mice similar to those for skin. The RBE pertaining to lumbar cord irradiated with single doses of neutrons from 16 MeV deuterons on beryllium is higher than that for skin: with fractionated irradiation preliminary results using doses to produce 10% myelopathy at one year post-irradiation also indicates a higher RBE than for skin [W37].

283. The RBE for spinal cord is similar to that for skin and several other tissues. Experiments have been performed with neutrons on the spinal cord of rats [W6, V6] and mice [G5, G7]. In mice, single doses of at least 6.8 Gy were required to cause paralysis and this was increased to approximately 10 Gy in 10 fractions. However, in fractionated experiments, renal failure also occurred at a similar threshold of 10 Gy [G7]. With rats, single doses of more than 10 Gy are required to cause a small probability of paralysis and they were increased to approximately 18.5 Gy in 23 fractions [V1, V8].

284. *Brain.* By counting cell numbers in the subependymal plate of the rat brain, Chauser et al. [C11] observed that with x-ray doses of less than about

15 Gy there was a loss in cells followed by a slow recovery in numbers. With neutrons, a dose as small as 1.2 Gy caused a steady fall in cells at least up to 6 months, with no sign of recovery. As the response after x rays or neutrons is so different, RBE varies with the time of observation. At late times the RBE is higher than for skin.

285. In the clinic Catterall reported that after neutron treatments of 15.6 Gy in 12 fractions over 4 weeks, gliomas in the brain were controlled but some patients suffered a slowly increasing dementia [C33]. Similar results were also reported by Parker from Seattle. The dementia is associated with the development of microscopic areas of demyelination throughout the treated volume. In Edinburgh, Duncan and Arnott, treating gliomas with 13 Gy of neutrons in 20 fractions over 4 weeks, observed cerebral oedema at about 6 weeks after completion of treatment, which is not normally seen after x irradiation, but dementia was not observed.

6. Thyroid

286. An assessment of the RBE for radiation damage to rat thyroid has been made by using the end-point of impairment of its proliferative potential. Using monoenergetic 14 MeV neutrons, Malone et al. [M29] derived the "survival curve", for which the D_o was 3.1 Gy. However, this value is very high, as is the value of D_o of about 4 Gy for x rays, owing to the unorthodox interpretation of the term "survival". The RBE at about 1 Gy of neutrons was 3.2 and at about 5 Gy of neutrons was 1.8. These values are in the range of those found for other tissues, indicating that the thyroid is not particularly sensitive to neutrons.

7. Testis

287. The RBE for damage to the testis has been obtained by two end-points; weight loss or spermatogonial stem cell survival. Weight loss of testis after irradiation is due to the killing of spermatogonia. The dose response curves obtained using this technique are biphasic with both x rays and neutrons, indicating a population of about half the total cells being more resistant [K18, H32]. With x rays there is no repair of sublethal damage in testis and the same is true for neutrons. When two doses of either radiation were given either 4 or 7 days apart, the dose-effect curves were not different from those obtained with single treatments [S22].

288. Hornsey et al. [H32], using neutrons of Ed = 16 MeV(Be) observed an RBE of 2.5 for neutron doses of less than 0.5 Gy and of 3.2 for larger doses. Geraci et al. [G19], using neutrons of Ed = 21 MeV(Be), obtained an RBE of 3.0 at low dose levels, but did not investigate at high doses. De Ruiter et al. [D26], using 1-MeV neutrons, obtained values at 5.5 and 4.1 at lower and higher levels, respectively. These results are consistent with the differences in neutron energies used (see section IV.C). Hornsey's results are therefore unusual in that over the dose range studied the RBE decreased with decreasing dose, which is the opposite of results found with other organized tissues (see Figure XIII). The reason for this difference is not clear.

8. The eye

289. The lens of the eye is avascular and, therefore, it may be concluded that it is also rather hypoxic. The RBE would, therefore, be expected to be about 1.5 times higher than for well-oxygenated cells and tissues, because of the reduced oxygen effect with high-LET radiations. Experimental RBE values have been determined by a variety of workers [B16, M25] and do seem to be higher than for other tissues at similar values of dose per fraction. For example, Merriam et al. [M28] obtained values of 4.5 at 1.8-MeV neutrons up to 9 at 0.43-MeV neutrons. The x-ray doses in their experiments were about 5 Gy.

290. Bateman et al. [B34] obtained much higher RBE values with 0.43-MeV neutrons, but these were for the comparatively low doses required to increase the probability of causing opacities in a highly susceptible mouse strain. Di Paola and others [D42] also measured high RBE values, increasing with decreasing dose per fraction from about 8 with 0.12–0.5 Gy of neutrons to about 20 with 0.01 Gy of neutrons. These values were also for increasing the probability of causing opacities, as in Bateman's experiments, but the RBE values were low. The RBE for 0.43-MeV neutrons would be expected to be higher than for other energies (see section IV.C).

291. The higher RBE for lens opacities generally found is borne out by the report of Abelson et al. [A11] that cyclotron workers exposed to neutrons over periods ranging from 10–250 weeks were observed to have lens changes with a mean dose of about 1 Gy of neutrons. In a trial of fast neutrons in radiotherapy, Roth et al. [R18] observed no changes with less than 0.8 Gy given as 12 fractions but slight permanent loss of vision with 2.2 Gy or more.

9. Haematopoietic tissues

292. The RBE for non-stochastic damage to stem cells of the haematopoietic system is low and varies little with dose per fraction [F28, B33, G19]. This is because there is little accumulation and repair of sublethal damage in these cells with x rays and virtually none with neutrons. RBE, therefore, mainly reflects differences in D_o, which are small.

293. There is also a dosimetric factor which will cause the neutron RBE to be low in bone marrow. Bone has a low hydrogen content so that the absorption of neutrons will be less than in other tissues because of the lower probability of collisions with protons. This is in contrast with an excess production of secondary electrons by photoelectric absorption of x rays because of the high mineral content in bone. However, Broerse and Barendsen [B33] conclude that although these dosimetric factors do play a significant role, there are indeed intrinsic differences between the biological response of cells of the bone marrow compared with many other tissues.

294. The lack of repair capacity is also seen in lymphocytes. The majority of untransformed lymphocytes are very radiosensitive, but the RBE values for killing unstimulated human lymphocytes, rat lymphocytes or white cells in mice are about 1 and for lowering the transformation index about 2 [G19, H31]. With photons, the haematopoietic tissues are more sensitive than the intestine, so animals which survive the early

intestinal syndrome may die later from the haematopoietic syndrome. This is not normally the case with neutrons, the intestine usually being the limiting factor in whole-body irradiation.

10. Blood vessels

295. The effects of radiation quality on the response of blood vessels has not been extensively studied. There are only a few studies with fast neutrons. In the intestine the RBE for leakage of albumin and PVP was estimated to be 3.4 ± 0.4 [T12] and 3.0 ± 0.5 [L10]. The RBE for capillary endothelium in subcutaneous tissues in the rat has been estimated by Broerse et al. [B35], using 14 MeV neutrons. For neutron doses between 2.5 and 5 Gy the RBE was 1.8–1.9. These values are similar to those found for skin and intestinal epithelium. The results of Aarnoudse and Lamberts [A12] suggest that the RBE for radiation-induced atheromatosis in hypercholesterolaemic rabbits depends on dose. A neutron dose of 5 Gy was more effective than the same dose of x rays, whereas for a dose of 10 Gy neutrons were less effective.

296. Stearner et al. [S23] conducted an electron microscopic study of changes in the microvasculature of the mouse ear between 12 and 20 months after sublethal whole-body fission neutron irradiation. There were degenerative changes in the smooth muscle of arterioles which are seldom seen after x irradiation. Although vascular damage was not sufficiently severe to be quantified, evaluations indicated more severe arteriolar degeneration after a total dose of 2.4 Gy of fission neutrons fractionated over 24 weeks than after the same single dose. This is the reverse of the normal fractionation effect.

F. MIXTURES OF NEUTRONS AND X RAYS

297. It is difficult from current knowledge to predict how a combination of low- and high-LET radiation will affect normal tissue tolerance and how the components of a mixed beam might add to produce a given degree of biological response. In principle, the treatments could either be simply additive or there might be some interaction between the different radiations to give enhanced damage. Information from cell studies in vitro is equivocal. Durand and Olive [D29] found that neutrons apparently caused a reduction in recovery from sublethal damage inflicted by x rays, whether given before or after x irradiation. They also found that the shoulder on the neutron cell survival curve did not represent recoverable sublethal damage. Others [R19, N6] found some interaction between the sublethal damage inflicted by x rays and neutrons when the two radiations immediately follow each other. It has been demonstrated in the stem cells of the intestinal epithelium that the rate of recovery from sublethal damage appears to be independent of its source [H24] and it has been suggested by Gragg et al. [G16] and by Hornsey et al. [H33] that recovery from sublethal damage with a neutron beam is simply due to its low-LET component. However, the presence of the high-LET part of the beam, which only inflicts lethal damage, will cause the total accumulation and repair of sublethal damage to appear less than with a photon beam. If the two radiations are separated by 24 hours, when recovery from sublethal damage is complete, then the effects are simply additive [H38].

298. There is little information on the effect of mixed treatments of neutrons and photons on either slow repair or potentially lethal damage, but there is evidence that tissues which have been treated with neutrons carry unrepaired damage for long periods. The tolerance to a subsequent course of x rays is less in a tissue previously treated with neutrons than in one previously treated to the same level of damage with x rays [H8, F9]. This observation may be particularly important for exposure to mixed beams for an extended period.

G. OTHER TYPES OF HIGH-LET RADIATION

299. Biological experiments have been performed with α particles, protons, negative π-mesons and with heavy ions. All of these particles have the property of increasing the LET with increasing penetration into tissue, before the particles are brought to rest. Fast protons in the range of 50–660 MeV have been shown in a wide range of biological materials to possess an RBE value close to unity. The same value would be expected to apply to man [R33]. For π-mesons the entrance particles have properties similar to those of sparsely ionizing radiations. This is also true for high energy protons and alpha particles. π-mesons have a "star region" of maximum dose deposition and maximum LET in which the oxygen effect is reduced and the RBE raised, but both to a rather lesser extent than with fast neutrons. In the peak region the increase in RBE is primarily the result of less sublethal relative to lethal damage after π-mesons relative to x rays [Y4]. The Bragg peak for alpha particles and protons is extremely sharp, and in this region of a millimetre or two the dose and LET are increased by a large factor relative to the entrance characteristics. Heavy ions also have a large peak dose and may reach LET values of about 1000 keV/μm for very short distances, just before the particles stop. These particles would then be expected to have high LET values: for example, a figure of approximately 10 was found for liver injury [R33].

H. SUMMARY

300. Throughout this section the emphasis has been on effects of fast neutrons. For single treatments sufficiently large to cause non-stochastic injury, neutron RBE values range between 1 and 5 compared with photons, depending on the neutron energy. Included within this range is a factor of about 2 in the variation of RBE for different tissues. Repair from sublethal damage is less with high-LET radiation, so that in some cases there is no further "dose sparing" by increasing fractionation beyond two fractions. Also the dose rate effect with high-LET radiation is small. This will cause an increase in RBE with decreasing dose per fraction (and thus with increasing number of fractions). Where cellular repopulation is important (skin or intestine) there is no reason to think that it will be dependent on the quality of the radiation and the sparing which occurs with x-irradiation will also apply to neutrons. For slowly dividing tissues, for which radiation damage occurs a long time after irradiation, repair by repopulation will be small for both x rays and neutrons. Since other repair processes after high-LET radiation are limited, the neutron dose which may be tolerated if given over a long period may not be significantly greater than that in a single acute exposure.

V. INTERNAL IRRADIATION BY RADIONUCLIDES

301. When a radionuclide is introduced into a living mammal, tissues absorb a proportion of the energy of transition to the stable nuclide. The energy per unit mass of tissue is largely delivered by radiations emitted by the radionuclide or its daughters during their decay, and constitutes a radiation dose. The biological effects of the deposition of energy in a tissue are usually reported in the literature in relation to the most accurate expression for the dose obtainable, which is often simply the activity introduced per unit weight of animal (Bq kg^{-1}). However, other derived or measured quantities are also given such as the tissue specific activity (Bq g^{-1}), the mean dose rate (Gy s^{-1}), and the mean cumulative dose (Gy). The latter might be thought to provide a useful quantity for comparison with the total dose delivered for the same effect by external irradiation, and forms the basis for the present recommended protection limits for internal exposure to radionuclides [11].

302. To interpret the results of studies in different species and to relate them to those involving external irradiation, it is necessary first to consider briefly the relationships between the various expressions of the dose from radionuclides. Then the factors which may influence the biological effects of a given dose will be discussed. Data obtained from studies in experimental animals together with the results of therapeutic, accidental and occupational exposures in man will be reviewed together in this chapter.

A. DOSE RELATIONSHIPS

303. Although the activity of a radionuclide introduced into an animal is of major importance in determining the dose to the tissues, it does not uniquely characterize it. Direct measurements of the dose are not often carried out owing to the technical difficulties involved in the use of dosimeters in vivo. Radiation doses and dose rates are therefore usually calculated and a recent ICRU report [19] has provided a review of the methods available, particularly with reference to the clinical use of radionuclides.

304. In this chapter some of the expressions occurring in dose calculations are discussed in order to illustrate the physical and biological factors which may be expected to influence the dose delivered to a tissue following the administration of a given activity of a radionuclide.

1. Mean dose rate

305. The mean dose rate $\overline{\dot{D}}$ (Gy s^{-1}) to a target tissue v in animal from activity A_r (Bq) of a radionuclide contained in a single source tissue r is given in general form by [19]

$$\dot{D}(v \leftarrow r) = A_r \sum_i \Delta_i \Phi_i (v \leftarrow r)$$

The summation is taken over all the i types of particle emission from the radionuclide, where particle is used in the sense defined by ICRU [19] for directly and indirectly ionizing particles. Δ_i (J) is the mean energy of the particles of type i emitted per nuclear transformation and is a constant determined entirely by the characteristics of the radionuclide. Φ_i (kg^{-1}) is called the specific absorbed fraction and is defined as the fraction of the energy of particles of type i emitted in the source tissue which is absorbed per unit mass of the target tissue. It depends on the nature and energy of the particles, the attenuating characteristics of the tissues and the geometry of the source and target regions.

306. The mean dose rate to a target tissue v from activity A_o contained in the whole animal is obtained by summation of the contributions given in the above equation for all the tissues in the body. This can be expressed as

$$\overline{\dot{D}} = \sum_r A_r \sum_i \Delta_i \Phi_i (v \leftarrow r)$$

where $\sum_r A_r = A_o$. The target tissue may be an organ or a region of microscopic dimensions. The mean dose rate is usually a function of time.

307. Calculation of the mean dose rate necessitates obtaining values of Φ_i and A_r, and these are usually calculated using physical or biological models to extend the applicability of the theoretical and experimental data which is available. Typical models are discussed in [19] and tabulations of useful data are appended to assist in such calculations.

308. It is clear from the above equation that the mean dose rate to a given tissue arising from a given total activity will be affected by the size of the organs contributing to the irradiation and in general will be dependent on the species as well as on normal individual variations. Alterations over a period of time may also be expected due to changes in the geometry of structures caused by radiation effects, disease, natural ageing or growth.

2. Mean cumulative dose

309. The cumulative dose $\overline{D}$ (Gy) averaged over a target tissue v for a time t (s) is given by the time integral of the mean dose rate $\overline{\dot{D}}$. When the geometry of the source and target regions remains constant, the above equation can be integrated to become

$$\overline{D} = \sum_r \tilde{A}_r \sum_i \Delta_i \Phi_i (v \leftarrow r)$$

where the quantity

$$\tilde{A}_r = \int_o^t A_r dt \qquad \text{(Bq s)}$$

is called the cumulative activity [19].

310. The cumulative activity is usually derived from measurements of the concentration of activity in an organ as a function of time after administration of the radionuclide and biological models are again used to extend the applicability of the data [19] to other tissues.

311. The many factors which influence the mean cumulative dose received by an organ following the administration of a given activity to an animal are those which affect the cumulated activities in the various tissues in addition to those already discussed affecting the specific absorbed fractions.

312. The cumulated activities in the body depend on the intake of activity, its transport, metabolism and re-utilization, as well as its excretion. These factors, in turn depend on: the characteristics of the material introduced, the nature of the radionuclide, its chemical

and physical form, the chemical and physical form of the carrier; the method of introduction of the activity, its distribution in time, route of entry, means of introduction; the animal species, weight, sex, age, condition, response to diet, etc.

313. Every element has its own characteristic metabolism in the body, although the presence of the carrier may affect it. The solubility of the carrier in body fluids, in particular, may determine the initial transport and excretion of the activity. The metabolism of an animal may be significantly altered if the activity incorporated is sufficiently high to produce radiation damage. After a period of continuous introduction of activity, the concentrations in the body may reach an equilibrium state, and the dose then delivered to tissues largely depends on the total time of irradiation, and may be relatively easy to determine. In general the distribution of the mean cumulative dose in the body tissues is not the same as the distribution of activity, but is related to it in a complex manner.

B. FACTORS INFLUENCING BIOLOGICAL EFFECTS

1. Temporal distribution of dose

314. The dose rate to a tissue is generally a function of time due to decay of the activity and metabolism or transport of the radionuclide in the body. For insoluble radionuclides in the gut, for example, the temporal distribution of dose to the gut wall is usually determined by the speed of passage of the gut contents. In most cases repair of sublethal damage will usually occur during exposure and the effectiveness of the mean cumulative dose will be much reduced over that from a single short exposure to external x-irradiation, although some damage will still occur.

315. A basis for relating the effects of radionuclides to fractionated radiotherapy has been suggested by Bigler [B59] using the time, dose and fractionation factor, TDF, concept of Orton and Ellis [O1]. However, the validity of these concepts has yet to be established. The dose rates involved are variable and considerably lower than those used in brachytherapy (> 0.3 Gy/h) for which the procedure was developed. In addition, the critical dose rates may not be represented by the mean dose rate to the organ but rather by the dose rate delivered to critical structures within it [B60].

2. Spatial distribution of dose

316. The biological effects of radionuclide decay are caused by one or several of the following processes [K40]: emitted radiation; chemical transmutation; nuclear recoil; change of atomic charge. The emitted radiation produces effects at distances depending on its penetration whereas the last three essentially produce effects within molecular dimensions close to the site of the disintegration.

317. Since the radiosensitive structures of cells are located at specific sites (for example, in the nuclear DNA) the biological effects of radiation depend on the microscopic distribution of energy along its path. Radionuclides emitting alpha particles causing dense ionization along their tracks, may be expected to be many times more effective than similar distributions of beta- or gamma-emitting radionuclides in producing tissue damage for the same absorbed dose.

318. The relationship of the sensitive site to the point of emission of the radiation is important. Radionuclides which emit a significant amount of energy in the form of Auger electrons may simulate the dense ionization produced by high-LET radiation. Figure XV shows results of calculations of the average energy deposition per disintegration in spheres of various diameters for ^{125}I and ^{3}H, in comparison with the mean energy transferred to the same volume by a 5 MeV alpha particle with a LET of 100 keV/μm [H56]. When the volume considered is sufficiently small, the energy deposited by the decay of ^{125}I is greater than that transferred by the alpha particle, whereas that deposited by the decay of ^{3}H is more than an order of magnitude smaller. The energy deposited in individual events is governed by stochastic processes and considerable variation about the mean values can be expected.

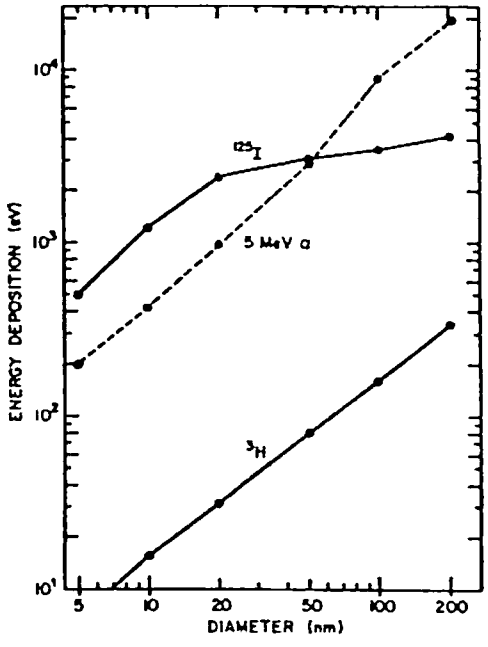

Figure XV. Average radiation energy deposited in spheres of various diameters by decaying ^{125}I and ^{3}H (solid lines), or by a 5 MeV alpha particle traversing the sphere (dashed line) [H56]

319. Experimental studies using labelled DNA precursors have shown [K40, F49] that the decay of ^{125}I located in the DNA of mammalian cells is 10–100 times more lethal per disintegration than ^{3}H in a similar molecular position. In comparing the doses to the cell nucleus in synchronized Chinese hamster cells [H56] ^{125}I-iododeoxyuridine was much more effective in causing cell death (LD_{50} : 0.45 Gy; D_o : 0.74 Gy) than either ^{3}H-thymidine (LD_{50} : 3.8 Gy; D_o : 0.74 Gy) or external x-irradiation (LD_{50} : 3.3 Gy; D_o : 2.3 Gy).

320. Radionuclides uniformly distributed in tissues or emitting particles with ranges which are large compared to cellular dimensions produce relatively uniform spatial distributions of dose. The biological effects are then determined by the temporal distribution of average tissue dose and the quality of the radiations emitted.

321. When radionuclides, particularly the alpha emitters, have heterogeneous concentrations within the tissues on a microscopic scale (i.e., a microdistribution)

and also emit particles with ranges comparable to cellular dimensions, their efficacy for producing a given effect is determined by the spatial relationship of the radionuclides as well as by the distribution of dose to the radiosensitive structures within the cells [F48]. If the localization of the radionuclide and the radiosensitive areas are congruent, the effectiveness of a given average tissue dose may be much enhanced both due to localized processes such as transmutation, which are associated with the disintegration, and to the particular microdistribution of dose.

322. The microdistribution of dose in tissues may also be important in comparing the relative efficiency of uniform and locally non-uniform distributions of activity [F48]. The dose microdistribution and other localized effects of radionuclide decay such as transmutation may be particularly important in considering the effects of radionuclides incorporated into specific vital molecules such as hormones or enzymes which control the metabolic functions of tissues and systemic processes.

C. EFFECTS ON TISSUES

323. The object of this section is to review information on non-stochastic effects of radionuclides which are likely to be of some significance for the health of contaminated individuals. The data are obtained from studies in experimental animals and reports of therapeutic, accidental and occupational exposures in man. Although one of the most important physical variables influencing the effects of radionuclides is the nature of the radionuclide itself, the emphasis of this Annex is on the radiobiology of individual tissues. Accordingly, the effects are here classified in relation to the tissue rather than the radionuclide.

324. The data on man are of most importance since species effects may be expected to be significant, not only because of inherent differences in the radiosensitivity of corresponding tissues, but also because of the differences in scale, morphology and metabolism, which determine the distributions of the dose delivered by a particular radionuclide. Often information concerning the radiation dose delivered for a given effect is not available, but even where it is, it should be remembered that the dose may be estimated to the time when the effects became evident, and the events producing the effect may have occurred at a much earlier time and for smaller dose. This concept of "wasted" dose has been reviewed by Mole [M52].

1. Gastrointestinal tract

325. Radiocolloids have been used in radiotherapy for the reduction of fluids accumulating in serosal cavities as a result of malignant disease. The colloid labelled with a suitable beta-emitting radionuclide (^{32}P, ^{198}Au, ^{90}Y) is introduced into the cavity and irradiates the tissue surfaces and disseminated neoplastic cells in the fluid while sparing deeper tissues. From autopsy data it has been estimated [H57] that 5550 MBq colloidal ^{198}Au in 400 ml saline injected into the peritoneal cavity resulted in total doses to the retroperitoneal lymph nodes, the omentum and the peritoneal serosa of about 77.5, 67.5 and 47.5 Gy, respectively. Mild radiation sickness and haematological complications have been recorded and sometimes persistent leukopaenia. Ileus and gastrointestinal complications have been seen up to ten years after treatment, at which time the serosa was found to be thickened and fibrosed. Adhesions and fragility of the bowel wall have been noted affecting the whole of the small intestine [H57].

326. When given in sufficient intraperitoneal amounts to mice both ^{32}P and ^{198}Au colloids can cause morbidity and death. Such effects were observed in a study using both radionuclides [H58]. After 15 days with 2–4 MBq of ^{32}P and 5.5–11 MBq of ^{198}Au there was marked blunting of the mucosal folds in both large and small intestines. Chronic inflammation was observed in the submucosa with slight fibrosis. Architectural changes in the myofibrils of the smooth muscle were also seen leading to early interstitial fibrosis and diffuse myofibrillar degeneration. However, since the distance from serosa to mucosa in mice is less than 1 mm (compared to more than 2 mm in humans) it is difficult to extrapolate these results to man.

327. Acute irradiation of the G.I. tract from injected insoluble beta emitters has been studied in rodents and dogs [S51]. The radiosensitive cells are in the crypts located beneath the mucosal surface at depths of some 0.2 mm in the large bowel of the rat and some 0.8 mm in that of the dog. The dose delivered to these cells depends on the energy of the beta radiations, the mass of the intestinal contents and the residence time of the radionuclide in any particular segment of the bowel.

328. In the rat, the LD_{50}s for suckling, weanling and adult animals for ^{106}Ru-^{106}Rh given by gavage were 55, 670 and 330 MBq/kg, respectively, and about 0.2 TBq/kg for ^{147}Pm in adults [S51]. In the neonatal animals the lower ileum showed the principal signs of damage and there was evidence that the ^{106}Ru-^{106}Rh pair, like ^{141}Ce [I6], ^{95}Nb [M53] and the actinides [S51] is absorbed into the epithelial cells of the mucosa in the immature small bowel. In the adults receiving a normal diet the main pathology was seen in the caecum and lower large bowel while the insensitivity of the weanlings was thought to be due to the relatively rapid transit of the gut contents in these segments of the young animal. Deaths occurred in the adults when 280 MBq/kg ^{106}Ru-^{106}Rh and 0.16 TBq/kg ^{147}Pm were exceeded, usually in the first or second week after treatment. Radiation doses to the target cells in the caecum were estimated to be similar for both radionuclides and suggested a $LD_{50/10}$ for ingested insoluble beta emitters in the rat of about 33 Gy [C26].

329. In dogs fed with ^{106}Ru- ^{106}Rh, the earliest death was at nine days after a dose of 130 MBq/kg but the survival time could not be closely related to the dose and one animal survived nearly 21 weeks after receiving 110 MBq/kg [S51]. Following ingestion of 92–150 MBq/kg the mucosa of the mid and lower colon were usually denuded at focal sites within eight days, and frequently the damage was irreparable. Animals surviving acute death had persistent diarrhoea until they were killed or died. The LD_{50} for acute death from ingested ^{106}Ru-^{106}Rh was estimated to be 130 MBq/kg and the $LD_{50/180}$ for delayed death, 100–110 MBq/kg [C26]. Direct measurements of the radiation dose carried out by means of thermoluminescent dosimeters sutured into the G.I. walls showed that the LD_{50} dose in the dog is about 40 Gy distributed over approximately 18 hours to critical tissue in the large bowel, regardless of the mode of death.

2. Bone and cartilage

330. Internal irradiation of bone has been investigated in various species following the administration of osteotropic radionuclides [V15]. It is convenient to divide these bone seeking radionuclides into two broad categories, volume and surface seekers, according to their basic metabolic behaviour [M55]. The alkaline earths, radium, calcium and strontium are volume seekers, distributing over a long period of time throughout the bone mineral by chemical exchange. From the blood stream they are rapidly transferred to accessible bone surfaces before concentrating in osteocytes involved in active mineralization and often ultimately being buried beneath new bone. Radium, unlike calcium or strontium, may remain for several days on the bone surfaces, particularly around the Haversian canals. Short-lived isotopes like ^{224}Ra may largely decay and irradiate these surfaces before they are incorporated into bone matrix. Plutonium and thorium are examples of the surface seekers which accumulate on the periosteal and endosteal surfaces, and may be resorbed or buried during growth or remodelling of bone. Plutonium is also concentrated in bone marrow, both as aggregates in macrophages and diffusely by a mechanism which is not understood.

331. Significant internal irradiation of bone in man has resulted from the deposition of isotopes of radium in the skeleton. ^{226}Ra and ^{228}Ra have been studied extensively since 1947 in groups of watch-dial painters, radium chemists and patients given radium therapeutically [A28, L36, S53]. Records in the United States have now been centralized at the Centre for Human Radiobiology at the Argonne National Laboratory, Chicago [R39]. ^{224}Ra was also given to about 2000 patients in the Federal Republic of Germany between 1944–1951 for the treatment of tuberculosis and ankylosing spondylitis [S54, S55]. ^{224}Ra at lower dosage is still used for treating ankylosing spondylitis in adults.

332. Severe bone dysplasia resulting in fractures especially of the long bones, vertebral collapse and severe bone pain has been associated with burdens of ^{226}Ra and ^{228}Ra [E24]. The effects of these isotopes cannot easily be distinguished in man [M56]. Hasterlik and colleagues [H59] have listed the following lesions seen on routine radiological examinations, often in subjects without symptoms: coarsening of the trabecular pattern; localized areas of bone resorption; patchy sclerosis; small and large bone infarcts; aseptic necrosis.

333. Some 20 years after the deposition of radium in the skeleton, characteristic punched-out areas alternating with areas of increased density are seen in the skull [L37]. The long and flat bones have a moth-eaten appearance. Increase in the number and severity of the lesions demonstrated over a period of years, occurs together with a progressive decrease in the body burden of radium. However, it has been concluded [H59] that body burdens in excess of 0.004 MBq ^{226}Ra are necessary before the radiographic lesions can be distinguished from those normally associated with ageing.

334. The microradiographic appearance of bone in subjects carrying radium burdens is similar to that found in dogs long after treatment with ^{226}Ra [J18] or ^{90}Sr [R40] and characteristic of vascular damage. Large numbers of Haversian canals are seen to be plugged with densely calcified material and the osteocyte lacunae may also be affected [H62, R40, L38]. In addition to complete plugging, a greater number of canals are found with highly calcified minor lamellae [H62] although large and bizarre resorption cavities are also present [J18].

335. Spiers has suggested [S56] that the skull lesions associated with radium burdens are related to the relatively high marrow dose to be expected in these areas. Measurements of mean path lengths in trabecular bone and in marrow cavities [S67] have enabled calculations to be made of the mean dose to the marrow spaces and to the endosteum, considered as a tissue layer of thickness 10 μm adjacent to trabecular surfaces [I1]. In the human skull the ratio of the mean path length in trabeculae relative to marrow spaces in the parietal bone was found to be 1.31 as compared to 0.16–0.30 for other bones, and the fraction of marrow irradiated was calculated to be some three times greater [S56]. However, on the assumption that a terminal radium burden of 0.37 MBq ^{226}Ra was evenly distributed through a 7 kg skeletal mass, the accumulated mean marrow dose would only be 5–10 Gy in 50 years whereas the dose to endosteal tissue would be 30–40 times greater. In parietal bone the marrow within range of the alpha particles would receive a dose 3–4 times greater. A quality factor of 20 would apply to all these doses [P60].

336. Radium-224 largely irradiates bone surfaces and sites of active mineralization at the time when the blood level is high. It has been estimated [S55] that the dose from ^{224}Ra to the endosteal surface in man is some nine times higher than the average skeletal dose whereas for ^{226}Ra it is less than two-thirds. Growth retardation, as measured by height, has been reported [S54] in 70% of children who had been injected with ^{224}Ra at 1–5 years, 44% injected at 6–14 and 12% injected at 15–20 years. Abnormal bone growths classified as osteochondromas were seen [M57] in 15% of the 204 juveniles receiving a mean skeletal dose of about 11 Gy from injections 0.85–1.7 MBq ^{224}Ra/kg over an average period of 11 months [S58]. These exostoses mostly developed in the long bones at sites where the metaphyses incorporated the activity; 73% were in males who have a natural preponderance of the hereditary tumours. Tooth breakage was also seen [M57] with maximum frequency of 15% in the 59 children injected between 16–20 years, although teeth are fully formed at this time. The tooth loss is characterized by resorption of the tooth near the gum line and breaking off of the crown. Similar changes have been induced in rats following the administration of ^{224}Ra and ^{226}Ra [R41] and in dogs with ^{239}Pu [T19].

337. Bone dysplasia in animals resulting from the administration of most bone seeking radionuclides has been widely reported. The early uptake of sufficient activity in epiphyseal growth cartilage, in the endosteal surface of the metaphysis and in the periosteal surface of the diaphysis, may rapidly destroy osteogenic tissue and damage the blood supply, causing a reduction in the rate and amount of growth. Irradiation to a high dose over a long period may result in bone fibrosis, necrosis and fractures at characteristic sites.

338. MacPherson and colleagues studied in great detail the inhibition of growth in weanling rabbits injected with 3.7 or 2.2 MBq/kg ^{90}Sr [M58]. Cellular damage was shown by an increase of disintegrating cell nuclei and decrease in mitosis in an area of high uptake in the metaphysis. A total dose of about 0.74 Gy received at a rate of about 0.08 Gy/h was sufficient to

cause a noticeable effect. The damage resulted in a thickening of the cartilage plate with failure of resorption. Damage to the blood supply, shown by leakage of red cells into the tissues, was noted after some 8 Gy at 3 days after injection, and in the animals receiving several tens of Gy the damage was so severe that the thickened cartilage plate became separated as a bar of dead bone. Fibrosis occupying marrow spaces between the trabeculae was seen after some 30 days and cumulative doses of 190 Gy. These animals had a marked reduction in tibial growth rate and ultimate shortening of the limb, whereas no difference in growth from control animals was seen for the animals receiving lower doses.

339. The incidence of radiation-induced bone fractures has been reported in the beagles at Utah [T19]. Radiation-induced fractures are unique in that they involve a minimum amount of pain and inflammatory response. Following single I.V. injections the fracture rate increased rapidly above 0.12 MBq/kg ^{226}Ra and ^{228}Ra, 0.033 MBq/kg ^{239}Pu and 0.0037 MBq/kg ^{228}Th [T20, T21]. Fractures due to ^{90}Sr were only seen in one animal who received 3.7 MBq/kg. The anatomical distribution depended on the radionuclide. Fracture healing was low in animals treated with ^{228}Th and ^{228}Ra but was high for ^{226}Ra and ^{239}Pu, 80% of the rib fractures induced by 0.11 MBq/kg ^{239}Pu being repaired in a satisfactory manner. The incidence and time of appearance of fractures is related to the average skeletal dose. Of the significant number produced in dogs by an activity level of 0.11 MBq/kg ^{239}Pu the earliest occurred approximately 390 days post-injection with an average skeletal dose of about 32 Gy [T19].

340. In beagles at Davis, California, kept on a regime of continuous intake of ^{90}Sr and ^{90}Y in the diet from mid-gestation to 1.5 years of age [M69], few fractures occurred at the highest levels of intake with maximum body burdens of 13.1 MBq ^{90}Sr delivering an average skeletal dose of 133 Gy over 2 years [M68]. The smallest dose from ^{90}Sr for which any radiographic bone damage was observed was about 70 Gy by 10 years of age, and occurred at an intake level of 0.44 MBq/d resulting in a maximum body burden of 1.7 MBq.

341. In the beagles given a total activity of 3.1 MBq ^{226}Ra in 8 semi-monthly intravenous injections starting at 14 months of age, 25% of the animals suffered fractures within six months of the last injection [M69]. In these cases the bone marrow had received an average dose of less than 50 Gy [M68]. Trabecular coarsening occurred in 100% and fractures in 50% of animals given a total activity of 1 MBq ^{226}Ra. The earliest fractures appeared soon after the last injection at 18 months, when, by extrapolation of the reported dosimetry, about 8 Gy would have been given on average to the skeleton.

342. Cartilage is inevitably irradiated during intra-articular injections of radioactive colloids for the radiotherapy of chronic synovitis. ^{198}Au-colloid was used initially [A27, M54] but its gamma-ray emission is more penetrating than is necessary to sterilize the cells of the synovium. In addition, the small size of the colloid particles results in substantial leakage of activity from the joint cavity and accumulation in the regional lymph nodes [T18]. The pure beta emitters ^{90}Y-silicate citrate and ^{32}P-chromic phosphate as colloids are currently used for the therapy of knee joints [R38]. For other joints such as in the hip, or the fingers, the less penetrating radiations from ^{186}Re-sulphide or ^{169}Er-citrate, respectively, may be used [I7]. The activities administered have been determined empirically to prevent cartilage necrosis or flexion deformities, while minimizing the failure rate of the radiation synovectomy. For the knee some 110–180 MBq ^{90}Y is commonly used and the dose delivered to the membrane is estimated as about 60–80 Gy [S52]. The dose falls rapidly beyond about 2 mm from the synovial surface [B61]. The colloid is phagocytosed into cells on the surface of the synovial membrane, although some is deposited on fibrin in the synovial fluid [W41]. Two cases of knee joint rupture have been reported, presumably arising from cartilage necrosis [D44].

3. Lung

343. The lungs of miners of uranium, fluorspar and other minerals are subject to internal irradiation from radon and its daughter products present in the air of mines in concentrations varying widely between $<10^3$ and 10^6 Bq per cubic metre of air. Radon diffuses rapidly through the body and the greater part is exhaled within its half-life of 3.5 days. Its immediate daughter products with a collective physical half-life of some 20 min become rapidly attached to the dust in the air of the mine and a high proportion of the activity breathed may be deposited in the respiratory tract. For a full discussion of these problems see Annex D. The induction of lung tumours in these workers and the possible influence of other ambient factors such as tobacco smoke on the induction of neoplastic and non-neoplastic diseases of the respiratory tract in man are also treated in Annex L.

344. In animals internal irradiation of the lung by radionuclides has been studied following the inhalation or intra-tracheal instillation of radioactive particles. The radiation dose delivered to tissues by a given radionuclide depends on its initial distribution of deposition and its rate of clearance from the lung.

345. Soluble materials may be cleared from the lung within a few days by rapid absorption into the blood and by transport to the oesophagus by mucociliary action followed by swallowing. They are then translocated throughout the body and may remain for long periods in the skeleton or in other tissues depending on their biochemical properties. Insoluble materials may remain in the lung for years, being cleared by local dissolution or transport (probably as intact particles) to the bronchial and tracheobronchial lymph nodes. The concentrations in regional lymph nodes may become many times those in the lung and in both tissues radioactive particles may form locations for the delivery of high radiation dose rates.

346. A comprehensive review of the radiation effects of radioactive particles deposited in the lungs of experimental animals has been published by the ICRP [I8]. Non-neoplastic pulmonary lesions resulting in early death occur when the activity is deposited in sufficiently high concentrations. Lower concentrations result in progressive fibrosis and may lead to death from pulmonary insufficiency. Data available from several animal species suggests that such non-stochastic processes might be expected to occur after an alveolar deposition of more than 0.37 kBq/g lung of alpha-emitting radionuclides [I8].

347. Rats receiving lung burdens of 0.22–0.74 MBq/g lung of relatively insoluble $^{238}PuO_2$ and $^{239}PuO_2$ died

within a few days from severe pulmonary oedema [S59]. Radiation pneumonitis caused early death in rats exposed to a cumulative dose of 98 Gy from a burden of about 0.15 MBq/g lung from relatively soluble $^{253}EsCl_3$ [B62]. In baboons, initial lung burdens of 3–10 kBq/g lung $^{239}PuO_2$ resulted in death at 1–6 months [M59]. The earliest deaths were due to alveolar oedema and vascular injuries, but after 2 months the alveolar septa were thickened and collagen deposits and progressive fibrosis led to respiratory insufficiency and death.

348. Deaths within 500 days due to radiation pneumonitis and pulmonary fibrosis were seen in dogs exposed to high concentrations of relatively insoluble forms of beta/gamma emitting radionuclides such as ^{90}Y, ^{91}Y, ^{144}Ce, and ^{90}Sr in fused aluminosilicate particles [M60, R42, B60, H60, S60, H61]. The alveolar septa were seen to be thickened with hypertrophic and hyperplastic alveolar lining cells. Frequently the alveoli were filled with protein material. Various degrees of fibrosis occurred, including fibrotic thickening of the pleura. The extent of fibrosis was increased in the longer surviving animals [J19].

349. The rate of dose delivery to lung is an important factor in determining the cumulative radiation dose and the time for death. ^{90}Y having a half-life of 64 h, requires a relatively low cumulative dose to produce a given effect and such effects will occur earlier; on the contrary, ^{90}Sr with a half-life of 28.8 a requires a higher cumulative dose and the effects are delayed. The smallest initial lung burdens to cause death in dogs within 500 days from radiation pneumonitis and pulmonary fibrosis ranged from 22 MBq/kg for ^{90}Y to 1.1 MBq/kg for ^{90}Sr [H60, S6O]. However, the cumulative dose delivered ranged from 93 Gy to 400 Gy and the minimum time to death from 7.5 days to 184 days, respectively.

350. A similar effect of dose rate may be seen for alpha emitters where the half-lives are long and the variable is chiefly the rate of clearance from lung. Death caused by respiratory insufficiency in beagle dogs resulting from pulmonary fibrosis occurred about 1600 days post-exposure to a lung burden of insoluble $^{239}PuO_2$ at levels >0.74 kBq/g lung [W42]. However, similar deaths were observed in less than 1000 days following exposure to the more soluble $^{238}PuO_2$ at levels >0.37 kBq/g lung [P30]. The greater solubility of $^{238}PuO_2$ than of $^{239}PuO_2$, attributed to the high specific activity of ^{238}Pu [F50, F51], was indicated by the faster clearance from lung and the ten times greater retention of ^{238}Pu in the skeleton at 70 months post-exposure [B64, P31]. Similarly, following exposure to the even more soluble ^{238}Pu nitrate at initial levels of about 0.37 kBq/g lung, death occurred in less than 300 days [P32].

351. In rats with initial lung burdens smaller than those necessary to produce acute effects, lungs are seen to have a smaller infiltration of serum proteins but an increasing deposition of fibrin and proliferation of bronchiolar epithelium and alveolar lining cells up to a year after exposure [S59]. Early hypoxaemia results in a compensatory increase in the blood mass and circulation time, although haemoglobin and erythrocyte concentrations are normal [K41]. A second phase of hypoxaemia appears at 8 months and at this time the total haemoglobin and erythrocyte mass remains unchanged. Early ultrastructural changes consist of an increase in the length of the air-blood pathway due to oedema [A32]. Later, proliferation of connective tissue cells increases the thickness of the basement membrane. The hypoxaemia is thus consistent with alveolar-capillary blockade.

352. In dogs quite small lung burdens (about 0.26 kBq/g lung $^{241}AmO_2$) produce local areas of dense pulmonary fibrosis and mineralization with bronchiolar and alveolar cell hypoplasia [T22, B65]. There may be marked fibrous pleural thickening and obliterative fibrosis of small arteries, together with some dense peribronchial fibrosis. Larger burdens produce functional changes such as increased respiration rate, decreased vital capacity and decreased partial pressure of oxygen and oxygen saturation [T22, B66]. In baboons lung burdens of 37–74 Bq/g lung $^{239}PuO_2$ lead to progressive fibrosis and respiratory insufficiency culminating in death 1–3 years later [M59].

353. A different sequence of events has been observed in the Syrian golden hamster following 15 weekly instillations of ^{210}Po with a half-life of 138 d [L40, A33]. Transient radiation pneumonitis and hyperplasia of the bronchiolar epithelium were observed together with a progressive epithelization of alveoli with a large variety of cell types. The latter became the dominant lesion at 30–180 days after the last instillation. This difference in pathology is presumably due to a species effect.

4. Liver

354. Internal irradiation of the liver for therapeutic purposes has been carried out in patients with colonic cancer using ^{32}P-phosphate colloid immediately following colonic resection [G34]. 550 MBq were injected in equal amounts into catheters located in the superior mesenteric and coeliac arteries. Previous trials in rats [N14] had shown that when the colloid was injected into the arterial supply of the gut, it became well mixed in the portal circulation and 70% of the activity was fairly uniformly distributed in the liver. A total cumulative dose of some 50 Gy given to the liver by this means has caused no significant tissue damage or functional changes, within the first year of follow-up, although a temporary radiation hepatitis was seen in one of the three patients one month after injection [G34].

355. In another much larger trial [A34], ^{90}Y-resin microspheres together with a chemotherapeutic agent, 5-fluorouracil, were injected into the hepatic artery to treat liver metastases in patients with primary cancer of the colon and rectum. 3700 MBq ^{90}Y was used, calculated to give a beta-radiation dose of some 100 Gy to the liver. No significant effects were associated with the internal irradiation in 25 patients surviving on average 26 months.

356. Following the injection of a pharmaceutical preparation containing soluble ^{224}Ra, irradiation of the liver arises both from the decay of the radionuclide during its initial deposition in soft tissues and from that of its daughter products with their own characteristic distributions in the body. ^{220}Rn is readily soluble in lipids and ^{212}Pb is bound to red cells as well as concentrating in the kidney and liver. In man chronic liver disease, usually cirrhosis, has been reported in 8% of 106 adult males injected with ^{224}Ra for the intended therapy of tuberculosis and in 3% of 329 patients treated for ankylosing spondylitis [S58]. The average activity of 0.84 MBq/kg given to male patients with

tuberculosis was more than double that administered for ankylosing spondylitis. The incidence was not significant in women and it was suggested that this might be related to the greater exposure of men to known liver toxins such as alcohol [S58]. Fifteen of the 18 cases were identified between 12 and 24 years after administration of the activity. The radiation dose to the liver has not been reported.

357. Many studies of patients receiving thorotrast as an intravascular contrast agent for angiography have shown an unusually high incidence of non-malignant liver disease [V17, D45, K42]. In 1237 patients traced in Portugal [D45], 2.7% of 931 deaths were attributed to liver cirrhosis or fibrosis. Some 25 ml of thorotrast was usually injected corresponding to an activity of about 0.022 MBq $^{232}ThO_2$ [K43]. The radiation dose delivered to tissues is difficult to estimate. However, the mean alpha dose to the liver of a 70 kg weighing man at 30 years after injection of 25 ml of thorotrast has been calculated to be 7.5 Gy [K43]. For nine Japanese patients who died of liver cirrhosis after a latent period of 21–41 years, the dose rates to liver were estimated to be between 0.17–0.53 Gy/a [K42] providing cumulative doses between 4.7–16.8 Gy [K42, K50].

358. Massive internal irradiation of the liver can produce liver cirrhosis in rats, rabbits and dogs [M61]. In rats injected with 38 MBq/kg ^{144}Ce and 0.25 MBq/kg ^{239}Pu nitrate liver cirrhosis was found in all the animals surviving beyond 200 days. The liver doses received were 160 and 57 Gy, respectively.

359. Hepatic changes induced by ^{239}Pu have been observed in the dogs at Utah [T23]. Following a single intravenous injection of 0.11 MBq/kg tetravalent ^{239}Pu the activity deposits in the hepatic cells and remains for 2–3 months before being transferred to the reticulo-endothelial cells lining the sinusoids. The evidence suggests that the transfer occurs on the death of the parenchymal cell and is related to dose. The lesions produced are principally hepatic cell necrosis followed by regenerative changes. Significant regeneration was seen at doses as low as 0.62 kBq/kg ^{239}Pu with mean cumulative liver doses of less than 0.8 Gy. Regeneration was sufficient to maintain normal liver weight, except for some dogs given the highest doses of 0.11 MBq/kg ^{239}Pu. In these cases liver atrophy was observed as early as 474 days from a dose of about 23 Gy. Based on the appearance of ascites, atrophy was probably significant as early as 350 days from doses of 15–17.5 Gy.

360. Decreased phagocytosis in liver was shown in mice after intravenous injection of polymeric ^{239}Pu (0.67 and 1.33 mBq/kg). At the time, when this effect became manifest, the accumulated liver dose was estimated to have been greater than 20 Gy. The depressed function coincided with the translocation of Pu from the liver to the lung and kidney [K49].

5. Kidney

361. Severe renal disease has been frequently found in patients who had received injections of ^{224}Ra [S58]. Kidney insufficiency and a wide range of renal disease were the recorded causes of death in nearly 13% of 222 patients. In both the living and dead subjects the incidence of recorded disease was 3.7% of 373 and 6.7% of 239 patients injected with a total activity grouped in the ranges of 0.015–0.52 and 0.53–2.4 MBq/kg, respectively. However, such evidence for a dose-related effect must be considered with some caution because the higher dose group contained larger numbers of patients originally affected by tuberculosis and the use of different drugs in the two groups may have affected the incidence of kidney disease.

362. A characteristic radiation nephritis together with a significantly increased serum phosphorus have been observed in beagles injected with 0.037–0.11 MBq ^{228}Th/kg [B79, C27]. ^{228}Th continually generates its daughter ^{224}Ra and some of this reaches the blood stream and is redeposited in the tissues with its own characteristic distribution. The average total dose to the kidneys contributed from ^{228}Th, ^{224}Ra and its daughters has been estimated as some 10–30% of the average skeletal dose [M62], less than approximately 3.6 Gy [S77].

6. Thyroid

363. The thyroid is regarded as a radioresistant organ from the point of view of cell death and failure of function. Results are available from irradiation in its unstimulated normal state in order to reduce metabolic rate and to control symptoms of angina in patients with cardiac insufficiency. At least 300 Gy is required to cause total ablation within a short time, e.g., 2 weeks. This can be achieved with single oral doses of 1850–3700 MBq of ^{131}I, resulting in an uptake of about 37 MBq/g in the thyroid [G12].

364. Unavoidable external irradiation of the thyroid sometimes occurs in the treatment of head and neck cancers. Several authors have observed hypothyroidism after normal fractionated therapy, e.g., [M23]. These authors reported five cases of myxoedema within 4–12 months after doses of about 25–49 Gy received by the thyroid. Rogoway et al. [R15] reported on patients treated for Hodgkin's disease developing myxoedema after irradiation of the thyroid to about 40 Gy in a fractionated treatment. Of these, 4% developed myxoedema after receiving both external radiation and lymphangiography, whereas no patients receiving either lymphangiography or the external radiotherapy alone were observed to develop hypothyroidism. This result was attributed to an increased radiosensitivity of the thyroid after stimulation into increased activity caused by the iodine present in the contrast medium used for lymphangiography.

365. There are numerous reports of reduced thyroid function caused by irradiation with ^{131}I or ^{125}I. About 90% of the radioactivity is concentrated in the colloid but the dose delivered by the relatively energetic beta/gamma emissions from ^{131}I is distributed fairly uniformly throughout the gland. Iodine-125, on the other hand, decays by electron capture and each disintegration is associated with a cascade of x rays and Auger electrons [D43]. A number of the latter have energies below 3 keV and about one-quarter of the radiation dose is delivered to the thyroid by electrons with a range of less than 0.4 μm in tissue. The sites of hormone synthesis, situated in the apices of the follicular cells close to the colloid-cell interface must therefore receive a significantly higher dose than the more distant cell nuclei. The mean dose to the gland from ^{125}I (in contrast to ^{131}I) is therefore somewhat higher than the dose to the nuclei of the parenchymal cells. Difficulties may be expected in extrapolating animal data to man owing to the difference in the scale and morphology of the cells in different species.

366. Several clinical trials of ^{125}I for the treatment of hyperthyroidism have been initiated on the basis that the reproductive capacity of the thyroid tissue is more radiosensitive than hormone secretion. Some estimates [G37, L42] have suggested that the microscopic dose delivered at the colloid-cell interface is about four times that at the nucleus, and about twice the dose averaged over the gland, although these factors depend on the gland mass and the colloid fraction.

367. As with other cell types and tissues, it appears that irradiation of the thyroid at low dose rate allows time for the repair of sublethal damage. In cell survival studies in rats [G35] a study on the effects of x rays, ^{131}I and ^{125}I gave D_os of 4.5, 55 and 94 Gy, respectively, when the mean dose to the gland was used for comparison. The extrapolation number for x rays was 1.7 whereas for radioiodine the survival curves were exponential from the origin. The difference between ^{131}I and ^{125}I was attributed to the relative sparing of parenchymal cell nuclei due to the inhomogeneous dose distribution from ^{125}I, particularly when it was noted that about 30% of the proliferating cells would be stromal and located at greater distances from the active colloid than the follicular cells.

368. Electron microscopic examination of thyroid tissue following irradiation has indicated that ^{131}I produces diffuse damage whereas ^{125}I produces localized effects at the colloid-cell interface [L41]. From experiments using rats, several workers have concluded that ^{131}I is less effective than ^{125}I in disturbing hormone synthesis than in affecting the response to TSH [G36, V18, L41]. However, Jongejan and van Putten found no such evidence and concluded that the ratio of $^{125}I/^{131}I$ activities necessary to produce similar effects on iodine uptake, serum T4 and damage to thyroid structure lay in the range of 11–17 [J20]. Gross et al. had calculated a ratio of 16 for both the mean radiation dose to the gland and the radiobiological effect as determined by radioiodine uptake suppression [G36].

369. A large body of data exists for treatment of hyperactive thyroid glands, usually by orally administered radioactive ^{131}I. In its hyperactive state the thyroid is more radioresponsive. Werner et al. [W22] observed a return to normal, or even hypothyroidism after fractionated doses of 1.5–3.7 MBq ^{131}I, giving estimated total doses of 2–8 Gy. A greater proportion of children than of adults responded, as has also been reported by Einhorn and Wikholm [E12]. Somewhat higher doses are normally used to reduce elevated function and if hypothyroidism results it is permanent rather than transient [F12]. The hypothyroidism develops slowly. In 7.5% of the cases it is apparent within the first year [W22, B23], and subsequently 3% per year of the patients develop symptoms up to 26% at 7 years [B23].

370. The total dose delivered to the gland depends on the uptake and rate of biological clearance. For diagnostic doses with a relatively long retention in the thyroid, the ratio of total doses delivered per unit activity of ^{131}I and ^{125}I, is as low as 1.6 for an uptake of 25% [M63]. However, ^{131}I delivers some seven times the initial mean dose rate to a 20 g thyroid compared with that from an equal activity of ^{125}I [S50].

371. Mean activity levels of ^{125}I were used for therapy in single and, where necessary, multiple doses ranging between 37 and 1480 MBq, corresponding to concentrations between 0.44 and 37 MBq/g thyroid [A35]. It is difficult to compare the frequency of induction of hypothyroidism between groups, because of variations in the populations treated and their diets. However, at least two centres [B67, S61] have abandoned trials because the results showed no improvement on those obtained with ^{131}I. A reduction in the dose necessary to reduce the incidence of hypothyroidism was accompanied by an unacceptable increase in the rate of persistent hyperthyroidism. Follow-up periods have been too short to indicate whether the rate of delayed hyperthyroidism from ^{125}I is lower than that following treatment with ^{131}I [B67]. Clinically, the loss of function in hypothyroid patients is not considered very serious and can be easily managed by administration of synthetic thyroid hormone, providing the late appearance and insidious nature of the symptoms are recognized.

372. In 1954 following a thermonuclear explosion at Bikini radioactive fallout was deposited on the Marshall Islands. Inhalation or ingestion of iodine radioisotopes (principally ^{131}I, ^{132}I, ^{133}I, ^{135}I) by the population resulted in exposure of the thyroid glands to significant internal, in addition to external, irradiation. Within nine years thyroid nodules were noted in children who had received the highest dose on Rongelap Atoll [L43]. In a subsequent follow up over the next 15 years [L43], 67% of individuals exposed at ages below 10 years and 15% of the remainder, developed nodules which have since been surgically removed. Doses to the thyroid were estimated to lie in the ranges 10.2–42.6 and 5–30 Gy, respectively.

373. Five children exposed at ages below 5 years showed some degree of growth retardation and two boys developed myxoedema [S62]. A recent study [L43] has shown that the population as sampled on Rongelap Atoll have a significantly impaired thyroid reserve as indicated by a smaller increase in T4 following TSH stimulation. Additional biochemical evidence such as basal and TRH induced serum TSH, and serum T4 concentrations suggests that at least four of 43 subjects have impaired thyroid function some 25 years after a thyroid dose from mixed radioiodine isotopes, estimated in three of these to be less than 3.5 Gy.

374. There is little data on the incidence of hypothyroidism in subjects receiving small radiation doses from radioiodine [H69, H70]. Preliminary results of a study of patients receiving ^{131}I for diagnostic uptake tests [U3] have indicated an incidence of 1.8% within an average follow-up period of 16 years. Hypothyroidism became evident in 2.0% of 146 patients and 3.3% of 151 patients who had received doses in the range of 0.31–0.80 and 0.81–19 Gy, respectively. However, in a study of 1378 children exposed to ^{131}I fallout, the incidence of overt hypothyroidism over a similar period of follow-up was not found to be significantly different from that in 3801 non-irradiated controls [R51].

375. Radiation-induced damage may not result primarily from effects on the thyroid parenchymal cells. In culture, these are rather radioresistant [D21] and they also appear unresponsive in the whole animal. Rather, the effects could be mediated via an autoimmune reaction, initiated by a large sensitizing dose of thyreoglobulin into the circulation [M23, B23, B13] or by radiation effects on the microvasculature, particularly after acute doses [R1]. Another possible explanation could be the impairment of long-term proliferative potential of epithelial cells.

7. Gonads

376. The effects of intramuscular injections of 0.048 MBq/g body weight ^{32}P on the ovary and testes of 30-day old mice have been studied at autopsy 30 days later [S63]. The ovaries showed severe damage with complete absence of normal oocytes or follicles. The seminiferous tubules of the testis were affected non-uniformly. Sperm cells were seen in considerably reduced numbers. Sertoli cells and interstitial cells were not affected.

377. Samuels studied the localization and oocyte survival in the ovaries of mice following intra-peritoneal injections of ^{210}Po which became localized in the follicular cells [S64]. Significant loss of oocytes occurred at four days after injections of 37 mBq/g body weight with an apparently non-threshold dose-effect relationship. There was no dependence on the age of the animal between 21–150 days. An activity of 3.7 Bq/g body weight destroyed oocytes at all stages of maturation within 30 days, at which time no pathological changes were seen in the uterus. In comparison with external ^{60}Co irradiation (see section IV.A.), the RBE appeared to depend on dose rather than dose rate and was thought to become as high as 50 from a mean dose of 110 μGy to the ovary resulting in a primary oocyte survival of 79%. For a cell survival of 2.7% at 30 days an RBE of 4.8 was calculated from a mean dose to the ovary of 54 μGy.

378. Activities of 0.18–0.74 MBq ^{90}Sr injected intravenously in female mice on the 11th day of pregnancy seriously affected the oocytes in the developing ovaries [R44]. After the maximum dose, the total number of oocytes relative to those in unirradiated controls was 21% at 56 days and 15% at 170 days post-partum. The reduction in cells at all stages of development was strongly dose-dependent but the naked oocytes and the young follicles appeared to be the most sensitive. Over a relatively short period of 100 days the irradiated mice produced litters of normal size and frequency, indicating that the pool of mature follicles was sufficiently large to compensate for the losses in young oocytes.

379. Further work by the same authors showed a strong relationship between the loss in oocytes and the time of administration of the activity [R45]. ^{90}Sr is more effective in the mouse the later it is injected between 8 and 19 days of the intra-uterine life. However, it has been shown using external irradiation [B68] that the sensitivity of the oocytes decreases markedly between the 15th and the 19th day, increasing only again at birth. It has therefore been suggested [R45] that some of the ^{90}Sr activity injected after the 15th day when the foetal skeleton has started to ossify, will be incorporated into it and together with ^{90}Y provide an additional source of irradiation to the ovary. In the foetal mouse the gonads are within the range of many of the beta rays originating in the skeleton. This might also account for the very marked effect of ^{90}Sr administered just before birth when the oocytes are in the radiation-sensitive dictyate stage. An activity of 0.011 MBq ^{90}Sr given to the mother at this time produced a significant reduction in naked oocytes at 56 days post-partum, [R46] even though the mean activity measured in the ovaries at 10 days post-partum was only 17 mBq kg^{-1} ^{90}Sr with 9.2 mBq kg^{-1} ^{90}Y (wet weight).

380. Tritium can be incorporated into all parts of the living animal, particularly as ^{3}HOH. The effects on the ovary have been studied [D46] in 14-day old mice following continuous administration of ^{3}HOH to the mothers in the drinking water during pregnancy and lactation. Oocyte survival decreased exponentially without threshold in the range of 3–410 kBq/ml body water, as measured in the urine. The LD_{50} was 74 kBq/ml, which would deliver a radiation dose of 0.0044 Gy/day. Continuous external γ-irradiation of the mice with ^{60}Co from conception to 14 days post-partum showed that the higher gamma dose rates were more effective in cell killing, but that the response was definitely smaller than that using ^{3}H, with an LD_{50} of about 0.01 Gy/day. The RBE therefore varied inversely with dose, ranging from 1.6 for 0.5 Gy of gamma rays to 1.9 for 0.25 Gy and up to 2.8 for the lowest exposures.

381. The effect on mice of ^{99m}Tc given as pertechnetate in daily intravenous doses to pregnant and lactating females has been investigated [L44]. The tissue distribution, and response to injected $NaClO_4$, of ^{99m}Tc in the foetus, was different from that in maternal tissue, and suggested the involvement of Tc in foetal metabolism. Significant effects on the body weight of mature mice were found extending into the third generation from doses as low as 185 kBq/d, giving about 10 mGy to the primary foetus during gestation. Hairlessness and sterility were observed in mice exposed to ^{99m}Tc in the milk secreted by lactating mothers given 1.8–18 MBq/d. However, it is difficult to distinguish radiation effects from the chemical toxicity of technetium since no stable isotope exists.

8. The eye

382. An increased incidence of cataract has been noted in patients who had received injections of Peteosthor containing ^{224}Ra, principally for the treatment of ankylosing spondylitis or tuberculosis [S58]. Periods of 7–26 years have intervened between therapy and cataract diagnosis. Since cataract is normally rare in young people, an incidence of 4% at ages between 14–46 years in 204 patients receiving ^{224}Ra as juveniles was particularly striking. In adults the incidence was 1% in 300 men receiving less than 0.53 MBq $^{224}Ra/kg$ and 4.5% in 155 of those receiving greater doses.

383. If radium isotopes are concentrated in the pigmented cells of the iris, as has been observed in dogs and rodents [T24], the emitted alpha radiation may well affect cell division in the lens and account for the induction of cataract. However it has not yet been determined if these lesions have a special character or are similar to those produced by uniform external irradiation. In addition, a possible association with any prolonged drug therapy or with the diseases originally affecting the patients cannot be excluded at this time.

384. Introduction of polymeric plutonium nitrate into dogs by inhalation has been found to result in an accumulation of about 0.01% of the total activity in the eye [S39]. The radiation dose received by the cornea was greater than that received by either the lens or the aqueous humour. No changes in the retina were observed for doses of less than 10 mGy, but local retinal dystrophy occurred in 75% of animals receiving doses of 1.7 Gy and 30% of those receiving 10–100 mGy.

9. Haematopoietic tissues

385. The late effects of chronic irradiation of the bone marrow by radium has been studied in female dial painters first employed before 1930. An analysis of the serum protein levels [P33] suggested a slight increase in α-2 globulin with age in those groups with the higher intakes of activity > 37 kBq/kg. There was little evidence for late effects of radium on white cell counts [P35]. A symptom-free but statistically significant reduction in haematocrit was found in the groups receiving the highest skeletal doses [P34], especially those with greater than 10 Gy, although these did not contain a higher frequency of low haematocrit values suggestive of anaemia. The dose rate to marrow within trabecular bone of a man with a 37 kBq burden of ^{226}Ra has been estimated to be about 16 mGy/year [M64].

386. The use of radioiodine to treat patients with metastatic thyroid cancer is generally limited by the dose to the bone marrow [B69]. In a large series in which the majority of patients had previously received a total surgical thyroidectomy, the activity of ^{131}I-sodium iodide administered was chosen to deliver 3 Gy to the blood. After nausea, depression of the bone marrow proved the most frequent serious complication.

387. Radiophosphorus, ^{32}P, has been widely used since 1939 in the treatment of patients with primary polycythaemia. Single or multiple doses are given until the patients red cells are reduced to acceptable levels. Spiers et al. [S65] have reviewed a series of patients given single doses of 144–222 mBq ^{32}P and showed that the dose rates to bone marrow follow a single exponential decay with a half-life of 6.7 d. The cumulative dose to the bone marrow was calculated to be 1.42 Gy per treatment or about 0.24 Gy/37 mBq injected. Late non-stochastic effects of such treatments have not been reported.

388. Following the demonstration of selective uptake of sulphur in chondrosarcoma [G38] and to a lesser extent in chordoma [W43], attempts have been made to treat these malignant tumours with ^{35}S injected as Na_2SO_4 [A36, B70, M65]. In a recent series [M65] doses of 185–222 mBq/kg were administered intravenously and the treatment repeated at intervals determined by the clinical and haematological response. A maximum of eight treatments were given over 88 weeks but in 13 patients the cumulative activity administered was in the range of 370–1780 mBq/kg. For an administered dose of 1110 mBq/kg it was calculated that the average radiation dose to normal cartilage and bone marrow was 40.5 and 9.9 Gy, respectively. From 70 to 90% of the activity was excreted in the urine over the first three days and most of the activity in the blood cleared with a biological half-life of 12 hours. In most patients the first dose had a minimal effect, but with each successive dose the prompt marrow depression increased and recovery became less complete. Thrombocytopaenia, leukopaenia and finally anaemia developed progressively and were dose-related. Only one patient with chondrosarcoma showed unequivocal improvement and all patients developed severe marrow hypoplasia, especially with respect to megakaryocytes and myelocytes.

389. Haematopoietic death has been described in the dogs at Utah given a series of single intravenous injections of various bone seeking radionuclides. Of those given 3.6 mBq/kg ^{90}Sr three died due to severe progressive thrombocytopaenia, leukopaenia and anaemia. Perivascular cuffing of central veins in the liver (which is characteristic of myeloid leukaemia) was also described together with myelofibrosis in some cases [D47]. The lowest average dose received one year before death was 38.4 Gy [M66] to the skeleton.

390. Following a single intravenous injection of 555 kBq/kg body weight of ^{239}Pu in mice, a moderate reduction in the apparent half-survival time of erythrocytes was measured [J24]. Polymeric plutonium entering the circulation is engulfed by the reticuloendothelial cells of the bone marrow, which are consequently subjected to continuous localized alpha-particle irradiation.

391. A single intravenous injection of 104 MBq ^{55}Fe in high specific activity (37 mBq/μg) causes early death in mice with severe depletion of haematopoietic cells in bone marrow and spleen, and atrophy of lymphoid tissues [L45]. Iron exists almost exclusively in intracellular form in the body and ^{55}Fe with a long half-life (2.7 a) is continually re-utilized. The radionuclide decays by electron capture depositing 75% of its decay energy within a range of 1 μm. The median survival time for animals given 52 MBq and 26 MBq ^{55}Fe was 117 and 439 days, respectively, in comparison with 847 days for controls. In these irradiated animals there was only slight atrophy of lymphoid tissues and nodular haematopoiesis of the regenerative type was sometimes seen in the spleen. However, they developed a dose-dependent pancytopaenia which was attributed to the inhability of the inactivated stem cells to replenish the loss from the various haematopoietic cell lines due to radiation damage. The effect was primarily seen in the erythroid series.

392. The chronic effects of ^{65}Zn have been studied in the rabbit [L46]. Zinc is a trace element influencing the activity of many enzymes and hormones and essential to the function of certain enzymes such as carbonic anhydrase. Following daily oral administration of ^{65}Zn as zinc chloride, the activity becomes very widely distributed in body tissues, reaching equilibrium within 3 months with a maximum concentration in the liver [A37]. ^{65}Zn decays mainly by K-capture associated with the emission of several short-range Auger electrons. The function of vital molecules into which the ^{65}Zn is incorporated would almost certainly be altered by transmutation of the radionuclide as it decays, in addition to any localized effects caused by the particles emitted and the radiation dose delivered.

393. The morphological changes observed in the blood-forming tissues are directly related to the level and duration of the continuous ^{65}Zn administration. In a group of animals given activity levels of 0.37 mBq/kg providing mean whole-body doses of 4.5 Gy/day, histological examinations after 3–5 months showed hyperplasia of the reticulo-endothelial elements in the spleen and lymph nodes, the appearance of foci of extramedullary haemopoiesis, and an increase in the number of cells of the white series in the bone marrow [G39]. Seven of the 20 rabbits in the group died during this period, 3 from bronchopneumonia with pleurisy and pericarditis and the remainder from a necrotic suppurative process spreading over the lymph nodes. Such inflammatory lesions of the lymph nodes may be considered characteristic of the chronic action of ^{65}Zn and have been attributed to the progressive formation of antibodies to proteins of the animals own tissues [F32]. Suppuration of cervical lymph nodes has been noted after 11–12 months in animals given activity

levels as low as 3.7 kBq/kg/d with corresponding mean whole-body doses 40 μGy/d [G39].

394. For sufficiently high levels of administered ^{65}Zn activity, erythopoiesis and lymphopoiesis are progressively depressed leading to the appearance of abnormal erythrocytes, reticulocytopaenia and lymphocytopaenia [B71]. At intermediate levels few such changes are seen, but at low activity levels [R47], providing mean whole-body doses of 40 μGy/d, there is an initial depression of erythropoiesis followed after 6–12 months by hyperplasia of the red and white series and marked reticulocytosis in the bone marrow. In the peripheral blood there is persistent reticulocytosis and transient increases in the number of lymphocytes, neutrophils and basophils. A similar apparently stimulating effect on haematopoiesis is observed for low dosage of other radionuclides such as ^{35}S [K44]. However, the granulocytic series seem to be particularly sensitive to exposure to ^{65}Zn [B72]. There is a gradual increase in the relative and absolute number of the young neutrophils in the bone marrow and an intensified release of rod nuclear neutrophils into the blood.

395. The haematological effects of inhaled radionuclides arise both from irradiation of haematopoietic tissue by activity translocated from the lung, and also by direct irradiation of the blood circulating in the lungs and the other tissues containing active deposits. The effects are therefore highly dependent on the solubility of the inhaled particles in the body fluids, and on the half-life and metabolism of the radionuclide.

396. The chlorides of the beta/gamma emitting radionuclides ^{90}Sr, ^{144}Ce, ^{91}Y are relatively soluble in the lung and are rapidly deposited in the skeleton. After their inhalation at high activity levels in dogs, deaths occurred in the following 12–44 days as a result of marrow hypoplasia, panleukocytopaenia, terminal haemorrhage and bacterial infection [M67]. The cumulative average beta dose to the skeleton to death ranged from 6–13 Gy arising from long-term retained burdens of 2.7–3.7 mBq ^{90}Sr/kg body weight, 5.2–11.8 mBq ^{144}Ce/kg body weight and 7.4–20 mBq ^{91}Y/kg body weight. For lower retained burdens, animals survived this acute phase and exhibited smaller depressions in the blood elements.

397. After inhalation of sufficient activities of the transuranic radionuclides in rodents and dogs, leukocytopaenia [B65, S59, B73] and depression of myelopoiesis have been observed [B66]. However, in dogs a dose-related lymphocytopaenia was the earliest and most consistent effect seen following inhalation of both transuranic radionuclides and insoluble particles containing beta/gamma radionuclides. Lymphocytopaenia has not been associated with either illness or premature death of the animals.

398. Lymphocytopaenia was observed in dogs within 2 weeks after exposure to high lung burdens of plutonium [W42, B74, P32, B73] and within 400 days following depositions of about 3.7 Bq/g lung $^{239}PuO_2$ with dose rates of more than 2.4 mGy/ day delivered to lungs and lymph nodes [Y5]. It was not seen in the 3–6 years following depositions of < 7.4 Bq/g lung [P36]. For lung burdens of 111–1480 Bq/g lung it became apparent after 1 year and persisted throughout life [P37]. From a review of the animal data it has been concluded that the magnitude and delay in onset of lymphocytopaenia depend on the dose of alpha-emitting radionuclides but can probably be detected after pulmonary depositions of ≥ 18.5 Bq/g lung [I4].

399. For beta/gamma emitters in fused alumino-silicate particles the lymphocyte response in dogs depended on the radionuclide [J21]. For short-lived ^{90}Y where the irradiation must have been largely confined to the lung, the maximum lymphocyte depression occurred 7–14 days after exposure with recovery to normal levels by 50 days. For ^{91}Y, depression occurred more slowly and by two years there were indications of recovery. For ^{144}Ce, the depression occurred during the first 200 days and was maintained over the remaining two years of observation. For ^{90}Sr the dose-related depression of lymphocytes was progressive over two years and was seen to persist for at least 2000 days [S66]. A reduced function in the surviving lymphocytes has also been demonstrated but it is not known whether T or B lymphocytes are primarily affected [B75].

400. Irradiation of the tracheobronchial, mediastinal or hepatic lymph nodes may also result from radionuclides translocated from the lungs. The mode of transfer of the activity from lungs to lymph nodes is unknown but for insoluble particles such as $^{239}PuO_2$ is probably mediated by macrophages. Concentrations of such particles can accumulate over a period of years to reach many times the levels in the lung, and retention of the activity in the nodes may be very prolonged.

401. Lesions of lymph nodes following the inhalation of alpha-emitting radionuclides and ^{144}Ce in fused alumino-silicate particles have been described in rodents and dogs [S59, D48, H61]. The primary lesions in nodes containing active deposits are characterized by lymphadenitis and fibrosis with some degree of depletion of the germinal centres. Lymphoid atrophy has also been observed following the administration of high levels of plutonium even in nodes without active deposits.

402. Following exposure to $^{239}PuO_2$ in dogs the histological changes observed in lymph nodes up to some 400 days proved to bear little relationship to the estimated cumulative radiation doses [Y5]. This was possibly due to variations in the rate of activity concentration and temporal distribution of the dose delivered to tissues. However, the changes correlated well with the mean dose rate, appearing to have a threshold at which no pathology was observed of some 50 mGy/ day to the lymph nodes from an initial deposition of about 1.1 kBq/g lung. At 400 days after depositions of more than about 3.7 kBq/g lung, lesions were apparent in nodes receiving mean dose rates of more than 70 mGy/day. Lymph node lesions have also been seen at much longer times after lung depositions of $^{239}PuO_2$ as low as 26 Bq/g lung [B76].

10. Vascular system

403. Vascular damage can lead to the development of sclerotic changes in internal organs following chronic irradiation. A form of nodular periarteritis affecting small and medium sized arteries was noted in 22%, 18% and 7.5% of rats surviving beyond 200 days from a single oral administration of 83 mBq/kg ^{106}Ru, 0.018–18 mBq/kg ^{144}Ce and 63 mBq/kg ^{137}Cs [M61].

404. Vascular changes were studied in the bones of the dogs from Utah contaminated with bone-seeking

radionuclides [J22]. The most sensitive measure of a vascular action was the length of vessels per unit area obtained from microphotographs. Table 14 shows the lowest values of injected activities, burden time and skeletal dose, where significant vascular reduction occurred in the compacta.

D. SUMMARY

405. Taking into account the difficulties of calculating the doses delivered to tissues from internal irradiation, this limited review of the data indicates that the effects of beta- or gamma-emitting radionuclides are not inconsistent with those expected from comparable mean tissue doses delivered at low dose rate by external x irradiation. The distribution of tissues affected is determined by the particular spatial and temporal distribution of the radionuclide in the body.

406. Alpha-, low-energy beta- and Auger-electron-emitting radionuclides produce microdistributions of energy around a disintegrating atom which sometimes coincides with a radiosensitive structure in the tissue, resulting in an enhanced effect. The enhancement with respect to external x irradiation may be expressed by an RBE factor which also takes account of effects due to the quality of the emitted radiation, the density of ionization and other results of decay, in particular the transmutation of the atom. RBE's as high as 50 for ^{210}Po and nearly 3 for ^{3}H have been reported for damage to oocytes in the mouse.

407. Another possible delayed effect of irradiation by radionuclides may be the indirect damage to tissues caused by alterations in metabolism or by autoimmunity. The low dose from iodine radioisotopes necessary to produce long-term impairment in thyroid function, as indicated by the data from the Marshall islanders, and also that from ^{65}Zn found to produce lymph node necrosis in rabbits call for further study.

VI. THE ROLE OF VASCULAR AND LYMPHATIC DAMAGE

408. Many factors other than direct effects on parenchymal cells may affect tissue response to irradiation, including hormonal changes, reactions mediated through the nervous system and modifications to the vascular system. Such changes have been considered in sections II. H and I, III. H and V. C, while the damage to vascular and lymphatic tissues is discussed in more detail in the present chapter in relation to the irradiation of organs and tissues. The role of vascular and connective tissue damage as a possible cause of generalized non-specific effects leading to life span shortening in whole-body irradiated animals is treated separately in Annex K.

409. Irradiated tissues frequently show vascular changes, particularly at late times after irradiation. For this reason, and because the turnover time of the endothelial cells is generally thought to be long, i.e., between 2 and 24 months (reviewed by Hirst et al. [H4]), it is often postulated that vascular damage is the common pathway for late radiation injury [R1]. This is the reason why radiation damage to blood vessels is discussed in a separate chapter. It should however be pointed out immediately that, owing to the intimate association of vascular and parenchymal elements, it is extremely difficult to decide whether long-term effects on parenchymal cells are the direct consequence of irradiation, or the indirect result of failure of the vascular or connective tissue elements.

410. After doses of radiation in the radiotherapy range, tissues which show no early reactions in parenchymal cells often show progressive vascular changes over a period of many months. Histological changes in blood vessels and interstitial fibrosis precede atrophy of parenchymal cells in liver [I2, R20], kidney [M10, C17], heart [F31] and lung [J3, M7, A13]. In general, changes in vascular function have been observed before severe late atrophy of tissues. Several authors have specifically noted that functional vascular changes precede damage to cells which are dependent on the vascular supply [G2, H39, K21, G21]. Increased vascular permeability is observed in the lung and in the mesentery before signs of fibrosis are apparent [T13].

411. These observations suggest that impaired vascular function may cause tissue atrophy at late times after irradiation. However, in the CNS, the situation is more complicated. At moderate doses (10–20 Gy) vascular lesions predominate after a long latent period, but higher doses (> 40 Gy) cause white matter necrosis at earlier times, in the absence of severe vascular lesions [H14, H41, V9]. This may be interpreted as an early response, which only occurs above a certain threshold for the glial elements [H42]. Sequential studies have also been performed in order to examine in which cells the damage is first expressed [P22]. Changes in lymphatics have been noted in the radiotherapy dose range. Alteration in lymphatic morphology occurs rather earlier than in blood vessels [A23, Z6, B47].

A. MORPHOLOGICAL CHANGES

412. Many descriptive studies of gross changes in blood vessels have been made, particularly for the skin. The time course of changes differs in different tissues, probably in relation to the death of surrounding parenchymal cells. The pattern of response also differs in different vascular elements, perhaps in relation to differences in the blood vessel walls. In capillaries and sinuses the endothelial cells are the main components of the vessel wall, whereas in venules, veins, arterioles and arteries, the thicker walls contain structural elements consisting of elastin, collagen, fibroblasts and smooth muscle cells. In the largest vessels the walls are sufficiently thick to require their own capillary network. Vascular damage can be roughly divided into early, intermediate and late changes.

413. Early changes occur roughly within minutes to days after irradiation. The earliest visible change is erythema, resulting from dilation of the capillaries. After very high doses of the order of 10 Gy this may occur within hours; after lower doses (1 Gy) erythema occurs after a few days. It has been postulated that histamine-like substances, released from dying epithelial cells, may cause this effect in skin [D30, E14]; however, capillary dilation has also been observed in the heart [F31] in which no early cell death occurs. Electron microscope studies have shown abnormalities in lung endothelial cells within 3 hours of exposure to 20 Gy [M30]. Vacuolation and lifting of endothelial cells has been observed within the first month after irradiation, preceding changes in the lung epithelial cells [P6]. In skin, vacuolation of endothelial cells has been observed within 10 days [Z3] but at this time many

epithelial cells have also died and the vascular changes may be a response to these dying cells.

414. Intermediate changes occur within approximately six months. Within each organ they show a patchy distribution with some areas being normal, whilst in others degenerative changes are apparent. In both lung [P6, M30] and heart [F31], electron micrographs show cytoplasmic swelling and endothelial cell sloughing. Thrombi sometimes obliterate capillaries. In some tissues, e.g., heart and kidney, endothelial changes precede changes in the parenchymal cells [P22]. Changes in the other components of larger vessel walls are seen at this time, e.g., effusion of plasma proteins leading to oedema, which is not drained by the lymphatics. It has been suggested that this protein leaking progresses to the hyalinization that characterizes large arteriolar lesions [Z3].

415. Late changes which are seen after about six months consist in degeneration of the walls of arteries, arterioles and capillaries. Endothelial proliferation at this time may lead to "sausage segments" by partially or completely obliterating the lumen [W26, M43]. Thickening of the basement membrane [P6, M31] and replacement of the lumen by collagen [P6, A13] also occur. Gross external changes, described as telangiectasis, are seen in many irradiated tissues [R21]. In the arteries and arterioles, tortuosities are also seen, with regions of dilation and constriction [H43, B37, L21]. Loss of endothelial and smooth muscle cells occurs and increased amounts of acellular material, including collagen, are deposited in vessel walls [R1, H40, Z3, W26, W27]. Changes in blood vessels and a reduction in their number can also be shown by computer analysis of microangiography results [E21].

B. FUNCTIONAL CHANGES

416. The function of the vasculature is to carry an adequate supply of nutrients to all parts of the body and to remove the waste products. Blood flow, vascular volume and vessel permeability have all been studied by means of radioactive tracer techniques.

417. In order to study blood flow, a radioactive tracer may be introduced into the blood (e.g., ^{42}K or ^{86}Rb) and the extraction in different tissues assessed from the incorporated radioactivity. Alternatively, the tracer may be introduced directly into the tissue (e.g., ^{22}Na, ^{99m}Te, ^{122}Xe) and its rate of clearance via the blood stream assessed. For the extraction studies the isotopes used must be taken up and retained by cells, whereas for the clearance assays the isotope must be freely diffusable [S25, K22, L22].

418. Early experiments to measure vascular permeability involved the intravascular injection of dyes which bind the plasma proteins and assessment of the degree of blueing of the tissue [R22, R23]. More recently large molecules have been used, labelled with radioactive isotopes, which would not normally diffuse across the vessel walls (e.g., albumin). Increased permeability leads to leakage of these molecules and to a greater accumulation of radioactivity in the tissues. The studies often require sequential sampling, or sampling at a fairly long time after intravenous administration of the labelled molecules. It is easier to interpret these permeability studies if an independent estimate of the blood volume can be made and this is often achieved concurrently by using radioactively labelled red blood cells (e.g., by ^{51}Cr), which do not cross even a leaky vessel wall [S26, J8].

419. These techniques have been used in studying a wide variety of irradiated tissues, after a range of different x-ray doses, and over different observation periods. Some of the studies are reviewed below.

1. Skin

420. This has been the most widely studied tissue in various species including rodents, dogs and pigs. In early studies using dyes in rabbit skin, waves of increased permeability were observed after 1–30 Gy. The exact timing varied in the different studies partly due to the different skin areas investigated [R24]. An early phase was seen almost immediately [P23, J9] with a second phase beginning at 20 minutes and lasting a few hours [E14, R24, J9]. Further waves of reaction were seen extending over the first month [J10, J11]. The threshold dose at which a measurable change was observed was about 1 Gy [J12].

421. Other studies were carried out on rabbits [M32], guinea pigs [S27], and rats [L23] using a variety of labelled proteins. Changes in permeability are observable for several weeks, but return to normal by 6 weeks after 10 Gy in rats. In general, rats and mice appear to be less sensitive to permeability changes than rabbits and guinea pigs [R25].

422. In dogs, the leakage of dextran molecules of varying size has been tested after 10–40 Gy. Some effect was observed at all doses with a peak at 2 weeks. With increasing dose the size of the dextran molecules that could leak out was increased [A14].

423. Blood flow changes are more variable than permeability changes, with both increases and decreases being reported at various times after irradiation. In general, changes are not observed until many months after irradiation. For example, no changes were observed in rat skin until 10 months after doses up to 40 Gy ([K21], Van de Mereck quoted by [D31]) after which time flow was reduced with a threshold dose of 15 Gy. In mouse foot skin flow was increased during the first 20 weeks after 10×4 Gy to 10×7 Gy [H44]. In tail skin, no change in resting blood flow was seen, but the hyperaemic response observed after releasing temporary occlusion was reduced, suggesting impairment of vascular function several months after irradiation [D32]. Glatstein [G2] could detect no changes up to 12 months after 15 Gy in mice but Hopewell [H45] observed increased blood flow and decreased vascular volume in hamster cheek pouches between 2 and 12 months after 20–30 Gy.

424. Pig skin has been investigated both by tracer techniques and by assessing the ability to vascularize a skin flap attached by a single pedicle. Above a threshold dose of 8 Gy more rapid flow was observed at 3 weeks, followed by a reduction at 12 weeks and a return to normal at 1 year. There may be a second decrease at 18 months [M33, H46]. Similar changes have been observed after 38 Gy/6 fractions/18 days, but after 80 Gy/30 fractions/39 days only slight changes were seen during the period 3–12 months [H46]. The skin flap assay of vascular function showed a progressive failure from 0–6 weeks after 20 Gy with no further change to 28 weeks [P24, W28]. Similar

changes were observed after 6 fractions/18 days or after 30 fractions/39 days [W28].

425. Human skin has been studied by thermography [W29] and by clearance of ^{22}Na [R26]. In the isotope studies, blood flow was measured up to 10 years after cumulative doses of 36–200 Gy. Of 37 patients studied, only one showed reduced clearance in the irradiated skin and 12 showed increased clearance despite the appearance of dense fibrosis, scarring and atrophy [R26]. A more recent analysis of this data suggests a trend towards reduced flow at later times after exposure [D31]. The thermography studies showed increased flow during early acute erythema (2–3 months) [W29]. Studies of blood vessels in patients developing radiation ulcers have been made using isotope techniques. After fractionated radiotherapy with doses between 40 and 120 Gy a reduction in circulation was noted together with sclerosis and fibrosis and an increase in the probability of blood clot formation. Blood and lymph vessel occlusion was observed which affected other tissues, e.g., nerves, bones and lungs. Disturbances in circulation sometimes led to swelling of the extremities [B46, B47, B48, B49]. There is little information about the response of blood vessels to vasoactive substances. The response to pharmacological mediators such as Compound 48/80 or carrageenan (all of which cause increased permeability) is not significantly affected by doses of 5–200 Gy of x rays to the rat foot [M34, V10].

426. Irradiation does affect the response to physiological agents involved in the regulation of blood flow to a tissue. The vessels of the rat foot show a reduced response to acetylcholine (vasodilation) at 24 hours and at 4–6 weeks after 30 Gy, but no change in the response to noradrenaline (vasoconstriction) [M34]. However, Lindop et al. [L21] found an increased response to adrenaline in the mouse ear between 1 and 55 weeks after exposure, with a threshold of 15 Gy. Indirect evidence suggests that blood vessels lose the capacity to respond to stress by vasodilation at late times after irradiation. The hyperaemic response of both the mouse foot [H44] and mouse tail [D32], which is normally observed on release of a temporary vascular occlusion, is reduced 4–6 months after exposure.

427. In conclusion, the lowest dose at which observable effects have been seen is 1 Gy for permeability changes in rabbit skin [J12] and 15 Gy or 8 Gy for blood flow measured in rats [K21] and in pigs [M33], respectively.

2. Intestine

428. Several authors have reported early changes in vascular permeability in the gastrointestinal tract after irradiation but it is difficult to say whether these could also be related to the early death of epithelial cells within the first 3 days. Willoughby [W30] found an increased capillary permeability in the vascular bed of the rat small intestine which began at about 18–24 hours and reached a maximum at 72 hours after 15 Gy of x rays to the abdomen. Turner and Fowler [T12] and Bromfield and Dykes [B38] measured ^{131}I-serum albumin leakage in the small intestine of rats after whole-body irradiation. Significant leakage occurred from the intestine at 3–5 days after doses of 5 Gy or more. Harris and Noonan [H47] observed two waves of increased permeability from intestinal blood vessels after whole-body irradiation. Doses of 7.5 or 15 Gy induced an initial peak at 3–4 hours and a second increase at 24 hours. Graham [G22] observed a biphasic increase in permeability after 8 Gy whole-body irradiation, with an early increase during the first hour and a second prolonged phase between 8 hours and 7 days. Vatistas and Hornsey [V3] also showed increased permeability, the extent of which was dose-dependent with a threshold of about 2.5 Gy. After whole abdomen irradiation of rats, Davies and Gamble [D33] observed increased permeability within 24 hours after 5–10 Gy.

429. Recently, changes have been studied in mesenteric vessels, in isolation from the ileum they supply, enabling the separate effects on vessels and parenchyma to be distinguished [H40]. In these experiments the vascular response was studied from 3 weeks to 24 months after 20, 30 or 45 Gy. Increased permeability was observed within 6 weeks after the two higher doses, with a maximum at 3 months and a return to normal by 12 months. A second phase was observed at 18 months. Very little change was observed after 20 Gy. Changes in blood volume and in vessel diameter were observed over the same period for single doses greater than 20 Gy. Thus, the dose required to cause changes in blood vessels could be greater when they are not in close contact with dying parenchymal cells, although the experiments referred to only involved larger blood vessels.

3. Cartilage and bone

430. Kember and Coggins [K25] investigated the effects of x rays on the epiphyseal blood supply to growing cartilage in young rats to test the hypothesis that the primary cause of damage would be to the blood vessels [M37]. After 9 Gy (soft tissue dose) there was a reduction in the number of blood vessels but those remaining seemed normal. Before the number of vessels was restored, damage to the cartilage plate was fully repaired. There was stunting in growth from this dose, but this was fully explicable on the basis of the parenchymal cell survival [K1]. It was concluded that damage to the vascular supply was not the primary cause of stunting.

431. Blood vessels in the vicinity of the cartilage plate pass through small channels (20 to 35 μm diameter) in the bony plate before reaching the cartilage space adjacent to it. Depending on the energy of the x rays used, the dose to the blood vessels may be increased by the presence of the bone. When this was accounted for, Kember and Coggins [K25] noted that even after doses of about 30 Gy in a single treatment to vessels passing through the bony plate, some vessels remained active. However, with doses of this magnitude, some clones of cells in the growth cartilage aborted at 5–6 weeks after irradiation. The possibility that this resulted from vascular injury at these higher dose levels could not be ruled out.

4. Lung

432. In spite of the numerous histological reports of oedema in irradiated lungs there are few studies of vascular permeability. Travis et al. [T13] observed increased vascular permeability in rat lung at 4 and 8 weeks, but not at 2 and 12 weeks, after 20 and 40 Gy to the hemithorax, while 5 Gy had no effect. In similar experiments on the mouse lung, Hornsey [H52] observed significant leakage at 4 weeks, which persisted

at 8–18 weeks. The effect was dose-dependent with a threshold at about 10 Gy. Maisin [M7] found an increased permeability at 30 minutes and at 3–7 days after 20 Gy to the mouse lung. Between 7 and 18 months there was a gradual decrease in permeability.

433. Long-term sequential studies of pulmonary blood flow in rats demonstrate reduced flow at 1–3 months after doses in excess of 10 Gy to one lung (Rana, quoted by Keyeux et al. [K21]). Blood flow returned to normal by 4–5 months after 10 Gy, but a prolonged depression of flow was observed after doses of 12.5 and 15 Gy. A dose of 20 Gy caused a complete arrest of the circulation within 6–12 months. Further experiments using ^{133}Xe injected intravenously, confirmed that there were two different phases of response [K21]. Clearance was allowed at 7–14 days, preceding the acute phase of radiation pneumonitis and the subsequent slowing of blood flow after 70 days coincided with the development of permanent histological lesions.

434. Glatstein [G2] used ^{86}Rb to measure vascular function after irradiation of one lung in the mouse. The uptake of ^{86}Rb decreased 3–4 months after single doses of 11 or 15 Gy, but subsequently returned to normal levels. Experiments in rats by Jovanovic et al. [J13] indicate that the volume of lung tissue irradiated is important. Following irradiation of one lung with 10–20 Gy, blood flow was reduced during the acute phase (up to 90 days) and also during the late phase (4–18 months). By contrast, irradiation of both lungs with doses of 5–15 Gy was followed by an increased blood flow during the acute phase. A reduced flow from poorly ventilated lung alveoli was observed during the later phases, but there was no significant change in the ventilated region.

5. Liver

435. In studies of liver circulation, the clearance from the blood of colloids which are taken up by Kupffer cells has been used as an index of hepatic blood flow. This is a reasonable method providing there is no accompanying change in the ability of Kupffer cells to function. Therefore, only the studies in which liver cell function has been assessed separately are discussed.

436. Fridrich and Schäfner [F32] observed decreased clearance of radiogold colloid, which was attributed to reduced blood flow, immediately after doses of 5 to 20 Gy to the livers of mice. The fact that uptake in spleen remained stable suggests that delayed clearance is not due to radiation damage to the reticulo-endothelial system, since if this were the case phagocytosis in the spleen would increase compensatorily. Impairment of the indocyanine green (ICG) clearance was reported by Paumgartner et al. [P25] at 2–11 days after local proton irradiation of the liver. Experiments with bromosulphtalein and labelled rose bengal ([K24, W32], Royer quoted by [D34]) indicate that the hepatic cell function is not affected during the first few weeks after irradiation so that clearance studies give a measure of blood flow at these times.

437. In an attempt to evaluate the function of both the hepatic cells and the vascular network, Keyeux et al. [K21] used colloidal gold to measure circulatory changes and labelled rose bengal to measure liver function in rats. A single dose of 15 Gy caused a transient marked reduction of liver blood flow index, but only a slight depression of hepatocyte function, during the first month. Between 2–28 months there was a gradual reduction in both blood flow index and liver function. A dose of 7 Gy caused no significant late changes but 15 and 30 Gy had comparable effects.

438. There is also one study of hepatic blood flow which does not depend on active uptake by liver cells. Using the ^{86}Rb extraction method, Glatstein [G2] showed no significant change in liver blood flow in mice after local single doses of 10 or 15 Gy up to 12 months after radiation exposure.

6. Kidney

439. The effective renal plasma flow (ERPF) may be estimated by measuring the disappearance of a tracer such as hippuran from the blood following a single intravenous injection, providing the tracer used is cleared by the kidneys. The disadvantage of this technique is that any impairment of the secretory function of the kidney tubules will also result in apparent reduction of the effective renal plasma flow. Although isotope clearance and extraction methods are not subject to this disadvantage, the ^{85}Rb extraction method has only been used in one study on mice.

440. The majority of experimental investigations into renal function have been in dogs. Mendelsohn and Caceres [M10] measured renal function after 20, 27.5 and 37 Gy, given in 13 days to the remaining kidney in unilaterally nephrectomized dogs. After 20 Gy there were no significant changes in renal blood flow. After the higher doses there was a temporary increase in both blood flow and tubular secretion during the first week, followed by a depression in function which reached a minimum at 9–11 weeks. This subsequently returned to normal by 36 weeks after 27.5 Gy but remained at 70% of the controls after the highest dose. Concannon et al. [C19] irradiated both kidneys of dogs with 19, 25 and 31 Gy in 12 fractions over 13 days. All doses caused persistent depression of renal blood flow from 10 to 60 weeks. Gup et al. [G21], using subcutaneous exteriorized kidneys, observed decreased renal plasma flow at 5–7 months after 5 and 10 Gy as single doses, and after 10 and 20 Gy in 10 fractions over 19 days. There were no histological signs of radiation-induced damage. Maier and Casarett [M36] used radiohippuran renograms to evaluate renal function in dogs. At 4–6 weeks excretion was reduced after 10 and 20 Gy but not after 5 Gy.

441. In pigs, the renal plasma flow is progressively reduced between 1–6 months after exposure [H12]. The single dose required to reduce function to 30–40% of normal at 6 months was 12.6 Gy. This was defined by the authors as the "tolerance dose". There was a further reduction in flow during 9–24 months, the tolerance dose falling to between 10.7–12.6 Gy [H48]. After fractionated treatments the maximum depression of plasma flow was observed at 6 months. There is good agreement between the data for pigs and dogs.

442. Estimation of renal function in rodents has been limited because of the small physical size of the animals. Smith and Boss [S28] measured renal function in exteriorized rat kidneys after single doses of x rays. No changes in renal blood flow were observed during the first 4 weeks after 25 and 30 Gy but 40 Gy caused a depression in flow at 28 days. Chauser et al. [C8] measured renal plasma flow in the rat at late times after

localized irradiation of a single kidney in situ. Doses of 10 Gy caused no effect by 20 weeks. Doses of 20 and 30 Gy caused total kidney failure by 12 and 20 weeks, respectively, with accompanying histological damage.

443. Thus, by the classical methods for measuring ERPF, there is a reduction in blood flow which is dose and time dependent. Similar results have been obtained using the ^{86}Rb extraction method in mice [G2]. Two months after irradiation of both kidneys with single doses of 11 to 19 Gy, blood flow had decreased and it continued to decline for at least one year. The effect was dose dependent and preceded fibrosis by several months.

444. An extensive study of renal function in man has been performed by Avioli et al. [A15]. They observed an early decrease in renal plasma flow during fractionated therapy as soon as a dose of 4.5 Gy had been accumulated. After completion of therapy there was a progressive fall in plasma flow which persisted for 12 months after cumulative doses of 20 and 24 Gy.

7. Central nervous system

445. Although the central nervous system is highly sensitive to slight decreases in oxygen and glucose supply and histological examination of irradiated brain and spinal cord indicate that there are radiation-induced lesions in blood vessels, there are few studies of vascular function in the CNS after local irradiation.

446. There is evidence that the blood-brain barrier is impaired by ionizing radiation. Permeability to protein, phosphorous, iodine, sodium and chloride can be increased [K23]. However, labelled proteins are probably the best agents with which to demonstrate gross permeability changes in the capillary endothelium [N7]. In rats, a dose of 100 Gy to the head caused no significant leakage of intravascular albumin between 1–96 hours [K23]. But, in the rabbit, permeability of the blood-brain barrier to albumin was increased at 24 hours after x-ray doses of only 8 Gy [W31]. Mogil'nitskiy and Brumshteyn (quoted by Keyeux [K23]) observed leakage of protein into the pericapillary spaces of brain vessels in dogs at 48 hours after 10–30 Gy and Clemente and Holst [C18] found that vascular permeability was increased in monkeys. The most severe changes in the blood-brain barrier were seen less than a day after doses of 45 and 60 Gy but 15 Gy also caused a detectable effect. Later effects have been studied in monkeys. No changes in the blood-brain barrier were seen before 28 weeks after 35 Gy but then increased permeability was observed until 40 weeks [T14].

447. Leith and Gaugl [L24] measured cerebral blood flow in the rabbit using an electromagnetic flow probe placed round the internal carotid artery. Doses of 100 Gy caused a transient decrease in flow at 1 hour and a further decline between 3–6 hours. However, Keyeux [K23] found that 200 Gy to the rat brain caused no change in blood flow at 48 hours, although blood volume was increased.

448. Delayed effects have been observed after lower doses. Keyeux et al. [K21] used local irradiation of the rat brain, and showed no change in blood volume at 8.5 months after 15 Gy, but blood flow was increased, with a threshold dose between 10 and 15 Gy. Moustafa and Hopewell [M35] observed modifications in vascular function after 20 and 30 Gy, but no changes after 5 or 10 Gy. The first change occurred 3 months after irradiation when there was a reduced blood flow. At 6 and 9 months blood flow was increased but by 12 months it had returned to normal.

449. Conflicting results have been obtained in the monkey, following localized irradiation of the right occipital lobe [T14]. Blood flow in both white and grey matter was reduced 28 weeks after a single dose of 35 Gy. At 40 weeks there was some recovery in the grey matter but not in the white. Changes in human brain haemodynamics have also been noted during acute radiation sickness [G27, T16, G29].

C. ENDOTHELIAL CELL SENSITIVITY

450. Since endothelial cells are present in all blood vessels, and since damage to these cells has been observed as one of the first pathological changes in many tissues [P22], several attempts have been made to measure their radiosensitivity. Because the turnover times for endothelial cells are very long, from 2 months to 3 years [H4, T3, S4, E15, S29], it is generally assumed that radiation-induced cell death would not occur for many months or years. However experiments on rats, rabbits and guinea pigs, in which the number of endothelial cells was counted in defined areas of the aorta, demonstrated a decrease in endothelial cell numbers at 5–11 days after irradiation. It was postulated that this was the result of interphase death. The dose required for 25% loss of cells was 4.9 Gy for guinea pig and 9 Gy for rabbit and rat. In these experiments the estimated values of D_q were 2.5 Gy for guinea pig, 8.3 Gy for rat and 8.8 Gy for rabbit [S43, S44]. More recent data [K4, H4] indicate that a small subpopulation of cells may exist with a cell cycle time of about 1 day. Therefore the kinetics of endothelial cells and their mode of death after irradiation are not known with sufficient certainty.

451. Other attempts to measure endothelial survival curve parameters have mostly involved stimuli to induce proliferation and to speed up expression of radiation damage. If the stimulus is applied before irradiation, the resulting survival curve refers to proliferating endothelial cells and may not be relevant to the normal slow turnover state. If the stimulus is applied after irradiation, the time of stimulation is found to be very important, owing presumably to repair of a slow type of potentially lethal injury [V2, R3].

452. Several studies have also been undertaken of endothelial cell survival in culture [N8, D35] but the survival characteristics of cells in vitro are mostly similar and not always the same as for cells in vivo. Essentially three methods have been employed in measuring in vivo endothelial survival parameters: (a) skin grafting, which stimulates growth of capillary loops linking host to graft; (b) stimulation of blood vessels in a subcutaneous air pouch by local application of agents such as croton oil or uric acid; (c) a technique of continuous labelling in utero which has been applied to the bone marrow [H64].

453. One of the earliest estimates of cell survival curve parameters was reported by Hopewell and Patterson [H49] in pigs. Three weeks after irradiation of a local area of skin, grafts of irradiated and unirradiated skin were transposed. Irradiated grafts on normal vascular

beds survived whereas normal grafts on irradiated beds sloughed off, indicating that the vascular bed was the important component. Capillary loops were visualized in the graft by injecting a dye at 48 hours after grafting and counting the number of loops linking host to graft. A dose-response curve with a D_0 of ~ 10 Gy and a D_q of ~ 3 Gy was derived from these data.

454. Reinhold [R27] obtained a D_0 of ~9 Gy after irradiating an area of a subcutaneous air pouch in the rat. Endothelial cell proliferation was stimulated by the local application of uric acid and the number of capillary sprouts was counted 5 days after stimulating division.

455. In later experiments, however, Reinhold and Buisman [R2] obtained a much lower value of D_0 by a modified version of the same system. These studies gave a survival curve with a D_0 of about 1.7 Gy, an extrapolation number of 7 and a D_q of about 3.4 Gy. Split dose experiments at 24 hours, using an initial dose of 5 Gy gave a D_2–D_1 value of about 3 Gy. The major difference between the two series [R27] and [R2] is that in the second experiment a longer period was allowed between proliferative stimulus and assay.

456. Van den Brenk [V11] has also used a longer follow-up period. Granuloma pouches were raised in the rat subcutis less than 5 minutes before irradiation by injecting air and croton oil beneath the panniculus carnosus. Both air pouch and adjacent tissue were irradiated. Thirteen days later, the air pouch was excised and opened. In unirradiated pouches a small confluent layer of granulation tissue formed. In irradiated pouches, discrete colonies of vasculature developed which could be counted, enabling endothelial cell survival curves to be plotted. These had a D_0 of 2.4 Gy, an extrapolation number of about 2 and a D_q of about 1.8 Gy. In later experiments, Van den Brenk et al. [V2] found no significant change in survival parameters if the radiation was given immediately before raising the air pouch. In these experiments, D_2–D_1 for the 24-hour interval was found to be 1.8 Gy after a first dose of 1.45 Gy.

457. It is not clear why the above investigations gave such widely different values for D_0. Cell survival parameters in vitro for a rapidly growing cell line of endothelial cell origin have been estimated to have $D_0 \simeq 2$ Gy, $N = 2.3$ [N8]. It seems that high values for D_0 (9–10 Gy) are obtained if the time interval between endothelial cell stimulation and assay is short [H49, R27]. It may be speculated that lethally-irradiated cells may perform one or two divisions before they die, maintaining functional integrity of the capillaries for a few days, whereas a later assay might detect the death of these cells and loss of the capillaries.

458. When the time between irradiation and subsequent stimulation is extended, repair of potentially lethal damage may occur before the damage is expressed. The three weeks between irradiation and grafting in the experiments of Hopewell and Patterson [H49] may have allowed repair of potentially lethal damage and this may account for the high D_0 observed. Van den Brenk et al. [V2] observed a dose sparing of 5–6 Gy when a 2–3-week gap was allowed between irradiation and the raising of the air pouch. Similarly, Reinhold and Buisman [R3] observed a repair phenomenon if the interval between irradiation and the uric acid stimulus was delayed for up to 60 days. The time course of the repair appeared to be exponential and had the effect of increasing the D_0 from 1.7 to 2.4 Gy for an interval of 16 days. This type of repair might be related to "slow repair" discussed earlier. In addition, repair of Elkind-type sublethal injury was observed in split-dose experiments, with a survival ratio of 5.

459. Gillette et al. [G23] studied the neovascularization after surgery on irradiated dogs' eyes. They suggested that cells stimulated before irradiation were more sensitive than cells stimulated after irradiation but their data are unconvincing. A split-dose increment D_2–D_1 of 3.5 Gy was obtained whether surgery was performed before or after irradiation.

460. Hirst et al. [H4, H40] measured depopulation and subsequent repopulation of endothelial cells in the mesenteric arterioles. A surprisingly early wave of depletion was observed, being more consistent with a short cycle time for 1–2% of the cells, than with a uniformly slow turnover of all cells. The subsequent repopulation was consistent with a D_2–D_1 of 7 Gy (as measured in split-dose experiments) and a D_0 in excess of 5 Gy. The rate of depopulation of the smooth muscle cells is, however, consistent with a generally slow turnover of all cells.

461. The above results suggest that the radiosensitivity of endothelial cells in vivo may be impossible to define because cells which attempt division soon after irradiation will be more sensitive than those that attempt division at later times when a significant amount of repair of potentially lethal damage may have occurred.

D. MECHANISMS UNDERLYING VASCULAR DAMAGE

462. A number of different mechanisms leading to the observed changes in vascular function have been postulated; they may be relevant at different times or after different doses in each of the tissues studied. The suggestions include widening of intra-endothelial cell gaps, changes in the amount of pinocytosis, changes in membrane permeability, depletion of cells, hyperplasia, leaking of proteins and development of fibrosis. The time course and extent of some of these individual changes are likely to be influenced by death of surrounding parenchymal cells. Hence the pattern of response must be considered separately for fast-recovering tissues such as intestine and skin, and for slow-turnover tissues such as lung and heart. In general, an early phase of dilation and increased permeability accompanies the early wave of desquamation which occurs in both intestine and skin. This has not been extensively investigated in slowly proliferating tissue. It is generally found that tissues show a gradual decrease in blood flow and an increase in permeability is seen at later times.

463. Gaps between endothelial cells have been observed in electron microscopic studies of skin within 10 days of irradiation [H50]. Maisin [M30], however, suggests that increased pinocytosis causes the increased permeability, although the correlation between these two is poor [M38].

464. Parenchymal cell death will produce chemical mediators (e.g., histamine or 5-hydroxytryptamine) increasing small vessel permeability [W33]. This has actually been postulated as the cause of the early changes observed [D30, V10]. The mediators in the late phase do not appear to be the same as those in the early

phase, and may involve release of lysosomal enzymes which cause the release of vasoactive polypeptides from plasma proteins [E14, M32, J14, J15, S30, E16].

465. At longer time intervals, e.g., 1–6 months after moderate doses, changes in endothelial morphology and in cell number are observed in rapidly and slowly proliferating tissues [P6, C17, A13, H40, Z3, W27, M39]. Vacuolation, sloughing and cell depletion have been observed in several tissues and this is probably the phase when direct damage to the endothelial cells is being expressed. At six weeks a good correlation has been shown between endothelial depletion in mesenteric arteries, and increased permeability, but not at later times [H40], probably because of other influences such as deposition of collagen.

466. At late times after irradiation, a reduction in blood flow with constriction and occlusion of blood vessels are seen. These changes have been attributed to localized proliferation of endothelial cells, which protrude into the lumen [M17, C17, H43] and have been related to the increased thymidine uptake seen in rabbit heart endothelium at 30–70 days [F33]. An alternative postulate relates to the insudation of the vessel walls by plasma proteins and their replacement by collagen leading to thickened walls, which limit the vessel diameters [Z3]. The processes are clearly complex and any or all of the changes which have been described may occur with time after irradiation.

E. COLLAGEN DEPOSITION

467. A characteristic of late radiation damage in tissues is an increase in the amount of acellular material. In particular, collagen is increased, although small foci of oedema and fibrin may also persist for many months or even years after treatment [R1, W34]. Moreover, the microscopic and biochemical appearances of collagen may be abnormal because the fibres tend to lose their orientation and take on a dense hyaline appearance [W34, G43].

468. Several authors have suggested that the increase in collagen is the final stage in the resolution of oedema fluid and fibrin which are observed at early and intermediate times after irradiation [R1, J3, L23, J16], and that fibrosis in vessel walls and intercellular spaces finally leads to parenchymal cell death. The sequence of changes observed in many irradiated tissues actually supports this view. Vascular changes and interstitial fibrosis precede atrophy of parenchymal cells in liver [I2, R20], kidney [M10, C17], heart [F31], lung [J3, M7, A13, J16] and brain [H14, P21]. On the contrary, other authors suggest that radiation has a direct lethal effect on parenchymal cells [H41, E17, C20, R28, Z4, M40], and that parenchymal cell death is followed by replacement fibrosis as a secondary effect when the cells cannot be regenerated [F34]. Therefore, collagen synthesis after irradiation is of interest.

469. In general, the concentration of collagen in adult tissue is maintained by a balance between synthesis and degradation. Radiation could upset this balance, either by altering the number of cells involved in synthesis or degradation, or by affecting the synthesis and degradation of collagen by surviving cells. Synthesis is measured by incorporation of labelled precursors (proline or glycine) after irradiation; degradation is measured by labelling before irradiation and following the subsequent loss of activity. In skin and in granuloma tissue, synthesis is depressed and degradation is increased for 3 weeks after 7.5–15 Gy locally, or 7.5–10 Gy whole-body irradiation [N9, A16, T15, K26, K27, O11]. Similar changes have been seen in muscle but not in tail tendon collagen [K26, K27]. With whole-body irradiation some effects may be secondary to starvation [K27], and after localized irradiation decreased degradation of collagen in granulation tissue has even been seen [R29, W35].

470. The depression of collagen synthesis taking place within 6 hours of irradiation is attributed to a direct effect on collagen biosynthesis, but the decrease at 2–3 weeks is attributed to reduced cell numbers available for synthesis [R29]. Collagen production per cell is increased, possibly because of less degradation, resulting in an accumulation of insoluble collagen.

471. The relevance of these early changes to the development of late radiation fibrosis is questionable. Degradation is inhibited only during the first three days after exposure [R29] whereas late radiation fibrosis develops over several months and gradual increases in the total collagen of adult rat skin have been measured between 4 and 12 months after irradiation [K28].

472. Radiation fibrosis may be the result of progressive organization of exudate from damaged blood vessels [R1, J3, L23, J16, R30]. An increase in the number of mononuclear cells, including fibroblasts, has been observed in irradiated tissues in which collagen also increases [J3, M7, R20, F31, D30, M39, R30]. This increase may persist, suggesting active collagen synthesis at months or even years after exposure [J3, R20, F31, M39, W34]. Increased collagen deposition has been observed after 36 weeks in mouse lung [L11] and at 20 weeks in mouse kidneys [C8] with a threshold between 10 and 20 Gy.

473. The collagen that is produced is less soluble than normal [O11, R29] but the detailed differences in chemical structure and cross linking are not known. External changes in pH may influence polymerization and thickness of collagen fibres and fibrin may be involved in collagen hyalinization [B39, W36].

F. CHANGES IN LYMPHATICS

474. Since the network of lymph vessels and lymph nodes forms an integral part of the vascular system, radiation effects on the dynamics and permeability of the blood vessels may result in reactive changes in the lymphatic system. In particular, the latter usually reacts to reduce circulatory disturbances caused by damage to the blood vessels, either through increasing drainage by lymph vessels or by opening of lymphatic-venous communications.

475. In general, the lymphatic vessels can withstand high doses of radiation before their function is impaired. Hodes and Griffith [H51] found no change in lymph flow in irradiated rats at 3–6 weeks after 22 Gy. In an extended study, Engeset [E18] also found no disturbances in lymph flow up to 1 year after 30 Gy to the rat limb. At later times lymph flow was not interrupted but was directed into newly formed vessels as fibrosis obstructed the original channels. Similar findings are reported in dogs by Sherman and O'Brien [S31]. Hind limb irradiation with 10–36 Gy did not affect lymph flow for 18 months after exposure.

476. The Sandison-Clark rabbit ear chamber was used by Van den Brenk [V12] as an experimental system for studying the effects of external radiation on lymphatics. A dose of 40 Gy did not induce endothelial swelling sufficient to cause blockage of lymphatic vessels up to 15 months after irradiation. Doses exceeding 50 Gy were required to cause destruction of lymphatic vessels. Lenzi and Bassani [L25] concluded that the threshold was even higher, i.e., 60 Gy in rabbit uteri. They described some dilations and varicosities which became progressively more pronounced after 80 Gy. The lymphatics were tortuous, varicose and rigid but patent in all cases.

477. Lymphangiography has often been used to estimate lymph flow in patients who have received therapeutic doses of radiation. In some early observations radiation to total fractionated doses of 20 Gy or greater did not appear to cause a reduction in flow up to 1 year after exposure [L25, P26, V13, A17, M41] although lymphatic vessels may appear rigid and flattened [L25] and lymph nodes may be reduced in size and increased in density [K34, Z6] or destroyed [A17, M41]. More recent work suggests doses in the lower limit of that range. In a study of 32 patients who developed skin ulcers between 6 months and 15 years after radiotherapy lymphatic changes were observed, including narrowing of the main vessels, anastomoses and the opening of vessels normally in reserve [B48, B47, Z6]. In some cases there may be leaking of contrast medium and the development of collateral lymphatic circulation [A18] but, in the majority of cases, lymphatic vessels did not undergo any marked changes in configuration [A17, M41].

478. Lymphangiography can only give a rather crude estimate of lymph flow rate but it can demonstrate cessation of flow either from intraluminal causes or from extravascular compression due to fibrosis. Results of lymphangiographic studies in man show that there is a progressive decrease in the size of irradiated lymph nodes reaching a minimum at 9–12 months after therapy. However, although lymph nodes become fibrotic the nodal sinuses remain patent. Irradiation per se does not cause obstruction of lymph vessels although perivascular fibrosis may cause a deviation of lymphatics.

479. In conclusion, lymphatic vessels in experimental animals and in man appear to be rather radioresistant. In most cases, large doses (single doses of 40 Gy to rats, fractionated dose of 75 Gy in 60 days to man) do not cause a change in lymph flow at 6–15 months after exposure. Any changes of lymph flow have frequently been found to be due to extravascular fibrosis, while irradiated lymphatics remain fully patent.

G. SUMMARY

480. After doses of radiation in the radiotherapy range, progressive morphological changes occur in all elements of the vasculature such that at late times after exposure vascular function is reduced. In general, changes in vascular function are observed before the occurrence of late atrophy of tissues, which suggests that vascular damage plays an important role in all late radiation injury after such relatively high doses.

481. Table 15 summarizes threshold doses for detectable changes in vascular function. Abnormal vascular permeability tends to occur at lower doses than marked reduction in blood flow. For any given species there is a wide variation between the threshold doses for different tissues, e.g., for the rat these range between 5 Gy in the mesentery to 15 Gy in the liver. These differences may of course reflect the different assay techniques used. However, it is also likely that they reflect intrinsic differences in various sections of the vascular system in different tissues. It should be recalled, finally, that the general response of a tissue depends on both the parenchymal and vascular components and that it may not be possible to view either in isolation.

VII. SUMMARY

482. Although the effects of irradiation on some body tissues were considered by the Committee in more recent specialized reviews, the whole field of morphological and functional changes in irradiated normal tissues of animals and man had not been systematically evaluated since 1962. A re-examination of the whole subject was therefore carried out with the main objective of identifying for each tissue and for various modalities of irradiation the effects and the doses that may become critical for the function of that tissue. As a secondary objective the Committee wished to analyse the main physical and biological factors which might modify these doses and effects. These objectives required a study of the dose-time relationships in each tissue, based on both animal data and on the observation of clinical effects in man.

483. The study was confined to the so-called non-stochastic or deterministic effects. Whereas the effects referred to as stochastic take place in one or a few cells and appear in an irradiated population as hereditary effects or tumours, the non-stochastic ones affect many cells and appear as tissue damage. In general, non-stochastic effects require that a minimum dose, called the threshold dose, be delivered before they can be detected. The clinical severity of the injury increases with increasing dose. The time of appearance of tissue damage is very variable as it may span from a few hours or days to many years after exposure, depending on the type of effect and on the characteristics of the particular tissue.

484. The concept of dose threshold is difficult to define and must be discussed in relation to each tissue and effect because it depends to a large extent on the sensitivity of the measuring technique. The loss of functional capacity of a given tissue, for example, may actually exhibit a much higher dose threshold than the appearance of subtle ultrastructural changes detectable only by sophisticated technology. Similarly, there is a need to distinguish between the threshold of appearance of clinical changes which have clear pathological connotations. While recognizing that these concepts have important practical implications, the Committee felt that a thorough discussion of tissue pathology was beyond the scope of this study which was primarily aimed at an assessment of the effects as reported, irrespective of their significance for practical purposes.

485. The amount of information that has accumulated on these subjects during the last twenty years is very large and an interpretative, rather than a comprehensive, treatment was therefore necessary. This was facilitated by the significant advancement in knowledge

of the basic mechanisms of cell and tissue response to irradiation. The premise of the Committee's review is that the non-stochastic response of a given tissue to radiation depends primarily on the level of killing of the component cells and that the degree of damage and its time of occurrence are related to the special way in which each given tissue is structured. Therefore an introductory treatment of the basic concepts of radiation effects on cells and tissues was required. In this part of the Annex the Committee discussed the mechanisms and the phenomenological characteristics of cell survival as a function of time and dose, repair phenomena, the normal mechanisms of cell proliferation in tissues and the changes induced by radiation thereupon. All this should be viewed as a unifying frame of reference for the specialized and systematic analysis of effects in various tissues.

486. Although the analysis of the Committee has considered separately the animal and the human data, the similarities between the observed effects warrant a common summary of the subject matter, with the necessary qualifications to point out major discrepancies.

487. In skin the early radiation reactions may increase from a temporary reddening through various degrees of severity to ulceration and necrosis. Late changes involve thinning of the skin, loss of hair, colour changes and dilatation of the blood vessels. In order to produce observable changes in animal skin by external irradiation, doses of the order of 7 to 10 Gy must normally be administered in acute exposures. However, this tissue has a very large capacity to repair radiation damage and thus, if radiation is delivered over a long time period, up to 5 times or more doses may be tolerated. Observations on radiotherapy patients generally confirm these findings. With single acute treatments temporary loss of hair results in man after 3–5 Gy and reversible changes cause no serious consequences. The area of skin irradiated is important, with more severe changes appearing for larger irradiated areas. A number of biological variables are known to influence the level of the threshold dose: among them the anatomical location of the skin, the age of the irradiated person, and the normal skin colour. Mucosae exhibit changes analogous to those seen in the skin at similar doses.

488. The blood and blood-forming cells appear to be particularly sensitive. The lymphocytes and the stem cells are inactivated by doses of a fraction of a Gy causing the disappearance of these cells from the bone marrow and the circulating blood. Blood forming organs have however a remarkable capacity for regeneration and may show complete recovery. In man, the haemopoietic system is also one of the most sensitive tissues. Responses may be observed after 0.5–1 Gy, whether given in a single exposure or as a series of small fractions. If depression of the peripheral blood cells is too severe death may occur, due to infection (loss of white cells) or to haemorrhage (loss of platelets) which are the major symptoms of the so-called haemopoietic syndrome. The LD_{50} for man lies in the range of 3–5 Gy.

489. External irradiation of the gastrointestinal system may lead to a variety of acute and chronic symptoms ranging from dyspepsia and diarrhoea with loss of fluid and blood, to localized ulcers and bowel strictures and obstructions. The review has treated separately the various sections of the gastrointestinal tract, since they are not uniformly sensitive. Considering the early forms of radiation injury, the stomach in man may tolerate up to 40 Gy of long-term fractionated treatment. The small intestine may also withstand fractionated doses of conventional radiotherapy of the order of 30–40 Gy. The large intestine is even more resistant and shows only transient symptoms at similar doses, while the oesophagus appears to tolerate up to 60 Gy. The late consequences of these large doses (particularly those given to large volumes) are little known and difficult to quantify. The liver is a very slowly proliferating organ, but its component cells may be stimulated into division by different types of injury including radiation: this could unmask latent damage that would not otherwise become apparent. In animals, single doses of over 10 Gy are necessary to induce permanent changes in liver and these doses may be increased up to six times upon extended fractionation. In man, liver is now known to tolerate 40–50 Gy in 30 days given to parts of the organ, the threshold for measurable effects being around 30 Gy of conventional fractionated radiotherapy.

490. The lung is regarded as being the most sensitive organ in the thorax and after moderate doses pneumonitis may develop which leads eventually, through a complex chain of pathological reactions, to fibrosis and loss of function. With whole-body irradiation and providing bone marrow function is maintained, the maximum dose which may be tolerated by lung is approximately 8 Gy, if given over several hours. The sensitivity of the lung with respect to long courses of irradiation is moderate. This is because it possesses a large capacity to repair intra-cellular damage, although it lacks the proliferative ability to reconstruct, by cellular repopulation, its elaborate structure. Doses of the order of 40 Gy in conventional radiotherapy (i.e., in 30 fractions) may lead to an appreciably increased incidence of complications. Among other thoracic organs, the heart is regarded, on the contrary, to be rather radioresistant in experimental animals where it shows only microscopic changes in the muscle cells and blood vessels after moderate doses. In man, a high incidence of cardiac complications consisting mainly of pericarditis and eventually fibrosis is seen after long fractionation courses to total doses in excess of 60 Gy.

491. The urinary system shows a wide range of sensitivities and among the various organs the kidney is believed to be the most vulnerable, followed by the bladder and the ureters. Acute and chronic nephritis followed by hypertension and proteinuria usually result from high radiation doses to the kidney. In experimental animals, morphological and physiopathological changes have been reported after single acute treatments with threshold doses between 5 and 12 Gy. With long-term fractionation these doses might be increased by a factor of at least 3. In man, 20–24 Gy in 3–4 weeks produce evident alterations in kidney function, so that the tolerance dose is normally regarded to be around 23 Gy in five weeks. In both man and animals the kidney appears to be more sensitive at around the time of birth. Doses of 55–60 Gy in 4 weeks are regarded as the tolerance doses for urinary bladder erythema, ulceration and eventually fibrosis.

492. The reproductive organs are particularly sensitive. Irradiation of the testis causes temporary sterility, which may become permanent after larger doses. The testis appears to be unique in that its component cells cannot undergo repair. Continuous

irradiation causes more, rather than less, damage than single acute treatments. In man, acute doses as low as 0.1 Gy have been reported to cause temporary sterility, although doses in excess of 2 Gy and possibly up to 6 Gy are needed to produce permanent aspermia. Many years may be necessary for complete recovery of the production of spermatogonial cells after severely damaging doses. The adult ovary is more resistant than the testis because, by the time of birth, the oogonial cells have all progressed to the more resistant oocytes. However, if irradiation is delivered to the developing ovary, fractionated treatments to a total of 2 Gy may cause severe damage in dogs and monkeys. Permanent sterility is caused in women by single doses in excess of about 3 Gy, or higher fractionated doses.

493. The threshold doses applying to the central nervous system differ for different structures. The lesions consist in alterations of the fibre structure, loss of myelin, encephalitis and necrosis. The damage is believed to result, at least in part, from primary lesions of the blood vessels and it is irreversible. The central nervous system, like the lung, has limited capacity for regeneration but a large capacity for repair of intracellular damage. An increasing amount of information in animals supports the view that structural damage to the nervous cells may occur after doses of 1–6 Gy. These doses may produce cellular degeneration of the brain some months after treatment with destruction of sections of the cortex. In man the tolerance dose for the whole brain is around 55 Gy delivered in 5–6 weeks, but morphological changes are seen after 10 Gy of fractionated treatment. Threshold doses for the spinal chord are lower, in the region of 35 Gy in 4 weeks.

494. Irradiation of growing cartilage leads essentially to disturbances in the process of bone formation, with resulting deformities. Growing cartilage is known to be one of the most sensitive tissues and the threshold dose to cause growth stunting is probably small and possibly zero. In the young animal, about 3% stunting per Gy has been reported. In children, total doses of 10 Gy or more given in daily fractions over a few weeks are sufficient to cause some degree of reduced growth. The younger the child, the more severe the degree of stunting. Mature cartilage, on the other hand, may tolerate up to 70 Gy in prolonged fractionation schemes. In general, adult bone is considered to be fairly resistant and doses of 65 Gy given in 6–8 weeks do not normally cause necrosis: there may be however predisposition to fracture, depending on the mechanical stress normally exerted on the bone.

495. Of the many tissues in the eye (lacrimal glands, conjunctiva, cornea, sclera, retina) the lens appears to be the most sensitive to radiation, with production of lens opacifications or clinical cataract. Initial effects are seen in man after 2 Gy of acute exposure. In animals which are particularly prone to the development of cataract, like the mouse, much lower doses are usually required to cause earlier cataract than normal. Fractionated irradiation may be rather less effective in increasing the threshold dose than in many other tissues. As to the endocrine organs, in the adult the pituitary is regarded as radioresistant. Adrenals respond to the stress of irradiation in such a way that it is difficult to assess the amount of direct effects on them. The thyroid is a slowly proliferating tissue in which radiation effects may become apparent after many years. Doses of the order of 10 Gy in a single treatment are necessary to cause morphological damage to cells and signs of malfunction.

496. The time sequence between changes in the blood vessels and parechymal tissue lesions suggests that vascular injury may play an important role in all radiation-induced disturbances appearing in tissues (cell loss, fibrosis). After high doses of radiation, such as those used in clinical radiotherapy, morphological damage is known to occur in blood vessels and long after exposure these changes may lead to disturbances of the vascular function. Threshold doses for relatively subtle changes, such as abnormal vascular permeability, tend to occur at lower doses (down to 5 Gy) than more marked functional injuries like the reduction in blood flow (10 Gy or more). A detailed study of available data suggests that blood vessels located in different tissues may have different thresholds of reaction and that the overall response of a given tissue may depend on the joint response of the parenchymal and vascular components, in such a way that it may not be possible to view the reaction of either component in isolation.

497. The Annex examined for each tissue the effects produced by radiations of different qualities (particularly by fast neutrons) that are known to produce, dose for dose, a higher degree of biological effects than x or gamma rays. For single acute doses sufficiently large to cause detectable non-stochastic injury, the relative biological effectiveness (RBE) of neutrons is in the range of 1–5 times that of x or gamma rays. The RBE increases in the course of fractionated treatments with the decrease of the dose per fraction or with the increase in the number of fractions. For tissues where post-irradiation repopulation is important (skin, intestine) there is every reason to expect that repopulation is independent of the quality of radiation; for slowly dividing tissues repopulation will be small with all radiations. However, since other modalities of repair are relatively less effective for neutrons, the doses of this radiation that could be tolerated if given over a long period of time will not be much greater than the doses for the same radiation given as acute exposures.

498. Consideration of the non-stochastic effects produced by beta- or gamma-emitting radionuclides administered internally showed that tissue injuries are usually consistent in type and degree with those caused by comparable mean tissue doses of external irradiation at low dose rate. The tissues affected by treatment with a given nuclide depend on the particular distribution of that nuclide in the body; the amount of injury depends on the radiation characteristics and on the temporal distribution of the energy delivered. Models to relate the temporal distribution of absorbed doses from a radionuclide to that of fractionated external irradiation on the basis of equal effects have not yet been fully explored. There are also uncertainties concerning the microdistribution of the energy delivered to the biological targets within the cells and they affect the assignment of precise RBE values to radionuclides emitting non-penetrating radiation, such as alpha particles and low-energy Auger electrons.

VIII. NEEDS FOR FUTURE RESEARCH

499. In general, this Annex has shown that non-stochastic damage is observed only with doses that are considerably greater than those producing stochastic injury. Nevertheless, further study of non-stochastic effects is important. The preceding chapters have repeatedly emphasized that the expression of non-stochastic injury is dependent on the proliferation kinetics of the tissue and on the relationship between the proliferating

cells and those responsible for the tissue-specific functions. There is generally a lack of information about the relationships between the various normal cell kinetic parameters and the timing and extent of injury. In addition, little is known of radiation-induced changes in proliferation kinetics during or after irradiation, particularly under chronic exposure conditions. Information is especially scarce for tissues with long turnover times in which the response is normally manifest a long time after irradiation.

500. Although a considerable body of data exists on tissue effects after single doses of irradiation or after a small number of dose fractions, there is a need for more information about effects of long term fractionation or continuous irradiation lasting over a significant portion of an animal's lifetime. Similarly, mathematical models which account for fractionation effects need to be extended to very long treatment times in order to confidently extrapolate existing data on man. Clearly the experimental and theoretical aspects of this problem need to be carefully related.

501. The translation of loss of clonogenic capacity of individual cells to impairment of tissue function is extremely complex and variable from tissue to tissue. In most cases the target cells of composite tissues and organs are not known: new techniques and much research on methodology are needed to gain information about them and the pathways of injury leading to functional impairment. The role of blood vessel damage and whether it is a primary or secondary effect of irradiation is unclear. Further studies are also needed on the pathogenesis of radiation induced fibrosis and sclerosis.

502. New and more sensitive and quantitative endpoints are needed to study effects of radiation in a range of tissues, including endocrine organs, reproductive organs, central nervous system, lung, liver, kidney, eye, haematopoietic tissues, etc. Of special interest are changes occurring late after irradiation. The existence of possible relationships between early and late responses would also be of importance for the quantification of long-term damage. Remote consequences of partial-body irradiation have as yet received scant attention. In recent years there have been great advances in knowledge of the immune system, but few comparable radiation studies have been made, particularly at low doses and dose rates. Also, in animal investigations little attention has been paid to alterations in response as a function of animal age or stage of development.

503. A reasonable body of data exists on RBE as a function of dose per fraction, but mainly for early effects and at doses greater than a few Gy. Below this dose level or at low dose rates little information exists. Data is also lacking on tissues which show damage late after irradiation. In complex organs the RBE may vary from one cell type to another so that the measured overall response of the organ may be qualitatively different with radiations of different LET. Such effects require careful examination.

504. Of fundamental importance in the response of tissues to long term irradiation is their capacity for repair. Intracellular repair mechanisms leading to repair of sublethal damage, potentially lethal damage and, in some tissues, slow repair are as yet not well understood and further knowledge of the mechanisms of cell killing and repair are required. Repair by regeneration is also an important factor, but after irradiation this may be incomplete and there may be replacement of functional parenchymal cells by fibrosis. Repair of all types requires further investigation after both low- and high-LET radiations for precise quantitative evaluations in all tissues.

505. The response of tissues to deposited radionuclides is often very difficult to evaluate owing to uncertainties in the dose distribution, together with variations in activity with time. This is particularly true where the decay scheme is complex. Efforts should be made to define the dosimetry more accurately. Studies are needed of effects of radionuclides emitting short range particles (e.g., Auger electrons), particularly where they are deposited in critical structures or molecules.

506. Quantitative results in man are urgently needed, but difficult to obtain. New methods to derive data from radiotherapy patients are required as is the continued careful monitoring of any situation of human exposure to doses resulting in stochastic damage to individual tissues or to the whole body. There are wide differences in the type and severity of the non-stochastic effects considered in this Annex. For practical applications it is important that attempts should be made to quantify this damage in terms of the degree of detriment.

Table 1

D_2-D_1 values for various tissues

Tissues	Species	Endpoint	D_2-D_1 (Gy)	Ref.
Skin	Pig	Radiodermatitis	5.0-7.0	[F1]
	Rat		8.9	[F2]
	Mouse		5.0	[D3]
	Mouse	Epidermal clones	3.5	[W4]
			5.7	[D3]
Oesophagus	Mouse	LD/50	5.6	[H2]
			8.5	[P1]
Gastrointestinal tract	Mouse	LD/50	4.5	[H3]
		Macrocolony assay	4.0	[W5]
Cartilage	Rat	Growth stunting	4.0	[D4]
			3.5	[K1]
Lung	Mouse	LD/50 (both lungs)	4.0-5.0	[F3]
			3.5	[P2]
Spinal cord	Rat	ED/50	9.5	[W6]
			6.0	[V1]
Testis	Mouse	Clonal assay	3.0[a/]	[W7]
Haemopoietic tissues	Mouse	Spleen nodules	1.0	[T1]
Endothelial cells	Rat	Stimulated dermal blood vessels	3.0	[R2]
		Colonies in granuloma pouch	1.8	[V2]
		Cell counts in mesentery	7.0	[H4]

a/ Decreases with increasing time between fractions.

Table 2

Changes in proliferation after irradiation of skin (Fractionation data) [D1]

Species	Fraction number	Overall time	Increment Gy/day	Doubling time (days)	Ref.
Pig	5	5-28	0.25	4	[F10]
Mouse	2	7-14	0.30	3.2	[D3]
		14-21	0.29	3.2	[D3]
Human	up to 25	up to 35	0.28-0.34	3	[C4]
Mouse	15	17-35	0.32	3	[D14]
Mouse	2	1-7	0.70	3.2	[C5]
Mouse	5	4-9	0.90	1	[F16]
Plucked skin					
Mouse	2	1-6	1.00	1	[W11]
Mouse	2	1-7	0.48	2	[E7]
		7-14	0.42	2.3	[E7]
		14-21	0.29	3.3	[E7]

Table 3

Threshold skin erythema doses for single doses of x rays

Species	Dose (Gy)	Area irradiated	Reference
Pig	10-15	Approximately 20 cm^2	[F10,W38]
Rat	10	Whole foot	[F2]
Mouse	10	Whole foot	[F12]

Table 4

"Threshold doses" for damage to kidney of various species

Species	Dose (Gy)	Type of injury	Ref.
Dog	< 20	Tubular function	[M10]
	6	Renal enzyme changes	[P7]
	6	Functional and enzymic changes	[Z1]
	5-10	Decrease in size and mass, histological and functional changes	[M11]
Pig	10	Function	[H12]
Rabbit	~ 12	Probability of lethality	[C7]
Rat	5	Hypertension	[L13]
	5	Nephrosclerosis	[B11]
	< 10	Functional and enzymic changes	[K8]
	10	Plasma flow and collogen deposition	[C8]
Mouse	5	Nephrosclerosis	[B12]
		Accelerated glomerulosclerosis	[G1,C9]
	< 10	Blood flow	[G2]
	8	Lethality after unilateral nephrectomy	[P8]
	10-15	Inhibition of growth	[D1]
	10	Decrease in weight	[G3]

Table 5

$LD_{50/30}$ (haemopoietic syndrome) for different species

Species	Approximate weight (gm)	LD_{50} a/ (Gy)	LD_{50} b/ (Gy)
Mouse	25	9.0	6.4,7.1
Desert mouse	30	15.2	
Gerbil	40	10.5	
Hamster	80	9.0	6.1,8.6
Rat	200	9.0	7.1
Guinea pig	800	2.6	4.5
Marmoset	3000	2.0	
Rabbit	3500	8.4	7.5
Monkey	4000	4.0	6.0
Dog	12000	2.7	2.5
Sheep	45000	1.6	2.1
Goat	50000	2.3	2.4
Man	70000	3.0 c/	3.0 d/
Swine	200000	2.0	2.5
Burro	400000		2.5

a/ [H6]
b/ [B7]
c/ [L17]
d/ [B18]

Table 6

Summary of threshold doses in experimental animals

Tissue	Endpoint	Single dose (Gy)	Multifractions or continuous irradiation (Gy)
Skin a/	Threshold erythema	~ 7	≥ 10
Oesophagus a/	LD/50	~ 20	50 in 10 F
GI tract	LD/50	8-15	2 Gy/day
Cartilage and bone a/	Stunting	1 Gy resulted in 3-5 % stunting	
Heart a/	Fibrosis, death	> 20	
Lungs a/	LD/50	≥ 10	50 in 30 F
Liver a/	Histological changes	> 10	30-60 in 10-20 F
Kidney a/	Various	5-15	Sparing by fractionation
Central nervous system a/	Neurophysiological changes	3	
	Paralysis	~ 15	~ 100 in 60 F
Thyroid a/	Malfunction	10	40-100 continuous
Pituitary	Weight loss of the animal	1-6 in the very young. Very large doses in adults	
Adrenals	Weight loss of glands	4-6	
	Permanent changes	~ 20	
Testis	Sterility	3-10	0.0012-0.006 Gy/day
Ovary	Reduction in cells and fertility	Very large species	~ 2 fractionated
Eye a/	Lens opacities	3-5	11-14 fractionated
Haemopoietic	LD/50		
	Cell depletion	2-15	~ 0.5 Gy/day

a/ These tissues have been specifically irradiated, as opposed to whole-body treatment.

Table 7

Atomic bomb survivors by clinical symptoms and signs of radiation injuries [016]

Degree of severity	First week	Second week	Third week	Approximate mortality and time of death in weeks
Very severe (Group I)	Nausea and vomiting (+++) Fever, apathy, delirium, diarrhoea (+++) Oropharyngeal lesions (+) a/ Leukopaenia (+++)	Fever (++) Emaciation Leukopaenia (+++) Anaemia Haemorrhagic diathesis (±) Epilation (±)		100 % first and second
Severe (Group II)	Nausea and vomiting (++) Anorexia Fatigue	Fever (++) Leukopaenia (+) Anaemia (±)	Anorexia, emaciation, fever, diarrhoea, epilation (+++) Oropharyngeal lesions (+++) Haemorrhagic diathesis (+++) Leukopaenia (++), anaemia (++)	50 % third to sixth
Moderately severe (Group III)	Gastrointestinal b/ syndrome (++)	Leukopaenia (+)	Anorexia, emaciation, fever, diarrhoea, epilation (± ~ ++) Oropharyngeal lesions (± ~ ++) Haemorrhagic diathesis (± ~ ++) Leukopaenia (++), anaemia (+)	Less than 10 % sixth or later
Mild (Group IV)	Gastrointestinal syndrome (±)	Leukopaenia (+)	Fever (±) Epilation (±) Oropharyngeal lesions (+) Haemorrhagic diathesis (±) Leukopaenia (±)	None

a/ These lesions (ulcerations) occurred on all mucous membrane surfaces but were more prevalent in lymphoid areas than elsewhere. The tonsil, pharynx, larynx, nasal passages, and tongue were frequently involved.

b/ Gastrointestinal syndrome includes nausea, vomiting, anorexia, and diarrhoea. (+++)(++)(+) and (±) connote grade of symptoms and signs in order of decreasing severity and frequency, such that ± indicates that the symptom was not always present. Approximate ranges of kerma are 4.5 to 6 Gy (or more) Group I; 2-4.5 Gy Group II; 2-3 Gy Group III; 1-2 Gy Group IV. Estimates of these doses are subject to change but it is anticipated that the modifications will not be large.

Table 8

Acceptable doses from conventional radiation therapy a/ [R1]

Structure irradiated	Injury after 5 years	1-5% Acceptable dose (Gy)	25-50% Acceptable dose (Gy)	Irradiation field
Skin	Ulcer, severe fibrosis	55	70	100 cm^2
Oral mucosa	Ulcer, severe fibrosis	60	75	50 cm^2
Oesophagus	Ulcer, stricture	60	75	75 cm^2
Stomach	Ulcer, perforation	45	50	100 cm^2
Intestine	Ulcer, stricture	45	65	100 cm^2
Colon	Ulcer, stricture	45	65	100 cm^2
Rectum	Ulcer, stricture	55	80	100 cm^2
Salivary glands	Xerostomia	50	70	50 cm^2
Liver	Liver failure, ascites	35	45	whole
Kidney	Nephrosclerosis	23	28	whole
Bladder	Ulcer, contracture	60	80	whole
Ureters	Stricture, obstructions	75	100	5-10 cm
Testes	Permanent sterilization	5-15	20	whole
Ovary	Permanent sterilization	2-3	6-12	whole
Uterus	Necrosis, perforation	<100	<200	whole
Vagina	Ulcer, fistula	90	<100	5 cm_3
Breast, child	No development	10	15	5 cm^3
adult	Atrophy and necrosis	<50	<100	whole
Lung	Pneumonitis, fibrosis	40	60	lobe
Capillaries	Telangiectasia, sclerosis	50-60	70-100	
Heart	Pericarditis, pancarditis	40	<100	$whole_2$
Bone, child	Arrested growth	20	30	10 cm^2
adult	Necrosis, fracture	60	150	10 cm^2
Cartilage, child	Arrested growth	10	30	whole
adult	Necrosis	60	100	whole
CNS (brain)	Necrosis	50	<60	whole
Spinal cord	Necrosis, transection	50	<60	5 cm^2
Eye	Panophthalmitis, haemorrhage	55	100	whole
Cornea	Keratitis	50	<60	whole
Lens	Cataract	5	12	whole
Ear (inner)	Deafness	<60		whole
Vestibular	Meniere's syndrome	60	100	whole
Thyroid	Hypothyroidism	45	150	whole
Adrenal	Hypoadrenalism	<60		whole
Pituitary	Hypopituitarism	45	200-300	whole
Muscle, child	No development	20-30	40-50	whole
adult	Atrophy	<100		whole
Bone marrow	Hypoplastic	2	5.5	whole
		20	40-50	localized
Lymph nodes	Atrophy	35-45	<70	
Lymphatics	Sclerosis	50	<80	
Foetus	Death	2	4.5	

a/ Usually the 1-5 % acceptable dose is considered reasonable in radiotherapy; 25-50 % is not.

Table 9

Doses causing temporary or permanent sterility of human ovary

Effect	Tolerance dose (Gy)	Ref.
Temporary or reduced sterility	1.5 fractionated a/	[T17]
	1.7	[G13]
	4	[P18]
	12 fractionated (3/day)	[R34,P18]
	174 (in 3 series/2.5 years)	[G14]
Permanent sterility	3.2	[G13]
	2.5-5 fractionated	[R34]
	4	[P18]
	6.25	[P19]
	8-10	[L20]
	2 (in 3 series/2 years)	[J71]
	6.25-12 fractionated (30F/6 week)	[R16]
	6-20 fractionated (30F/6 week)	[L16]
	3.6-7.2 fractionated (2-4F)	[D20]

Table 10

Doses causing temporary or permanent sterility of human testis

Effect	Tolerance dose (Gy)	Ref.
Temporary sterility	0.1-1.0 fractionated	[S45]
	1.5-3	[H20]
	1-2 fractionated	[H55,S46]
	2.5	[G13]
	4	[O10]
Permanent sterility	2-3 fractionated	[H55,S45]
	9.5	[C12]
	6	[H21]
	5-6	[G13]
	4.5-6 fractionated	[L16]

Table 11

Effects of radiation on the human eye [H25]

Tissue	Effect	Dose (Gy)	
		Single dose	Fractionated dose
Lid skin	Early erythema	4-6	6 x days$^{0.33}$
Lacrymal gland	Atrophy	20	50-60 30F/6 weeks
Conjunctiva	Late teleangiectasia		30-50 (3-5 weeks)
Cornea	Early oedema and keratitis	10	30-50
Sclera	Late atrophy		200-300
Retina	Early oedema		30-35
	Late degeneration		30-50
Lens	Cataract	2-10	4 x days$^{0.17}$

Table 12

N and T factors for neutrons compared with x rays

Tissue	Damage	Neutrons	x rays		Neutrons		Ref.
			N	T	N	T	
Subcutaneous	Fibrosis		0.24	0.11			[E4]
Skin	Erythema desquamation	16 MeVd/Be	0.26	0.11	0.04	0.11	[F30]
Tail	Necrosis	14 MeVd-T	0.39		0.00		[H28]
Tail	Erythema desquamation	16 MeVd/Be	0.39		0.03		[A10]
Lung	Pneumonitis	16 MeVd/Be	0.27	0.07	0.00	0.00	[F8,H30]
Spinal cord	Myelopathy	14 MeVd-T	0.44	0.03	0.00		[V1,V8]
Spinal cord	Myelopathy	16 MeVd/Be	0.38	0.00	0.00		[W6,H66]
Brain	Necrosis	16 MeVd/Be	0.38	0.00	0.00	0.00	[H67]
Small intestine	Crypt damage	16 MeVd/Be	0.29		0.00		[W2]
		50 MeVd/Be			0.00		

Table 13

Threshold skin erythema doses for fast neutrons

Species	Dose (Gy)	Area irradiated	Ref.
Pig	5	Approximately 20 cm^2	[B30]
Rat	4	Whole foot	[F2]
Mouse	5	Whole foot	[F26]
Man	2	Approximately 20 cm^2	[F14]

Table 14

Lowest injection, burden time, and skeletal dose where significant vascular reduction occurs after various radionuclides [J22]

Radionuclide (kBq/kg)		Days post injection	Skeletal dose (Gy)
41	^{226}Ra	1900 days	23
3.5	^{239}Pu	2200 days	3.5
6.3	^{228}Ra	2500 days	5
1.2	^{228}Th	1900 days	2.5
3700	^{90}Sr	1000 days	80

Table 15

Threshold doses for changes in vascular function (single treatments)

Tissue	Species	Functional study	Threshold dose (Gy)	Reference
Skin	Pig	Flow	8	[M33]
	Rabbit	Permeability	1	[J12]
	Rat	Permeability	20	[L23]
		Flow	15	[K21]
	Hamster	Flow	20	[H45]
Intestine	Rat	Permeability	5	[T12]
	Mouse	Permeability	2.5	[V3]
Mesentery	Rat	Permeability	5	[D33]
	Mouse	Permeability	20	[H40]
Lung	Rat	Permeability	20	[T13]
		Flow	10	[K21]
	Mouse	Permeability	10	[H53]
		Flow	11	[G2]
Brain	Monkey	Permeability	15	[C18]
	Dog	Permeability	10	[K23]
	Rabbit	Permeability	18	[N7]
	Rat	Flow	10	[K21]
Kidney	Man	Flow	4.5/3F	[A15]
	Pig	Flow	~ 12	[H12, H48]
	Dog	Flow	10	[M36]
	Rat	Flow	10-20	[C8]
	Mouse	Flow	11	[G2]
Liver	Rat	Flow	15	[K21]
	Mouse	Flow	5	[F32]
			> 15	[G2]

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ANNEX K

Radiation-induced life shortening

CONTENTS

Introduction

1. Since the 1958 and the 1962 reports of UNSCEAR [U1, U2] the Committee has not presented a review of the cumulative evidence in the field of non-neoplastic long-term effects of whole-body irradiation. The scope of this Annex is to consider the data available in order to ascertain:

(a) The existence and extent of life-span shortening in irradiated animals and man and the relationships of life shortening to the physical and biological variables which may influence this effect of radiation;
(b) The extent and ranges of the physical and biological components of this effect which might be attributed by careful pathological analysis to either real non-tumorous conditions or to specific neoplastic diseases;
(c) The range of doses within which a non-specific radiation effect may be identified and measured;
(d) Whether such a non-specific shortening of life may be similar to the normal biological aging process.

Although answers to some of the above questions may be difficult in the light of the present biological and radiobiological knowledge, the Committee believes that a review of the field may be of value as a selective collation of the existing information. All data in the human species have been grouped for convenience in chapter IV. Causes of death due to non-stochastic effects are dealt with in Annex J.

2. Due to its coherence and wide acceptance, the international system (SI) of units of measurements has been employed wherever possible. The use of SI has resulted in the replacement of the former unit of absorbed dose, the rad, by joule/kilogram and in a special name of the unit, the gray (Gy), with one Gy being equal to 1 J/kg and to 100 rad. Similarly, the unit of exposure, the roentgen (R), has been replaced by C/kg, where one C/kg is equal to about 3876 R. Furthermore, the unit of activity, the curie (Ci), has been replaced by the reciprocal second and its special name, the becquerel (Bq), where 1 Bq is ($1/3.7\ 10^{10}$) Ci.

3. The use of the SI units poses problems in the presentation of results, except those obtained in the recent past. Due to the simple relation between the rad and the gray and that between the curie and the becquerel it is possible to easily perform these conversions. This has been done throughout this Annex. For the quantity exposure, however, it has been decided to employ the units provided by the authors.

4. The relation between exposure and absorbed dose and the recent tendency to use the latter in quantifying irradiations presents another difficulty. As an example, for soft tissues exposure to 1 R of low-LET radiation results in an absorbed dose of about 0.009 ± 0.0005 Gy, when the quantum energy is more than about 25 keV and electron equilibrium exists. However, the variation in absorbed dose can be far greater for other tissues (e.g., bone). Other uncertainties arise when animals larger than the mouse are irradiated. In these cases the conversion depends on whether the exposure quoted is that in free air or the mean exposure in the animal. In the more usual case of free air exposure, there is a complex relation between exposure and absorbed dose, depending on the size of the animal, irradiation geometry and radiation energy. For these reasons no attempt has been made to replace quoted exposures by corresponding absorbed doses.

A. HISTORICAL BACKGROUND

5. Radiation-induced life-span shortening was described first in the rat by Russ and Scott [R1] and in the mouse by Henshaw [H1]. They reported that irradiated animals had a shorter life span and appeared to age more rapidly than their non-irradiated controls. These and other observations led quite naturally to the establishment of a conceptual link between the life-shortening action of radiation and natural senescence. In 1952 Brues and Sacher [B1] discussed the problem of radiation-induced long-term radiation lethality. These authors recognized that single acute exposures to radiation tended to displace the Gompertz age-mortality function upward, while chronic exposure throughout life increased the slope of this function. Other techniques of analysis by the cumulative or the impulse lethality functions were also proposed as quasi-empirical actuarial and kinematic descriptive approaches. A comparative review of radiation lethality in various mammalian species, particularly under conditions of chronic treatment for the entire duration of life was presented by Sacher in 1955 [S1].

6. Although the treatment of this subject had proceeded quite far by 1958, there was little coverage of it in the 1958 report of the Committee [U1]. At that time the analysis of the biological end-point was not very sophisticated. It had been established that the pathogenesis of early death was due to the failure of self-renewing systems in the body, but that the precocious extinction of an animal population as revealed by actuarial analysis, was due to different mechanisms. However, there seemed to have been poor discrimination of the two mechanisms. In particular, no attention was given to the actuarial approach which had already been advocated by Sacher [S2] and Brues and Sacher [B1].

7. Although the review presented by Mole at the First International Congress of Radiation Research [M1] criticized the idea that radiation-induced life shortening might be equivalent to natural aging, this notion gained acceptance as a result of some observations on animals surviving doses in the lethal range made by Henshaw [H1] and later by Alexander [A1]. The "equivalence" idea was first based on actuarial observations of an increase in mortality rate from all causes of death, with an apparent shift of diseases characteristic of older age to younger age groups. The occurrence of phenomena typical of the old age in survivors (greying of the fur, cataracts, loss of reproductive capacity, etc.) tended to support the hypothesis of "equivalence". However, Upton in his 1957 [U3] and 1960 [U4] reviews warned against the attempt to establish a close relationship between certain effects of irradiation and aging, because not all age-dependent changes were affected similarly by radiation and the incidence and severity of the various diseases differed in control and irradiated animals.

8. Comfort [C1] discussed similarities and differences between natural aging and radiation-induced life shortening. His review is an important effort to define basic concepts and to differentiate between the various biological effects observed but his analysis of data according to dose and time is less elaborate than elsewhere. Storer and Grahn [S3] presented an accurate review of information available. This paper is still of interest for reference purposes. Neary [N1, N2] regarded theories of aging as belonging to one of two main groups: those interpreting aging as due to random

events in a population of supposedly uniform individuals; and those examining the individual and its component cells. Neary proposed his own theory, based on the analysis of original data on irradiated mice. According to his formulation aging proceeds in two successive stages, induction and development, each characterized by appropriate parameters. Although no attempt was made at the time to identify these stages, experiments reported later from the Soviet Union [V8, V9, V11, V12] tend to show that induction consists of the spontaneous occurrence of lesions in cellular DNA and development (promotion) in the activation of endogenous viral genomes by chemical carcinogens or radiation.

9. Another interesting contribution was provided by Casarett [C2]. By a critical comparison of natural aging and of late radiation effects, he proposed that radiological aging can be ascribed to the damage of endothelial cells of the fine vasculature, leading to fibrotic changes of the arterioles and of the interstitial collagenous substance. These mechanisms would be followed by loss of parenchymal cells, replacement fibrosis of the organs, loss of the functional reserve capacity and, eventually, by an increased susceptibility to trauma, stress and disease.

10. In recent years research tended to be more experimental than theoretical, except perhaps for the work of Sacher and Grahn [S4], Grahn and Sacher [G1] and Sacher [S5] who further elaborated previous ideas in an attempt to derive, from a refined analysis of the data, a basis for a comprehensive theory of a natural and radiation-induced aging. Attempts towards a better systematization of the experimental data were also carried out in contributions from scientists of the Soviet Union [A11, K26].

11. A recent report of Walburg [W1] was essentially a critique of the concept of non-specific life shortening, especially at the low doses of practical interest. Walburg came to the conclusion that life-shortening effects after irradiation may principally be explained by the induction or acceleration of neoplastic diseases. This conclusion was supported by Storer [S6]. These and other [K26] authors recognized that at higher doses other mechanisms of death prevailed.

B. METHODOLOGY

12. Life shortening can only be assessed on the basis of death, an end-point that can be defined rather precisely in time. However, it is usually more informative to know also the reasons why an animal dies. To ascertain the cause of death is often difficult and, in some cases, impossible as death is often the result of a variety of causes all acting jointly. This is particularly true as animals grow older [D1, A2, D2] because aging animals of all species (but particularly of the long-lived ones) die with multiple lesions, contrary to early death where there is often a single pathological cause. In old animals the number of possible causes of death increases and the primary or precipitating cause is difficult to diagnose. Most irradiated animals die of diseases which are unrelated to radiation exposure and this complicates the identification of the terminal pathological syndromes. Thus, multiple disease conditions, and interactions between diseases in the same animals should be correlated with parameters such as age and dose to provide a meaningful interpretation of the pathology at death.

13. The first difficulty with much of the work reviewed, particularly with the earlier contributions, is the lack of careful pathological observations on the animals at death, or a refined multifactorial analysis. Many experimental series are therefore difficult to interpret, as the representation of the life-span shortening, which may be accurate with respect to time, masks the complexity of the biological end-points. Another difficulty is that even when good pathology is available, information is usually collected at death. Under these conditions it is impossible to assess the contribution of each specific cause to life shortening, since there is no reason to presume that all causes are equally accelerated by radiation. Serial sacrifice experiments could, in principle, provide such information, but these require considerable time and effort and such reports are therefore not common in the literature [K1, C3, A3].

14. Apart from the difficulties in defining and describing a complex effect such as life shortening, quantification can create problems by giving implicit support to one or another possible interpretation. Interesting comments have been made by Mole in this respect [M2, M3]. He points out that it is not immaterial to think of the effect as a differential between the life span of the control population (t_0) and the life span of the irradiated animals. If it is postulated that survival after a given dose (t_D) is a function of that dose, it is implicitly ignored that animals may die of some unrelated pathology, and there is no implication that the effect of radiation may persist up to the end of life. If, on the other hand, the postulate is that the differential life time ($t_0 - t_D$) is a function of the dose, then the implication is that the effect of radiation may be equivalent to natural aging. No problems arise for single acute exposures given at young ages or for duration-of-life experiments, because under these conditions the two postulates are compatible. However, when experiments with various t_0 are involved, that is, when groups of animals are started on a course of irradiation at variable ages, one could come to quite different conclusions from the same experimental data simply by accepting one or the other postulate.

15. By definition, life shortening is an effect that must be estimated statistically by comparing irradiated and non-irradiated animal populations. The different ways of describing and expressing the effect quantitatively include the mean or median life span, the per cent cumulative mortality or the age-specific mortality rate. All these may be regarded as compounded expressions of specific and non-specific causes, acting within each individual to decrease fitness and ultimately to cause death.

16. Life shortening is expressed in days of life lost and since the time to death has a statistical variability, life shortening may be represented by one of the following statistics: shortening of mean or median age at death, shortening of mean or median survival time. In these cases the effect is given in units of time. Alternatively, the effect can be given as a percentage of control values and in such cases the per cent shortening of the mean or median age at death or the per cent shortening of the mean or median survival time would be the relevant parameters. It should be noted that the percentage effect as measured by the shortening of the mean or median age at death is not equivalent in most cases to that measured as per cent shortening of the mean or median survival. Although it would have been desirable to use the same method of expressing the effect

throughout this Annex, it was impossible to do so due to the lack of suitable data in the documents reviewed.

17. Mean and median life span are the average duration of life experienced by the animal population and the time required for 50 per cent of the animals to die, respectively. These statistics do not offer any indication of the variability of the phenomenon with time: they are therefore, as such, unsatisfactory parameters for any statistical analysis. The curve describing the extinction of the population in time is more informative as it shows the time when this process begins and ends and whether it has taken place regularly. Irregularities of the curve may sometimes be attributed to specific causes or set of causes. Both the mean and the median life span can be easily calculated and the per cent cumulative mortality as a function of time can be readily plotted.

18. The age-specific mortality rate is a more elaborate parameter. It expresses the instantaneous rate of mortality of the animals at risk as a function of age. The change over time is the main disadvantage in using this parameter. The main advantage lies in its sensitivity in measuring the changes in the distribution of times at death. It should be recalled that the displacement of the age-specific mortality rate curve for irradiated animals above the curve for non-irradiated controls does not measure days of life lost, but the increased rate of dying at a given age. The trend of this parameter in time and any irregularity in it are extremely useful to identify possible specific causes of death.

19. In estimating mortality rates it is desirable that assessments be independent of the proportion of animals that have died by any given time, i.e., that the estimate should be truly non-parametric with respect to survival. To this end, different formulas for its calculation have been proposed and may be utilized in radiation experiments [U5]. Upton, Kastenbaum and Conklin [U6], in an analysis of the age-specific death rates in irradiated LAF1 and RF mice pointed out that beyond a certain age this parameter tends to assume an exponential trend and that death rate curves specific for certain diseases vary in shape and slope. These observations emphasize the complexity of the relationships between dose and disease incidence. Therefore, the generalized notion that irradiation may advance the onset of old-age diseases is an oversimplification in the light of the variability observed with respect to specific injuries.

20. Other refinements in the analysis of life-shortening data may be introduced in order to account for the effect of competing diseases. It has long been known that the estimates of final incidence of diseases occurring late in life may be affected by the rate of mortality at times preceding the onset of these diseases [M4, F9]. Hoel and Walburg [H2] have compared various interval techniques of analysis with a non-interval technique by Kaplan and Meyer and have come to the conclusion that the latter may be used with advantage when the age at death of the animals is known. This technique has been employed for analysing the significance of the difference between treatment groups with respect to their cumulative mortality. There are also techniques to adjust the comparisons of mean ages at death, according to the presence of competing, lethal and non-lethal, diseases. Using these techniques Walburg [W1] has analysed some existing data on life-span shortening in experimental animals and has convincingly shown the usefulness of such methods in discriminating between specific, i.e., neoplastic, and non-specific life shortening.

21. Risk estimates for long-term somatic effects of radiation exposure have mainly been based on the incidence of fatal tumours. In principle, an improvement in these estimates could come from consideration, in addition to cancer incidence, of the mean ages at death. Sato et al. [S52] proposed an index which takes into account the contribution of each cause of death to life shortening. This index is the sum of three terms. The first reflects the tumour incidence, the second the changes in mean age at death from each cause of death and the third is an interaction factor for the preceding two terms. If radiation exposure increases the incidence of a given death cause and shortens the respective mean age at death, the index gives a large positive value. On the other hand, an increase in incidence of a late occurring cause of death gives a small positive or even a negative value for the index. The paper has a numerical example based on animal data.

C. THEORETICAL FOUNDATIONS

22. Although it is the primary object of this Annex to review and discuss experimental data on life-span shortening, it is impossible to do so without some background information on the hypotheses of aging. Such information is given in the next few paragraphs in a very simple form and is limited to those hypotheses that were proposed in the field of radiation research. More comprehensive discussions of the various theories of aging are, for example, in Strehler [S7], Walburg [W1], Vilenchik [V8], Nikitin [N13].

23. Gompertz in 1825 found that the age-specific mortality rate in man as a function of age increased exponentially over a considerable portion of life and assumed that this phenomenon reflected an exponential decline with age of some vital system. In the field of radiation research Brues and Sacher [B1] first introduced a mathematical approach to long-term mortality based on the observation of Gompertz and this was followed later as a basis for the analysis of experimental data and for many theoretical formulations. According to this approach, the survival characteristics of a group of individuals may be described by actuarial functions. One of the most widely used is the Gompertz function.

24. The Gompertz function $\ln \Omega(t)$ is the logarithm of the age-specific rate of mortality which is defined as [S16]

$$\Omega(t) = -\frac{1}{N}\frac{dN}{dt} \qquad (1)$$

where $\Omega(t)$ is the age-specific mortality and N is the number of animals surviving up to the time t. Linearity of the Gompertz function with time implies that

$$\Omega(t) = P_0 e^{P_1 t} \qquad (2)$$

where P_0 and P_1 are positive constants. Experience shows that a single acute dose of radiation is followed (after a period of latency) by an upward displacement of the Gompertz function without change in slope and that the amount of displacement with respect to the control is a function of dose. In other words, acute irradiation changes the constant P_0 in equation (2),

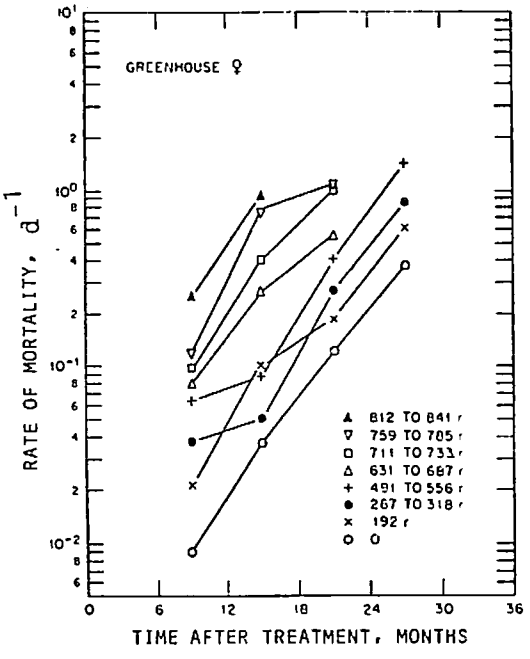
without affecting P_1. If single exposures would affect median survival, t_{med}, linearly with dose D, then

$$t_{med}(D) = a - bD \quad (3)$$

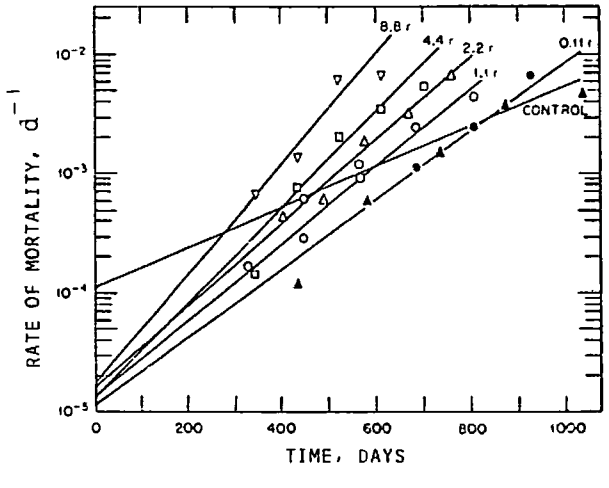
where a is the median survival time of the control group and b a dose-dependent constant. Chronic irradiation, on the other hand, characteristically increases the slope of the Gompertz function proportionally to intensity of irradiation, so that

$$t_{med}(I) = a\, e^{-cI} \quad (4)$$

where $t_{med}(I)$ is the survival time following duration-of-life exposure at dose rate I and c is a dose rate-dependent constant. These basic trends of the rate of mortality in irradiated mammalian populations are shown in Figure I.



A. Gompertz plots for LAF1 mice (females) after single acute exposures to gamma radiation. Data from Furth et al. [F2] *plotted by Sacher* [S2]



B. Gompertz plots for LAF1 mice (both sexes) under daily exposure to gamma radiation. Data from Lorenz et al. [L6] *plotted by Sacher* [S2].

Figure I. Basic trends of actuarial parameters in irradiated mammalian populations. In the mouse exposure to 1 R will result in an absorbed dose of approximately 0.009 Gy

25. The assumptions underlying such interpretations are that the Gompertz function is a measure of the amount of aging injury present at any given time. Acute exposure increases this amount of injury initially and for the rest of life. However, if a new induced injury adds to the residual present injury at any given time or to the underlying aging injury, one should expect a change in slope produced by chronic irradiation, with a divergence from the control slope proportional to the amount of daily dose administered. It should be clear that such characteristics of the actuarial functions are not necessarily related to the form of the dose-effect relationships, which may themselves be linear or not, as discussed in the next chapter.

26. In 1952 [B2, B3] and again later in a more complete form [B4, B5] Blair formulated a model of the relationships between radiation dose and life shortening. This model postulates that total injury is linearly proportional to dose and that such injury is only in part reparable. Recovery from reparable injury proceeds exponentially at a rate proportional to its magnitude; while, on the contrary, the irreparable portion of injury would accumulate linearly with dose. Finally, reparable and irreparable injuries add and death occurs when the effect of their sum is proportional to the remaining life expectancy. Starting from these premises, Blair developed simple equations relating dose and injury under different conditions of exposure and showed that some of them conformed to the then available data. Blair's formulation stimulated much research to ascertain the amount of reparable injury and the kinetics of repair under a variety of experimental conditions but was recognized later as an oversimplification leading to incorrect estimates and as such inadequate to account for the form of the dose-injury functions.

27. Mewissen et al. [M5] developed a complex equation relating life shortening to chronic whole-body irradiation and applied this formula to the irradiation of the burro. The formula is based on an analysis of the injury, which is also assumed to consist of a reparable and an irreparable fraction. Wasted radiation is accounted for by the transformation of a latent into an actual injury at a given measurable rate. The numerical parameters of the equation may be computed from experimental results in cases of chronic and acute irradiation. Weekly exposure to gamma radiation of burros, between 175 and 2800 R, with corresponding mean survival times of 9 weeks to 1 week, were the time-dose conditions in which the above formula was found to apply. They are clearly of little value to the present discussion referring to low dose rates and to extended survival times. Storer [S8, S9] in a review of data on recovery rates and their possible relationships to life shortening showed that the mean rate at which mice recovered from radiation exposures, which if acute would result in acute death, could be related to the number of fractions delivered daily, rather than to the size of the exposure. This and other observations suggested modifications of the original formulation of Blair.

28. Krebs, Brauer and Kalbach [K3] measured the kinetics of non-recoverable injury by exposing C3H female mice to conditioning irradiations (600 to 1500 R) and then estimating at different times (4 to 20 weeks) the injury remaining. This estimate was obtained indirectly by taking the $LD_{50/30}$ values on the preirradiated mice. A proportionality between conditioning dose and reduction in tolerance to x rays, as measured by a reduction of $LD_{50/30}$, was found; however, the

injury parameter did not account for the observed mortality when animals were chronically irradiated. Further work [K4, K5] suggested that different recovery components with different half-times could be shown to apply to acute and chronic radiation exposure conditions.

29. Complete disappearance of residual damage was seen by Alexander and Connell [A4] three weeks after conditioning exposures of 600 to 1100 R prior to $LD_{50/30}$ determinations. Spalding et al. [S10] gave conditioning fractionated doses of gamma rays (2.4 to 12 Gy) or of fission neutrons (0.9 to 4.5 Gy) to RF female mice and, after a repair period of 3 months, exposed them for the rest of their lives to a dose rate of 0.5 Gy d^{-1}. They found that radiation-induced damage had a permanent and irreversible component, that at least a part of this damage was proportional to the dose and measurable in terms of reduction of survival time, and that fission neutrons produced about five times as much irreversible injury as gamma rays. Always with the same animals, an investigation of the two-component theory of Blair [B4, B5] under the assumption that the half-time of the reparable component was 7 days and that the irreparable injury would be equivalent to 5% of any given dose, showed that such a formulation was only useful under a limited range of exposure conditions.

30. The above limited discussion of the results of a vast amount of literature shows that short-, medium- and long-term mortality are produced from different pathogenetic mechanisms. There is probably more than one single formula to account for the variety of mechanisms. Further, no single recovery time or residual injury value can define all of the conditions of protracted exposure. The constants applicable to acute injury may to some extent predict the results of exposures to within about 100 days and 15 Gy in the mouse, but for longer times and low doses a new set of relations between injury and recovery must be established [G1].

31. Neary [N1, N2] also proposed a model, based on the observation that the great majority of animals in a population die during the last part of the life span. The preceding period of life, in which deaths are relatively few, is called "induction" by Neary, who defines it as a state of intracellular changes and intercellular reactions proceeding insidiously and without marked functional impairment. When a certain level of this type of change is reached, the second stage sets in quite abruptly. This stage, called "development" involves a different level of organization and is sustained by physiological interactions proceeding autonomously and autocatalytically and culminating in death. The most interesting feature of this model is that once development sets in further inductive change is superfluous and therefore irradiation during development has comparatively little effect. This point was emphasized conceptually by Mole [M6] and by Mole and Thomas [M7] in the notion of "wasted radiation". Neary suggested that small radiation doses would essentially act by shortening induction without affecting development, and also showed that there was a good correlation between the results of experiments on mice [N3] and the formal requirements of the model. Kohn and Guttman [K6] pointed out, however, that the model, derived from results of duration-of-life exposure was difficult to apply to results derived from acute irradiation experiments. Experimental evidence has more recently been reported [V8, V12] in support of a two-stage model of aging.

32. In a paper published in 1956 Sacher [S2] proposed a model in which all individuals in a population were assumed to be initially identical. However, with time, due to fluctuations in the physiological state of the animals and to external stresses, there was a progressive change and a dispersion in the physiological state of the population. In this model, when a fluctuation of large amplitude in the homeostasis of an animal takes place, death ensues. By a mathematical description of a physiologic fluctuation process, it is possible to derive an approximate relationship between the rate of mortality and the mean physiologic state of the population. The relationship has the form of a linear function of the logarithm of the mortality rate with respect to the mean physiologic state of the population at any given age.

33. A more analytical presentation of this theory and of the derived functions can also be found in other papers [S4, S12]. In a later contribution [S13] attempts were made to interpret lethality in terms of very simple cell population kinetics, without building into the models known parameters of cell kinetics such as maturation time or feed-back control of self-renewing systems. Other features of cell kinetics, with special regard to lengthening of the generation cycle upon continuous irradiation, were discussed in another paper [S5] as possible causes for a cumulative lesion related to the life-shortening effect. Cytogenetic injury due to rearrangements of chromosomes has also been considered to account for radiation-induced life-span shortening [S14].

34. A critical comparison between the model of Blair and that of Sacher is contained in Sacher and Grahn [S4]. The latter model assumes linearity and additivity functions formally equivalent to those contained in the former, although Blair postulated the existence of only one component of recovery from injury, which operated soon after exposure and caused the injury to fade away exponentially. When the equations derived by Blair were fitted to the cumulant lethality function of Sacher the fit failed, owing to significant systematic deviations. In addition, the mean recovery time estimated from Sacher's data was 4 to 10 times longer than the recovery value of 5 days accepted by Blair on the basis of fractionation experiments. For these reasons Sacher and Grahn [S4] rejected the central assumption of Blair referring to the single linear component of recoverable injury. All the remaining assumptions of Blair are included in the more generalized formulations of Sacher. The assumptions are that radiation injury is proportional to dose and to dose rate; the recovery rate from this injury is proportional to the amount of injury present and is independent of age; death occurs when the sum of all injuries reaches a given value, called the lethal bound; radiation injury is additive to the injury accumulating due to age; and that age-cumulative injury is linear with age.

35. Stover and Eyring [S15] and Eyring and Stover [E1] developed a steady-state theory of mutation rates and applied it to the survival data of beagle dogs injected with ^{239}Pu and ^{226}Ra. The fits of the experimental data obtained by the use of this model were good and allowed the identification of various mechanisms of death caused by the two nuclides. The formalisms developed in this series of papers adequately describe the experimental data and may be of use in further interpretations.

36. Sato, Nakamura and Eto [S16] performed calculations of the life-shortening effects of radiation as a function of dose and dose rate under the assumption of linearity of the Gompertz function for both acute and continuous exposure. They showed that within the range of doses usually employed with mice the values of percentage life shortening are not appreciably changed if the survival time is measured as mean, median or mode.

37. Iberall [I3] examined the various models of radiation lethality in great detail and attempted a unitary description of the various modes of death, from those due to very high acute doses to those due to low chronic treatments, through an analysis of much experimental data. In so doing he illustrated the level of complexity required for a careful mathematical description of the actuarial properties of a population. This description pointed towards the isolation of five or six possible conditions affecting lethality as a result of the various irradiation regimes. The paper supplemented the studies of Sacher and Grahn [S4] with a widespread examination of the entire problem from a mathematical point of view.

38. Another model for life shortening by late effects of ionizing radiation was developed by Scott and Ainsworth [S47]. It applies to data in the mouse and it is specific for doses much below the $LD_{50/30}$. It focuses on the number of individuals with life-shortening injury and variations due to dose, dose rate and quality of radiation. For these individuals the survival time distribution differs and shows earlier times to death as compared to other members of the population without life-shortening injury. The results of the model's analysis are consistent with available data at comparatively low doses, including the convex upward life-shortening responses. The model predicts enhancement of effects after fractionated exposure to ^{60}Co gamma rays and an approximately linear response in most cases of acute exposure to low-LET radiation. The model also provides a means of extrapolating between mouse strains or age groups, an extrapolation which can be achieved by changing a single parameter [S48].

39. Finally, other publications should be cited for completeness, where the problem of long-term chronic exposure to carcinogenic agents in general (or specifically to radiation) was addressed, in an attempt to account for both the increased incidence and the early displacement of the tumours induced which, in turn, cause shortening of life span. In this context the papers of Blum [B27], Druckerei [D11], Albert and Altschuler [A15], Hug [H20] and Mayneord and Clarke [M32] should be recalled as valuable contributions. However, these papers refer to tumour induction and not to life shortening in general and have therefore a narrower approach to the problem under discussion here than many of the papers cited previously. They should be kept in mind mainly in view of the general conclusions to be arrived at in this Annex.

D. LIFE SHORTENING AND AGING

1. Specific and non-specific life shortening

40. There is considerable discussion in many of the papers reviewed about the specificity or non-specificity of the life shortening observed in a variety of experimental situations. Semantic considerations as well as important reasons of substance have complicated this issue. It should first be recognized that speculations about specificity often conceal the lack of good pathological analysis. Life shortening must be due, if properly assessed, to some specific cause. However, the word specific has been taken to mean that the irradiated animals die earlier than their controls with a characteristic spectrum of diseases or causes of death different from the spectrum seen in the non-irradiated controls.

41. Since it is well known that not all diseases are readily induced by radiation, to expect that radiation acts non-specifically in shortening the average life of an animal population would be to reject all radiobiological experience. Recently the discussion has been more reasonably centered on whether or not radiation may produce life shortening by induction of tumours and how much of the observed shortening can be accounted for by neoplastic diseases. Though never defined clearly, the words specific and non-specific have therefore been taken to indicate neoplastic and non-neoplastic contributions to life shortening. Under these conditions, the question of specificity of the life-shortening action is legitimate and of great practical significance.

42. In discussing the problem of specificity, ICRP publication 14 [I1] and Mole [M2, M3] point out that in order to detect a general non-specific deleterious effect of radiation, long-term survival data should first be corrected for diseases known to be specifically induced by radiation. The concept of life shortening is ambiguous as it may be regarded either as an overall measure of deleterious effects or as a measure of the effects remaining after allowance for the induction of tumours and other defined diseases. Non-specific life shortening, if it exists, must have some basis in damage to biological structures and functions. Actually, some damage, anatomical or functional, may be shown for some tissues [C4, D3, C5], but not for all. Under these conditions an increase of causes of death related to damage in those particular tissues may be expected. The resulting effect should be a change in the spectrum of diseases induced in irradiated animals. On the other hand, one could envisage that damage to body components such as the blood vessels or the connective tissue, which are uniformly distributed in the body, could be the cause of non-specific life shortening at high doses. However, it appears unlikely that damage to blood vessels in skin, muscle and fat tissue results in changes ultimately affecting the vital capacity of an individual, whereas damage to blood vessels of the kidney, the brain, the heart can be expected to result in important changes affecting the capacity for survival. Thus, if the determining factor is the anatomical location of the damaged blood vessels, again a change in the spectrum of diseases compared to the spectrum of diseases of unexposed animals would be expected in irradiated animals.

43. In conclusion, the notion of non-specific life shortening is compatible with that of aging (advanced or accelerated) induced by radiation. The two concepts are inevitably linked with the demonstration of the principle that radiation, although advancing the instant of death, does not modify the spectrum of normally occurring diseases. This demonstration is difficult in practice and probably impossible to visualize as the mechanisms that may be hypothesized for non-specific effects will also change the spectrum of diseases appearing in irradiated animals. Such change is incompatible with the notion of aging or of non-specific life shortening.

2. The phenomenon of aging

44. Attempts to show that irradiation may non-specifically age animals were begun with observations that radiation did produce life shortening and that irradiated animals showed phenomena similar to those observed in old age (greying of the fur, appearance of cataract, loss of fertility). Although it should have been clear that the resemblance was only superficial [M3], the hypothesis of radiation-induced aging gained momentum and stimulated much work. The interested reader may refer to the following reviews – which are some of the many available – for more detailed evaluations of data obtained in experimental animals [A1, A11, U4, C2, C32, H3, C6, C7] and in man [A4, A6, F1, B6].

45. Difficulties in experimental work on aging are related to its definition, to the lack of any direct measure of senescence other than in terms of life span, and to the impossibility of deciding whether pathological processes in old animals are the causes of aging, the effects of aging or indeed aging itself. The only acceptable generalization is that in mammals the age-specific death rate increases as a function of time in a roughly exponential manner by a constant factor for each year of the adult life. That is, that the probability of death per unit time increases with age (see control curves in Figure I). However, to accept this generalization as a measure of aging requires the assumption that aging of each individual is paralleled by the average changes of the population to which the individual belongs. In addition, there are uncertainties in sorting out, both for the individual and for the population, intrinsic and environmental factors, primary and secondary effects, specific and non-specific phenomena.

46. Radiation is by no means the only agent producing life shortening. Other treatments have often been reported to produce similar effects in conjunction with radiation experiments. These life-shortening agents include various types of toxins and non-specific toxic substances [C8, C9] or cytotoxic drugs [C10, A4, U6, C11, D4] in various combinations and dosages. It appears from all the data that the effect of these agents is in general less readily induced than the effect from radiation and that the diseases leading to precocious death are specific for each drug.

47. In the context of the hypothesis of radiation-induced aging, the concept of differences between advanced or precocious aging on the one hand, and accelerated aging, on the other has been discussed repeatedly (see, for example, [C2] and [C7]). The two notions can be formally visualized in terms of the theory of radiation injury of Blair [B2, B3, B4, B5]. If one assumes that aging in an individual is determined by the sum of deleterious irreparable injuries accumulating in time; that radiation causes irreparable injuries which may add to the aging injuries; that beyond a given level of injury death of the animals occurs; that such processses within each animal may also be reflected by the Gompertz curve; then a displacement upward of this curve without change of its slope would be interpreted as precocious aging, whereas an increase of the slope would be formally equivalent to accelerated aging (Figure I). However, such definitions may hold formally but are difficult to verify experimentally.

3. Mechanisms of aging and life shortening

48. In spite of the above important considerations of principle, attempts were often made to identify a possible effect of life shortening with some non-specific, diffuse, subclinical deterioration of tissues that might advance the onset of all old-age diseases to roughly the same degree. There are a great variety of non-tumorous degenerative changes in irradiated tissue [U4, C7]. Some of these superficially resemble senescent changes, although on closer inspection there are profound dissimilarities between radiation-accelerated and senescent lesions [W1, M3]. Among the least equivocal mentioned by van Cleave are [V7] the following: involution of the cartilage discs, involution of the thymus and all lymphatic tissues, lymphocytopenia, marrow hypoplasia, atrophy of the iris, atrophy and dysplasia of skin and degeneration of the skin collagen, degeneration of the elastic walls of the arteries, nephrosclerosis with glomerulosclerosis, dysplasia of the lens epithelium, vacuolization and degranulation of endocrine glands, involution of testis and ovary, generalized progressive fibrosis of the arteriocapillaries and generalized increase in fibrillar density of the interstitial connective tissue.

49. Casarett [C7] proposed a "histopathological theory" of natural and radiation-induced premature aging. It rests on the notion that the most generalized deleterious change in aging mammals is an increase of the histohematic barrier, the layer of connective tissue between blood and parenchymal cells, with an increase of arteriocapillary fibrosis. Functionally, a loss of selectivity of the barrier to nutrients and to wastes and a decreased efficiency of circulation are the consequences of such changes. Under these conditions a decrease of parenchymal cells and functions follows with more fibrosis and loss of vasculature becoming progessively more serious with time and leading to increased susceptibility to infection, stress, degenerative and neoplastic conditions and eventually to death.

50. Irradiation advances such an increase of the histohematic barrier and ensuing consequences, to various degrees in various tissues, depending on the sensitivity of the constituent parenchymal cells. Non-specific damage to the endothelium of the fine vasculature directly or indirectly caused by radiation would be the primary cause. The consequent morphological (interstitial oedema, increased fibrillar density) and functional changes (loss of reserve capacity of single organs reflecting gradually and progressively on other parts or on dependent organs) would tend to perpetuate and to increase themselves by circular reactions where the natural and radiation-induced aging would not be separable any longer.

51. The basic notions of Casarett's model [C7] appear to be well founded, as it is known that radiation may cause an interstitial fibrillar density and capillary fibrosis. The mechanisms of these phenomena have recently been discussed by Streltsova [S58], by Gerber [G1] who has examined the possible pathways responsible for fibrosis and by Hopewell [H16] who has particularly addressed vascular changes. But whether the initial endothelial and connective changes operating in natural and in radiation-induced aging may be the same, remains to be demonstrated as do the further steps of Casarett's hypothesis, which should be set on firmer ground [W1]. In addition, more recent information on the radiosensitivity of the endothelial cells [R11] seems to cast considerable doubt on the applica-

bility of the hypothesis to very low doses and dose rates and to confine its applicability to the region of the intermediate to high doses.

52. The hypothesis that late effects of radiation on the duration of life may be brought about via alterations of the immune system can also be entertained. In this respect two possible mechanisms of action can be envisaged. The first implies that auto-immune diseases are possible causes of a diffuse deleterious action. Alternatively, life shortening can be viewed as the result of an earlier appearance and a higher incidence of tumours, elicited in turn by radiation-induced immune disturbances. In no case does the effect of life shortening have a truly non-specific character, because an acceleration or an advancement in time of old-age diseases without changes in their spectrum could hardly be expected as a result of such mechanisms.

53. In 1972 the Committee extensively reviewed the effects of radiation on the immune response and considered the general question of radiation as it may relate to auto-immunity and possibly to aging [U15]. At the time there were few results on irradiated animals consistent with the hypothesis of a breakdown in the balance of self-tolerance leading to auto-immune conditions. On the whole the data were thought to be inconclusive as far as positively showing any such effect.

54. Studies of the late effects of radiation on the immune system are relatively few and their results vary according to the test system and radiation doses [S46]. In general, intact animals examined individually many months after exposure to moderate doses (1.5 to 6 Gy) of x or gamma rays showed little if any changes of their immunologic competence [S45, S46]. On the other hand, lymphoid cells derived from these animals and examined for various immunologic functions frequently show significant delayed effects [see S46 for a review]. However, this reduced immunologic competence could be due to an artifact resulting from a dilution of the lymphocytes or from suppression of lymphocyte functions by an excess of non-lymphoid elements in the test cell preparations. Reduced immunologic competence may or may not be compensated by a change in the total number of lymphoid cells in the whole animal. The radiation dose, the age at exposure, genetic and environmental factors (particularly the microbiological flora) could affect the expression of late immunological affects and, hence, the life span of the exposed animals, if radiation-induced shortening of life is indeed related to a dysfunction of the immune system.

55. A life span study performed with Biozzi mice specifically selected for a high or a low antibody response has some relevance to the present discussion. It was shown in that study [C30] that mice with a low antibody response had a higher incidence of spontaneous malignancies and a shorter life span than others of the same genetic background having a high antibody response. On the other hand, it is known that total lymphoid irradiation performed on NZB/NZW mice with a high incidence of an auto-immune disease reversed the expression of this condition and thus produced a prolongation of survival [K22].

56. In a comprehensive review of the immunological action of radiation Anderson and Warner [A10] discussed three general hypotheses for the possible induction or acceleration of auto-immune processes. The first one suggests that radiation can alter tissue constituents to create new auto-antigens or to release previously inaccessible components. The second possibility is action via somatic mutations thus leading to the emergence of auto-reactive clones. The third is action through the imbalance of natural mechanisms of regulation controlling the potential auto-immune expression. Several studies are in favour of the third mechanism but at the present time few definitive statements are warranted. The first statement is that the interplay of regulatory mechanisms in the immune system is so complex and variable that radiation effects are hardly predictable and at present cannot be extrapolated with any confidence from one experimental situation to another. Secondly, although immunological mechanisms may actually operate at high radiation exposures and cause extensive tissue damage, their possible relevance at the low doses of interest for radiation protection can only be viewed with great reservations given the present state of knowledge.

57. The Committee has reviewed in its 1977 report [U14] the role of the immune system in the pathogenesis of radiation-induced tumours. The conclusions pointed to a secondary role of immune reactions in the development of neoplastic conditions, particularly at low doses and dose rates. No new information has appeared since then that might change this general proposition. A most recent review of the subject [S46] confirms the above conclusion and therefore indirectly supports the view that, whatever the role of tumours in radiation-induced life-span shortening, there is as yet no clear evidence that the role is mediated through immunological mechanisms.

58. There are other hypotheses of aging that have been considered either alone or in conjunction with radiation and for which some experimental evidence has been claimed. The older theories were discussed by Walburg [W1] and their applicability to a possible effect of premature aging was criticized as mortality data and causes of death in irradiated animals indicate a life-shortening action essentially related to tumour induction. According to that analysis, exposure of mammals to life-shortening doses of radiation almost uniformly fails to accelerate lesions characteristic of senescence.

59. Recently other hypotheses related to molecular changes have been considered. Cutler [C31] reviewed the concept of primary aging processes. This term covers causes which can underlie many different specific disease processes at the organismic level and many age-related losses of function resulting in a progressive decline of general health. At the molecular level, cross-linkage between biologically important molecules effected by various agents (free radicals and their derivatives, aldehydes) may be postulated to be at the origin of natural senescence and of possible radiation-induced changes. This hypothesis has received little experimental support when applied to cellular and extra-cellular constituents such as collagen, age pigments, etc. It can, however, be more attractive when applied to information transfer molecules such as DNA or to structures such as chromatine. For these cellular constituents a more systematic approach might be envisaged.

60. Work by Vilenchik [V8, V9, V10] and others [L20] was directed to illustrate the similarities between the changes in the DNA induced by aging and by radiation, showing that spontaneous DNA lesions

result from thermal degradation of DNA at normal body temperatures and lesions may also be induced by free radicals such as $OH^{\cdot}$, which are known to be responsible for radiation-induced damage. Accumulation in this molecule of various lesions (alkali-labile sites, DNA-protein bonds, changes in the circular dichroism spectra) as a function of age has been taken as valid confirmatory evidence of a hypothesis of age-related multistage DNA damage advanced in the past [V8]. For a review of the free-radical theory of the aging process see [H21].

61. DNA damage is, however, only the initial step in reactions of this kind, as it is well known that this damage can be repaired. Hart [H17] discussed the most recent data concerning another complementary working hypothesis. This envisages the aging process as a sequence of events involving the induction of the DNA damage and its subsequent manifestation at the physiological level. The ability of the system to repair DNA damage and the redundancy of the genetic information for vital functions within the system are the factors controlling the manifestation of such damage. Alterations in one or both of these mechanisms are expected to modify life expectancy. Since it is known that DNA damage and repair is also involved in radiation carcinogenesis, the hypothesis has been entertained [V8, V10] that physiological aging and carcinogenesis (both spontaneous [V8, V10] and induced [V9]) may be inhibited by error-free repair systems. Although interesting and often supported by some indirect evidence, all the above hypotheses have not yet been sufficiently formalized and their general applicability has not been extensively tested to warrant more than the present mention.

4. Conclusions

62. In summary, although at some stage research on aging was advocated on the ground that radiation might represent a unique tool for the study of senescence [C7] resulting efforts have been rather unproductive. Data in animals and man lend no support to the view that radiation may cause premature aging or that the carcinogenic effect observed is only part of a more general effect of acceleration of aging [B6]. Attempts to identify a possible life-shortening action with non-specific diffuse changes in tissues, particularly of the connective and vascular structures have been difficult and are probably inapplicable at low doses and dose rates. Information about a possible role of the immune system via an increased incidence of autoimmune conditions or a favouring influence on tumour acceleration or induction are few and contradictory. In any case, such mechanisms are not expected to yield non-specific life shortening without changes in the spectrum of old-age diseases.

63. Therefore, in view of the difficulties of defining aging, of the lack of reliable parameters of senescence, of the impossibility of distinguishing between specific and non-specific causes of aging and between genetic and ambient factors, of the generally negative conclusions to be drawn from the available data, the Committee decided to limit the present analysis to the only effect of radiation that has been shown convincingly, namely the shortening of life span. It would in fact be unreasonable under the extremely undefined conditions discussed above, to carry out an analysis of the physical and biological variables affecting such an ill-defined effect as aging. Pending clarification of the points reviewed previously, the relationships between radiation-induced life shortening and aging (if indeed the latter effect exists to justify such relationships) will not be taken up again for discussion in the rest of this Annex.

I. THE EFFECTS OF PHYSICAL VARIABLES

64. Establishing a relationship between the degree of life shortening and the characteristics of the acute or chronic exposure to radiation is important in determining criteria and levels for human exposure. Such a relationship may also be useful in order to indirectly validate hypotheses and models of the nature of aging and on the similarity between natural and radiation-induced senescence. Experiments on single acutely-delivered doses are the simplest of all possible models. Single-dose irradiations are not interesting for radiation protection purposes, but represent the most efficient means of exposure, as under these conditions the action of any repair system is minimal. On the other hand, there are experimental treatments such as the duration-of-life exposure which may more closely resemble the situations of interest in practice. These yield, dose for dose, less effect than the acute exposures. Between these two extremes there is a whole range of exposures where any given amount of effect can be obtained by infinite combinations of many interrelated variables. These include the number and size of the dose fractions, the radiation-free time interval between fractions, the time over which a given radiation treatment extends, the total accumulated dose, the instantaneous dose rate, etc. All these variables interact for any given radiation treatment to produce the final effect on survival and it is in practice extremely difficult to design experiments allowing their separate analysis. It should also be added that each experimental system has its own biological, physiological and pathological characteristics (to be examined in chapter II) and that an end-point such as life shortening may be the result of an infinite number and type of underlying biological effects.

65. Having thus recalled the complexity of the problem at hand, the following irradiation conditions will be considered in turn; single acutely-delivered exposures; continuous life-time irradiation; the effect of dose rate; the effect of fractionation; protracted exposures; and the effects of different types of radiation. The various effects will be examined in the sections thought to be most relevant. However, a certain amount of overlapping and repetition is unavoidable in comparing the various conditions of irradiation. The problem of partial-body exposure will be dealt with in chapter III.

A. THE EFFECTS OF ACUTE SINGLE DOSES

66. In the following section the effect on long-term survival of acutely-delivered single doses of radiation is examined. The data are reviewed with the criterion of considering together all information pertaining to a given species. The data are arranged according to the time of publication to give some historical perspective. As it was often found that data on low- or high-LET radiation were included in the same paper, the review will consider the information pertaining to different types of radiation together. A summary of the numerical values to be derived from the documents reviewed is given in Tables 1 and 2, where low- and high-LET data are tabulated separately.

1. Mouse

67. The earliest data of Gowen and Stadler [G2], Grahn and Sacher [G3], Furth et al. [F2], Kallman and Kohn [K7], Storer and Sanders [S17], Storer et al. [S18], Boone [B8, B9] and Nowell and Cole [N4] will only be mentioned in this context. The essential information in these reports may be derived from Tables 1 and 2.

68. In 1960 Upton et al. [U5] reported on a very extensive series of data (the Greenhouse experiment) on late effects including life shortening in LAF1 mice (6 to 12 weeks old) exposed at a nuclear test site. Nineteen groups of 220 mice each were exposed to gamma rays from 1.79 to 7.82 Gy. Neutron doses in eight groups ranged from 0.28 to 2.5 Gy. Mean survival times were obtained for each exposure group and tested for linearity versus dose. In both sexes, for the gamma as well as for the neutron data, significant departures from linearity were observed and the best interpolation to these data was a curvilinear quadratic relationship fitted empirically. The authors felt that the shape of the curve should be taken with some reservation, particularly since later tests with more refined dosimetric methods (which in this particular instance left something to be desired) gave more nearly linear dose-effect relationships.

69. In the Greenhouse series [U5] the Gompertz plot of irradiated mice showed a displacement upwards and to the left of the control curves for both sexes. Life-span shortening was reported to be due to premature onset of all diseases observed in normal aging mice. The onset of old-age diseases was advanced to essentially the same extent by any one dose, an exception was thymic lymphoma whose incidence was greatly increased in both sexes. There was no consistent relationship between frequency of neoplasia and dose, because the incidence of some tumours (thymic lymphoma, granulocytic leukaemia, tumours of the ovary) increased but that of others (reticulum cell sarcoma, mammary sarcoma) decreased with increasing doses within the dose range studied. Thus, no overall clear-cut relationship could be established between life-span shortening and tumour incidence. It should be pointed out that the classification of lymphoreticular tumours in the mouse is a controversial issue and that these diseases are different in many respects with regard to similar conditions seen in man.

70. Some of the data from the Greenhouse experiment (male and female animals receiving up to 2.67 Gy) were analysed again by Walburg [W1] on the basis of the original pathology data and with appropriate corrections for competing probabilities of death [H2, H4]. A significant life-shortening effect was observed when all causes of death were considered together; but when only non-neoplastic deaths were taken into account there was no advancement in time of mortality due to these diseases. Walburg therefore concluded that evidence of life shortening due to non-neoplastic causes was lacking, although these experiments are often cited as an example of non-specific life shortening.

71. Using data from work on six mouse strains irradiated with single doses of x rays around the $LD_{50/30}$, Grahn [G4] reported a curvilinear type of relationship with dose. By appropriate correction for animals dying of leukaemia and ovarian tumours, he was able to eliminate much of the variability between strains and sexes and to analyse the whole process culminating in life shortening to produce a basic injury parameter (0.28 d of life lost/R or 19% life lost for irradiation at the $LD_{50/30}$) applying to all strains and sexes. Other factors, specific for life shortening due to leukaemia and ovarian tumours, could be superimposed on this basic parameter to give predictable amounts of effect at any dose and for any strain and sex. Other data by Vogel, Frigerio and Jordan [V1] are summarized in Table 2.

72. Lindop and Rotblat [L1, L2] reported on experiments with SAS/4 inbred mice exposed to single whole-body irradiation (50–780 R, 15 MeV x rays). When the percentage of survivors was plotted against age for each dose group, the life-shortening effect for the pooled sexes had a good fit to a linear relationship with dose without apparent threshold. The data suggested that life shortening was the result of a loss of early life and not of a contraction of the time scale. Lindop and Rotblat [L2] established the cause of death of these animals and came to the conclusion that life shortening was not due to induction of specific diseases but to the forward displacement in time of all causes of death. In this respect radiation could thus be considered as a cause of aging, although not identical to natural aging, as the relative ages of onset of the various diseases were different in irradiated and control animals.

73. Storer's [S19] data on RF/J mice were limited to a single exposure of 400 R of 250 kVp x rays administered at the age of 90 days. They are summarized in Table 1. Storer also performed other experiments [S20] on DBF1/J female mice treated at three months of age with graded exposures (100, 300, 500 R) of 250 kVp x rays. Under these conditions shortening of median survival followed a linear non-threshold function of dose. Autopsies performed on large samples of the animals showed that tumour incidence was not increased by radiation exposure, although tumours tended to occur earlier. The time interval between irradiation and the occurrence of a significantly increased death rate was inversely related to the size of dose, as though low doses required longer times for the injury to become manifest. On this basis Storer postulated that in experiments where animals are sufficiently long-lived (or the latent period is sufficiently short) so that the elevation of the death rate may show over the time interval in which essentially the whole population is dying out, life shortening will be proportional to radiation dose. But with low doses or short-lived animals a curvilinear relationship may apply.

74. Upton and collaborators [U7, U9] performed an exhaustive series of experiments on RF/Un mice irradiated with various doses and dose rates of 1 and 5 MeV neutrons, 250 kVp x rays and ^{60}Co gamma rays. At high dose rate (about 0.1 Gy/min or higher) both with x rays and with 1 MeV fast neutrons, the shape of the curves appeared distinctly non-linear (convex upwards). With x rays within the 3 to 30% range of life shortening the days lost per Gy at the various doses varied between 56 and 2 at progressively higher doses, with differences between male and female animals. With fast neutrons between about 20 and 50% of life shortening, the days lost per Gy were between 21 and 3, again with differences between the two sexes. In these animals death was characteristically associated with neoplastic and degenerative diseases common to the natural aging, except for animals treated with high doses in which death was attributed to necrosis and aplasia of the lymphatic and haemopoietic tissues. The shape of the dose-survival curve (for both neutrons and

x rays) may conceivably be explained by differences in the effects responsible for life shortening, as not all effects which may contribute to earlier death are identical in dose-response relationships. Leukaemia and other neoplasms could not entirely account for life shortening in this series of experiments.

75. Data on induction of neoplasia in the experiments described above were reported in a paper by Upton, Randolph and Conklin et al. [U9]. There is no specific discussion in this paper about the relationships with life-span shortening but some of the data (^{60}Co irradiation at high dose rates for single doses of 1 and 3 Gy) were analysed again by Walburg [W1], on the basis of rather careful macroscopic examination of the animals at death. There was no significant difference between control and irradiated animals when all causes of death other than neoplasia were considered. But when all causes of death including tumours were analysed together the difference between control and irradiated mice became very significant. It may thus be concluded that there was no significant residual life shortening when only the non-neoplastic causes of death were considered. This conclusion which is partly at variance with the conclusions of the authors themselves is to be attributed, in Walburg's view [W1], to the use of a more refined analysis of the lethality data.

76. Darden et al. [D1] also reported data on RF/Un female mice exposed to graded doses of 14 MeV neutrons (dose rate 0.01–0.02 Gy/min). The mean age at death of animals surviving beyond 30 days decreased with increasing dose, with a maximum difference between control and irradiated animals being observed in the 4 Gy group and amounting to 151 days or 27% of the control life span. Life shortening per unit absorbed dose was an approximately constant or slowly decreasing function of dose up to about 2 Gy, but at higher doses the efficiency/Gy tended to decrease, as in the series by Upton [U7]. Tumour induction could not entirely explain the life shortening observed, although thymic and myeloid leukaemia could account for most of the increase in mortality in irradiated groups.

77. By the use of a radioprotective agent (WR-2721 or S-2(3-aminopropylamino) ethylphosphorothioic acid) which protects against acute mortality more efficiently than it does against the life-shortening effects of radiation, Yuhas [Y1] expanded the range of doses studied. The shapes of the dose-response relationships were consistently different for the two strains studied. In the A/J strain the curve was linear non-threshold at low doses and came to a plateau in the high dose range. In the C57BL/6J life shortening was curvilinear over the entire range of doses. It is impossible to assess whether the radioprotective treatment altered the actual shape of the dose-response relationship in ways and amounts different for the two strains used. Actually, if one considers the dose relations obtained at doses below the $LD_{50/30}$ without the use of the WR-2721, a certain amount of curvature can be seen in both sets of data, perhaps more pronounced in the C57BL/6J.

78. In a more recent experiment Grahn, Fry and Lea [G5] gave LAF1 hybrid mice of both sexes single exposures of ^{60}Co gamma rays in the range of 390 to 900 R. Mean after-survival showed a curvilinear trend with dose. The principal life-shortening effect was attributable to excess tumour mortality up to 390 R, while at higher exposures the loss of life expectancy was not paralleled by a further increase of tumour incidence. Walburg [W1] commented on these data and interpreted them to show that when the life-shortening effect is 15% or less of the control the increased mortality is entirely attributable to induction or acceleration of tumours.

79. Clapp et al. [C12] reported on a large-scale experiment on life shortening and disease incidence in RF/Un mice irradiated with 300 kVp x rays (0.5–4 Gy) and with 60 MeV protons (0.47–3.72 Gy). The data indicated a flattening of the dose-response curve at doses in excess of 2 Gy and a reasonably straight trend at the lower doses. When animals dying from thymic lymphoma and myeloid leukaemia (which were induced in up to about 40 and 25%, respectively, of the mice) were removed from the calculations, the mean survival time of the remaining animals still showed a decrease as a function of dose. Gompertz's analysis confirmed that removing the leukaemic animals did bring the death rate curve nearer and more parallel to the control line. The curves, however, did not superimpose except at doses below 1 Gy. Thus, not all of the observed life shortening, particularly at doses above the $LD_{50/30}$, can be explained by the induction of leukaemia, as in male RF animals. A possibility does remain (but was not examined in a more recent publication, [C15]) that ovarian tumours occurring in 50% or more of the animals might account for the extra life shortening remaining after subtraction of leukaemia.

80. In his 1975 review Walburg [W1] refers to data in the male RFM mouse exposed when 5–6 weeks old to a single acute treatment of 300 R of 300 kVp x rays. Routine histopathology allowed the assessment of causes of death with reasonable accuracy and the data were corrected for competing probabilities of death. The cumulative mortality curves for all causes showed significant life shortening; when deaths attributable to leukaemia were excluded the cumulative mortality curves of the control and of the irradiated mice became superimposable, suggesting that radiation did not significantly induce or accelerate under these conditions other non-specific causes of death.

81. Ainsworth et al. [A7] irradiated male and female B6CF1 mice with single doses of gamma rays (0.9 to 7.88 Gy) and found that life shortening had a reasonably linear dose-response. In the case of fission neutron irradiation, however, the shape of the dose-response curve (0.2–2.4 Gy) appeared to be convex upward. Possible explanations for this shape of the relationship were suggested. They will, however, remain unclear until the causes of death will be completely worked out. A paper updating these experiments confirmed essentially the above conclusions [T4].

82. Data of life-span shortening induced by single acute exposures of 250 kVp x rays (100 to 900 R) were obtained by Maisin et al. [M8] in the course of experiments on the effects of chemical protectors. Data refer to male BALB/c mice (4–12 weeks old) and to male C57B1 mice (1 to 3 months old, 350 and 650 R). In spite of the dose-square form of the relationships for tumour induction an essentially linear decrease of the life span with dose was found for the two sets of data: the numerical values are given in Table 1. Pathological observations in these experiments were evaluated by the method of competing risks [M10] with a classification of the causes of death comprising various forms of leukaemia and solid tumours, glomerulosclerosis, non-neoplastic lung lesions and others. In the non-irradiated BALB/c animals tumours were mainly responsible for deaths, while in the normal C57Bl mice

other non-neoplastic causes were observed in the majority of cases. An increased and advanced incidence of specific diseases, mainly thymic lymphoma, was associated with radiation-induced life shortening in the low-to-medium range of exposures. For higher doses in excess of the LD_{50} life shortening was instead characteristically associated with glomerulosclerosis.

83. Very extensive data on RFM and BALB/c mice were presented by Ullrich and Storer [A8] and Storer et al. [S44]. The effects of dose, dose rate and radiation quality on life shortening and carcinogenesis were examined. Caesium-137 gamma rays at 0.4–0.45 Gy/min and 0.083 Gy/day (0.1 to 4 Gy total doses) and fission neutrons at 0.05–0.25 Gy/min or 0.01 Gy/day (0.05 to 1.88 Gy total doses) were used. Dose-effect relationships for life shortening at high dose rates will be examined here. In the RFM females a dose-squared or linear-dose-squared model described the data adequately between zero and 0.5 Gy, with the dose-squared component predominating after about 0.04 Gy. The curve for RFM male animals was thought to be linear. High dose rate neutron curves in both RFM and BALB/c females were linear in the range of zero to 0.47 Gy, with an ensuing decrease of effectiveness which gave rise to an upward convex trend up to 2 Gy. No specific discussion was given of the contribution of particular diseases to life shortening.

84. Metalli et al. [M9] irradiated hybrid male mice of the $(C57BLxC3H)F_1$ strain (100 d old, 250 kVp x rays, 1 to 7 Gy). A dose of 9 Gy with bone marrow infusion from isogeneic donors or with shielding of one leg in order to overcome the early effects of radiation on survival was also used. These procedures did not appear to appreciably alter the long-term survival of the animals. The mean after-survival of the mice as a function of dose could be reasonably fitted by a linear function. These animals had a spontaneous incidence of about 55 to 60% of reticulum cell sarcoma. The incidence of this disease was still quite high at 4 Gy but fell gradually at higher doses to about 5 % at 9 Gy. On the contrary, the incidence of glomerulosclerosis (which is very low in normal animals) increased to about 70% after 9 Gy. Since life-span shortening versus dose could be fitted by a linear regression, in spite of such profound changes in the spectrum of induced diseases, linearity should probably be regarded as a fortuitous event. The data are in no way reconcilable with theories which postulate a non-specific aging effect.

85. Some data have also been reported about a very extensive study designed by Spalding et al. [S22] to investigate in the same experimental series the effect of dose, dose rate, age at exposure and genetic background for a variety of late effects, including life shortening, by ^{60}Co gamma rays in mice. Preliminary data on C57Bl/6J mice [S54] indicate that in this strain, which has normally a very low incidence of neoplastic diseases at death, radiation-induced life shortening is not statistically significant at all combinations of doses, dose rates and age tested.

2. Other species

86. There are a few data of single-dose irradiation of rats. Hursh et al. [H5] irradiated Wistar male and female animals with 250 kVp x rays in the range of 150 to 600 R. A decrease of the survival time roughly proportional to exposure was found. The per cent reduction of life span/100 R was between 4.2 and 4.9 for male and between 2.8 and 4.0 for female animals. Inspection of the data shows an approximate linearity of the experimental points, although the error is fairly large, as the various dose groups included a maximum of 24 animals each.

87. Wistar females surviving an acute whole-body exposure to hypoxic irradiation (250 kVp x rays, 1000 R) showed some life shortening compared to controls. Tumours appeared sooner in the irradiated animals but their final incidence was not increased. This early onset of neoplasia was best explained as one aspect of the accelerated aging process, although other diseases prevalent in old rats (cataract, acute inflammations, epilation, skin ulcerations) were also accelerated to a comparable degree [L3]. Nephrosclerosis in 46% of these animals and increased blood pressure (the two conditions being rather unrelated) were reported as pathological findings in another paper by the same group [L5]. Also in the rat (female Long-Evans-Wistar hybrid) life-span shortening was observed after acute whole-body x ray exposures (250 kVp at 55 R/min) of 120, 240 and 480 R. Under these conditions the efficiency of the treatment per unit dose was found to vary from 0.60 to 0.76 to 0.52, respectively, at the above-mentioned exposures [L4].

88. In experiments by Kimeldorf, Phillips and Jones [K8, K9] young adult male guinea-pigs from an SPF Hartley colony were exposed to a simulated fission spectrum of fast neutrons. The median life span of the controls was 828 days; of the 1 Gy-exposed animals, 730 days (12% reduction); of the survivors in the lethal dose range (1.2–1.6 Gy), 698 days (16% reduction). Both values of the median life span were significantly lower than control survival. In a related study [K9] young adult male rats (94 to 110 d of age) were treated with 2.15 to 2.3 Gy from the same neutron source. Although this dose was sublethal to the animals at 30 d, the median life span was reduced by about 22%. It was concluded that the dose range producing acute mortality in the guinea-pig is less effective in reducing life span than a sublethal dose in the rat. The reduction in median life span per unit dose is, however, comparable for the two species.

89. There are a few data obtained by Kohn and Guttman [K11] on the Chinese hamster. Although this animal is more resistant to the acute effects of irradiation than other rodents under similar conditions, the late effects tend to be more severe, at least judging from the life-span shortening. In fact, 5.5 Gy of x-ray whole-body exposure caused a loss of 32 weeks (corresponding to about 30%) of the life span remaining at the age of 230 days. At higher doses, for each increment of 1 Gy above 5.5 Gy and up to 9.5 Gy there is an additional approximately linear loss of life span of 20 weeks up to a per cent life-span reduction of 93%.

90. Hulse [H18] reported recently some data on rabbits exposed acutely to 4.4–14.1 Gy of gamma rays or to 1.8–5.5 Gy of fission neutrons. Although the irradiated animals died earlier than the non-irradiated controls, the difference was statistically significant only after the highest neutron doses. The earlier deaths could be accounted for by an increased incidence of tumours, of which a large spectrum was observed, while other phenomena associated with natural aging (particularly nephrosclerosis and teeth degeneration) were not changed or were even decreased after irradiation.

91. An experiment on the life span of 360 normal and irradiated female beagle dogs has been reported by Andersen and Rosenblatt [A2]. At 10–12 months of age the dogs were given single or fractionated 250 kVp x-ray treatments to a total of 100 or 300 R. All irradiated beagles had a shorter life span than controls. For single-dose treatments the life-span shortening relative to controls amounted to 9.5% and 20.7% in the 100 and 300 R groups, respectively. The average life-span shortening per 100 R amounted to 6.7%. Mortality rates were calculated for the last 6 years of life and the Gompertz slopes were found to be similar for all control and treated groups, except that the irradiated dogs attained higher rates of mortality earlier in life than controls. Major causes of death were tumours and chronic diseases (nephrosclerosis, heart failure, pancreatitis) with no obvious qualitative differences between control and irradiated animals. However, malignant neoplasms developed at an earlier age in irradiated dogs, thus accounting in large part for the life-span shortening.

92. The above data were reanalysed by Walburg [W1] by the method of Kaplan-Meier [K2] for competing causes of death, the analysis being limited to controls and to dogs exposed to 100 R, where sufficient numbers were available. For ages at death beyond 3000 days (an epidemic of canine distemper or a vitamin-E deficiency altered the pattern of early deaths to some extent) there was a significantly increased rate of mortality in the irradiated dogs with respect to normal animals. However, this increase disappeared when the neoplastic deaths were excluded from the comparison. Thus, in Walburg's opinion, the data are in accordance with the view that all the radiation-induced shortening of life seen at relatively low doses can be explained by induction or acceleration of neoplasia.

93. Experiments on life-span shortening in large animals were also carried out. In the burro irradiations with single and fractionated doses of gamma rays and with single doses of neutron-gamma radiation from the detonation of a nuclear weapon have been performed [B10]. Results on this series are not sufficiently advanced for any definite conclusion. In the cow, single and fractionated doses of gamma rays were also administered in April 1960 for a life-span study [N5] but the experiment was terminated in 1973. The relevant data are of no use for life-span shortening since more than half of the animals were still alive when the experiment was ended.

3. Data analysis

94. Most of the data pertaining to the effects of single acute doses of x and gamma rays in the mouse are summarized in Table 1 and are plotted together in Figure II which shows the percentage of life-span shortening as a function of dose. The data in the Figure refer to about 35 experimental series performed on about 20 strains of inbred, outbred of hybrid mice of both sexes and various ages, performed in various laboratories around the world since 1956. A large scatter of the experimental points would not be unexpected under such conditions and in fact the agreement among such very heterogeneous data appears rather surprising. The variability about each experimental point (which is available in many of the experiments, although not in all) has not been plotted as it would be expected to be accounted for in the variability between series and could not in any case be used to weigh the points in the analysis to follow. In order to avoid including animals dying from early radiation effects, mice surviving less than 60 days were excluded. The analysis was limited to doses of up to 900 rad and to corresponding maximum effects of about 60%. In order to standardize the abscissa dose scale a conversion factor of 1 R = 0.0095 Gy was used. The ordinate scale is the percentage of life-span shortening (calculated from mean or median values as they were available) by comparison with the life span of non-irradiated mice, irrespective of the duration of life of the normal animals or of the pathology at death.

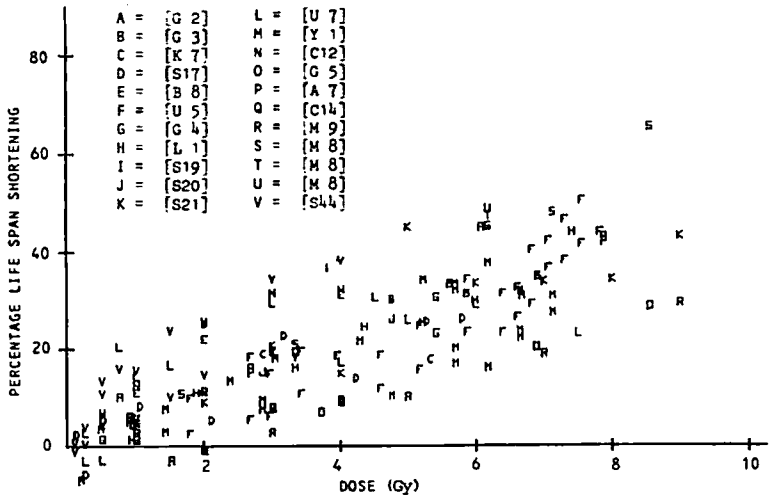


Figure II. Dose-effect relationship for life shortening in the male and female mouse following single acute exposure to x and gamma rays. Various experiments

95. The nature of the plot in Figure II is such that for very high doses a saturation of the effect must become manifest, although it may reasonably be assumed that within 50–60% no saturation might distort the plot. In the absence of any information as to the possible form of the dose-effect relationship a non-weighted linear regression was first interpolated to the data, according to the formula

$$y = a + b D \qquad (5)$$

where y is the percentage of life shortening, D is the dose and a and b are the coefficients of the regression.

The calculated least-square solution to the above equation was

$$y = (1.524 \pm 1.873) + (4.806 \pm 0.264)\, D \qquad (6)$$

and it gave an R^2 value of 0.747 implying a moderately good correlation. Although at inspection of the data a higher-order component was not clearly apparent, its existence could not be excluded and therefore the following relationship was also fitted

$$y = a + b\, D + c\, D^2 \qquad (7)$$

which yielded the following solution

$$y = (0.853 \pm 1.989) + (5.639 \pm 0.120)\, D - \\ - (0.115 \pm 0.020)\, D^2 \qquad (8)$$

The R^2 of this fit was 0.749.

96. The data obtained in the mouse by neutron irradiation (see Table 2) were similarly plotted on a common graph as in Figure III which includes doses up to about

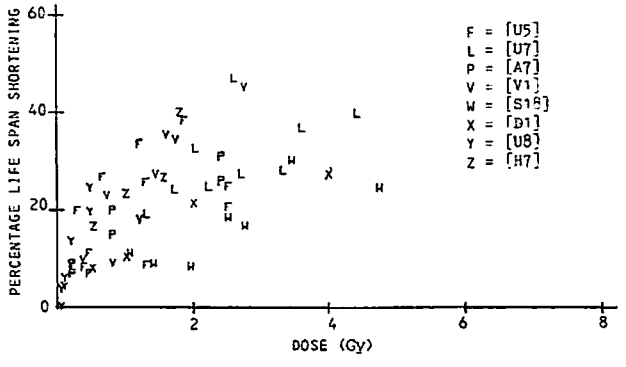


Figure III. Dose-effect relationship for life shortening in the male and female mouse following single acute exposure to fast neutrons. Various experiments

5 Gy and life-span-shortening effects up to about 50% of normal. Only the results with monoenergetic-, fission- and weapon-neutrons delivered acutely were included, for a total of 14 series and 4 different strains of mice. Inspection of the data makes it immediately apparent that the nature of the dose-relationship is in this case quite different from that observed with x and gamma rays. This impression is confirmed when the following equations are fitted to the data with the following results

$$y = a + bD \qquad y = (6.896 \pm 3.082) + (8.107 \pm 0.200)\, D \\ (R^2 = 0.565) \qquad (9)$$

$$y = a + bD + cD^2 \qquad y = (3.044 \pm 2.799) + \\ + (17.885 \pm 0.521)\, D - (2.731 \pm 0.202)\, D^2 \\ (R^2 = 0.683) \qquad (10)$$

Clearly, none of these two relationships provides a satisfactory interpolation to the neutron data, because the first fails to show the initial steep rise and the second shows a maximum of effect between 3 and 4 Gy and bends down rapidly towards lower values. This effect is difficult to interpret. The following relationship was also fitted [K10]

$$y = a + b\sqrt{D} \qquad (11)$$

and it yielded the following solution

$$y = (1.289 \pm 3.022) + (17.140 \pm 0.204)\sqrt{D} \\ (R^2 = 0.694) \qquad (12)$$

The square-root relationship seems to fit the data fairly well as it adequately describes the increase of effect seen at very low doses of neutrons and the ensuing levelling-off of the data for doses up to 5 Gy, along a slope roughly parallel to the slope of the low-LET radiation dose relationship.

4. Conclusions

97. In conclusion, data are not available in the mouse for x or gamma rays below 0.1 Gy and the scatter of the experimental points is such that for doses below about 1 Gy apparent life lengthening (rather than life shortening) may be found, depending on the variability of the control and irradiated groups of animals. Although errors affecting the above numerical constants must be fairly large under the conditions of the analysis performed, the life-shortening data for the mouse may follow a linear non-threshold relationship as a function of the x- and gamma-ray acute dose, indicating a life-shortening efficiency of about 5% per Gy down to the smallest doses. The data may, however, also be fitted by a linear-quadratic function, where the quadratic term is negligible and thus does not give rise to an appreciably different relationship within the errors of such an analysis or give rise to substantially different quantitative conclusions.

98. Analysis of the data in the various experimental series and an inspection of Table 1 makes it quite obvious that in any given instance the dose-effect relationship for life shortening may be linear or curvilinear (with upper concavity or convexity). The actual shape of any such curve depends on the interplay of the biological variables (strain, sex, age) with dose, which results in a different spectrum of life-shortening diseases or pathological conditions at the various doses. The observation that the combination of a variety of experiments produces a linear relationship cannot therefore be considered to depend on any particular biophysical law, at this stage of the analysis. It may simply reflect the fact that when all experimental conditions and all the resulting life-shortening effects are averaged over a number of different series, they combine by chance to produce an approximate linear relationship with dose. Therefore, taken as such, this observation may have no special meaning in the interpretation of the life-shortening action, but may be regarded as a very interesting observation in practice. It shows, in fact, that in a highly non-homogeneous mammalian population where all ages, sexes and strains are represented, the use of a linear function to describe the dose-effect relationship for acute exposures to x and gamma rays is not unreasonable.

99. Under the conditions of the present analysis, the neutron data at the energies available are best described by a relationship having a convex upward trend with dose, such that the efficiency of low neutron doses is higher than that of higher doses. The numerical value of this higher efficiency will be discussed in section II.D. It should be again stressed that there is no fundamental biophysical reason why the shape of the neutron curve is of the form roughly described by the above equations, as the same observations pointed out before for the x- and gamma-ray data can be expected to apply to the neutrons as well. However, the form of the neutron relationship is curvilinear (convex upward)

within a range of effects where a linear function applies to low-LET relationships. As saturation phenomena with respect to the expression of the biological damage may not be expected under such conditions, the only way to interpret the neutron data is to assume that the shape of the relationship reflects some primary biophysical difference in the mode of action of low- and high-LET radiation, particularly at the low doses.

100. The effects of single acute exposures of low-LET radiation on animals other than the mouse are summarized in Figure IV, in comparison with all the

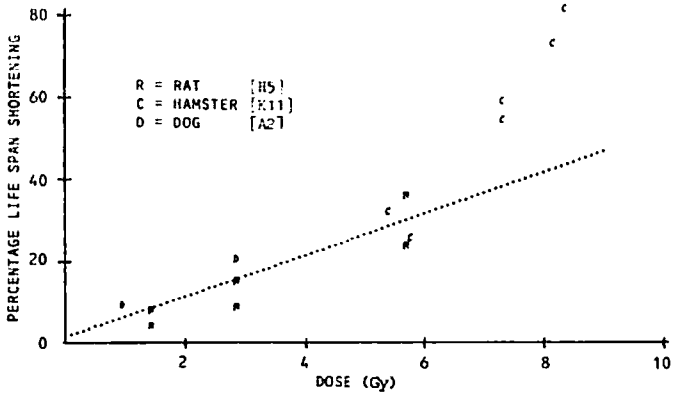


Figure IV. Dose-effect data for life shortening in various mammalian species following acute single exposure to x and gamma rays, compared with the response of the mouse. The dotted line is the best fit to the data for the mouse in Figure II, as in equation (6). Various experiments

mouse data. On inspection, no large differences may be traced from the small series reported in the literature. This is particularly true for the data for the rat, that are well superimposable up to 5 Gy with the mouse response. The effect on the dog has only been examined at relatively low doses and the data are perhaps on the high side of the data for the mouse. The Chinese hamster, on the contrary, has only been examined at doses in excess of 5 Gy and the data are suggestive of a concave upward trend. Among the species tested, however, the variability of the response is apparently rather small.

B. THE EFFECT OF CONTINUOUS LIFE-TIME IRRADIATION

101. The "duration-of-life" exposure condition has been used since the very beginning and is documented in the early papers of Henshaw [H1], Evans [E2], Lorenz et al. [L6] and Boche [B11]. It has been widely utilized in the experimental series of Sacher and Grahn [S4] who have largely contributed to the interpretation of this type of data and is still in use [N6, N7]. In case of internal irradiation from radionuclides of long half-life it is the only possible irradiation condition. Exposure for the entire life represents a base-line condition of irradiation useful for comparison with other exposure types such as the acute single-dose. In this respect it has the advantage of mimicking an exposure pattern which is of most practical interest. Research workers [G1, G6] have pointed out other advantages, such as the linearity of the relationship between the log mean after-survival of the animals and the daily exposure level. That property may facilitate the description of the effect and justify comparisons between various animal species or various types of radiation.

102. On the contrary, others believe that the terminated exposure technique, rather than the exposure to death may be more apt to give unbiased answers. Based on evidence from irradiated DBA mice, Mole [M6] examined the concept of what he called "wasted radiation" for exposure to death, that is, the amount of radiation administered in excess of that strictly required to kill the animals. Mole showed that under some conditions of exposure the wasted radiation amounted to over one-half of the mean accumulated dose. This implied that the duration-of-life exposure condition was unsuitable to establish precise dose-time relationships for life shortening. Actually, the mean accumulated dose would have been overestimated on account of the wasted radiation and the mean survival time would have been put in doubt by the fact that each specific biological response to radiation might have taken a different and characteristic time to develop. According to Mole [M6], for these reasons it is preferable to use terminated exposure conditions.

103. The concept of wasted radiation was used by many research workers, although often without much experimental basis, to account for data that could not otherwise be explained. The concept stems from the notion that each specific disease or pathologic condition has a latency time between induction and clinical manifestation; there is also more time intervening between the appearance of the disease and its development to a lethal condition. The biological arguments underlying the concept of wasted radiation are well founded but there are different views as to the practical importance of this concept as the amount of wasted radiation appears to be either negligible [L7] or very substantial [M6] under different experimental conditions. Sacher and Grahn [S4], Grahn and Sacher [G1] and Sacher [S23] have repeatedly criticized the concept of wasted radiation pointing out that it does not lend itself to any easily testable implications. In their opinion, there are changes in the effectiveness of a given dose with an increase of the protraction time (see section I.C.) and under appropriate circumstances these changes may at least in part be interpreted as being due to an effect of wasted radiation. According to Grahn and Sacher [G1] this concept is contradicted for rather high doses and short survival times (the concept was actually derived from experiments at 200 to 25 R per day and on the $LD_{50/30}$ end-point); but for long protraction periods the idea would be unjustified as no amount of radiation may be considered as truly wasted.

104. In continuous exposure until death, time and dose cannot be experimentally separated from each other. Thus, it becomes difficult to isolate the dose that would have been given in excess of the minimum required to kill the animal within a given time from an end-point such as the life-span shortening, which is measured in units of time. An additional difficulty lies in the nature of the biological event of death which is a final end-point in survival experiments, whereas in experiments on tumour induction, for example, it is possible to account in part for the wasted radiation by computing the dose absorbed at the tissue of interest up to the time of the first appearance of the tumour or to some such extrapolated time [F3, M11, M12].

105. It is natural therefore that, in spite of its wide acceptance, specific work to experimentally test the concept of wasted radiation has not been very extensive. In fact, this concept has a shortcoming in the difficulty of its experimental analysis and in the precise evaluation of its importance under each specified experimental condition. There appears to be little hope that these problems will be settled in the near future. Any conclusion concerning the relevance of this notion in the interpretation of radiobiological experiments in animals or, more so, in human radiation biology must remain open for the time being.

106. The available evidence of the biological effects of chronic radiation exposure for the whole life of the animals is reviewed in the following. This field has been reassessed at various times, among others, by UNSCEAR [U1], by Sacher and Grahn [S4], Grahn and Sacher [G1], Grahn [G6], Sacher [S14]. The reader is referred to those contributions for more extensive coverage of the subject. The life-shortening effects of incorporated radioisotopes are considered in a separate subsection.

1. Mouse

107. All known experiments on irradiation for the duration of life [H1, H6, H7, E2, B11, L6, L8, S2, N3] were reviewed by Mole in 1957 [M13] and his paper was made a part of the 1958 report of the Committee [U1]. Only 5 of 11 known reports (see [M13] for a complete list of references) contained sufficient details for the reconstruction of a curve showing the decrease of the mean survival time versus the dose per week. Fast-neutron as well as gamma-ray data were plotted together with the dose scales in the ratio of 1 to 13 (see Figure XIV). The agreement of the experimental series was, at least for the mouse, surprisingly good and exposure levels of 10 R per week or higher of gamma rays shortened the mouse life in a reproducible manner. There were eight experimental estimates at weekly exposures of less than 10 R (or its neutron equivalent) and in none of them the duration of life was significantly different from the respective control value. Taken at face value, these data suggested therefore an apparent threshold at dose rates below 10 R per week or its neutron equivalents.

108. Moos et al. [M14] and Yusken et al. [Y2] carried out experiments on CFW mice of both sexes, individually caged and irradiated with 400 kVp x rays at daily exposures of 2 to 512 R. The survival time of the mice decreased as the daily dose increased but the decline was not very rapid up to 8 R per day. Exposure of up to 4 R per day allowed the animals to accumulate 600 to 1400 R before one-half of the mice died. About 2900 R of accumulated radiation was given at 16 or 32 R per day. In a subsequent paper Moos [M15] tested the possible existence of a threshold in the same mice. He showed that variability of the control population and of the animals receiving 2 R per day was the same or could not be resolved statistically and concluded for a continuous effect of life-span reduction down to the smallest dose rates tested.

109. Of particular interest to the problem of life-time irradiation are the data by Sacher and Grahn [S4] on more than 5000 LAF1 male and female mice given ^{60}Co gamma-ray exposure starting from the age of 100 days. These data represent up to the present the most complete and exhaustive experimental series on this subject. The exposure levels used were 36, ranging from 5 to 200 000 R per day and corresponding mean survival times from about 500 days to 6 hours. The daily exposures between 5 and 2500 R (giving mean after survival times of 5 or more days) were delivered during 12 or 15 hours per day; higher daily doses were given almost continuously. Dosimetry was particularly accurate and fully discussed.

110. Survival data were analysed by an empirical function of survival time and dose rate, the cumulant lethality function, C_L, defined as

$$C_L(t^*) = \frac{1}{I}\left(1 - \frac{t^*}{t_o}\right) \qquad (13)$$

where I is the daily exposure in R, t^* is the mean after-survival at dose rate I and t_o the mean after-survival of controls. The first derivative of this function, called the impulse lethality function, S_L, allowed the identification of four distinct phases of injury with peaks at 0.5, 5, 13 and 40 days and these times could be related to different modes of injury to the nervous system, the intestinal epithelium, the leukopoietic and the erythropoietic marrow, respectively (see Figure V). A plot of the log mean after-survival versus the daily dose was found to be very nearly linear for mean after-survivals in excess of 60 days. This procedure allowed the assessment of life-shortening coefficients with small uncertainties. The paper by Sacher and Grahn [S4] contains a full discussion of the mathematical formalism underlying the cumulative lethality functions. This represents an advancement in the identification of the phenomenology of radiation injury and lethality.

111. Lesher et al. [L9] reported on the pathology of these animals, in an attempt to establish the cause of death. The daily exposures of 5 and 12 R per day were considerably more carcinogenic than higher exposure rates, and the lower carcinogenic efficiency of the higher dose rates was tentatively attributed either to the earlier death of the more heavily irradiated animals or perhaps to a "therapeutic" effect on the potentially transformed cells as the dose rate increased. It was found, in general, that the duration-of-life exposure yielded fewer tumours per R of accumulated exposure than single or terminated irradiation regimes. Tumours of the genital tract and a higher incidence of lymphoma were responsible for the much higher tumour incidence in female mice. Furthermore, some diseases were accelerated in the irradiated mice and some were not.

112. Sacher and Trucco [S13] analysed a model for mammalian radiation lethality and recovery, which was essentially based on the kinetic characteristics of self-renewing cell populations. The model assumes that

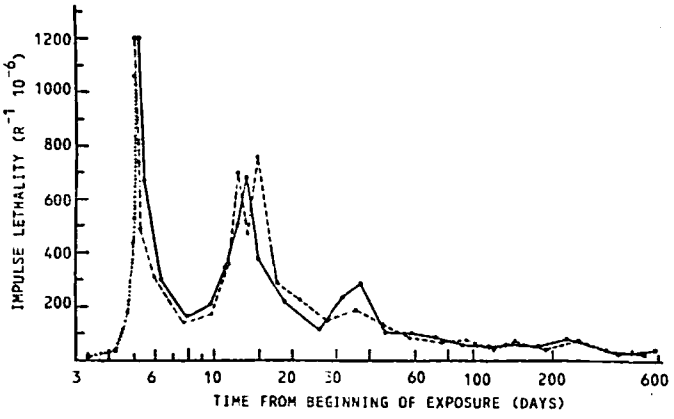


Figure V. A plot of the impulse lethality function versus time from the beginning of exposure in duration-of-life experiments. The data are for LAF1 male (solid line) and female (broken line) mice exposed to cobalt-60 gamma radiation at exposures from 5 to 200 000 R d^{-1}. Data from Sacher and Grahn [S4]

population growth proceeds at a rate proportional to cell number but that growth is constrained, so that each cell population attains a given stationary size. The rate of growth is therefore the product of two terms, one of which is a monotonic function of the size of the population and the other is a function of the difference between actual size and limiting size at any given time. Based on these simple assumptions Sacher and Trucco produced a complex phenomenological theory which was applied to radiation data on survival after split doses, multiple fractionation and protracted continuous exposure and showed some qualitative agreement between the curves obtained experimentally and those predicted by the model. However, the formulation of this theory is not sufficiently developed and may be regarded as a first attempt towards a more comprehensive treatment.

113. In another paper Sacher, Grahn, Fry et al. [S5] examined the late consequences of gamma-radiation with respect to two major categories of effects: the incidence of tumours of the reticular tissue and the life shortening induced by all causes other than the reticular tumours. The data were obtained from male and female mice of four different genotypes exposed in duration-of-life experiments (^{60}Co gamma rays, 0.3 to 56 R per day). In agreement with that observed on the LAF1 mouse [S4] the data showed that the log mean after-survival plotted as a function of the daily dose followed a very nearly straight line.

114. The Gompertz transforms of these data (see Figure VI) for all causes of death were slightly convex upward and formed a fan of lines of increasing slope with increasing dose rate with small differences between genotypes. When the cumulative incidence of four tumour types (reticular, pulmonary, hepatomas, ovarian), summed over the four genotypes was plotted as a function of daily dose, three tumours showed a modest increase in incidence with a peak at 6 R per day or less followed by a sharp decline. Reticular tumours, on the contrary, rose to a peak between 24 and 32 R per day and then showed a sharp decline at higher daily dosages. This phenomenon was explained in terms of the hypothesis put forward by Gray [G7] which postulates two phenomena (induction and cell killing) acting together but with different dose dependencies in the relevant target cell populations.

115. In the experiments under discussion [S5] the log mortality rate data for all causes except leukaemia plotted as a function of age indicated in the BCF1 mouse a linear rise at all daily dose levels. The slopes of these lines increased with increasing dose levels to form a fan of lines intersecting with the control slope at 100 days, at which time exposure began (see Figure VII A). These slopes plotted on a semi-logarithmic scale as a function of the exposure rate (R per day) gave linear

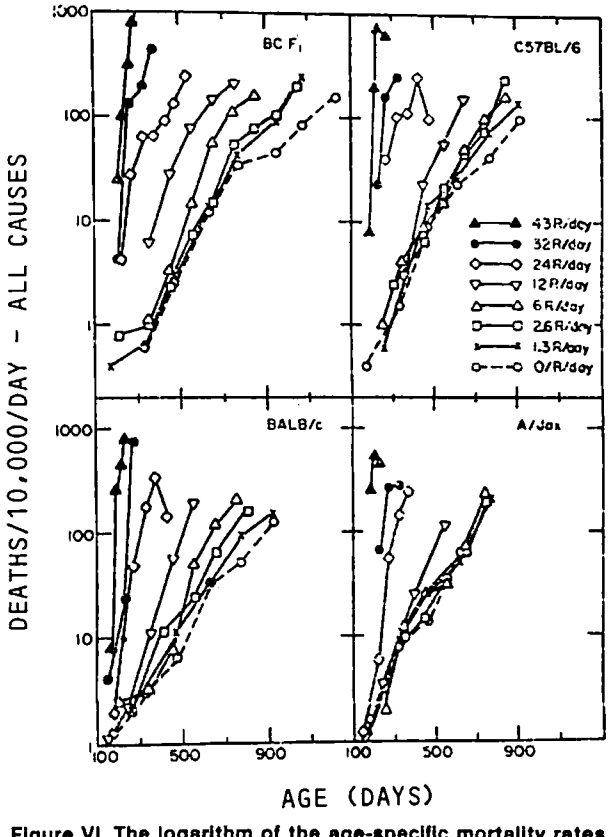
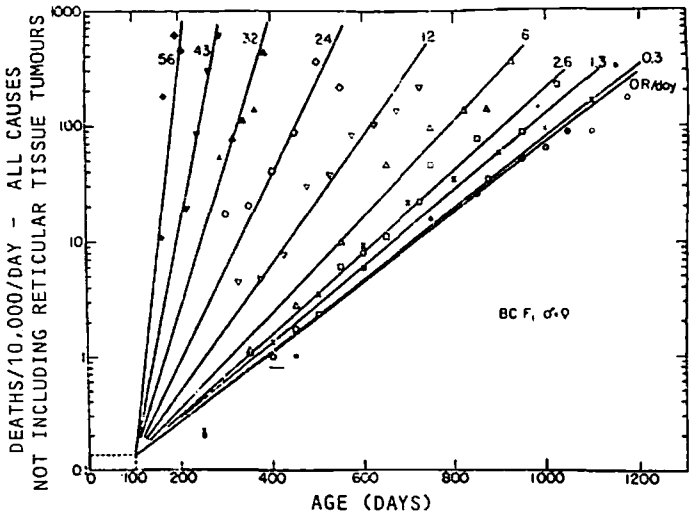


Figure VI. The logarithm of the age-specific mortality rates for all causes of death (Gompertz transform) in mice of four different genotypes (BCF1, C57BL/6, BALB/c, A/Jax) plotted as a function of age. Mice were irradiated in duration-of-life experiments at the exposure rates shown. Data from Sacher, Grahn, Fry et al. [S5]

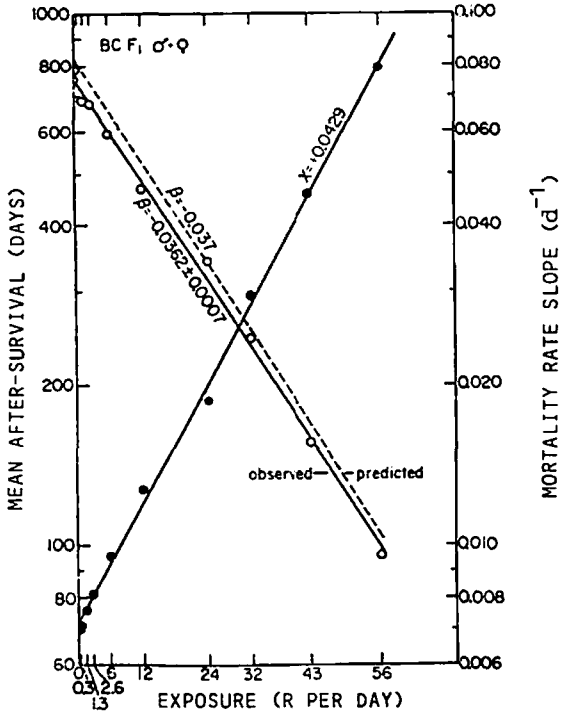
relationships and thus justified the conclusion that the slope of the Gompertz lines increases exponentially with daily dose (see Figure VII B). Finally, this paper [S5] has interesting aspects concerning the cellular mechanisms of life shortening because it provides some link between phenomena at the whole-body level and at the cell population level.

PANEL A



The logarithm of the age-specific mortality rate (Gompertz transform) for all causes of death except leukaemia in BCF1 mice of both sexes irradiated in duration-of-life experiments at the exposure rates shown. Straight lines were fitted by least squares through the control incidence at 100 days of age when the exposure began.

PANEL B



Plots of the Mean After Survival (MAS, open circles) and of the slope of the Gompertz transform (closed circles) versus exposure level. Data are for BCF1 mice of both sexes, as in panel A. The dashed line is that predicted by MAS from the estimated Gompertz slopes in order to show the consistency of the relationships. The lines were fitted by least squares analysis.

Figure VII. Changes of the Gompertz transform as a function of exposure rate in duration-of-life experiments [S5]

116. Another paper by Grahn, Fry and Lea [G5] summarized a number of studies on various strains of young adult mice exposed to various levels of ^{60}Co gamma radiation ranging from 0.3 to over 30 R per day and discussed the problem of a "non-specific" life-shortening effect as opposed to a "specific" effect, that is the induction of neoplasia. Data from mouse strains BALB/c, C57BL/6 and their F_1 hybrid show a steady increment of mortality associated with neoplastic disease upon irradiation as the age increases and the daily exposure increases up to a few R per day. An excess mortality from non-neoplastic conditions with respect to controls was seen only at 6 R per day and above. Thus, the risk of early or excess death from radiation exposure at intensities of the order of 100 or 200 times the background is related entirely to the

increase in incidence and to the shift in the time of appearance of the neoplastic diseases.

117. Sacher [S14] pointed out that when the slope of the Gompertz curves obtained at various daily doses is plotted as a function of the daily dose on a double logarithmic scale for two mouse strains, the LAF1 [S4] and BCF1 [S5], the resulting relationship can be resolved into two straight lines (Figure VIII). At

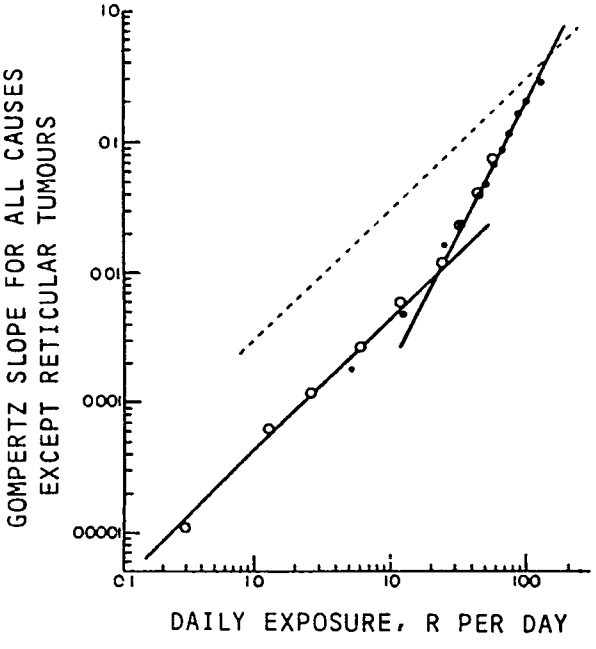


Figure VIII. A plot of life shortening to daily exposure for mice treated with life-time gamma-ray exposure. Life shortening is measured by the increase of slope of the Gompertz function in irradiated as compared to control populations. Open circles refer to BCF1 and closed circles to LAF1 mice. The dashed line corresponds to the inferred relationship for single exposures with constant effectiveness per roentgen of $0.003\,R^{-1}$. Data from Sacher [S14]

exposure rates below 24 R per day the data lie close to a first-power trend while above this value they conform closely to a second-power trend. At about 24 R per day the contribution of the two terms is equal.

118. New data were recently reported [T5] on the life shortening in $B6CF_1$ mice given weekly exposures to ^{60}Co gamma rays (0.07, 0.174 or 0.319 Gy per weekly fraction) or to 0.85 MeV fission neutrons (0.0067, 0.0167 or 0.0267 Gy per weekly fraction) either for 60 exposures or for the duration of life. The amount of life shortening produced by the life-long or by the terminated exposure regimes was essentially identical, so that the two series were analysed as a single experiment. The data are generally in good agreement with those reported from other laboratories.

2. Other species

119. One hundred day-old male and female guinea-pigs were started on a fractionated course of radiation (^{60}Co gamma rays) for the entire duration of life [R2]. Together with a number of control animals, groups receiving 1.35 R, once or four times a week; 2.6 R, 5 times a week; 6.0 R, 4 times a week; 24 R, once a week; 6 R, 6 times a week; were included for a total of 344 animals. The relationship of the log mean after-survival time against the weekly exposure in R was approximately linear and the life-shortening coefficient came to about 0.06 days/R, in close agreement with the data of Lorenz et al. [L6]. At 5.4 R per week a paradoxical early decrease of mortality was noted in males for which no explanation could be given. Fatty degeneration of the liver, chronic kidney diseases, spleen amyloidosis and various tumours were noted in the animals in no obvious correlation with life-span shortening.

120. The survival of goats was followed by Hupp et al. [H8] and by Hupp [H9] for groups of 11–12 animals for each sex submitted to chronic ^{60}Co gamma-ray exposure (3, 7, 15, 30 and 40 R/20 hour day). Great individual variability was observed in the survival time at all except the highest exposure level. The lethality pattern observed was quite different from that of mice and rats. Females exhibited little exposure rate response in the range of 7–40 R per day, while males accumulated the maximum exposure at 7 R per day. Rats and mice, on the contrary, accumulate maximum exposures at 30–50 R per day [G6].

121. Casarett [C16] reported briefly on the survival data of dogs (1000 kVp x rays, 5 days per week at daily exposures of 0.06, 0.12 and 0.6 R per day beginning at 21 months of age). The accumulated exposures at death in these three groups varied between 122 and 257 R; between 243 and 465 R; and between 1088 and 2198 R, respectively. Average ages at death were 13.8, 13.2 and 12.3 years, respectively, the control age being 13.0 years. Median death age was 13.1 years in the control and 14.1, 13.8 and 12.7 years in the irradiation groups, respectively. In addition to these groups, a similar fractionation scheme was applied in other groups, giving 3 R per day in 10 minutes for 5 days per week for a total of 25, 32 and 42 weeks. Two other groups received 300 and 375 R whole-body at rates of 10 and 64 R per minute, respectively. For these latter groups no survival data were reported. More recent data for the dog are also to be found in [N7] (see subsection II.A.1).

3. Data analysis

122. The effect of life shortening induced by continuous exposure may be analysed as a function of the dose rate of the treatment or against the total dose received (at the various dose rates) from the beginning of exposure to death. There is enough data for the mouse to examine both types of dependencies and to attempt some descriptive analysis.

123. Figure IX shows the percentage life shortening induced at various dose rates. All data available for various strains and sexes have been grouped, separately for the cases of neutron and of low-LET radiations. The graph therefore includes all the variability expressed in these experiments. The data by Moos et al. [M14, M15], although qualitatively following a similar trend, have quite different quantitative relationships and cannot be considered with the other series. The x- and gamma-ray data include seven different series performed on five strains of male and female mice; the neutron data include seven series on four strains and both sexes.

124. The nature of the plot in Figure IX is such that the low dose rate end of the abscissa is greatly expanded. Sigmoid relationships of the type

$$y = 100\,(1 - e^{-\alpha A}) \qquad (14)$$

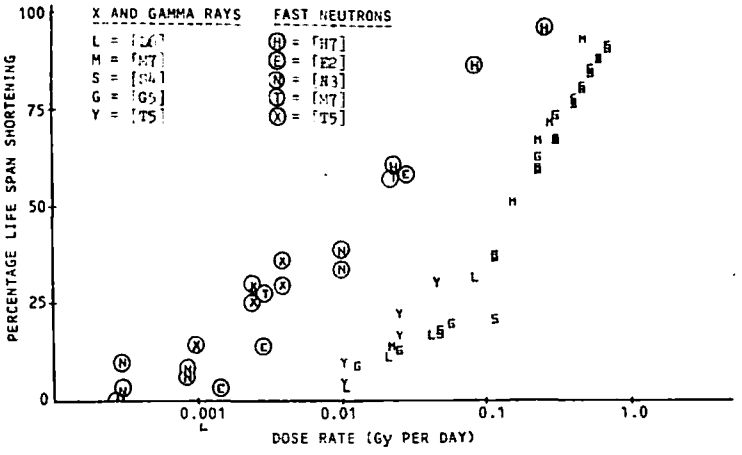


Figure IX. The relationships between dose rate and the life-shortening effect following duration-of-life exposures to fast neutrons and low-LET radiation in the male and female mouse. Various experiments

where A is the dose rate in Gy per day, may reasonably be fitted to the data. When a non-weighted curve was fitted to the data by a least-square method, the solutions were, in case of the low-LET radiation

$$y = 100\,(1 - e^{-3.89\,A}) \qquad (15)$$

and in the case of neutron irradiation

$$y = 100\,(1 - e^{-44.14\,A}) \qquad (16)$$

By inspection, the above relationships interpolate the low-LET data quite adequately, but fail to properly follow the fairly high effect seen at the very low doses of neutrons and the tendency of the x-ray and neutron data to merge in the high dose region of the graph. The relationship

$$y = 100\,(1 - e^{-a\sqrt{A}}) \qquad (17)$$

which fits the neutron data with the following values

$$y = 100\,(1 - e^{-5.078\sqrt{A}}) \qquad (18)$$

seemed more adequate for that purpose.

125. Another analysis is one where the percentage life shortening is plotted versus the dose accumulated at the various dose rates under duration-of-life exposure. Data obtained in the experimental series shown in Figure IX are plotted separately for the x and gamma ray and for the neutron series in Figure X. For

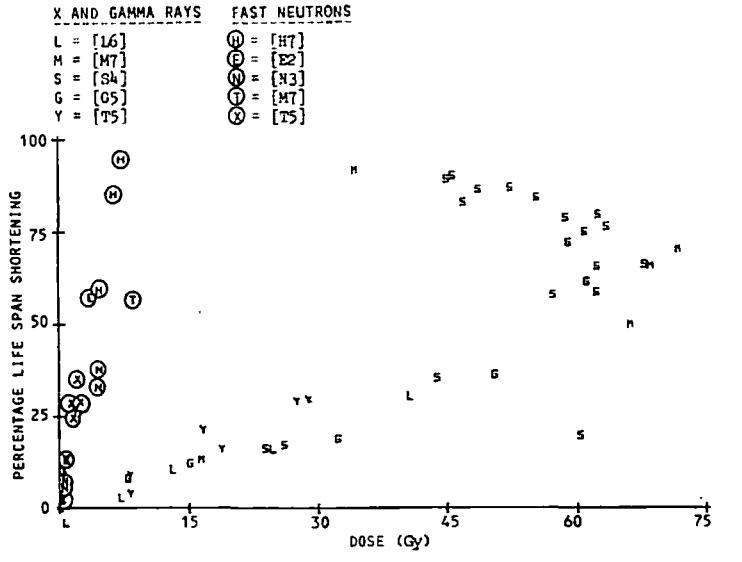


Figure X. Relationship between the total accumulated doses of fast neutrons and low-LET radiation in the male and female mouse, following exposure for the duration of life. Various experiments

increasing doses the life-shortening effect of low-LET radiation also increases in an apparently linear fashion at low doses and then with a progressively accentuated upper concavity to doses of about 60 Gy administered for the duration of life at dose rates of about 0.2 Gy per day.

126. At higher dose rates the life shortening continues to increase but, owing to the progressive reduction of life span, the accumulated dose decreases and the curve bends backwards towards the origin. Such an effect was previously described by Lorenz et al. [L6] and may be predicted by the theories of Blair [B5] and Sacher [S1]. Although this observation is not immediately apparent from Figure X, all along the curve the data obtained at approximately similar dose rates are reasonably well clustered together. This immediately points to a relationship between the three quantities under study in the graph: dose, dose rate and life-shortening effect.

127. In order to describe the data with a maximum of precision, an attempt was made to fit a curve where the three quantities cited would all contribute to determine the final shape of the relationship. The following

equation was assumed to reasonably interpolate the data

$$y = b\,D\,e^{cA} \qquad (19)$$

where y is the percentage of life-span shortening; D the dose and A the dose rate; b and c are proportionality constants. Such a relationship cannot be adequately fitted in the absence of some function relating dose and dose rate. In order to find such a function the simplifying assumption of an exponential decrease of the life span with increasing dose rate was made for any given total absorbed dose

$$T = T_0\,e^{-A/A_0} \qquad (20)$$

Since the total absorbed dose is the product of the duration of life and the dose rate

$$D = A\,T \qquad (21)$$

it follows that

$$D = A\,T_0\,e^{-A/A_0} \qquad (22)$$

A plot of total absorbed dose versus dose rate for data belonging to the same experiments in Figure IX was found to agree reasonably well with an expression of the above type. Therefore, the previous relationship was fitted to the experimental data, yielding

$$D = 698.81\,A\,e^{-3.687\,A} \qquad (R^2 = 0.97) \qquad (23)$$

128. By the use of the above relationship a fit of the experimental data was then attempted with optimization of the various parameters to achieve the minimum square deviations. The experimental points from the fitted curve gave the following solution

$$y = 0.7253\,D\,e^{1.469\,A} \qquad (24)$$

in which the functional relationship between A and D is given by the above expression (equation 23). Figure XI

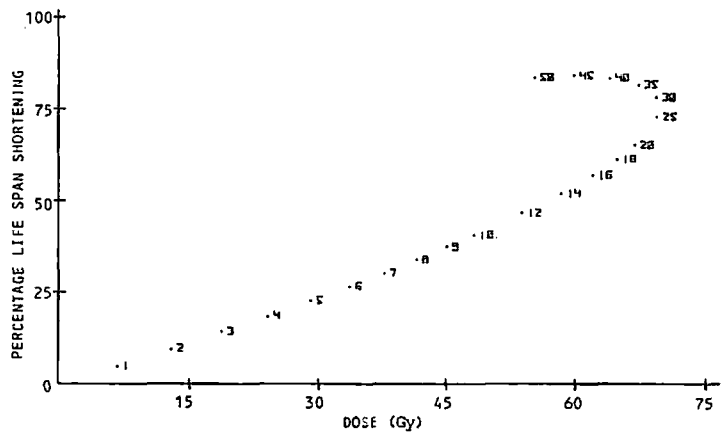


Figure XI. Best fit of the low-LET radiation data in Figure X. The numbers in the body of the graph are the dose rates (10^{-2} Gy per day) at which the doses specified in the abscissa are cumulated during the entire life of the animals

represents the best fit to the experimental data in Figure X and provides for each dose (in the abscissa) the percentage of life shortening to be expected (on the ordinate) at the dose rates (in Gy^{-2} per day) specified at the various points along the fitted curve in the body of the graph.

129. The neutron data in Figure X deserve separate mention because for them the very characteristic trend of the x- and gamma-ray data in duration-of-life experiments has not been verified. On the contrary, the data available may point to a continuously increasing effect of life-span shortening without any inflection in the trend. The data are too few and too scattered to establish with certainty such a difference in shape. It may be speculated that the effectiveness of the neutron treatment in duration-of-life experiments is so high compared with x and gamma ray that the bending of the curve is not possible in view of the short life of the irradiated animals. But it should also be noted that the experimental points in excess of about 60% of life shortening (where the curvature becomes apparent with the low-LET radiation) are only two of the same series and therefore insufficient to confirm a difference of shape. In any case, the point is of little practical significance because the doses involved are extremely high.

4. Conclusions

130. In duration-of-life experiments the variables "time" and "dose" are linked and difficult to resolve experimentally. Data in the mouse were analysed by the Committee as a function of the dose rate and showed an increasing life-shortening effect following an exponential function of the dose rate, up to a maximum of 1 Gy per day. Neutrons appeared to be more effective in causing life shortening, particularly at dose rates of 0.001 Gy per day or less.

131. When analysed as a function of total cumulated dose, life shortening appeared to be induced according to a linear trend up to doses of 30 Gy of x or gamma rays. The percentage life shortening then followed a curve with a progressively accentuated upper concavity up to 60 Gy administered for the whole life at dose rates of about 0.2 Gy per day. At still higher dose rates life shortening continues to increase. However, as the animals have a shorter life, the dose accumulated decreases and the dose-effect relationship bends towards the origin. The same trend for the neutrons cannot be precisely established for lack of data.

132. It is of great interest to examine the change of effectiveness observed in the mouse between the single acute and the extremely low dose rate data. If the linear term with dose of the single acute exposure (about 5% life lost for 1 Gy) is divided by the slope of the curve for duration-of-life exposure obtained at, for example, a dose rate of 0.01 Gy per day (total dose about 7 Gy) the efficiency is lower by a factor of about 7. In the case of neutrons the experimental results show in some cases increased life shortening after increasing the exposure

time. But until further work clarifies the situation a precise comparison of acute and low dose rate data is not justified.

133. The guinea-pig, the goat and dog were also exposed for the duration of life and revealed differences from the mouse. The differences are related to the sensitivity of the various species to haemopoietic death or, more precisely, to the dose rate level at which the susceptibility of the bone-marrow becomes the main cause of life shortening. The guinea-pig was consistently more sensitive in two experimental series; goats showed differences between the two sexes and an increased response with respect to the mouse. There was evidence that the bending point of the curve as a function of dose (see Figures X and XI) may occur at dose rates consistently lower than in the mouse, so that the maximum dose that this animal may accumulate in duration-of-life experiments occurs at less than 10 R per day, as compared to the 20–40 R per day applying to the mouse. The qualitative response of the dog might be similar to that of the mouse, since the dependencies on the dose of the life-shortening effect change when haemopoietic or non-haemopoietic mechanisms influence survival. Quantitatively, the primary mechanisms of death might be neoplastic non-haemopoietic or possibly degenerative at dose rates below about 0.035 Gy per day, while in the mouse the relevant figure would be in the region of 0.2 Gy per day.

5. Internal irradiation

134. Irradiation by injected, ingested or inhaled radionuclides is a special form of localized chronic treatment which is worth considering in relation to its effects on the life span of contaminated animals and to the existence of any non-neoplastic life-shortening effect. Finkel, Biskis and Schribner [F5] examined the effect of ^{90}Sr in CF1 female mice injected at 70 days of age with nine acute doses between 1.3 and 8.1 Bq/kg. The same data with a more extended range of doses were also reported by Finkel and Biskis [F3] and made the object of a comparative analysis of life-span shortening and incidence of neoplasms. When plotted against dose, life-span shortening and bone sarcoma induction were not linear over the whole dose range observed. Life-span shortening and tumour induction appeared to be equally sensitive indicators of radiation damage. There was a good correspondence between life shortening and tumour induction up to a dose of 3.3 10^7 Bq/kg but at still higher doses, in spite of a decreased incidence of the bone tumours, life span further decreased.

135. Finkel's [F5] data were further analysed by Mays and Lloyd [M11]. Mice dying with bone sarcoma had a median life span from injection to death which decreased rather regularly with increasing average skeletal dose, owing to a shorter latency time of the bone sarcoma incidence at higher doses. An effect of life shortening induced by single injections of ^{90}Sr (3.7 10^4 or 7.4 10^3 Bq/g) was also described by Van Putten and De Vries [V2] on (CBAxC57BL)F1 hybrid female mice and these data plotted as the percentage of the control life span were rather close to those of Finkel et al. [F5].

136. Similar observations can be made regarding the data on rats by Moskalev, Streltsova and Buldakov [M16] as re-analysed by Mays and Lloyd [M11], since the average time from injection to death tended to increase as the dose decreased from 1.9 10^7 to 1.9 10^2 Bq kg^{-1}. A dose-related life-span shortening was reported by Brooks et al. [B12] in hamster injected with ^{90}Sr (7.4 to 185 10^3 Bq). The 50% survival times ranged from 90 days with 7.4 10^4 Bq g^{-1} to 1100 days at 7.4 10^3 Bq g^{-1}. In this species, however, myeloproliferative diseases rather than osteosarcoma were the most common pathological conditions observed.

137. Another bone seeker, ^{45}Ca, was studied in single injections by Finkel et al. [F5], and their data were analysed again by Mays and Lloyd [M11]. They were able to show that median survival time from injection to death in mice dying with bone sarcoma declined with increasing dose owing to a progressively early appearance of the bone tumours.

138. Sarcoma incidence in the bone tissue and life-span shortening were evaluated as a function of dose, dose rate and time in beagle dogs fed from mid-gestation to 1.5 years of age a diet containing ^{90}Sr [M17]. Under these conditions the observed life-span shortening was attributed mostly to radiation-induced tumours. Also, in the same paper a reduction of the delay time in the appearance of bone sarcoma with increasing activities administered was reported in dogs. The same observation was true for the same species in the experiments of Burikina [B13], thus confirming that a shortening of the induction period for tumours (giving rise to a shorter life span of the tumour-bearing animals) holds true also in the case of chronic uptake of the nuclide.

139. There is some information regarding bone-seeking alpha-emitters. In a further analysis by Mays and Lloyd [M12] of data on single injections of ^{239}Pu in CF1 female mice by Finkel and Biskis [F3, F6] a progressive decrease of the average survival from injection to death (for mice living beyond 200 days post-injection) was seen at increasing skeletal dose, even when the incidence of bone tumours at doses in excess of 11.5 10^4 Bq kg^{-1} decreased, rather than increased. At these very high doses there may of course be some question about how much a non-specific life-span shortening might have contributed to the observed decrease of the percentage tumour incidence.

140. Shortening of the latency interval of tumours induced by ^{239}Pu injection in rats was also shown by Bensted et al. [B14]. But in the same species chronic administration of ^{239}Pu—in spite of an increased incidence of osteosarcoma, leukaemia and marrow aplasia—was reported to produce minimal changes in the life span of the treated animals [B15].

141. The life shortening observed in dogs carrying osteosarcomas induced by various injected bone-seeking radionuclides (^{239}Pu, ^{228}Th, ^{228}Ra, ^{226}Ra, ^{90}Sr) were calculated by Dougherty and Mays [D5]. The accumulated skeletal doses up to one year before death were computed and used as the independent variable. In all tumour-bearing animal groups and for all nuclides tested the log of the time from injection to death was a linear function of the log average skeletal dose. Thus, not only was the average life span reduced by the appearance of bone tumours (whose incidence is a function of dose) but a further reduction of the life span was seen in tumour-bearing animals by the earlier appearance of tumours at higher doses. Based on life-span shortening, the approximate efficiency of the various nuclides relative to ^{226}Ra (taken equal to one) was $^{239}Pu = 6$; $^{228}Th = 8$; $^{228}Ra = 2.5$; $^{90}Sr = 0.07$ to

0.24. These differences could best be interpreted by taking account of the local site of energy absorption and of the type of radiation. The surface-seeking alpha emitters are substantially more effective than the volume-seekers.

142. In 1970 Eyring and Stover [E1] examined the life-span shortening from internal irradiation by ^{239}Pu and ^{226}Ra reported for beagle dog experiments [M18, S24, J1] making use of the steady-state theory of mutation rates [S15, S51]. They fitted cumulative survival curves as a function of the average skeletal dose accumulated by groups of dogs injected when young adults with various doses. There was a high correlation between the mean survival time and tumour induction with the average skeletal dose. The log of the dose was proportional to the 50% survival time and the experimental data followed two quite unrelated slopes at low and at high doses of injected ^{226}Ra. In the case of ^{239}Pu, on the contrary, the 50% survival times followed a linear function of dose at the low doses.

143. The analysis of life shortening was also extended to ^{228}Ra, ^{228}Th and ^{90}Sr in subsequent publications [S25, S26]. When the percentage of osteosarcoma induction was plotted against the percentage of the life shortening produced by each dose level of each nuclide, a life shortening of 60% was obtained when the tumour incidence reached 100%. At high dose levels the degree of life shortening was similar for all five nuclides but this similarity was not maintained at the lower dose levels. In the case of ^{239}Pu the incidence of osteosarcoma greatly exceeded the control incidence even at the lowest dose level where no life shortening relative to controls was apparent. In the case of ^{226}Ra progressive life shortening was seen at skeletal doses in excess of 21.2 Gy, where the occurrence of osteosarcoma was between 92 and 100% but practically no life shortening was found at skeletal doses between about 3.7 and 9.5 Gy, although sarcoma incidence in these groups was 10 to 20% and 42%, respectively.

144. From an analysis of data on young beagles injected with single intravenous doses of ^{252}Cf, ^{249}Cf, ^{241}Am, ^{238}Pu, ^{228}Th, ^{228}Ra, ^{226}Ra and ^{90}Sr Mays and Dougherty [M18] concluded that all or virtually all of the life-shortening effect observed at medium and at low doses of the nuclides is attributable to radiation-induced bone sarcoma. Thus, the thesis that the induction of neoplasia is responsible for all of the life shortening observed in the low-dose range of the experiments available was also confirmed for the case of a medium size mammal injected with a variety of bone-seeking radionuclides.

145. In the field of inhaled alpha emitters an experimental study in rats treated with ^{238}Pu, ^{239}Pu and ^{241}Am given as oxides or nitrates was reported [M19]. Survival time of the animals and latency time, frequency, location and histotype of the tumours were analysed as a function of the dose rate and of the dose distribution. An acceleration of tumour induction time (and therefore of after-survival time) with increasing dose and the existence of a non-neoplastic life shortening at high doses were also apparent. Similar findings were also obtained in dogs inhaling ^{239}Pu by Bair [B16] and by Park [P1].

146. In conclusion, a large variety of injected, ingested or inhaled radionuclides have been studied for their capacity to induce life shortening. The largest body of experimental evidence is for bone-seeking beta emitters (^{90}Sr and ^{45}Ca) or alpha emitters (^{226}Ra, ^{228}Ra, ^{228}Th, ^{238}Pu, ^{239}Pu, ^{241}Am, ^{249}Cf and ^{252}Cf) administered to different animal species under a variety of routes, doses and dosages. Very good correlations were generally found between life shortening and induction of bone tumours, thus justifying the conclusion that whatever reduction of life is apparent from the experiment it may entirely or almost entirely be explained by tumour induction or acceleration, except at extremely high doses where aspecific mechanisms of death may produce short-term mortality. This conclusion is very clear-cut and not surprising, as selective partial-body exposure is the mechanism operating in case of internal irradiation and, under these conditions, non-specific damage to the whole body cannot be expected. The data are therefore not strictly comparable to those from whole-body irradiation and the above conclusions carry little weight in respect to the problem of life-shortening specificity.

6. Uncommon findings

147. In some experiments involving life-time irradiation [L6] low doses of radiation led to an increase, rather than to a decrease, of the expectation of life. Here mice were exposed to 0.11 R of gamma rays daily. Although the increase was not statistically significant, it was confirmed in a subsequent test where differences between groups concerning the air conditioning and the temperature of the animal quarters made comparisons difficult. Sacher and Grahn (reported by [S3]) also noted no harmful affect of 5 R per day in three different strains of mice, following cumulative exposure to about 2500 R. Yuhas [Y3] reported life-span lengthening when old mice (15, 18 and 24 months of age) were exposed to 10 fractions of 140 R given over 12 days, whereas the same amount of radiation administered to 4 and 9 month old animals produced some life shortening. Similar observations were made repeatedly after relatively low single doses [G2, U7, S17, E3], as may be deduced from Figure II.

148. In addition to the above cases, life prolongation has also been reported following the interaction of suboptimal ambient temperatures and low radiation doses. Carlson et al. [C21] exposed male Sprague-Dawley rats at 25°C and 5°C to ^{60}Co gamma-irradiation for 8 hours per day during one year. The animals were caged individually and a parallel control group was run at each temperature. The dosimetry was such that the animals in the room at 25°C received from 38 to 96 mR per 24 hour-day and the exposed ones 895–931 mR per 8 hour-day. In the room at 5°C the respective dose rates were: control, 42–149; irradiated, 897–966. Oxygen consumption, food consumption, body weight and metabolism were checked routinely. The irradiated animals at both 5°C and 25°C lived over 20% longer than their respective non-irradiated controls, the half-lives observed were: at 5°C, control 240 days, irradiated 305 days; at 25°C, control 460 days, irradiated 600 days. No explanation was offered for this observation, except the suggestion that a mild injury might result in apparently beneficial effect by stimulation of cell and tissue repair and repopulation processes.

149. Trujillo et al. [T1] reported that RF/Un female mice showed a linear decrease with increasing age in their ability to withstand a standard cold stress (6°C to 7°C for 14 days). Mice exposed to protracted ^{60}Co gamma-ray exposure at 0.5 Gy per day and then

allowed to recover for 90 days showed a similar linear decrease with increasing radiation exposure in their ability to withstand the same cold stress. This radiation-induced effect was considered similar to life shortening by natural aging and was equivalent to 9.3 days per Gy.

150. In a rather more elaborate set-up Carlson and Jackson [C22] studied the interaction among radiation and high temperature. The animals were divided into 8 groups of 22 rats each, individually caged. Four of them were kept at 28°C and exposed to 0.29, 0.64, 2.60 and 4.18 R per day over a period from 4 to 16 months of age. The other four groups were kept at 35°C for the same length of time and exposed to 0.28, 0.60, 2.57 and 3.96 R per day. The age at which 50% of the irradiated animals died increased with increasing dose at all dose levels tested, with good statistical significance of the data, except for two points. It was suggested that ionizing radiation may have interacted with the environment in increasing longevity by stimulation of the repair processes. These experiments [C21, C22] are noteworthy, not only because they show an interaction between radiation and ambient temperature, but also for the finding that radiation in the region of 4 R per day or lower has (at all temperatures tested) increased, rather than decreased, survival. As to the first point, the observation has so far remained without confirmation; concerning the second one, it should be mentioned that Bustad et al. [B17] working on individually caged mice within the same exposure range but at normal ambient temperature could not confirm the data of Carlson. The problem therefore remains unsolved, as the different species or environmental conditions might have been responsible for the negative observations of Bustad.

151. Following the formulation of a theory on the statistical nature of mortality by Sacher [S2] and by Sacher and Trucco [S12] in which the death of an organism is viewed as a random event arising from the fluctuating nature of its physiological performance, these authors proposed [S32] a modification of the theory that makes it possible to account for the paradoxical observations described. Radiation (particularly at low doses) induces a decreased fluctuation of the signalling and control systems of physiological processes. As a result, the probability of a large fluctuation leading to an irreversible change is decreased. In essence, the decreased variability among the exposed compared to among the control animals, is the main effect of the irradiation and the improved survival at relatively low doses results from it as an occasional consequence.

152. The above model may provide a phenomenological explanation of life-lengthening effects in actuarial terms, but the intimate mechanisms through which such effects may be brought about are still unknown. Data showing stimulation of antibody formation [D10, L19], increase in phagocytic activity and lysosome content [T3] and activation of reparative enzymes by relatively low radiation doses [K24, V8] can, in principle, be cited in this respect, but their general applicability cannot be decided at present.

153. Biological variability of the control and experimental animal groups and long-term changes of the baseline reference values may have been responsible for at least some of the above observations and these cases should probably be viewed separately from the others in which interplay of environmental factors led to the phenomena under discussion. Kuzin [K24] considered that an increased resistance of the animals brought about by unfavourable environmental conditions may have been responsible for life span prolongation.

C. DOSE RATE, DOSE FRACTIONATION, PROTRACTED EXPOSURES

154. Results of other experiments are available in which radiations of different types were given at various dose rates in chronic terminated or in fractionated exposures to animals of various species. The experiments were sometimes made to examine the effect of a given regime of chronic terminated exposure. In other instances, the experiments were carried out to study changes in the dose rate; and in other cases in order to compare the effects of splitting a single dose into fractions separated by various time intervals. In all of these experiments the interplay of dose-time parameters is extremely variable and the final effect may be expected to be intermediate between the two extremes of the single or of the duration-of-life exposure. It is difficult and somewhat arbitrary to separate all this work into various chapters: however, the following will separately consider the effect of dose rate, of dose fractionation and of protracted exposure, in an attempt to draw more systematic conclusions about the different radiobiological variables. The effect on life span of the distribution in time of low-LET radiation has been discussed in [N14].

1. Dose rate

155. The papers where dose rate was examined as a separate variable in acute exposures or in the course of chronic terminated experiments are very few and all on mice. Vogel, Frigerio and Jordan [V1] reported that between 10 and 44 mGy min^{-1} of fission neutrons the effect on life span was independent of dose rate, although there was dependence for gamma rays in the range of 10 to 130 mGy min^{-1}. The efficiency of the treatment was lower at low dose rate. The experiments were performed on CF1 female mice irradiated with 13 brief daily exposures. In another series the mice were irradiated with single neutron exposures at 80 mGy min^{-1} or 2 mGy min^{-1} (0.36–1.74 Gy total dose). Survival did not differ within the above dose rates.

156. Vogel and Jordan [V3, V4] irradiated the same mice with fission neutrons and gamma rays (10 to 350 mGy min^{-1}). Four weekly doses of 2 Gy per week of ^{60}Co gamma or 1 Gy per week of neutrons were employed, delivered at variable dose rates. For both radiations, the lower the dose rate, the longer the life span of the animals. Lindop and Rotblat [L10] reported on the changes in effectiveness (expressed in weeks of life shortening per Gy) as a function of the dose rate at the extremely high intensities of 0.77 to 1580 Gy min^{-1}. They showed that the maximum effectiveness (5.7 to 6.2 weeks Gy^{-1}) was at around 10 Gy min^{-1}, but could not explain the loss of effectiveness at still higher dose rates. Oxygen depletion induced by these high intensities could not have been responsible for such an effect, as it was also seen in mice made artificially hypoxic.

157. Upton, Randolph and Conklin [U7] and Upton, Randolph and Darden [U10] used variable dose rates of gamma rays (0.8–0.01 Gy d^{-1}) or of fast neutrons (110 to 0.04 mGy d^{-1}) to induce life shortening on RF/Un male and female mice (total doses of 100 and 10 Gy,

respectively). In females, a consistent reduction of the gamma-ray effectiveness was seen at the lowest intensities, amounting to about a factor of 3, by comparison with acutely-delivered (0.067 or 0.8 Gy min^{-1}) doses. A further reduction to a factor of 6 was observed if continuous irradiation was carried out to the time of death of about 50% of the animals. For neutrons, loss of efficiency of continuous against acute administration was 0.9 and decreased further to 0.7 for exposures protracted to death of 50% of the mice. In male animals, the loss of efficiency of the gamma rays was even higher, amounting to 0.1 upon continuous administration and to 0.04 for irradiation protracted up to 50% survival.

158. Spalding et al. [S21] performed experiments on RF female mice irradiated with gamma rays (0.025 to 2.5 Gy h^{-1}, 1 to 12 Gy total dose). Within a given total dose the mean after-survival was changed more or less randomly with the dose rate. Biological and environmental factors such as individual variations in radiosensitivity and cage effects rather than any identifiable physical parameter were held responsible for these observations. Dose rate studies (gamma rays, 1 to 1000 Gy min^{-1}, 1 to 3 Gy weekly exposure for a substantial duration of the life span) were also reported by Willhoit and Wiggins [W5]. Some decreased effect at the lower dose rates was noted, but it was impossible to attribute the effect to any specific disease, owing to the lack of pathology.

159. In the experiments of Ullrich and Storer [U8] and Storer et al. [S44] on RF and BALB/c female mice lowering the dose rate of gamma rays led to a modification of the shape of the dose-effect relationship in the range 0.5 to 4 Gy from a very complex pattern at 0.45 Gy min^{-1} to a nearly linear shape at 0.083 Gy d^{-1}. The large difference in effectiveness was related to an upward displacement of the regression line in the 0 to 0.5 Gy range in the high dose rate groups. BALB/c females showed a similar trend, in that the 0.5 Gy dose point was displaced upward in the high intensity curve, suggesting a dose rate dependent injury component which saturated at high dose rates at about 0.5 Gy, similar to the one identified by Sacher [S2] in female mice given 2 Gy or more. The response to neutron irradiation of high (0.25 Gy min^{-1}) or intermediate (0.01 mGy d^{-1}) dose rate was somewhat different. In RFM mice the low dose rate was less effective at 0.24 Gy but more effective at 1.88 Gy than the high dose rate. In BALB/c mice little dose rate dependence was seen at low doses but at 1.88 Gy the low intensity was more effective. The results are somewhat less clear at lower doses.

2. Dose fractionation

160. The experiments reported in this subsection were performed by splitting a given dose or a series of doses into two or more fractions, irrespective of the time over which the total dose was administered. The dose per fraction, the fractionation interval and the total time to complete the course of irradiation are variables that interact to produce the final effect. They cannot be separated from each other under most of the experimental conditions used. Often the comparison is therefore between a dose given in a single treatment and the same dose over a very protracted course of fractionation. Only seldom is the accuracy of the data such that numerical protraction factors can be derived with the necessary degree of precision.

161. Sacher [S2] performed experiments on the life-shortening effect in the mouse of 400, 800 and 1200 R given in equal fractions 5 day/week over 2 or 8 weeks. The life shortening of mice dying from causes other than lymphoma decreased with increasing number of fractions, even though the effect of leukaemia induction increased by fractionation, as reported for the C57BL mouse by Kaplan and Brown [K12]. The dose fractionation experiments performed by Curtis and Gebhard in 1958 [C17] with fission spectrum neutrons and 250 kVp x rays in CF1 female mice did not show any change in effectiveness upon fractionation but the authors recognized the peculiarity of this finding and attributed it to the use of fairly large doses. In their opinion, the recovery rate from such doses would be essentially different in the x-ray and neutron groups, as compared to the recovery from small fractional doses.

162. Survival and leukaemia incidence were studied in RF male mice irradiated with 250 kVp x rays by Upton, Wolff, Furth et al. [U11]. After 150 R given in a single exposure the life span was 15.6 months and it increased to 16.3 and 16.5 months when this same exposure was split into two 75 R fractions and given 2 and 6 days apart, respectively. Similarly, 450 R given in a single treatment or in 3 equal fractions at 2 or 5 days interval changed survival from 10.3 to 10.8 to 11.1 months, respectively. These changes are small and of dubious significance, in spite of the relatively high number of mice per group. They could be attributed to changes in the incidence of reticular tissue tumours which are by far the largest part of the causes of death in this strain, particularly after irradiation.

163. Mole [M1, M20, M21] reported that when 1000 R of x rays were delivered in 10 daily fractions of 100 R the mean survival time was shortened by 10% with respect to controls. When the same total exposure was delivered in 100 fractions of 10 R each the mean survival time was shortened by 37%. Thus, spreading a given dose over a longer time would apparently increase the amount of damage. The same result was obtained on CBA mice when 750 R were given in a single dose or spread out over several weeks. In this case fractionation induced a change in the shape of the age-mortality curve and of the age-specific mortality rates owing to the appearance of more leukaemia deaths after the protracted than after the single exposure. It seems possible therefore that the important factor in this case might have been a change in the spectrum of the induced diseases rather than the fractionation per se.

164. Cole et al. [C18] examined in the LAF1 mouse the influence of 250 kVp x-ray fractionation. The incidence of leukaemia was increased significantly when 690 R were subdivided into 2, 4 or 8 equal fractions separated by 8 weeks, 19 days or 8 days, respectively. Irradiation shortened survival time in all groups, but the largest decrement was seen in mice receiving 8 exposures of 85 R, an effect which would be contrary to expectation if leukaemia had not specifically shortened survival in this case. In contrast, observations on nephrosclerosis showed a decreased incidence of this disease with fractionation from more than 50% in the mice receiving the single exposure to less than 10% in the group receiving eight fractions. Therefore, in these experiments nephrosclerosis was regarded as being mainly responsible for early death after the single dose, whereas malignancies specifically accounted for more than half of the deaths in the fractionation groups.

165. According to Vogel, Frigerio and Jordan [V1] fractionating 2.75 Gy of neutrons into 3, 4 or 10 separate daily exposures did not result in any significant difference of the mean survival time of CF1 female mice. Kohn and Guttman [K6] studied the effect of 520 R of 250 kVp x rays given as a single exposure or in two fractions administered 8 days apart on male and female CAF1 mice. Specifically with respect to the effect of fractionation, here again the results were unclear in showing any significant improvement in survival.

166. Vogel and Jordan [V5] examined on CF1 female mice the effect of fractionating a weekly dose (3 Gy of ^{60}Co gamma rays or 0.6 Gy of fission neutrons) into 1, 3 or 6 equal dose fractions per week. Both radiations were delivered at approximately 0.01 mGy min^{-1} and the treatments were continued for a total of 13 consecutive weeks, so that the mice were exposed to almost 40 Gy of gamma rays or 7.8 Gy of neutrons. The mean survival times of the gamma-irradiated mice were not significantly different whether they were exposed 1 or 3 times per week. There was some indication that a further dilution of the dose to 6 fractions per week might increase survival but the significance of the data could be questioned. No indication of a sparing effect of fractionation was, however, found in the neutron-irradiated mice.

167. Silini and Metalli [S27] showed in a small experimental series that survival time could be increased by a schedule of fractionation where a conditioning dose of 1.5 Gy was followed by 3.5 Gy given at 7 time intervals between zero and 48 hours. A positive regression of the data amounting to an 8% increase in survival time was detected. The kinetics of the phenomenon followed a pattern reminiscent of the short-term intracellular type of recovery described in cultured cells by Elkind and collaborators [E4].

168. Grahn and Sacher [G1] tested the effects of 450 and 750 R of ^{60}Co gamma-radiation delivered as single exposures or in two equal fractions separated by increasing time intervals from 3 hours to 28 days. The regression of survival time versus fractionation interval was negative in 3 out of 4 cases (2 doses x 2 sexes) but none of the regressions were significantly different from zero. The incidence of leukaemia was not consistently modified by fractionation and this disease was not specifically associated with life shortening, in contrast to results of other studies [G4, U11].

169. Ainsworth et al. [A7] reported that fractionation of a gamma dose of 8.38 Gy into 24 doses of 0.35 Gy administered over 23 weeks produced a "sparing effect" by approximately three-fold. On the contrary, a similar regime of fractionation with fission spectrum neutrons increased life shortening. This is a rather unusual observation in fractionation experiments, but it is in agreement with the theoretical expectation when the single-dose curve is, as in the case at hand, convex upward [R13]. Histopathological observations on pulmonary tumours could not explain all of the increased mortality resulting from neutron dose fractionation. Tentative explanations were offered, based on the differential acceleration of the lung tumour appearance or on the differential killing of potentially transformed cells in the lung. A more recent report [T4] confirmed the same conclusions in regard to the actuarial analysis but did not provide pathological data useful for their interpretation.

170. Storer et al. [S44] exposed RFM and BALB/c mice to 7 weekly doses of fission neutrons of 0.067 Gy (total 0.47 Gy) or to 0.235 Gy once every 4 weeks for 28 weeks (total 1.88 Gy). Animals exposed to a fractionated dose of 0.47 Gy had a life span not different from those given single high dose rate exposures or exposures at 0.01 mGy d^{-1}. BALB/c animals receiving 1.88 Gy had a survival time significantly shorter than that following a single exposure. RFM animals given fractionated treatment up to 1.88 Gy experienced the same survival as after single exposure and a significantly longer survival than following exposure at 0.01 Gy d^{-1}. It was concluded that the cause of death may critically determine the effectiveness of the fractionated exposure, although the authors were unable to provide an explanation for their observations.

171. Data on the effect of dose fractionation on life shortening were described by Hursh et al. [H5] in the Wistar male rat irradiated with x rays. Information on x-ray dose fractionation was also reported in the same animal species by Lamson, Billings and Gambino [L4, L11]. Increasing the number of fractions from 1 to 3 to 6 for the same total exposures of 120, 240, 480 R caused an increase of life span, compared to the same exposure in one fraction. The effect was dose-dependent in that it could be seen at the two higher exposures. Spacing of the fractions at intervals of 3, 5, 7 or 14 days did not influence longevity. It was concluded that fractionation after exposure in the 1 to 6 fraction range led to 30–46% of the sparing effect obtained by halving the total exposure in the 0 to 446 R exposure range.

172. In the Wistar rat Reincke et al. [R3] examined the effects on tumour frequency and life-span shortening of two different fractionation regimes of whole-body x-irradiation (300 R in 3 exposures over 2 months or 10 R in 90 exposures at daily intervals) and compared these regimes between themselves and with control non-irradiated rats. No significant differences in the overall incidence of tumours or on tumour types were observed. The average survival times were 20 and 25 months, respectively. Tumour induction rates and death rates were not different between the two groups, but some differences became apparent when age-specific rates due to neoplastic and non-neoplastic causes were compared. In general, all radiation effects were more pronounced in the group receiving 300 R x 3. There was no complete summation of the effects of the single doses and recovery processes were more effective after small daily exposures than after greater radiation exposures given at longer intervals.

173. Various schedules of fractionation as well as single exposures to 250 kV x rays were given to female beagle dogs by Andersen and Rosenblatt [A2]. For total exposures of 100 or 300 R, 4 equal fractions or 2 equal fractions given at 7, 14 and 28 days interval were administered. In general, differences between subgroups receiving fractionated exposures were apparent only in groups totalling 300 R. In these animals life shortening was increased when the total treatment time increased from 7 to 84 days. It was estimated that the decrease in life shortening produced by 300 R would be reduced from 23 to 10% as treatment time increased from 7 to 84 days.

3. Protracted exposures

174. The papers discussed in this subsection pertain to chronic exposures carried out with different radiations

on various animals. The heterogeneity of this work does not detract from the quality of some of the contributions in which many important conditions such as the protraction of dose administration or the duration of exposure (and therefore the cumulated total doses) are the variables under examination. The common feature is that in all cases exposures were terminated before a substantial part of the animals died, thus allowing estimates of the survival parameters under conditions in which the "wasted radiation" component was not effective.

175. The early contributions of Evans [E2] and Lorenz et al. [L6] are only cited here for completeness. The paper of Mole and Thomas [M7] is a systematic investigation of life shortening in CBA mice by changing the duration of exposure to daily irradiation of ^{60}Co gamma rays or of fast neutrons (mean energy 0.7 MeV). In the case of gamma irradiation, weekly exposures of 350, 210, 110 and 16 R for progressively longer times (4 to 30 weeks) and for the duration of life were tested. For neutrons, 0.16 or 0.02 Gy per week for 5 to 60 weeks or for the duration of life were the conditions tested. For both radiations, as the duration of exposure to a given daily dose (and therefore the total dose) increased, the mean survival time decreased. However, beyond a given point a further increase of exposure time and total dose produced no further effect. The lower the daily dose, the more survival time became independent of the total dose or of exposure time. The minimum dose or exposure time required to produce a maximum life-shortening effect could only be approximated. The shape of the cumulative mortality curves depended systematically on the particular level of daily dose and on the duration of the exposure, except possibly at the lowest daily doses. A summary of these data is given in Figure XII.

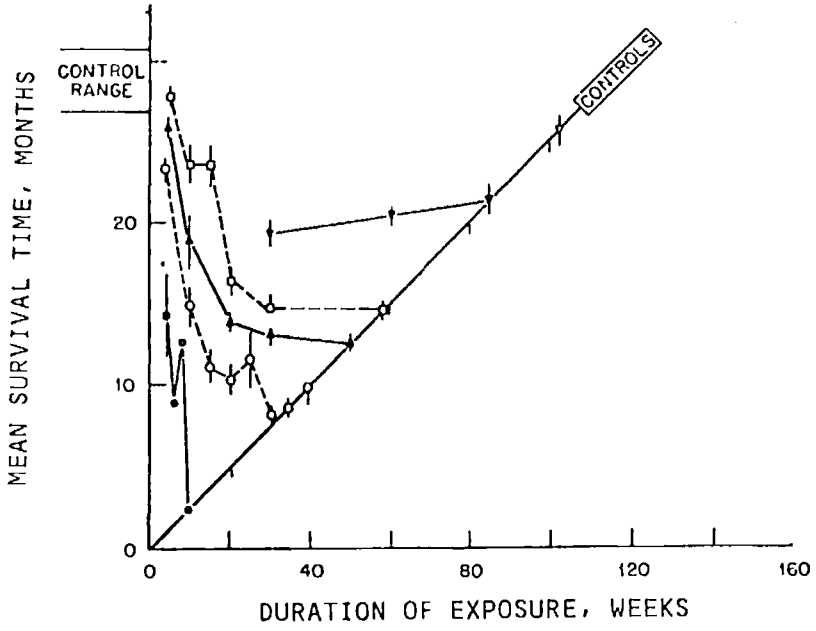


Figure XII. Mean survival times of female CBA mice after chronic terminated and duration-of-life exposures to gamma rays and fast neutrons. The nominal weekly exposures are: gamma rays, ● 350 R, O 210 R, □ 110 R, ▽ 16 R; fast neutrons, ▲ 0.16 Gy, ▼ 0.02 Gy. In duration-of-life experiments the mean survival time equals the mean length of exposure and therefore all points for such exposures must lie on the diagonal slope 1, as shown. Vertical bars show the range of mean survival time in various groups of control mice. Data from Mole and Thomas [M7]

176. Mole's paper [M7] contains, in addition to valuable experimental observations, a number of interesting points for discussion. Some pertain to the concepts of reparable and irreparable injury. Other points concern the problem of controlling and assessing biological variability in long-term experiments and here data are given for a discussion of the secular changes of the life span of the controls. Another observation relates to the presence of discontinuities in the response to chronic irradiation generated by biologically different modes of death. Data on the effect of acute versus chronic irradiation were also reported in the mouse by Curtis, Tilley and Crowley [C19] and are discussed elsewhere.

177. In the series by Bustad et al. [B17] hybrid (C57BLx101) mice were exposed for 8 hours daily from the age of 6 to the age of 58 weeks (that is for one year) to 0.1 R h^{-1} or 0.2 R h^{-1} of ^{60}Co gamma radiation. The cumulated total exposures were 290 and 480 R, respectively, after which the animals were taken out of the radiation field and followed for the rest of their life. Although the treatment did produce some differences in the average pattern of growth and longevity, in most instances these differences were found to be small relative to the variability of the normal samples.

178. Grahn, Fry and Lea [G5] also discussed the effect of protraction on mortality, showing that the risk of death from all and from specific causes is quite different if compared to acute exposure. Their data on LAF1 mice show that leukaemia death rate is reduced by a factor of 5 or more for daily exposure levels below 20–30 R d^{-1}. Data on all causes of death other than leukaemia show also a protraction factor which takes up different values (from 2 to 5) as the exposure rate decreases from 40 to 50 R d^{-1} to 12 or less R d^{-1}.

179. Spalding et al. [S28] exposed 13 groups of adult female RF mice to ^{60}Co gamma rays at about 0.028 Gy h^{-1} until a predetermined dose (from 4.57 to about 0.03 Gy) had been accumulated. As doses increased, there

was no accompanying increase of life shortening because any dose had about the same effect, amounting to an average of 83 days reduction of life. Assuming a linear relationship with dose in the range 0 to 0.47 Gy, the effect would be about 18 days per Gy, a value which is on the low side of those usually found for low-LET radiation (see Table 1).

180. The contribution of Russ and Scott [R1] on the rat should only be mentioned for historical reasons. Boche [B11] refers to some experiments in which rabbits received one year of treatment at daily exposures of 0.1, 0.5, 1.0 and 10.0 R. Life shortening was shown in various ways. Similar treatments were also given to a few dogs and when the experiments were conducted with irradiation for only a fraction of the life time at dosages below 1 R d^{-1} no effect on survival was noted. This was also true for monkeys.

181. The paper by Fritz et al. [F7] on the beagle dog is an attempt to clarify time-dose relationships after terminated chronic exposure to ^{60}Co gamma rays. Four exposure rates (5, 10, 17, 35 R d^{-1}) were used and the dogs (354 in total) were removed and allowed to die of natural death after total exposures of 600, 1400, 2000 and 4000 R. The experiment is still in progress but the provisional data are sufficient for a few tentative conclusions, as follows. The LD_{50} increased from 2.58 Gy delivered at 15 R min^{-1} to about 30 Gy at 10 R d^{-1}. Over this range of exposures the leading cause of death was haemopoietic damage. At 5 R d^{-1} or lower no definite LD_{50} could be determined: the haemopoietic function continued at a nearly normal rate and survival was sustained. The relatively high number of malignancies other than leukaemia observed among the few animals dead up to the time of the report suggested that tumours of the soft tissues in irradiated animals were significantly increased with respect to controls. It is yet too early to see whether a non-specific component in the life-span shortening may become apparent at the lowest dose rates.

4. Conclusions

182. On the whole, the modifications of the life span induced by changing the dose rate are rather variable. For single acute doses of low-LET beams, changing the dose rate from 0.004 to 0.4 Gy min^{-1} did not significantly alter the effect [S21]. When the dose rate varied between about 0.8 and about 1580 Gy min^{-1} [L10] the effectiveness of the treatments differed as a maximum by a factor of 1.6. Thus, acute treatments show little dependence on the dose rate down to 0.004 Gy min^{-1}. At lower dose rates, down to about 0.01 Gy d^{-1}, it becomes difficult to resolve changes due to the dose rate as such or to dose protraction over a time which allows adaptation of the animal to the treatment. Under conditions implying irradiations for weeks or months, the efficiency of the treatment with respect to acute doses may drop by a factor of 10 or even of 25 for extremely low dose rates and long irradiation times with accumulated doses involving less than 50% survival of the irradiated animals [U7]. With such extremely protracted irradiations the form of the dose-effect relationship may also change with various reduction factors for different total doses [U7, U8]. Modifications of the form of the dose-effect relationships are not surprising, as changes of the damage, repair and repopulation at the various doses would superimpose to changes of the biological system itself during physiological adaptation to irradiation. All these variables would be expected to change profoundly as a function of time and dose. There has been experience in changing the dose rate in the course of brief repeated exposures at daily or weekly intervals. For daily exposures, a dose rate dependence of ^{60}Co gamma radiation amounting to a factor of 2 has been found, but not for fast neutrons. Weekly fractions with higher doses and within a higher range of dose rates did, however, show some reduction of effectiveness even for neutrons [V3, V4].

183. In the case of neutrons, changing the dose rate between 0.08 and 0.002 Gy min^{-1} does not result in an appreciable loss of effectiveness [V1]. The data available at lower dose rates (250 to 0.04 mGy d^{-1}) given in protracted exposures [U7, U8] may be interpreted to show that the reduction of effect at the low intensities is modest, probably lower than a factor of 1.5. There may be question as to the significance of changes in the form of the curve within such a small range of variation. Thus, the dependence of life shortening on dose rate is modest for low-LET radiation and doubtful for neutrons, when treatments last a few hours to a few days. Only when extremely low dose rates and correspondingly long irradiation times are involved, do x and gamma rays (but not neutrons) show consistent reduction of effectiveness, of the order of a factor of 10 or 20.

184. Experiments performed by splitting a given dose into two or more fractions separated by a few hours to a few weeks [G1, S27] have yielded little increase in survival by the split dose. When fractionation intervals of progressively longer duration were tested with a given scheme, a tendency to a longer life span with an increasing interval between doses has sometimes been found, but the variations observed even for very long fractionation times are too small to make these observations clearly significant [G1, A2, S27].

185. It is very difficult to see an overall trend for more complex fractionation patterns. In some cases [S2, A2, A7, H5, L4, R3] dividing the dose into smaller and smaller fractions does lead to an increased survival time following x- or gamma-irradiation. So does the increase in the total treatment time for the same number and size of fractions. But in other cases [M1, K6, M20, C18] a paradoxical effect is observed, i.e., an increase of the life shortening upon dose fractionation. A changing spectrum of the various diseases contributing to life shortening with more leukaemia induced at longer fractionation times has been invoked to explain the observations. Neutron dose fractionation experiments have also been reported on mice with unclear results.

186. In spite of the absence of a component of wasted radiation that has been claimed to confound the analysis, the effects of chronic terminated exposures are more difficult to evaluate than the experiments involving duration-of-life exposure. In principle, for any given type of radiation, the effect to be expected should lie between the dose-effect relationships obtained for high dose rate acute exposures (see Figures II and III) and those operating under duration-of-life conditions (see Figure X). However, the most striking finding in these series is the modification of the dose-effect relationships taking place at progressively variable dose rates. These modifications, depending on the characteristics of the species and strains, determine the final outcome of any given course of irradiation. There are not enough data on any single species to analyse such a broad statement into any coherent

model as published data have essentially been obtained on two mouse strains [M7, U7] and other series [S11, S21, L6] have contributed relatively less information.

187. These data, involving x-, gamma-ray and neutron irradiations were analysed by Grahn and Sacher [G1] and their conclusions may be provisionally accepted. Apparently (see Figure XIII) the curve describing life shortening as a function of total dose accumulated for doses of 15 Gy or less or for protraction periods of 50 days or less shows an abrupt slope transition from an initial portion where the effectiveness of the treatment

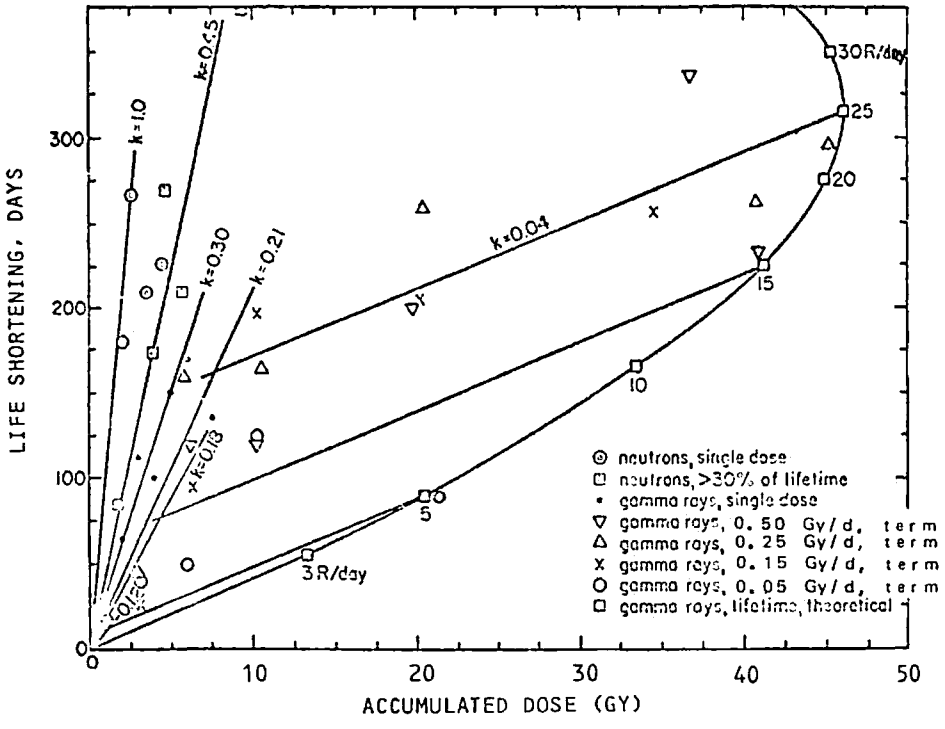


Figure XIII. Life shortening as a function of mean accumulated dose in RF female mice given various patterns of exposure (single, chronic terminated, duration-of-life) to gamma rays and neutrons. Data from Upton et al. [U7] as plotted by Grahn and Sacher [G1]

is of the order of 20–30 days of life shortening per Gy to a final slow-rising portion having an effectiveness of 4–5 days per Gy. This final slope applies to all protraction periods, including exposure for the duration of life; however, the point of transition between the fast-rising and the slow-rising segments of the curve is clear at 0.5 to 1 Gy d^{-1} but less so at intensities of 0.1 to 0.15 Gy d^{-1}. This flattening of response noted by Mole [M1] and by Sacher [S1] may be related to the establishment of an equilibrium between radiation injury and recovery mechanisms, which would depend on the kinetic modifications of the tissues that are important for long-term survival [S5, L13, L14, L15].

188. It may therefore be reasonably expected that the breaking point or transition in the dose-effect relationships depends also on the kinetic characteristics of the relevant cell lines, which are known to be species-specific. Such an analysis makes it also quite clear that conditions of protracted exposure may not be defined with respect to their life-shortening effectiveness by a single recovery constant or residual injury value valid for all conditions of protraction and all animal species. The neutron data would be such [G1] that when the transition from the fast- to the slow-rising portion of the curve is operative, the RBE would change from 2–3 to 5–15, as a result of the change in life-shortening effectiveness.

D. RADIATION OF DIFFERENT TYPES AND ENERGIES

1. Data

189. The action of different radiation is manifested through a change of effectiveness for the same amount of energy absorbed by the irradiated animal. The spatial distribution of the primary physical events that are responsible for the final biological effect is at the origin of these changes. Radiobiologically, the effect of densely-ionizing radiation becomes evident through an increased efficiency of the dose, by comparison with a sparsely-ionizing radiation. Under well specified irradiation conditions, when a given effect may be followed for a whole range of doses, the above phenomenon is expressed by the "Relative Biological Effectiveness" (RBE), a factor specifying the efficiency of the test treatment against a low-LET treatment assumed as the standard. X rays of around 250 kVp or ^{60}Co gamma rays may be used for this purpose: they are themselves of different effectiveness, the hard gamma rays being about 0.8 times as effective as the x rays. This Annex does not discuss the theoretical foundations of these concepts which are reviewed elsewhere [K10, R4] and are also discussed in Annex J. It considers only evidence regarding life shortening, according to the order of publication.

190. The early experiments on fission neutron RBE by Henshaw [H6], Evans [E2], Gowen [G8] and Neary et al. [N3] will only be cited. These experiments were analysed in the 1958 report of the Committee [U1] which discussed all data for the chronically irradiated rodent and summarized these in one graph [M13] (see Figure XIV). The percentage mean survival time was plotted versus the gamma-ray or the fast neutron

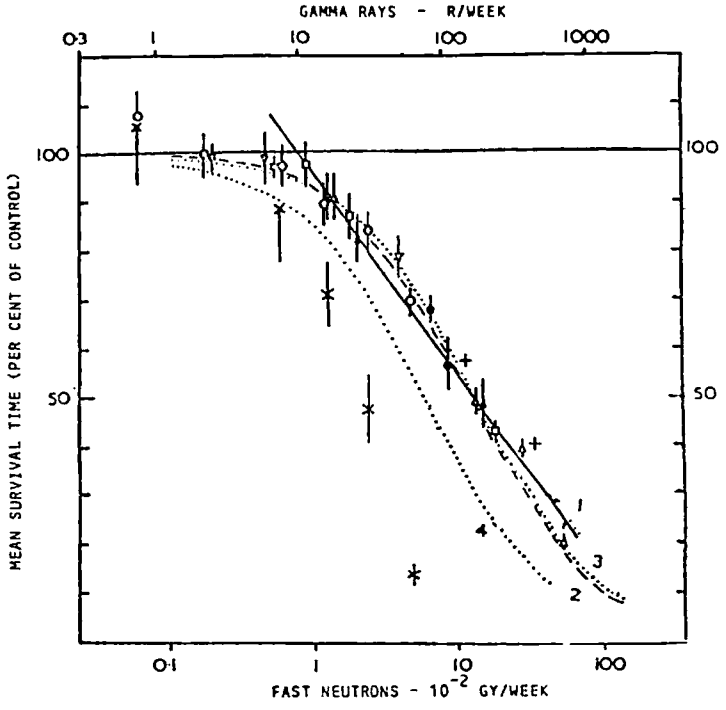


Figure XIV. Mean survival time expressed as percentage of the control survival, as a function of the weekly dose or exposure to fast neutrons or gamma rays. The gamma and neutron scales are in the ratio of 1 : 13. The symbols refer to different sets of data obtained on mice, rats and guinea-pigs by various authors, plotted by Mole [M13] and included in the UNSCEAR 1958 report [U1], as follows; Δ and ▽ [H7]; O and x, [L6]; □ [E3]; ■ [N3]; ▲ and ●, Neary et al., unpublished observations, + J. F. Thompson et al., Am. J. Roentgenol. 69 : 830-835 (1953)

exposure or dose rate. The data appear to be superimposable when the gamma- and neutron-scales were in the ratio of 1:13. From this it was deduced (in spite of some uncertainties in the comparison of data from different laboratories) that the RBE between fission neutrons and gamma rays applicable to life shortening in the rodent for chronic exposure was about 13. A study of x rays (250 kVp, 1.85 Gy min^{-1}) and of fast neutrons (fission spectrum, 2.7 10^8 neutrons cm^{-2} s^{-1}) was performed in CF1 female mice by Curtis and Gebhard [C17] following single or fractionated irradiations. The RBE for life shortening was estimated at 1.7. These results are difficult to interpret not only for the lack of an increase of RBE with fractionation, but also for the low RBE value of the acute exposures.

191. When straight lines were fitted to the data of Upton et al. [U5] on LAF1 mice irradiated with gamma rays or fast neutrons from a nuclear explosion, very similar RBE values of 2.1 and 2.3 were obtained in male and female animals, respectively. Mole and Thomas [M7] estimated the RBE of fission neutrons against ^{60}Co gamma with the same source of radiation and the same animals as reported previously [N1, N3, M13]. The life-shortening effects of about 0.16 Gy per week of fast neutrons or of 210 and 110 R per week of gamma rays were found to be equivalent both for terminated and for duration-of-life exposures. For all levels of response the neutron data were intermediate between the effects of these two intensities of gamma rays and nearer to those of the 110 R per week. The RBE was therefore estimated to be between 13 and 7, but nearer to the latter figure.

192. In a subsequent paper by the same group [N8] the RBE value was discussed for CBA mice chronically irradiated with fast neutrons as described in [N3]. The dose rates of the 0.7 MeV neutrons were 0.02 Gy d^{-1} or 0.003 Gy d^{-1}. Gamma irradiations were run at 0.16 or 0.023 Gy d^{-1}. Complete life-table data and cumulative survival curves were obtained in replicate experiments and several forms of dose-response curves were postulated to fit the data. RBE values around 10 were found, with a range of estimates between 8.6 and 15.0, according to the assumptions made. The data were thought to be inadequate to establish whether or not the RBE depended on the level of daily exposure.

193. The RBE of thermal column radiation, composed of thermal neutrons and hard gamma rays, was tested against 250 kVp x rays in experiments by Storer and Sanders [S17] performed on Swiss white mice. Since the neutron and the x-ray data could be fitted by a common linear non-threshold regression of per cent life shortening versus dose, the RBE had a value of unity. In another series, Storer et al. [S18] exposed CF1 female mice to neutrons or to mixtures of neutrons and gamma rays from an atomic weapon. The relative effectiveness of the neutrons was calculated to be 2.6 ± 0.9. In both series the RBE values for life shortening were in close agreement with those obtained for the production of acute effects.

194. In experiments by Vogel, Frigerio and Jordan [V1] CF1 female mice were exposed to daily doses of fission neutrons or gamma rays at dose rates of about 0.044 and 0.13 Gy min^{-1}, respectively. Groups of animals were given 13 brief exposures, each corresponding to 0.022 to 0.7 Gy d^{-1} of neutrons and 0.065 to 2.08 Gy d^{-1} of gamma rays. The neutron RBE was not increased over the figure of 2.8 previously obtained for acute single doses. Other experiments performed with 13 brief exposures of the two radiations given at 0.1 Gy min^{-1} indicated an RBE for median survival time of 2–3, in fairly good analogy with the figure of 2.8 for the $LD_{50/30}$ after single exposures.

195. Curtis, Tilley and Crowley [C19] reviewed the literature data on life shortening due to acute or chronic irradiation of mice with x rays or neutrons. They concluded that acute gamma doses could be up to 4 times as effective as chronic doses. For neutrons equal efficiency by acute and chronic exposures was the most common finding. Accordingly, the neutron RBE of about 2 for life shortening by acute doses may increase to about 8 for chronic treatments. Chromosome damage in the liver of animals was shown to behave similarly and these data were thought to provide some cellular basis for the differential action of low- and high-LET radiations. The data on chromosomes were also interpreted to indirectly support the hypothesis that mutations in somatic cells may be at the origin of natural and radiation-induced aging.

196. Sixteen-week-old female CF1 mice received 1 Gy per week of fission neutrons for 4 weeks at dose rates of 0.01, 0.03, 0.06, 0.35 Gy min^{-1}; or 2 Gy per week of ^{60}Co gamma rays at the same dose rates [V3, V4]. In all groups thymic lymphoma was the main cause of death and its incidence was not significantly affected by the dose rate. On the basis of mean survival time or of mortality curves, life time was reduced by about 65% by neutrons and by about 50% by gamma rays. The neutron efficiency was therefore higher than that of the gamma by more than a factor of 2. The mean survival times of both neutron- and gamma-irradiated animals were significantly shorter with 0.35 than with 0.01 Gy min^{-1}.

197. Vogel and Jordan [V5, V6] compared the lethality of fission neutrons produced by a CP-5 reactor to that of ^{60}Co gamma rays, both radiations being delivered at about 0.01 Gy min^{-1}. CF1 female mice were exposed according to a complex pattern of fractionation in which 13 weekly doses of 3 Gy of gamma rays were delivered as 1, 3 or 6 equal fractions per week. Since the arbitrary RBE value chosen was 5, the corresponding total weekly dose of neutrons was 0.6 Gy, delivered into 1, 3 or 6 fractions per week. The data showed that the postulated RBE of 5 was too high. Upton, Randolph and Darden [U10] reported that with fast neutrons the life expectancy of RF female mice was shortened by 80 days per Gy, irrespective of dose rate, whereas the life-shortening efficiency of the gamma rays decreased from about 30 days per Gy at 0.07 Gy min^{-1} to about 15 days per Gy at 0.05 Gy d^{-1}. The RBE increased therefore with decreasing dose rate from about 2.7 to 5.4.

198. In the experiments of Upton, Randolph and Conklin [U7] variable dose rates of x and gamma rays (0.80 to 0.01 Gy d^{-1}) and of fast neutrons (0.11 to $4\ 10^{-5}$ Gy d^{-1}) were administered to RF mice. There were also groups treated at about 1 Gy min^{-1} of both radiations. Gamma rays at the low dose rates were invariably and consistently less effective than at the high dose rates. Neutron effects, however, showed less dependence on the dose rate. The RBE evaluated on the basis of the average life-shortening effect (days/unit dose) was about 3 at high dose rates and it increased to about 8 for terminated chronic irradiation. When exposure continued until mortality reached about 50% of the mice, a further increase of the effectiveness to about 14 took place. Without knowledge of the dose rate to RBE relationships it was impossible to foresee whether higher RBEs might be found at even lower dose rates. Similarly, it was impossible to predict any trend at different neutron energies. However, since 5 MeV neutrons (from a Po-Be source) were essentially as effective as the 1 MeV cyclotron-generated neutrons in spite of the much lower dose rate ($3\ 10^{-8}$ to $1\ 10^{-4}$ Gy min^{-1} as opposed to 0.85 Gy min^{-1}) it was felt that neutrons of still higher energy might prove less effective.

199. Clapp et al. [C12] published an experiment in which the effects of acute doses of 300 kVp x rays (0.5 to 4 Gy) were compared with those of 60 MeV protons (0.47 to 3.72 Gy). Irradiation conditions were such that comparable LET values were obtained. The proton mean LET was estimated to be approximately 1.5 keV/μm within the animal's body. As expected on the basis of LET considerations, the protons RBE was 0.63 for life shortening and slightly less than 1 for all parameters, excluding the induction of ovarian tumours. Thymic lymphoma, myeloid leukaemia and ovarian tumours were increased significantly by radiation, while other alterations in the incidence and severity of diseases were minimal by comparison with non-irradiated mice. An RBE of 1.0 or slightly less would thus be applicable for most pathological parameters examined.

200. The experiments of Ainsworth et al. [A7] showed differences in the shape of the dose-response relationships which were linear with gamma rays and convex upwards with fission neutrons. The RBE was therefore dose-dependent. On the basis of more recent data from the same series [T4] the RBE for both single and fractionated exposures varied inversely with the square root of the neutron dose over the range of doses covered by the experiments. It was predicted that, depending on the method of calculation, the RBE at 0.01 Gy of neutrons would be 28–33 in male and 40–44 in female animals, for single exposures. For fractionated treatments the extrapolated RBE values would be 62–91 in males and 41–79 in females. Experiments are presently in progress to test the validity of these predictions. For duration-of-life or long-term fractionation exposures the RBE might be between 60 and 120 at 0.0005 Gy of neutrons per week, varying inversely with the –0.4 power of the neutron dose [T5].

201. The RBE of fission neutrons for life shortening, relative to ^{137}Cs gamma rays varied in the experiments of Ullrich and Storer [U8, S44] according to dose level. In the RFM female mice treated at high dose rates the two-component nature of the gamma-ray relationship produced RBE values increasing for progressively lower doses as the inverse of the square root of the dose in the dose range below 0.5 Gy. Such a trend would be predicted by the dual radiation action theory of Kellerer and Rossi [K10]. At doses above 0.5 Gy the RBE estimate (based on the ratio of the slopes of the linear regressions fitted to the gamma-ray and neutron experimental points) was 2.9. This value was similar to that observed within the same range of doses on the

BALB/c mice (3.0). In the experiments of Hulse [H18] on rabbits the RBE of fission neutrons was assessed at 3.5–4.0 for longevity.

2. Conclusions

202. The RBE experience on life shortening refers essentially to neutron irradiations in the mouse. For acute doses in the region of a few tenths to a few Gy of x and gamma rays (and equivalent doses of neutrons) RBE figures of 2 to 3 have generally been found. The evidence reviewed shows some increase of the RBE upon short fractionation courses and with decreasing dose rate down to hundredths of Gy of neutrons per day to figures of about 5–6. More consistent changes are found for extremely long courses of irradiation where RBE values of between 9 and 15 are quoted.

203. From the Committee's analysis of the mouse data in Figures II and III the RBE values that can be obtained for acute single doses of neutrons by pooling all available experience would differ at different doses. For acute doses of neutrons in the region of 0.01 Gy the RBE cannot be determined precisely from the data reviewed. The predicted values might be about 10, but values as high as 50 might be possible, depending on the assumed shapes of the dose-response curves.

204. The average RBE values applicable to exposures for the duration of life may be obtained from a comparison of the curves as a function of the dose rate shown in Figure IX. At 50% life shortening the neutron dose rate that would give the same effect as the x and gamma rays would be about 10 times smaller than that of the gamma rays. At dose rates corresponding to 0.01 Gy d^{-1} of low-LET radiation (and proportionately lower neutron dose rates) the effectiveness of the neutron treatment would increase to about 40. Alternatively, the RBE as a function of total accumulated dose might be calculated from the curves in Figure X where the RBE values applying to different levels of effect would be, between 10 and 20. It may be concluded that the RBE values derived in the mouse by the independent and comprehensive review of the Committee are in fair agreement with those that may be derived from the analysis of the single experimental series discussed in the preceding paragraphs.

E. SPECIFICITY OF LIFE SHORTENING

205. After the overall quantitative analysis in the preceding paragraphs, it is appropriate to review the problem of the specificity or non-specificity of the effect. Such a discussion presupposes the availability of experimental series with careful pathology of the animals at death or serial sacrifices to investigate the development of the pathology of aging. Experiments reported of this kind are very few and even when pathology is reasonable, any direct comparison with survival is made impossible by the presentation of the data. Therefore, the present section will be essentially qualitative. It will be based on the conclusions of the authors themselves which are often unsatisfactory owing to inadequate pathology (mostly macroscopic) or to insufficient statistical analysis. In other cases the conclusions of the experiments were biased by the models of action assumed in the interpretation of the data. However, in the absence of the original data, no better treatment of the subject matter is possible.

206. It was mentioned in the introduction on methodology that the usefulness and precision of the life-shortening data is often limited by the fact that increased risk from one life-shortening disease may be offset by the decreased risk for another. Unless efforts are made to establish the causes of death, information concerning the relative importance of disease states will not be obtained and the existence of mechanisms of death over and above those attributable to the diseases normally occurring in a given species or strain will not be proven. Identification of disease states at death or by serial sacrifice is in itself a difficult task, but it is preliminary to an appreciation of the relative significance of disease states. The relevant problems, particularly in rodents and in relation to life span studies, have recently been reviewed [H19].

207. It is easily appreciated that the quality of the pathology and its capacity for resolving different diseases will to a great extent condition the share of the non-diagnosed causes of death in a given experiment. In order to achieve good resolution, the pathologist should have experience of the animals used. Without going into details, it is well known that each species and strain of experimental animals dies with a characteristic set of pathological conditions. Data referring to the most common species of laboratory mouse [G19], rat [F10, W6, B26], rabbit [W7], dog [A14] and other animals [B25] may be found in reference publications. The variety of pathological conditions is very wide and their incidence extremely variable in each case. Most of the experience available on life shortening is in the mouse, where the variability of diseases between species is by now well documented. From an intercomparison of results in animal strains having different pathological characteristics an insight may be gained into the more general aspects of the life-shortening action.

208. Although the diagnosis of a given disease (or combination of diseases) in an animal is founded on objective criteria, the assessment of its significance to life shortening is to a large degree subjective, in that it requires an evaluation on the part of the pathologist as to the capacity by a given disease to produce death in that particular case. In principle one can think of a number of chemical and clinical examinations performed before death to aid in the diagnosis, but in small animals such as the mouse these cannot be carried out. Therefore, even under the best conditions of macro- and micro-scopic analysis, 20 to 30% of these animals die without an apparent cause. For them it may be assumed (but, of course, not proven) that death is due to true aging or physiological senescence [H19].

209. Once the pathological analysis has been performed, the actuarial data must be interpreted in the light of its results. In theory, correlation of the time at death with the occurrence of any specific disease makes it possible to assess in a given population the contribution of each nosographic entity to life shortening. Specificity or non-specificity of the life-shortening effect is essentially judged on these criteria. In practice, however, it should be emphasized that the occurrence of multiple disease conditions, particularly in old animals, and the problem of competing causes of death make this exercise difficult. It may not in fact be expected that the precision of the combined pathological and actuarial analyses may be higher than the resolution attaching to any of the two methodologies.

210. It is commonly reported [G4, S19, C12, L9] that correction of the data for animals dying of leukaemia

and of ovarian tumours, which are very common causes of death in the mouse, leads to a reduction of the large variability of the effect between strains and sexes and to a reduction of the life-shortening efficiency of the radiation treatment. This indicates that at least part of the reduction of life after irradiation must be attributed to tumour induction.

211. The first large experimental series where pathology was of such a quality to allow analysis of specific death causes was that of Upton et al. [U5]. The authors could establish no clear-cut relationship between shortening of life and incidence of tumours as the dose relationships for tumour induction had variable forms; some neoplasms increased and some decreased with increasing dose. These data gave impulse to the idea that radiation may cause non-specific aging by advancing all diseases by about the same degree for each given dose. However, a more recent re-evaluation by Walburg [W1], by a statistical method allowing for competing probabilities of death, justified the conclusion that life shortening, which was clearly apparent when all death causes were considered together, disappeared when tumours were excluded from the analysis.

212. Another set of data that was held to support the notion of non-specific life-span shortening was that by Lindop and Rotblat [L2]. The main conclusion of these investigations was that life shortening was due to advancing of all causes of death with respect to time, without change in the relative probability of each cause. It would be of interest to reconsider these data with a more refined statistical test [H2] in order to assess the reliability of the conclusion. This is particularly true as the pathology and the statistics of this experiment have been criticized [W1]. The authors did recognize differences in the relative times of onset of the diseases between control and irradiated animals. One may wonder therefore how these data may have been interpreted, as they were then and later, to support the existence of a non-specific effect of aging.

213. Storer in his 1965 [S20] series noted in the range of between 100 and 500 R of x rays a tendency of the neoplastic diseases to occur earlier in irradiated than in control mice. In the large series of Upton et al. [U7] and Upton, Randolph and Conklin [U9] microscopic pathology was not performed as a rule, but the quality of the macroscopic examination of the animals at death was quite good. The authors felt that the death of irradiated animals was characteristically associated with tumours and degenerative diseases of old age, but that neoplastic conditions could not entirely account for the reduction of life. When some of these data were reassessed by Walburg [W1] with more refined statistics, the life shortening in the irradiated mice was negligible if the tumour deaths were excluded, at least in the dose range of 1 to 3 Gy of gamma rays. This indicates that tumours did contribute substantially to life shortening. Similarly, Darden et al. [D1] and Walburg [W1] ascribed to thymic and myeloid leukaemia most of the mortality increase observed in RF mice irradiated, respectively, with neutrons and with x rays.

214. Grahn, Fry and Lea [G5] ascribed to excess tumour mortality the life shortening observed up to about 4 Gy, while at higher doses the decreased life expectancy was not accompanied by a parallel increase of tumour incidence. Maisin et al. [M10] on BALB/c and C57BL mice attributed life shortening at doses below the $LD_{50/30}$ essentially to thymic lymphoma and, at higher doses, to glomerulosclerosis. Similarly, malignant tumours at the low doses and glomerulosclerosis at high doses were identified by Metalli et al. [M9] as the main causes of premature death in irradiated mice. In the experiments of Lamson, Billings and Meek [L3] and Lamson, Billings, Ewell and Bennett [L5] acceleration of tumour appearance and nephrosclerosis were associated with life shortening in the rat; and the same was true for the dog in the series of Andersen and Rosenblatt [A2], according to the re-analysis of Walburg [W1].

215. Concerning duration-of-life exposure, the paper by Grahn, Fry and Lea [G5] contains a comprehensive discussion of the problem of specificity, based on data from different mouse strains. According to this analysis, the increment in long-term mortality at exposure rates up to a few R per day is associated with an increment of the neoplastic deaths which can entirely account (both as increased incidence and as accelerated appearance) for the relevant reduction of life. At exposure rates above 6 R per day an excess mortality from non-tumorous conditions becomes apparent. It should be added that data up to the present from the Argonne series on the life time irradiation of dogs are in agreement with the above conclusion.

216. Thus, the vast majority of data on rodent and non-rodent mammals, irradiated with sparsely- and densely-ionizing radiation and with acute or chronic doses, when properly analysed, appear to be consistent with the following conclusions. The life-shortening action observed on animals surviving the acute effects of irradiation, that is, after low-to-medium doses up to about the $LD_{50/30}$, may be essentially accounted for by an acceleration or an increased incidence of neoplastic conditions resulting in the premature death of some animals. From doses around the $LD_{50/30}$—but progressively more so at higher doses—other pathological conditions may also advance or accelerate death and among them the vascular changes leading to organ fibrosis, particularly of the kidney, have been described on irradiated animals. At these dose levels deaths from other non-stochastic effects described in Annex J would be expected. The hypothesis of a general deleterious action of radiation formally analogous to aging could, in principle, be entertained and, if so, it could not be disproved. However, if non-specific life shortening is viewed as an advancement in time of diseases normally associated with senescence without apparent changes in the spectrum of these diseases, no data are found to support such a concept. The notion of non-specific aging, based only on actuarial analogies and on superficial resemblances between irradiated and aging animals, cannot be substantiated by accurate pathology. Particularly at the low doses and dose rates of interest in radiation protection there appears to be no need to invoke any general non-specific noxious effect, because all the experience on animals does not require to postulate any other effect than tumour induction or acceleration to explain the reduced life expectancy observed after irradiation.

II. THE EFFECTS OF BIOLOGICAL VARIABLES

217. In this chapter the biological variables affecting the life-shortening response to irradiation are reviewed. The data refer to the genetic constitution of the animal species or strain, a major determinant of the response;

to the effects of age at irradiation, both in the intra- and in the extra-uterine life; and to the differential effect on male and female animals, because special physiological conditions or the expression of peculiar diseases in the two sexes may result in a variable amount of life shortening induced by a given dose. The effect of partial versus whole-body irradiation is considered in Section III.D. with other modifying biological conditions.

A. GENETIC BACKGROUND

218. Among the genetic variables, the inter-species and intra-species differences should be considered separately. In the first case, the object of the analysis is to establish a scale of sensitivity with respect to life shortening between various mammals, analogous to that repeatedly attempted for short-term survival (for an extensive discussion of these problems in relation to the acute radiation syndromes, see [B18]). In this connection the problem of data extrapolation to other species may be discussed. In the case of intra-species comparisons, the problem is that of analysing the character and the amount of life shortening in genetically different strains of the same species, in order to correlate the degree of radiation effect with some vital characteristics of the strain, such as longevity, age-specific rate of death and spectrum of spontaneous diseases. These experiments have been carried out so far in the mouse for the availability of inbred animals in large numbers and the relative ease of obtaining crosses of inbred genotypes.

1. Inter-species differences

219. It is well known that a large variability exists among various animal species in respect to life span and tumour incidence [B25]. The finding of a correlation between these two variables across various species might in principle be of help to put generalizations in the field of radiation-induced life shortening on a firmer basis. However, in view of the disease spectrum peculiar to each species, it can also be argued that generalizations not accounting for specific pathological characteristics would have heuristic significance but little practical value.

220. Attempts at inter-species comparisons in relation to life shortening with the objective of a projection to man, were discussed and proposed repeatedly. An approach based on the actuarial Gompertzian analysis of survival parameters was first put forward as a working hypothesis by Brues and Sacher [B1]. They envisaged that if the linear dependence of the log mortality rate on age (see Figure I) may hold for mammalian species of different life span, a common origin for the curves and a time-scaling factor may be chosen in such a way that actuarial functions belonging to various species may be made identical. Calculations of this kind using empirical constants obtained on mice and dogs indicated that in the absence of any recovery function the exposure of man to a continuously accumulated tolerance dose in use at that time (0.3 R per week) may decrease the human expectation of life by 10%.

221. On the basis of experiments by Henshaw [H1], Boche [B11] identified in the parameter α (the excess death rate per week divided by the exposure level in R per week for chronic irradiation experiments) the quantity that would be invariant for each species and might therefore allow inter-species comparison, because it expressed the susceptibility of that species to chronic radiation action. Based on the value of such a constant, Boche attributed about equal sensitivity to the rat, the dog and the mouse, a higher resistance to the rabbit and a higher susceptibility to the monkey.

222. Lorenz [L7] summarized the effects of long-continued whole-body irradiation of mice, guinea-pigs and rabbits. He accepted essentially the radiosusceptibility scale of Boche [B11] and discussed the problem of extrapolating the findings to man. He concluded that man should be considered to be as sensitive as the most sensitive animal found experimentally and on this basis proposed that an acceptable whole-body exposure might be 0.1 R per 8-hour day. Such an approach was criticized by Mole [M13] who pointed out the relativity of the criterion and the fact that extrapolation from animals to man required sufficient evidence of the similarity between man and other animals, to give confidence to the process of filling the gaps in our knowledge of human effects with experience on other mammals. Mole considered that in the absence of a satisfactory theory, efforts to define a relationship between daily dose and life span for survival times of the order of 95% or higher of the control values were hardly justifiable. On the other hand, it is only in this region of effects that extrapolation is of any interest.

223. In 1955 Sacher [S1] examined the evidence available on seven animal species (rabbit, rat, mouse, monkey, dog, burro, guinea-pig) treated with various acute or chronic doses and deduced for each species a cumulant lethality function (see section I.B.) describing the course of injury according to a given set of reasonable hypotheses. Regarding short-term lethality, the conclusion was that the most and least sensitive species investigated differed by a factor of about 10 in the steady-state or plateau values of their cumulant functions, while intra-species differences were within a factor of 4. However, the evidence available for long-term mortality showed considerably less species variation.

224. Blair [B4] and with him the 1958 UNSCEAR report [U1] by plotting together rat and mouse life-span-shortening data after acute irradiation and showing their good agreement on the basis of units of $LD_{50/30}$, implicitly recognized the existence of some relationship between acute and chronic survival response in these two species and the close similarity of their susceptibility to the long-term lethal action of chronic irradiation.

225. Boche's hypothesis [B11] that a given dose might produce the same proportional life shortening in different species has represented the basis of many attempts to derive life shortening per unit dose in man from laboratory animal data. The values proposed varied from 1 to 5 d R^{-1} [N1]. In Neary's model [N1] if the percentage life shortening per unit dose equivalent is taken to be the same for man as for the mouse, the absolute life shortening for the two species would be calculated at 8 d Sv^{-1} of chronic radiation. Thus, a person accumulating what was at the time a maximum permissible life-time dose of 2 Sv would suffer a life shortening of 16 days, instead of the figures of up to one year calculated on Boche's [B11] assumptions.

226. Spalding et al. [S21] attempted extrapolation of data obtained from mice that had been exposed to acute ^{60}Co gamma doses (1.1 to 12 Gy). They found

that if a mouse-to-man relationship of 1 day to 1 month may be assumed, similar conditions of exposure in man may be expected to cause a reduction of the mean after survival time of 900 to 1000 days per Gy of gamma-ray exposure.

227. Grahn and Sacher [G1] based their extrapolations on the linearity of the log mean after-survival in days as a function of daily radiation in rad or R, for mean after-survival of 25% or more of the control values. This linear trend of the mean after-survival was previously shown to hold for the mouse [S4] (see Figure XV). The coefficient of this regression is a species

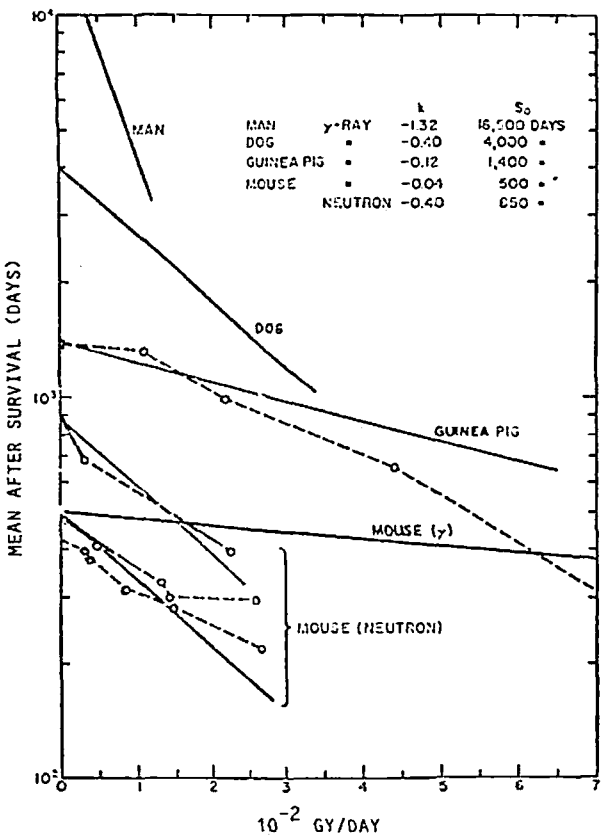


Figure XV. A plot of log mean after-survival as a function of daily exposure according to equation $S_I = S_0 e^{-kD}$ where S_0 is the survival and S_I the survival at dose rate I. The values of k and S_0 are shown for mammalian species. Data from Grahn and Sacher [G1]

constant [G9] and is related to the days of life lost per unit dose or the fraction of life lost per day. It may therefore allow one, when two points referring to a given species are known, to define the slope of the curve applying to that species. The ratios of the coefficients of regression would then be related to the ratios of life expectancies for non-irradiated populations or to the ratios of the age-specific mortality rate slopes. A radiosusceptibility scale may thus be constructed for man, dog, guinea-pig and mouse, on the basis of the slopes being in the ratio of 33:10:3:1 for life expectancies of 16 500, 4000, 1400 and 500 days, respectively. It may therefore be deduced that the relative sensitivity of the various species (expressed in per cent life shortening for unit exposure) was approximately the same for all species and in the ratio of: mouse = 1; guinea-pig = 1.8; dog = 1.25; and man = 1. Similar conclusions were also drawn by Sacher [S23, S14].

228. Grahn [G6] explored the problem of inter-species comparison further, starting from the notion of the exponential decline of mean after-survival with daily dose, which has been mentioned repeatedly (Figure XV). By comparing the vital statistics of two selected populations of male men and mice, he established that the ratio of time scale to equate the two populations is 10 mouse days = 1 man year, or 1 mouse day = 36.5 man days, a factor slightly higher than he previously used (33:1) [G1] and much higher than that used by Failla et al. (20:1) [F4]. In consideration of these other estimates Grahn selected a ratio of 1:30 for his calculations and established that the daily exposure to induce a 50% reduction of life expectancy in man was 0.65 R d^{-1}, compared with a 19.4 R d^{-1} in the mouse. Calculations for man and for other species showed that the guinea-pig was a relatively sensitive species in a framework defined by the mouse, dog and man. It should be pointed out that the life span and radiosensitivity values used for these calculations are very much at variance with those in the 1968 paper by the same authors [G1] and therefore the relative sensitivity scales in the two papers do not correspond.

229. Mole [M2] discussed in general terms the problem of extrapolation between species. He noted that experimental investigations are of value when they lead to quantitative generalizations that must include within themselves some allowance for any species difference. Mole mentioned three possibilities in this respect: the opacification of the lens of the eye, which may be inversely related to the body size or to the size of the eyeball; the susceptibility to the induction of bone tumours, which may be equal in all mammals; and the radiation sensitivity of mammalian oocytes, which may be inversely related to the metabolic activity or to the degree of lampbrush configuration of the chromosomes. Generalizations of such specific biological phenomena, rather than extrapolation of abstract matters such as mortality or life shortening should particularly be pursued. He further expanded these concepts [M3] and pointed out that in principle life-span shortening may be considered to be a meaningful parameter only when the spectrum of diseases in different animal populations receiving various doses is the same. In the absence of this condition, life shortening becomes simply a compounded but imprecise way of expressing differences in the incidence of pathological conditions that might be more adequately expressed otherwise.

230. An inter-species comparison of response in mice [S4, G6] and dogs continuously exposed to ^{60}Co gamma rays was reported by Norris, Tyler and Sacher [N7]. It was found in both species that plotting the log of the radiation-specific death rate (i.e., the difference of the reciprocals of survival times for the exposed and the control animals [S14, S29], see also Figure VIII) against the log of the dose rate gave rise to a dose-response with a slope of 2, indicating that the excess mortality increased with the square of the dose rate (Figure XVI). The phenomenon was seen over the whole range of dose rates in which damage to the haemopoietic tissues is the primary cause of death, that is above 0.2 Gy d^{-1} in the mouse. At lower dose rates in this species the slope was 1, indicating that injury was only a function of the total dose accumulated and independent of the rate at which it was given. Data available in the dog would suggest a similar inflection taking place below 0.035 Gy d^{-1}, but this suggestion will have to be proven by appropriate experimentation. The only point available for dogs below 0.01 Gy d^{-1} [C16] lies quite close to the curve for the mouse having slope of 1, which would be in favour of a roughly similar sensitivity of the two

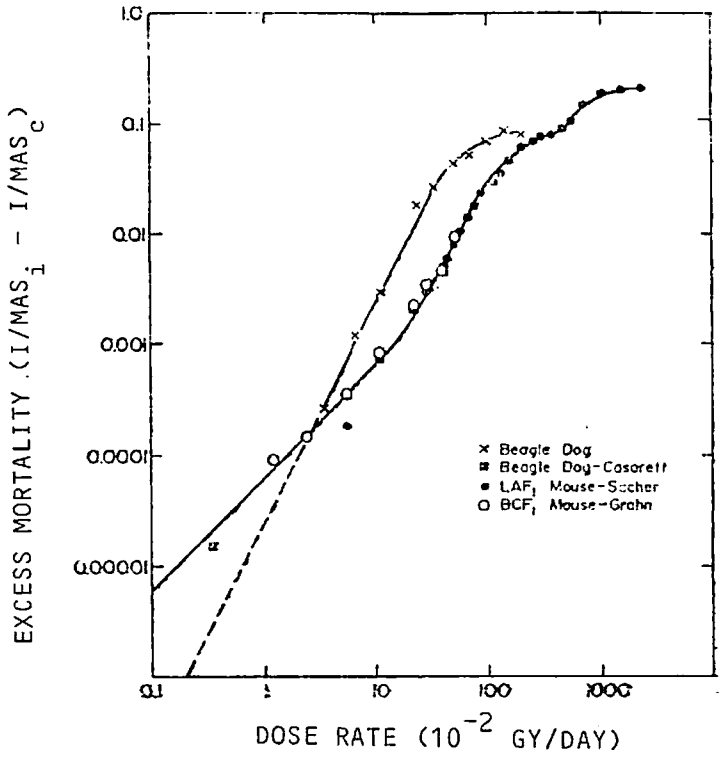


Figure XVI. A comparison of radiation-specific death rate in dogs and mice under duration-of-life exposure, as a function of the daily dose rate. Data from Norris et al. [N7]

species at the level where injury becomes independent of dose rate.

231. Grahn, Sacher, Lea et al. [G16] returned again to the problem of extrapolation from mouse to man on the assumptions [G6] that: the Gompertz slopes for mouse and man are in the inverse ratio of their susceptibility; the previously-mentioned ratio of 30:1 for mouse:man applies; and the ratio of slopes or the slope displacement has an identical relationship to the reduction of life expectancy in both species. They thus calculated that 2.5 Sv (i.e., 0.05 Sv a^{-1} which is the present limit of dose equivalent for workers x 50 years of working life) given chronically over a very long time would produce 15 days of life shortening for an average 100 day-old mouse and about 15 months for the average 20 year-old man.

232. At the same time Sacher, Tyler and Trucco [S50] extended their observations to 15 species of mammals from the orders of Carnivora, Arctiodactyla and Rodentia, exposed for the duration of life to gamma rays. The survival data analysed in terms of the radiation-specific death rate showed that for all species (with the exception of the black rat) the death rate increased as the square of the dose rate up to a break point above which death rate increased linearly with dose rate. A log-log plot of the co-ordinates of the breaking points showed a linear relationship, indicating that the species variation to chronic irradiation is due to a single parameter. A mathematical model based on the induction of cytogenetic damage was compatible with the findings and suggested that species susceptibility to continuous exposure could be related to an accumulation time for damage leading to chromosome breaks. At this level of analysis the actuarial parameters could be linked with the study of molecular lesions as discussed in "Mechanisms of ageing and life shortening" although filling the gap between the two approaches requires clearly much confirmatory work.

2. Intra-species differences

233. It is important to realize that a very large variability exists between different strains of the same species with respect to longevity and the incidence of leukaemia and tumours. Systematic data are available on rodents on differences in the life span and tumour incidence between inbred and hybrid strains. Life span in female mice may differ between strains by nearly a factor of three and in males by more than a factor of two [S56]. In 7 inbred strains the incidence of total tumours ranged from 7.3 to 44% in males and from 25 to 55% in females. Variability with regard to specific tumour types may be even higher, some strains not showing some tumour types at all [S55]. In rats very similar conclusions apply [A12, M30]. This extreme variability points, on the one hand, to the difficulty of generalizing findings in a given strain. On the other hand, the variability makes a given conclusion very significant if it holds in spite of strain differences.

234. The oldest contribution to the problem of strain differences in the response of mice to long-term radiation effects is that of Gowen [G8]. He studied two strains, the S mouse with a medium longevity and the Ba mouse with a long life span. Upon irradiation in the course of a nuclear test the S mice were shown to be considerably more resistant than the Ba ones and this pattern of response was similar to that observed after 98 kVp x-irradiation (exposures of 20 to 960 R). There were no good pathological observations reported, and it was argued that the resistance of the S strain to Salmonella might at least partly account for the differences observed, although the full basis of the radioresistance of these mice was thought to be more complex.

235. Grahn [G10] reported on the chronic lethality of five mouse strains: BALB/c, A/Jax, A/He, C3H1/He and C57BL/6. The survivors of single 200 kVp x-ray acute exposures (400 to about 700 R) were kept for

analysis of late effect. Weighted regression lines of life shortening versus dose showed no significant differences between the strains in either sex, although females were more sensitive per unit dose. There was no correlation between life-span reduction and control life expectancy, although such a relationship could be shown in respect to $LD_{50/30}$. In a second series daily ^{60}Co gamma exposures were tested at 11 exposure levels between 220 R d^{-1} and 6 R d^{-1}, covering the full range from acute to chronic responses. Partial data from crosses of BALB/c x C57BL/6 were also included. Preliminary data showed strain differences at all exposure levels; survival times were quite variable between strains but closely reflected genetic differences in control survival. The greatest life-shortening effect was seen in strains with a high incidence of leukaemia.

236. The conclusion of a more refined analysis of the above data [G4] was that all genotypes exhibited a radiation-induced life-shortening effect dependent on a single common primary injury parameter. For acute exposures the parameter could be expressed by the number of days of life lost per unit exposure, equalling 0.28 days R^{-1}. This parameter could then be combined with others to give equations predicting the life shortening for any combination of normal life expectancy, dose, and incidence of neoplastic conditions. After correction for leukaemia and ovarian tumour induction, life shortening for both sexes following exposure to 570 R was 111 days and exposure to the same $LD_{50/30}$ caused a constant proportion of life lost amounting to 19%. In duration-of-life experiments mean survival time and mean accumulated dose varied directly with control survival and therefore at each exposure rate strains having different control survival lost the same proportion of their life expectancy. With a few exceptions, the mean accumulated dose and the acute $LD_{50/30}$ were shown to be related to each other in that each had a common relationship to the normal life span.

237. Gowen and Stadler [G11] published also a large series of experiments in which ten different mouse strains (four pairs for each genotype) were initially exposed from mating to death to ^{60}Co gamma-irradiation (0.6 to 2.7 R d^{-1}) for 22 hours per day. The design and the analysis of this research, although involving irradiation for the duration of life, was centred more on the capacity of irradiation to stop the reproductive functions of these mice, than to shorten their life span.

238. Other analyses by the Argonne group [S5, G9] contain comparisons of the relative life-shortening effect of ^{60}Co irradiation to death in genetically different mouse strains and indicate the constancy of the slope of the relationship expressing the log mean after-survival against exposure rate. The linearity of this relationship over the exposure rate range between zero and 56 R d^{-1} was established for BCF1, C57BL/6, BALB/c and A/Jax male and female mice [S5], thus confirming previous findings with the LAF1 mouse [S4]. The control survival of the male and female mice of the 4 genotypes cited (8 groups in total) ranged from 466 to 796 days and these differences in life span curves were nearly parallel and were displaced from one another by the same amount of displacement of the control survival times.

239. The problem of the genotype relationship to long-term survival has also been considered by Holland and Mitchell [H10] who irradiated (300 R, 300 kVp x rays) 4 strains of male and female inbred mice (C3Hf/Wg, C57BL/6, RFM/Un, BALB/c), C3CF1 and B6FRMF1 hybrids and a cross between these two hybrids, C3CB6RFM. Females were shown to be, in general, more sensitive than males by a factor of 1.5. Within the same sex, substantial differences in sensitivity were also shown among strains. As these differences correlated well with the weight of the animals, it was suggested that the variation in susceptibility to life shortening may be at least partially accounted for by genetically-determined differences in the maturation rates of the various genotypes. After fission neutron irradiation at both high (0.25 Gy min^{-1}) or low (0.01 Gy d^{-1}) dose rate no appreciable difference in life shortening was found between RFM or BALB/c female mice in the experiments of Ullrich and Storer [U8].

240. Life tables for different strains of inbred and hybrid mouse strains have been reported, with data on life expectancy for parental, F1 F2, F3 and the first three backcross generations [G17]. These data refer to non-irradiated animals, but they could be used in radiation work on the basis of the repeatedly cited invariant life-shortening relationships with dose common to all mouse genotypes (4 days per Gy or 28 days per Gy for life-time and single acute exposure, respectively [G4]). In another paper Storer [S57] reported life table data on 9 inbred and 5 hybrid strains of mouse, non irradiated or exposed to 250 or 450 R of 250 kVp x rays. All these data may be regarded as initial attempts to a genetic analysis of the radiation susceptibility to life shortening in mammals. Such attempts must however be improved considerably in order to clarify the simple relationships of the kind mentioned above and how these may be translated into a variety of disease states in different mouse genotypes.

B. SEX AND BODY WEIGHT

241. Very often in the course of the papers reviewed mention is made of differential effects in the two sexes for various strains of animals. To review all these observations separately is probably unnecessary as in many cases they are incidental and not particularly relevant to the main physical or biological variable discussed in each specific paper. In this section only those papers are reviewed where such effects were particularly well substantiated and discussed. Emphasis is given to contributions where pathological observations were performed, in an effort to ascribe the differential effects to diseases or conditions affecting preferentially one of the sexes.

1. Sex

242. In the experiments of Neary et al. [N3] the mean survival time of the female animals was significantly greater ($P < 0.05$) than that of the males. When only the mean survival times between 30% and 100% mortality were considered in order to exclude early mortality, this sex difference remained evident. Sex differences in BALB/c, A/Jax, A/He, C3Hf/He and C57BL/6 mice were evident when data for female or for male animals of all strains were pooled and fitted by linear regressions as a function of dose. The reduction of mean after-survival for a given dose increment was about twice in female as in male animals [G10]. Ovarian dysfunction resulting in ovarian tumour formation was suggested as the possible cause of this difference. Grahn and Sacher [G3] also showed a

greater sensitivity of the females with respect to chronic life-shortening injury. With x rays of three different energies the reduction of life span averaged in animals surviving the $LD_{50/30}$ about 37% in the female and 29% in the male. Female mice were uniformly more sensitive than males when irradiated with gamma rays or fast neutrons [U5]. This was again attributed to the induction of tumours of the ovary or to hormonal disturbances. However, the RBE for neutrons against gamma rays was not significantly different between the two sexes.

243. After single-dose irradiation of one hybrid and five inbred strains of mice (200 kVp x rays, doses between 0.85 and 1.15 times the $LD_{50/30}$) strain differences within sex were not significant. The two sexes had, however, significantly different responses averaging for the males 0.28 days lost per R and for the females 0.81 days per R (all strains pooled). Differences tended to disappear when corrections were introduced for animals dying of leukaemia and of ovarian tumours. It should in fact be recalled that there are sex differences in the induction of leukaemia among different mouse strains [U14]. Life shortening in all strains after an acute treatment about the $LD_{50/30}$ seemed to be characterized by a single parameter applicable to all strains and sexes and expressed as a constant number, 28 days of life lost per 100 R. Combination of this primary injury term with other secondary parameters may provide equations predicting the final long-term effect for any combination of normal life expectancy, leukaemia incidence, ovarian tumour incidence and dose [G4].

244. In the experiments of Lindop and Rotblat [L1] the shapes of the survival curves were similar for males and females SAS/4 mice but showed small consistent differences in favour of a higher resistance for males. These differences were not such, however, to warrant a separate analysis of the life-shortening effect in the two sexes. Moos [M14] also reported no difference in longevity response with respect to the sex of irradiated animals (mice, CFW strain, 40–50 or 140–150 days of age) in the interval of daily dosage between 2 and 256 R d^{-1} of 400 kVp x rays.

245. In the series by Kohn and Guttman [K6] the animal's sex was shown to be an important factor for life-span shortening in CAF1 mice. During much of the adult life the female animals reacted to doses below 25 Gy, although the slope of the female dose-effect relationship between 2.5 and 4.0 Gy was less than that of the males. Late in life the females became less sensitive than the males. Here again, changes in the endocrine balance were reputed to be at the origin of such phenomena, in the sense that the female's changes in sensitivity may have been a manifestation of the increase and fall of ovarian endocrine function. Such a hypothesis is in accordance with the fact that continuous low-level treatment with oestrogen hormone increased the age-specific mortality rate of the BALB/c female mouse after x-irradiation [K13]. It is of interest that in the CAF1 strain the reduction of life span was not correlated with the induction of ovarian tumours, which were actually depressed and not enhanced at the doses used.

246. Sacher and Grahn [S4] showed that LAF1 female mice after life-time irradiation were slightly more sensitive than males in the 5–10 days period of survival but became consistently more sensitive in the 17–40 day period. In the mice surviving during the periods of 10–15 and of 40–130 days the difference between sexes was either much smaller or non-existent; at survival times in excess of 130 days females accumulated consistently higher doses than males. In the large experiments of Upton et al. [U7] on RF/Un mice no obvious effect of sex can be traced from the data. Protraction factors in male animals irradiated with gamma rays at low dose rates appeared to be in the same direction as in female animals but considerably more pronounced. Consequently, RBE data were different in the two sexes.

247. Sex differences in the A/J strain in regard to radiation-induced life shortening (x rays, single exposures, 150 to 600 R) were also seen by Storer [S30]. At exposures of 600 R the female animals lost nearly four times as many days of life as did the male mice. Qualitatively similar results in male and female mice were observed in the experiments of Ainsworth et al. [A7] and the apparent quantitative differences in response after single and fractionated gamma-ray and fast-neutron experiments could not be attributed with certainty to differences in body size (and therefore absorbed doses), to hormonal unbalance resulting from damage to the ovaries or to differences in the spontaneous or induced tumour incidence.

248. Holland and Mitchell [H10] studied life shortening (300 R of 300 kVp x rays) on four inbred male and female mouse strains (C3H, BALB/c, RFM, C57BL/6), on two hybrid strains (C3CF1 and B6RFMF1) and a four-way cross between both F_1 hybrids, C3CB6RFM. At the time of irradiation the mice were 5–6 weeks of age. In all strains and crosses a significant life-shortening effect was observed. Females were about 1.5 times more sensitive than males of the same strain and these data suggested a general and constant effect of sex under all conditions. Unfortunately, the data on the various modes of death are not yet available for a more complete interpretation of these observations. A higher sensitivity of RFM female mice accounted for by a rapid rise of life shortening over the dose range up to 0.5 Gy was also reported by Storer et al. [S44].

249. In experiments by Moskalev et al. [M22] performed on rats treated with fast neutrons (0.085 to 5.1 Gy) or 500 MeV protons (0.28 to 10 Gy) observations on life shortening were also reported. The average life expectancy of rats irradiated with the fast neutron beam did not depend on the animal's sex. The data by Rust et al. [R2] on the guinea-pig showed that the females were more responsive to life shortening by chronic gamma-ray exposure. This differential effect could not be correlated with the induction of tumours of the female generative organs.

2. Body weight

250. Body weight as a variable affecting long-term animal survival was investigated in mice by Holland et al. [H10]. Within the same sex, there were substantial differences in sensitivity among the strains tested and these differences were highly correlated with body weight at 6 weeks of age. The heavier animals were less resistant to radiation, i.e., showing a higher degree of life shortening. Previous analysis of body weight versus radiation resistance based on early effects and on mature animals had given opposite results [Q1, G12, R5] in that, within the same strain, adult animals with a higher body weight were shown to be more resistant.

However, in adult animals body weight is thought to reflect the general state of health and fitness and it is conceivable that the heavier (i.e., the healthier) animals, may be more resistant to a given radiation insult. If the comparison is among different strains and on maturing animals, given a more or less uniform state of health, the data of Holland et al. [H10] would be compatible with the hypothesis that body weight may be a measure of the rate of maturation and it is not inconceivable under these conditions that body weight is a parameter better correlated with radiation resistance than chronological age. It may also be further suggested, as the authors do, that some of the strain-specific differences in radiation sensitivity already discussed in subsection II.A.1 may be due to differences in the rate of maturation of the various strains or to other non-specified processes which are in turn highly correlated with maturation rate.

C. AGE AT IRRADIATION

1. Irradiation in utero

251. The available data on life shortening induced by in utero irradiation are examined first. According to Nash and Gowen [N9] who evaluated in multifactorial experiments the life spans of 647 mice irradiated in utero with exposures of 20 to 320 R at four different gestational ages, the reduction in longevity induced by the radiation treatment depends on the genetic constitution and sex, as well as on the dose and on the gestational age at irradiation. Rugh, Duhamel et al. [R6] followed the long-term survival of mice irradiated with mid-lethal in utero doses at 0 to 5 days post-conception (p.c.) and found no modification of the life span in animals that survived later than 30 days post-partum. This observation indicates that after the neonatal period there is little permanent damage of the in utero irradiation.

252. Non-inbred male and female RF mice were exposed to x irradiation in utero at ages ranging from 9.5 days p.c. to 1 year of extra-uterine age. Shortening of life span by doses of 50–400 R was more effective per unit dose at the higher exposure levels of 300–400 R and in age groups of 40–70 days. For exposure in utero life shortening was consistently less marked than for exposure after birth, but irradiation with high doses in utero (300 R at 14.5 days p.c.) gave rise to growth and developmental effects in a very high percentage of the animals (particularly males) which caused death in 6 to 7 months for causes which were not clear [U12].

253. Friedberg et al. [F8] tested the effect of fast neutrons (0.15 Gy) on mouse embryos in the pronuclear-zygote stage for their ability to shorten the life span or to induce tumours in animals surviving at least 30 days after birth. No differences were found between irradiated and control animals of the same sex for the following end-points: mean ages at death, cumulative mortality distributions and incidences of the principal neoplastic diseases. Sasaki et al. [S49] observed a significant shortening of life in mice irradiated at 16–18 days p.c. with 200 R of x rays. Mean life span was reduced by about 13% to 16%. Slight changes of the tumour spectrum were observed, with no excess of lympho-reticular tissue tumours. Female mice had a higher incidence of lung and pituitary tumours, while a prevalence of lung and liver tumours was found in males.

254. For the rat there are data by Reincke et al. [R7]. In her experiments Wistar animals were administered a single whole-body x-ray exposure of 270 R at 5 days before birth and at 13, 49 and 121 days after birth. Among other observations, life expectancy was reduced by about 3 to 6 months and this reduction was not influenced apparently by the age at exposure. In a subsequent paper Reincke et al. [R8] reported that 220 R five days before birth resulted in a long-term survival not significantly different from controls.

255. Sikov, Resta and Lofstrom [S31] studied the long-term mortality of rats surviving at the time of weaning, exposures of 20 or 100 R at 10 days p.c. and of 50 or 185 R at 15 days p.c. Life-span reduction appeared to be greater in females than in males where the effects observed were of doubtful significance. An interesting observation was that the $LD_{50/30}$ of an irradiation performed at 100 days of age decreased as a linear function of the dose of a previous irradiation carried out in the pre-natal period at all developmental ages. In the opinion of the authors such a linear dependence may imply a general decrement of fitness as a result of pre-natal exposure.

2. Irradiation during extra-uterine life

256. Experiments where the effect of the extra-uterine age has been examined as a biological variable affecting radiation-induced life span shortening are fairly numerous and cover a variety of different species, strains and conditions of irradiation. Kallman and Kohn [K7], Kohn, Kallman and Berdijs [K1] and Kohn and Guttman [K6, K14] studied the life-shortening response to x rays of male and female CAF1 mice, with special regard to the influence of age at irradiation. Exposure conditions were: 250 kVp x rays at a dose rate of about 0.4 Gy min^{-1} with two single doses of 2.6 or 5.2 Gy and a fractionated dose of (2.6 x 2) Gy given 8 days apart. Mice were irradiated when young (144 and 164 days of age) or old (385, 550 and 730 days) and followed with detailed pathology at death. The age interval covered in the mouse would correspond in man to a range of ages between 18 and 65 years. The last publication of Kohn and Guttman [K6] gives an account of the whole set of data, including a re-analysis of other previous data obtained on BALB/c mice irradiated at 5 months, 1.2 or 1.4 years of age. In general, some reduction of the life span was observed, although in some cases evidence of life shortening was small or even absent.

257. Old adult mice tended to show less life shortening than young ones, although the difference was not the same in all strains used owing to genetic differences. During much of the adult life the female animals were more sensitive to doses below 2.5 Gy. Later in life, however, the females, at least in the CAF1 strain, became less sensitive than the males. The life shortening in older animals was not associated (as in younger ones) with an increased induction of neoplasia, but rather with a decrease. In the CAF1 mice irradiation tended to reduce the number of animals dying with tumours and the tumour-bearing animals lived as long or longer than the non-tumorous ones. Aging (both premature or accelerated) as such was an inadequate explanation for these data because the irradiated animals appeared to age abnormally and usually died sooner than controls, the effect depending on age at exposure, sex and dose [K6].

258. Boone et al. [B19, B20] on CF1 female mice at ages from 1 day to 18 months reported changes in life shortening as a function of age at exposure. More precisely, after 4 Gy of x rays life shortening amounted to 40% of corols when in the age interval from 1 day to 3 months; it was then gradually decreased to 32, 14 and 7% of controls at 6, 12 and 18 months of age, respectively. Thus the life-shortening response decreased as a function of age. This effect could not be traced to the incidence of leukaemia or of ovarian tumours which were evaluated separately in these experiments. In other strains the situation may, however, be different. In the C57BL mouse, for example, age is a condition which alters the sensitivity to lymphoma induction. Kaplan [K15] showed in fact on animals at 2 weeks and at 1, 2, 3 and 4 months of age that lymphoma incidence is higher and the appearance time earlier for irradiation at the young ages than at the older ones.

259. Upton et al. [U5] considered in detail the variable "age at exposure" in relation to the life-shortening effects in both sexes on 9–12 week old mice. No differences were found of any significance for either sex and this observation was at variance with what was seen in the same animals with regard to early mortality, which was highest among young animals. Moos [M14] was also unable to find differences between the longevity of young (40–50 d) or old (140–150 d) mice within the range of doses of 8 to 128 R d^{-1}. However, such differences were seen at exposure rates of 2, 4 and 256 R d^{-1}, and the old mice were less resistant under these conditions.

260. In a series conducted on about four thousand RF/J female mice Storer [S19] examined the age-dependent changes in radiation sensitivity in normal and previously-irradiated animals. He obtained life-table data on all these mice, about one-half of which received at the age of 90 days 400 R of 250 kVp x rays. The rate of mortality from all causes in the irradiated mice showed marked departures from the Gompertz equation and this dose of radiation shortened the median life span to 63% of the control animals. Mortality rates for all causes other than leukaemia gave reasonably good Gompertz fits to the control and irradiated populations: life shortening amounted to 24 days per 100 R under the assumption of linearity between dose and effect. No latent period was found between exposure and the time when the mortality increase became detectable. The mortality rate of irradiated mice was at all times higher than in control animals. The $LD_{50/30}$ of the control and irradiated mice tested between 120 and 560 days of age declined linearly with age without effect attributable to the previous 400 R exposure. The mean after-survival following exposure to 100 R d^{-1} also declined with age in a complex manner, irradiated animals being generally more sensitive than controls. Finally, recovery rate tested by split exposures was found to decline sharply with age: the rates estimated in previously-irradiated animals were much lower than those in non-irradiated animals of the same age. From all these data Storer [S19] concluded that the tests applied were in fact measuring the damage inflicted to different cellular systems each of which aged at a different rate, in contrast with the notion of a non-specific life-shorteninig action.

261. Lindop and Rotblat [L12] made a systematic study of the effects of age, giving small single sublethal exposures of 15 MeV x rays to SAS/4 mice. They found that radiation given at 4 weeks of age produced an effect that was linear with dose in the range of 50–780 R. The life shortening produced by 100 R was about 4 weeks for mice irradiated at the age of 1 week; it increased to about 6 weeks for 5 week-old animals and then decreased steadily to a minimum of approximately 2 weeks for animals irradiated when 70–90 weeks old. A given reduction in life time in old animals represents a much greater loss of the remaining life than the same reduction produced at a young age. When the effect was expressed as a percentage of the remaining life span the increase in response at 5 weeks of age was still evident, followed by oscillations of the response between a maximum of 6% and a minimum of 3% reduction of the remaining life span.

262. In a subsequent paper [L16] life shortening was studied as a function both of the age and of the oxygenation conditions of the animals. For animals breathing air, assuming linearity of response at all ages, the life-shortening effect at 1 day and at 1, 4, 8 and 30 weeks of age was found to decrease as a function of age from 7.6 to 2.7 weeks per 100 R. Under hypoxic conditions a considerable reduction of the life-shortening effect was found at all exposures, amounting to a factor of three for mice irradiated at 8 and 30 weeks of age. However, when the mice were irradiated at 1 day or at 1 week of age hypoxia changed the linearity of the dose-response relationship to a convex upward curve, such that the protection afforded by hypoxia at low doses was large but at high doses small. The authors could not suggest a firm interpretation for such findings.

263. Johnson [J2] set up a simulated experiment where he computed the life shortening as a function of age at irradiation utilizing parameters and life-functions taken from Sacher's [S2] analysis of the LAF1 male mice exposed to fission neutrons and gamma rays in the Greenhouse experiments [U5, F2]. Irradiation was simulated by a displacement of the Gompertz function on the time axis. Johnson was thus able to show that a decrease in the life-shortening effect with increasing age was a necessary consequence of the hypothesis that ionizing radiation accelerates certain of the processes that characterize natural aging. The relationship of life shortening to age at irradiation varies however according to the actual form of the Gompertz function.

264. Age-dependent changes in the response to radiation (250 kVp x rays) were also observed in other experiments by Cosgrove et al. [C20] where LAF1 mice were given from 300 to 1200 R whole-body or partial-body when 10 weeks or 1 year old. At any given exposure level, a higher incidence of glomerulosclerosis was observed in animals irradiated at the younger age, presumably because the older animals did not survive long enough to develop as high an incidence of the diseases. Longevity was also reduced and the incidence of ovarian tumours increased in the young but not in the old irradiated animals.

265. Some data by Storer [S20] in mice are of interest to the problem under discussion. BDF1 females, when three months old, were exposed at doses of 0, 100, 300, 500 R of 250 kVp x rays. Median survival time was found to be reduced linearly with exposure and the slope of the linear non-threshold regression function amounted to a life-span reduction of 45 days/100 R. The changes in radiation response with advancing age and for various radiation exposures were evaluated in two ways: beginning at various ages, samples of previously-irradiated surviving animals were tested for their ability to survive successive daily exposure of 100 R; or, alternatively, they were tested for their LD_{50}.

266. Thirty-four samples of previously exposed animals were tested at ages ranging from 120 to 960 days with 100 R d^{-1} and resistance was assessed as mean survival time after initiation of this treatment. Resistance was found to follow a long plateau (the duration of which was dose-dependent) and to decline sharply at advanced ages. Pre-irradiated animals were less resistant than non-irradiated control mice of the same age and showed an earlier onset in the decline of resistance. Since the variability in radiation resistance increased with age and the differences in sensitivity between irradiated groups were reduced when the relevant comparisons were conducted at equal levels of mortality, Storer [S20] concluded that the test treatment was not actually measuring a phenomenon intrinsic to the aging process but was more simply an estimate of the incidence of diseases in the population examined. Similarly, the $LD_{50/30}$ test showed that resistance followed the same dependence on age as after the protracted exposure test. The conclusion was that the earlier onset in the decline of resistance of the more heavily exposed animals was in fact correlated with the earlier onset of morbidity in these groups.

267. In addition to presenting data on CBA female mice given acute doses of radiation (4.5 Gy of 250 kVp x rays at four ages from 100 to 670 days), Mole [M2] pointed out some difficulties in the analysis of such data. If the mean after-survival time is taken as the criterion of effect, then it is clear that the radiosensitivity of the animals decreases with age. But if it is assumed that the radiation-induced mortality depends on the mortality of the non-irradiated animals and the Abbott's correction is used to derive the net radiation-induced life shortening, then the curves of cumulative mortality show little difference with age. Mole also refers to similar unpublished data obtained with protracted exposures to gamma rays and fission neutrons. Such observations may imply that the life-shortening process proceeds independently of natural aging and thus the two phenomena are not correlated. However, in the absence of further information about natural aging itself, it should simply be realized that opposing conclusions may be reached by different analyses of the same experimental data.

268. In experiments by Yuhas [Y3] the sensitivity was studied of 4 to 24 months old C57BL/6J female mice to the life-shortening effects of 1400 R of 300 kVp x rays. Radiation was given in 10 equal fractions within 12 days. In the 4 months old animals the resulting life shortening amounted to 148 days but in older animals the same dose was considerably less efficient: in fact, life shortening amounted to only 30 days at 9 months and at the three oldest ages (15, 18 and 24 months) there was actually a lengthening of life of the order of 53 to 65 days.

269. The decreasing response with increasing age confirmed previously-reported data by Lindop and Rotblat [L12], Kohn and Guttman [K6], Jones and Kimeldorf [J3]. The data also confirmed the life lengthening in mice irradiated at very old ages. The compatibility of these findings was tested in relation to five different hypotheses. The data could not be accounted for in terms of insufficient time for expression of injury; or of the identity of normal and radiation-induced senescence; or of selective changes in the population of mice induced by early mortality; or by normal "attrition". They were instead consistent with the hypotheses that the sensitivity to the induction of certain diseases decreases with advancing age, irrespective of the time required for their expression; or, alternatively, that radiation given in old age may have a therapeutic effect on some neoplastic growths in these animals.

270. Ainsworth et al. [A7] examined the problem of age-sensitivity in B6CF1 male mice after single doses of 0.8 Gy of fast neutrons or 2.69 Gy of gamma rays. The mice were 115, 194 or 278 days old at the time of exposure. Irrespective of whether life shortening was expressed as a per cent reduction of the after-expectation of life or as per cent life shortening, there was some decrease with age of the effect per unit dose and this was shown to be greater after gamma than after neutron irradiation. The contribution of this change in sensitivity to the "sparing" effect of fractionation during a long course of treatment is thus proportionately greater with low- than with high-LET radiation. Life shortening and carcinogenesis by x rays in mice irradiated neonatally was also studied recently by Sasaki and Kasuga [S61] who attributed the reduction in mean life span to the high induction rate of liver and pituitary tumours and of thymic lymphoma.

271. The data available for the rat are similar to those just discussed for the mouse and show a dependence of life shortening on the age of irradiated animals. Jones and Kimeldorf [J3] treated male Sprague-Dawley rats with about 2.2 Gy of fast neutrons obtained by the Be (p,n) B reaction. They belonged to 5 different age groups of 1, 3, 10, 15 and 21 months. Survival rate and life expectancy were decreased and the age-specific death rate was increased by comparison with sham-irradiated litter-mate controls. The magnitude of these effects was inversely related to age at exposure from post-infancy up to middle age (10 months). At older ages there was no discernible change in life span with respect to control rats. In the opinion of the authors these data may be compatible with Neary's theory [N1] postulating an induction period in life which may be shortened by various treatments and an ensuing period of development, which would be relatively constant in duration. In the male Sprague-Dawley rat the period of development would begin in the age range of 10 to 15 months.

272. In a subsequent paper [J4] the relevant data for tumour induction were reported. There was an excess proportion of animals with one or more palpable tumours (compared to the control groups) after exposure at all except the oldest age (21 months), in spite of a significant life shortening only after exposure at the three younger ages. The percentage of animals with palpable tumours was higher in all groups (even for the group exposed at 21 months) in comparison with the control tumour-bearing animals. It should be recalled that this strain of rats has normally a very high incidence of radiation-induced tumours, particularly of the skin and skin adnexa, which may have altered to an unknown extent any more precise estimates of life shortening.

D. CONCLUSIONS

273. From all the data reviewed it may be concluded that among the biological variables determining the life-shortening response to irradiation there is sufficient data for discussions on the genetic constitution and on the influence of sex and of age at irradiation.

274. It is easy to understand that different species may show a different response in relation to the longevity of

each species and to its specific physiologic and pathologic characteristics. It is less easy to trace a common parameter or a set of parameters from which one can evaluate the sensitivity of a species and thus construct a susceptibility scale for inter-species comparisons or extrapolations. The analysis of survival parameters according to the actuarial model of Gompertz; the calculation of semi-empirical parameters such as the excess death-rate divided by the exposure rate in chronic irradiation experiments; the evaluation of the life-shortening effect normalized as a percentage of the control value and as a function of the acute $LD_{50/30}$; the hypothesis of a common life-shortening effect per unit dose normalized according to the respective life span of the species compared; were all criteria proposed in order to achieve the scopes mentioned above. On the basis of one of these parameters approximate scales of radiosensitivity were in fact proposed, of which the majority were obtained from gamma-ray chronic irradiation data (see Table 3). Most of these data agree in showing that the rat, the dog and the mouse are about equally sensitive, while (on the basis of very scanty data) the rabbit would appear to be less susceptible and the monkey, the goat and the guinea-pig perhaps more sensitive in terms of life lost per unit dose. Susceptibility for man is reported in one case to be higher (perhaps by a factor of two) and in another case to be similar to that of the dog and the mouse. It does not appear from the data that the differences between the various mammalian species tested is very large and the range within which all species may be included may possibly be a factor of two in both directions (taking the mouse and the dog to be in the middle of an ideal radiosusceptibility scale) or about a factor of five over the whole range of radiosensitivity of the species tested.

275. Intra-species or inter-strain variability has also been studied in the mouse, the species where different genetically-homogeneous strains are more easily available. When adequately looked for, differences between various strains (for the same sex) were easily observed. Little formal genetic analysis of the radiosensitivity parameters has been attempted and most of the data refer to irradiation for the duration of life. In general the amount of life shortening is correlated with the control mean survival time, in the sense that the proportion of life lost per unit dose is similar for the various strains having different life spans. Life shortening is also correlated with the expression of the pathological characteristics of the strains, since animals prone to the development of leukaemia and of ovarian tumours (the cases which have been more thoroughly analysed) show a greater amount of life shortening per unit dose. It is possible that the differences in response of the various strains may also reflect the maturation rate of the genotypes irradiated, as some data on the correlation of the response with the weight of maturing animals would suggest. When allowance is made for all these variables the mouse appears to respond according to a basic parameter, whereby the number of days lost per unit exposure for acute single doses equals 0.28 d R^{-1}. On this basic dose-response relationship all the factors mentioned above (in addition to other factors for sex and age) combine to give the final compounded value of effect for each particular situation.

276. In a few cases of the data reported, either no difference or small differences in sensitivity to life shortening were reported between male and female animals. In most other cases however invariably a higher sensitivity of the female animals was observed. The sensitivity factors reported were between 1.5 and 4. Ovarian dysfunction induced by irradiation and the incidence of ovarian tumours were generally reported to cause this differential effect, which tended to disappear when the data were appropriately corrected for the incidence of tumours of the genital tract or of leukaemia. The conclusion to be drawn from the vast majority of the data is that, within strain, sex has a constant effect which is mostly manifested by an increased incidence of tumours of the female genital tract.

277. The data for the rat show no obvious difference in results for either sex, while the results for the guinea-pig, in analogy with most data for the mouse, show an increased sensitivity of the females attributable to tumours of the genital tract. Body weight may also be a biological variable of interest in the final expression of life shortening, but it appears to be of rather minor importance.

278. With regard to the effect of age, after allowance for other conditions influencing reduction in longevity (genetic background and sex) most data show that irradiation in utero of the mouse produces less marked life shortening than irradiation during post-gestational ages. There may even be no long-term effect at all on the irradiated animals, particularly those surviving irradiation at the early gestational ages. The experience in the rat shows some reduction of the life span for irradiation of the foetal animals, but the effects observed are of doubtful significance and in any case not substantially different from the effects of the same doses given soon after birth.

279. With regard to the effect of extra-uterine age, the data are rather numerous but only pertain to the mouse and the rat. In both these species irradiation late in life invariably produces—all other factors being equal—less life shortening than treatment at younger ages. In the one case where no effect of age was found [U5] the range of useful ages examined was too short for any effect to be seen. In some instances the reduction of life shortening with age is preceded by a phase of increased susceptibility of the animals up to the time of sexual maturity [L12]. In other cases irradiation in old ages may even produce (for moderately high doses) an increase, rather than a decrease, of the duration of life [Y3] or no change with respect to control [J3]. The change in sensitivity between young and old animals may be up to a factor of three when the life shortening per unit dose is considered; if the effect is evaluated in terms of the percentage loss of the remaining life span, this amounts to a few per cent. In some experiments a correlation may be established between the degree of life shortening and the induction of tumours or of nephrosclerosis, but in other cases no such correlation may be found.

280. If life shortening is primarily or exclusively due to the induction of excess tumours, each of which has a distribution of times of expression, the age-dependence of life shortening may be due to the influence of latency on the life tables of the irradiated population. Thus, because of competing risks, some lives will be over before the induced cancers are expressed, an effect which obviously increases with the age at exposure. No specific test of this possibility has been reported in the literature. It may, however, account for all age-dependence. If it should only account for part of it, then the remainder may be attributed to a decreased susceptibility of certain pathological conditions. Another possi-

bility is that radiation in old age may have a therapeutic effect on some (presumably neoplastic) conditions already under development at irradiation. Caution should be used in the analysis of data from experiments in which animals were started on irradiation courses at variable initial ages as different analytical approaches to the data, in addition to implying different hypotheses of action, may lead to variable conclusions as to effect of age on the animals' radiosensitivity.

III. MODIFYING FACTORS

A. PHYSICAL TREATMENTS

281. Among the treatments that modify the life-shortening response to irradiation those of a physical, chemical or pharmacological, and biological nature are reviewed in this chapter. It should be realized that information on these subjects is very heterogeneous and not suitable for generalized conclusions. A review on life shortening, including also some original data, centred on various chemical and biological modifying factors, has been recently published [A16]. Among the physical treatments, those referring to irradiation given in combination with low- or high-temperature treatments have already been reviewed in subsection I.B.6.

282. In experiments by Gambino et al. [G13] Long-Evans female rats were irradiated over the whole body or only on the adrenals with 500 R and then exposed for three hours daily to 0°C. Reduced longevity was among the effects (retarded growth, cataract, fur greying, tumours) seen at long term in the whole-body-irradiated (but not in the adrenal-irradiated) rats. It amounted to about 20% of the normal control life span and it was not modified by the cold treatment. Other effects were also not modified, except perhaps for a slight reduction of the accelerated tumour onset seen in whole-body irradiated animals. Interpretation of these data is made difficult by the fact that the cold treatment as such has produced life-span reduction and changed the spectrum of diseases with a prevalence of inflammatory pulmonary conditions and a relative decrease of neoplasia [H11].

283. Some information is also available in regard to the modifying effects of a specific stress on long-term mortality of irradiated animals. Ordy et al. [U1] irradiated C57BL/10 mice on the brain with 5 Gy of 20 MeV deuteron beam with a highly significant decrease in longevity of the irradiated animals. They also observed a reduction of the late mortality in the animals undergoing periods of daily stress (cold, electrical shock, or both). Such an effect appeared to be statistically significant in some, although not all, groups of animals and was observed irrespective of whether they had been irradiated or not.

284. Reincke et al. [R9] submitted Wistar rats at 120 days of age to starvation for 9 days, water deprivation for 6 days or forced swimming. Animals that had passed through such severe stress before irradiation (280 R of x rays, single dose), lived longer than those receiving irradiation only. The differences in the survival curves were significantly different in three out of six possible comparisons. No influence of stress was observed on the tumour incidence. There was also no obvious difference in the swimming ability and in the decline of this ability with age between normal mice and mice irradiated with a single acute dose of 2.24 Gy of x rays at 20 weeks of age [N12].

B. PHYSICO-CHEMICAL AND PHARMACOLOGICAL TREATMENT

1. Anaesthesia, oxygen and hypothermia

285. The effects of hypoxia induced by various treatments will first be examined. Lindop and Rotblat [L12] showed some protective action of anaesthesia against early and late death. Protection appeared to decrease with dose rate in the interval 4.8–1620 Gy min^{-1}. Protection could not be ascribed to low oxygen tension in tissues by the anaesthesic drug, because there was no summation of effects by the anaesthesia and dose rate, particularly at the high dose rates. In other series of experiments Lindop and Rotblat [L12, L16] showed that when SAS/4 mice, anaesthetized with 20–60 mg/kg of Nembutal and breathing nitrogen 30–50 second, were exposed to a beam of fast electrons (15 MeV, 400 Gy min^{-1}) they had a considerably reduced life shortening, in comparison to other animals exposed in air. The protective effect of hypoxia was influenced by the age at exposure in that a dose-reduction factor of about 3 due to the nitrogen breathing was observed in animals of 8 and 30 weeks of age. In mice of 1 day or 1 week of age the shape of the dose-life shortening relationship was changed from linear to curvilinear, giving rise to a larger protection factor at low doses and a very small one at high doses.

286. Hypoxic hypothermia was also tested by Hornsey [H12] with respect to the possible modification induced by this treatment on life span. While hypothermia induced at the time of irradiation offered considerable protection (a factor of about 2.8) to the haemopoietic system whose failure is responsible for the early death of the animals, it did not protect to the same extent against long-term death. For the same dose administered to normal and to chilled animals the expectation of life was greater for the latter, but the nature of the data did not allow any precise estimate of the protection factor afforded by hypoxic hypothermia. Thus it appears that the protection by hypoxia already shown against the acute radiation effects extends also to the long-term effects, although perhaps not to the same degree.

2. Chemical radioprotective drugs

287. On the subject of chemical radioprotection Maisin et al. [M32] reported that mercaptoethylamine [MEA] (10 mg/rat, given 5 minutes prior to irradiation) was active in reducing the mortality rate during the first month post-irradiation but was incapable of modifying the late rate of mortality following irradiation of the head (1000–2000 R) or of the abdomen (900–1500 R). This drug was also without effect on the late mortality following irradiation of the abdomen and of the whole body with 600 R. In another series of experiments, MEA (425 mg kg^{-1} d^{-1}) and 2-aminoethylthiosulfuric acid (1000 mg kg^{-1} d^{-1}) were administered in the drinking water to Swiss mice that were exposed for the duration of life to ^{60}Co gamma rays at dose rates from 1 to 5 R h^{-1}. Mortality data were indistinguishable from those of controls drinking tap water and it was therefore concluded that neither of the drugs (which are active in the prevention of early mortality) had a protective action against chronic irradiation effects at drug levels accepted by the mice [A8].

288. Cosgrove et al. [C23] tested the effect of the radioprotective drugs aminoethylthiouronium (AET)

on (101 × C3H)F1 female mice following a wide range of x-ray exposures (300–1800 R) with or without parallel treatment with isologous bone marrow drug treatment was found to have a marked protective effect against early lethality, but its effectiveness in protecting against a reduction in longevity was equivocal. No effect was found on tumour induction, nephrosclerosis and lens opacities while induction of thymic lymphomas and greying of the fur were reduced by the drug treatment. Thus AET protected against some but not all long-term somatic effects and in no case the dose reduction factor approached that obtained against the acute lethal effects of radiation (40–50%). In another experimental series performed on male and female LAF1 mice by the same workers [C20] administration of AET before irradiation led to some reduction of kidney sclerosis but was again without effect in regard to the induction of tumours of the ovary or to the greying of the fur.

289. An attempt to maximize protection against 9 MeV irradiation was reported by Shewell and Wright [S33] who combined four different methods of protection: administration of cysteamine before irradiation, irradiation during nitrogen hypoxia, and administration of syngenic bone marrow and of antibiotics after irradiation. The $LD_{50/30}$ for the protected mice (C3H/Bi, 15 weeks old) was increased by a factor of 3.8 with respect to unprotected animals and this factor persisted throughout the long-term follow-up of the mice surviving early lethality. Greying of the hair and epilation also gave a dose-reduction factor of 3.8, but the appearance of radiation cataracts did not conform to the same pattern. It was therefore concluded that the protection afforded against the different effects had variable dose-reduction factors for each effect tested.

290. In Nelson's [N10] experiments irradiation followed various fractionation schedules: 80 R at intervals of 1 day up to total accumulated exposures of 640–1920 R; 80 R at intervals of 3 days for the whole life span; 160 R at intervals of 1, 3 and 7 days up to exposures of 480–1760, 1600–3250 and 2880–5760 R, respectively. Cysteamine at 4 mg per day for 24 days or at 4 mg per day twice a week was used as a chemical protector. The drug treatments by themselves, as well as the injection of physiological saline twice a week for the whole life, modified drastically the mean and median survival time of the irradiated animals. However, cysteamine unequivocally protected against mortality. The magnitude of the protective action depended on the accumulated exposure and on the time interval between fractions. At low accumulated exposures radiation injury was insufficient to show significant differences between protected and control animals, while for high exposures radiation injury was supralethal. The effect of fractionation intervals was often variable. No single dose-reduction factor could be derived from these experiments since the values of this factor vary in each series with exposure, fraction size and fractionation interval. However, cysteamine was shown to protect not only against the acute injuries but also against fractionated doses in the sublethal range. Any more precise assessment would be unwarranted owing to the toxicity of the drug and to the adverse effect of the administration procedure which influenced the survival of the animals rather substantially.

291. Yuhas [Y1] reported that the radioprotective agent WR-2721 [S – 2-(3-amino propylamino) ethyl-phosphorothioic acid] protects against acute death more efficiently than it can protect against the life-shortening effects of radiation, although the exact extent of this protection could not be directly and precisely estimated. It has, however, been shown [D6] that the ability of the drug to protect against life shortening varies with the size of the dose of radiation.

292. Storer [S30] investigated on A/J and C57BL/6J male and female mice the effect of four radioprotectors administered i.p. 15 min prior to irradiation. They were: paraaminopropiophenone (PAPP) at 40 mg/kg, mercaptoethylamine (MEA) at 200 mg/kg, amynoethyl-thiouronium (AET) at 200 mg/kg and 5-hydroxytrypt-amine (5 – HT) at 100 mg/kg. X rays of 300 kVp were given acutely at 150, 300, 600 R to the control animals and at proportionately higher exposures to the protected mice. Dose-reduction factors in the region of 1.5–1.8 were found for the various drugs with respect to the $LD_{50/30}$ of the x rays and the drug treatments had no significant effect on the longevity of the non-irradiated mice. Within the range of exposures tested, mean survival time decreased as a function of dose (with some sex and strain differences in the amount of response) with concave upward relationships, although the hypothesis of linearity could not entirely be rejected. The pooled data (all strains and sexes and drugs together) for control and for protected mice showed that mean life shortening was a curvilinear function of dose both with and without drugs and that the radioprotective treatment did afford some protection against life shortening. However, the extent of protection varied with strain, sex and drug. PAPP was found to be the most effective, followed by MEA, 5–HT and AET. The average dose-reduction factor for all agents and mouse groups was 1.35. All this shows that protection against life shortening is qualitatively and quantitatively different from protection against the acute lethal effects and results from a complex interaction of factors depending on strain, sex, drug and dose of radiation.

293. Other experiments on the subject of chemical radioprotection were reported by Maisin et al. [M8, M23] and summarized in Maisin et al. [M10, M24]. BALB/c and C57BL mice were given 100–2000 R acute exposures of 250 kVp x rays; causes of death were classified among 12 different groups and analysed for competing risks of death. In the BALB/c strain life shortening had a linear dependence on dose, except perhaps at very high doses. When AET or a mixture of radioprotectors (glutathione, cysteine, AET, MEA and 5-hydroxytryptamine) were administered prior to irradiation with various schedules of administration, they showed a significant protective action against late death. Under the hypothesis of linearity, the dose reduction factor for AET was estimated to be 1.23 ± 0.05 and that for the radioprotective mixture 2.1 ± 0.2, which values are significantly smaller than those applying to acute lethality (1.7 and 2.8 respectively). Radiation-induced shortening of life was attributed to specific diseases (thymic lymphoma, myeloid leukaemia, glomerulosclerosis, non-tumorous lesions of the lung). Protection was most effective against thymic lymphoma, but was also discernible for leukaemia and nephrosclerosis. In the C57BL mouse the data, although less complete, were essentially similar.

294. Maisin and his collaborators [M24] performed also another experiment where the mice were given fractionated treatments. Using a variety of different doses and fractionation intervals they showed for the irradiated-AET-protected mice a dose-reduction factor of 2.1 at 50% life shortening. Radioprotectors decreased significantly the incidence of thymic lymphoma, but

did not modify other causes of death. A paper was also reported on the same subject by Philip [P2]. In this case AET (300 mg/kg body weight) or 5-HT (75 mg/kg) were given i.p. 10 min prior to irradiation with 400 R (250 kVp x rays) to young Swiss female mice. Single exposures of 100, 200 and 400 R were also given to normal, non-protected mice. Life-span shortening, incidence of thymic or myeloid leukaemia, and the occurrence of tumours of breast, ovary, lung and uterus were the end-points evaluated. Dose reduction factors of 1.7 for AET and 1.4 for 5 – HT were calculated for long-term survival. These values were close to those obtained for short-term survival. For the induction of all tumours the respective dose-reduction factors were 1.5 and 1.4; for the induction of thymic lymphoma 1.8 and 1.6.

C. BIOLOGICAL TREATMENTS

1. Bone marrow transplantation

295. Syngeneic marrow transplantation was not very effective in protecting against reduction of longevity in Cosgrove's et al. [C23] experiments. This treatment inhibited the induction of thymic lymphoma, in accordance with other data [C13, K16, I12, C24] but did not alter the incidence of glomerulosclerosis, solid tumour induction (ovary, breast, lung, uterus) or lens opacities.

296. Experiments on the late somatic effects in syngeneic radiation chimaeras were performed by Covelli et al. [C13] on (C57BL × C3H)F1 male mice. Bone marrow treatment was effective in increasing survival of the animals within 60 days, but the mean and median after-survival of the mice irradiated with 9 Gy of x rays were not influenced by the number of cells injected (in the range of 8 10^4 to 1 10^7 cells/mouse). Irradiation with 9 Gy of 250 kVp x rays followed by bone marrow treatment was very effective in decreasing the incidence of reticulum cell sarcoma in long-term survivors but led to an enhanced incidence of other tumours (particularly of the malignant ones) by comparison with untreated animals. Irradiated bone-marrow-treated animals had a greatly enhanced and accelerated appearance of nephrosclerosis which was by far the most important cause of death between 600 and 700 days of treatment under these conditions.

2. Other treatments

297. In order to examine further the frequently reported finding of a greater sensitivity of the female animals to life shortening (see section II.B.) Holland et al. [H13] investigated the effect of ovariectomy on RFM mice. Castration had little effect on overall mortality rate, both alone or in combination with irradiation (300 R). It had, on the contrary, significant effects on specific spontaneous or radiation-induced diseases, as it reduced the incidence of lymphosarcoma and pituitary, harderian and adrenocortical adenoma and it increased the incidence of lung adenoma. For two other diseases, septic metritis and severe glomerulosclerosis, castration interacted with radiation in nullifying the increased incidence brought about by radiation. Although not strictly comparable, these findings seem at variance with those of Hamilton et al. [H14] who exposed LAF1 mice to 145 R d^{-1} and found that females had a greater sensitivity than males, judging by survival time. However, when the females were ovariectomized their survival became closer to, although still lower than, that of males. Thus, acute survival might be influenced by ovariectomy, as opposed to long-term survival.

D. PARTIAL-BODY IRRADIATION

1. Mouse

298. Although selective partial-body exposure may, in principle, be a good method for the study of the pathogenesis of the individual causes of death responsible for life-span shortening, data on this subject are comparatively few. In the mouse Kallman et al. [K7] reported on CAF1 females exposed to 250 kVp x rays. Partial-body irradiation was performed bilaterally on the thorax (weight of irradiated tissues about 7.6 g); on the right hemithorax (3.5 g) and on the pelvis (5.0 g). Three hundred and 500 R given to the whole body produced an appreciable shortening of life. Partial-body exposure on the chest or on the pelvis was much less effective than whole-body irradiation in terms of tissue dose units. The smallest whole-body doses were more effective than the larger per unit dose but the reverse was true in the case of partial-body exposure. In the partial-body exposure of one region the loss of life per unit absorbed dose (dose per unit volume of tissue) was not a constant in these experiments.

299. Boone [B8, B9] worked on mice of the same strain and sex irradiated on the whole-, lower- or upper-body with x-radiation in single doses. Whole-body irradiated animals (150 mice for each group) received 1, 2 or 4 Gy, shielded animals 2, 4 or 8 Gy and shielding was adjusted in order that the total weight of the tissues included in the irradiation fields would be the same. The integral dose to shielded animals was therefore equivalent to that received by unshielded ones receiving one-half of that dose. Inspection of the data showed a non-linear dose-effect relationship in all cases, with upper convexity. Whole-body exposure was most efficient for induction of life shortening; shielding of the lower body least efficient; shielding of the upper body was intermediate between the two. The only pathological data given were those referring to overall leukaemia and they are insufficient for any conclusion. Also, the significance of the differences observed between control and treatment groups and between the treatment groups themselves appears dubious.

300. Cosgrove and Upton [C25] exposed RF female mice to 250 kVp x rays, under Nembutal anaesthesia and the conditions studied were: irradiation on the whole body with 100 R or 300 R; 300 R to the upper, middle or lower third of the body: non-irradiated controls. Life shortening was appreciable after 100 or 300 R given whole-body but survival of the shielded groups was slightly, if at all, different from that of non-irradiated controls. Whole-body irradiation at both exposure levels increased the incidence of thymic lymphoma and in the 300 R group myeloid leukaemia was also increased; but none of the diseases was increased in shielded mice. Since partial exposure of any third of the body to 300 R produced less life shortening than did 100 R to the whole body, the effect was not correlated with the integral dose.

301. The experiments of Cosgrove, Upton et al. [C20] on LAF1 female and male mice are more concerned

with the induction of nephrosclerosis than with life shortening, but were performed on partially-shielded animals. They showed that shielding of the kidney prevented the induction of glomerulosclerosis and exposure of the kidney alone was as effective as whole-body irradiation for induction of this disease. Longevity was reduced by irradiation of the whole body or by exposure of the lumbar area to 1200 R at 10 weeks of age, but not when the same dose under the same conditions was given at 1 year of age. Partial-body exposures below 1200 R gave an insignificant reduction of the mean age at death.

302. Sato, Tsuchihashi and Kawashima [S34] reported that whole-body, head or trunk exposure to 400 R induced significant life shortening in ddN female mice irradiated when 10 weeks old with 200 kVp x rays. Lower-body exposure to the same amount of radiation did not result, on the contrary, in any reduction of the life span. Per volume dose, life shortening was maximum for the head exposure. Gompertzian plots of all groups were linear, but they did not bear any simple relationship between partial- or whole-body irradiation. Other experiments on ddY female mice [S60] yielded dose-effect relationships for life shortening by whole- or partial-body irradiation. Mean survival times following whole-body exposure decreased by about 7% per Gy. A dose of 1 Gy to the head or the lower body produced 8.5% and 9.7% shortening, respectively, but there was almost no further reduction up to 7.6 Gy. After irradiation of the trunk with 1.9 Gy life shortening amounted to about 14% of the control value and beyond this dose to about 1% per Gy.

303. An analysis of causes of death was carried out only for part of the experiments mentioned above. Histological data are available for animals receiving 6 Gy whole-body, 8 Gy on the head, trunk or lower body, or for non-irradiated controls [S43]. The increase in incidence of all tumours and of malignant lymphoma was significant in the whole-body exposed group. Head exposure enhanced the induction of tumours of the pituitary gland; trunk exposure that of ovarian tumours (with a depression of malignant lymphomas); lower body exposure gave the same tumour spectrum as the control. Judging by the mean after-survival of mice dying for the same cause, an earlier appearance of all causes of death (and particularly of the lymphoma) in irradiated than in control groups was apparent. The larger life shortening produced by the whole-body treatment was attributed to the high incidence of lymphoma and to the early appearance of lymphomas, lung and mammary tumours. The lower incidence of lymphoma in the partially-shielded mice was responsible for the low life-shortening efficiency of these treatments.

2. Rat and hamster

304. In the rat Maisin et al. [M23] and Dunjic et al. [D7] performed a study of the mean duration of life of a homozygous strain exposed under various conditions. They found that 600 R given whole-body gave a reduction of life span of about 41%; 850–1000 R to the abdomen alone reduced the life span by 18–34%. There were also groups irradiated over the thorax only (600–3000 R) or over the head only (600–2000 R). The survival curves had distinctly different shapes depending on the region of the body exposed and on the various modes of death showing at characteristic doses: pulmonary and oesophageal syndromes for thorax irradiation and delayed head or oropharyngeal syndromes for irradiation of the head. The authors suggested that the survival curve after whole-body irradiation could be a composite of the survival curves for partial irradiations of various types, an explanation that fails to account for the life shortening at doses far lower than those responsible for the modes of death mentioned above.

305. In other experiments young female Wistar rats were irradiated on the whole body or on sections of it (head, upper abdomen, whole body except the upper abdomen) with a single exposure of 1000 R of 250 kVp x rays under anaesthesia and therefore under slight anoxia. Mean and median survival times of the groups receiving partial- or whole-body exposure were all reduced compared to controls. Life shortening observed after partial-body irradiation was in approximate proportion to the weight of the irradiated tissues. Nephrosclerosis was not seen unless the upper abdomen was included in the irradiation field and, except for the kidney, the spectrum of diseases observed at death in control, partial-body or whole-body irradiated animals was very similar. Inflammatory diseases of the thoracic organs and benign and malignant neoplasms predominated [L17].

306. The results of Taketa [T2] were also obtained in the rat (adult male Sprague-Dawley, 9–11 weeks old) and involved exposure of the intact abdomen exclusive of the gastro-intestinal tract (which was surgically exteriorized and shielded) to 13, 35 or 50 Gy. A dose of 13 Gy to the intact abdomen resulted in 100% of the animals dying within 4 days of exposure. The same dose given to the abdomen without the intestine allowed survival of the animals to a mean life span of 262 days. But an increase of the dose to 35 or 50 Gy under the same conditions shortened the life span of the rats to 82 or 33 days, respectively. Results with the lower or the upper abdomen irradiated separately (with exteriorized and shielded intestine) were less clear.

307. Carsten and Innes [C26] working on female rats of the CFN strain irradiated with 250 kVp x rays showed that 6.5 Gy given to the lower body or 13 Gy administered to the upper body had a life-shortening effect of about 90 days (against a control value of about 700 days). The effect was statistically different from the control life span, but was very similar for the two treatments. Mammary adenofibromas developed in 60% of the normal aging mice. Acceleration of these tumours was induced by irradiation of the lower, but not of the upper, body. These tumours were a major cause of death in both the irradiated and the non-irradiated rats.

308. Chinese hamsters were irradiated whole- or partial-body with 250 kVp x rays [K11]. Judging by the life span, the upper half of the body appeared more vulnerable than the posterior half and the response to the whole-body exposure was largely determined by irradiation of the anterior half. This observation seems quite unique to this species and at variance with data obtained in the mouse [K7, B8, C25] and in the rat [D7, L17]. A significant increase of the incidence of tumours in irradiated animals was seen only for the ovary. Progressive capillary glomerulosclerosis was observed in all animals examined and this was accelerated by irradiation.

E. CONCLUSIONS

309. In conclusion, it appears that stress of a rather non-specific nature (cold, starvation, water deprivation, physical exercise, electric shock) may have some influence on the life span of the irradiated animals, owing presumably to some interaction between the effects of stress and of radiation exposure. These data are, however, too few, the treatments tested too unspecific and their underlying mechanisms too obscure to warrant undue generalization. Hypoxia induced by various techniques invariably results in protection against the life-shortening action of radiation, but the extent of this protection is probably less than that produced by the same treatments against acute radiation effects.

310. Treatment shortly before irradiation with a number of radioprotective chemicals (MEA, AET, 5-HT, cysteamine, PAPP and others) affords a certain amount of reduction of the life-shortening effect, by comparison with irradiated untreated controls. The nature and the dose of the drug; the dose of radiation in relation to the form of the relationship and to its possible modification by the drug treatment; the strain and sex of the animals; are all variables that may to some extent modify the final outcome of the drug-radiation interaction. The effect on longevity of these drugs is often smaller, sometimes marginal, by comparison with the effect produced by the same drug treatments on early mortality: dose reduction factors in the region of 1.4 to 1.8 may be derived. Some protective effect is also found with fractionated courses of treatment but not with duration-of-life exposures and low drug levels. The protective action of a single drug may cumulate with the effects of other drugs and with the action of concomitant treatments like anoxia, bone marrow transplantation, antibiotics. Whether the protective effects of the drugs on the life span operates through a decreased induction of tumours or of other non-specific conditions is not clear. However, the incidence of some diseases such as kidney sclerosis (which is responsible at medium-to-high doses for life span shortening) may be decreased by the action of radioprotective drugs.

311. Isologous marrow infusion acts essentially on short-term lethality: late survival is not correlated with the size of the marrow inoculum or with the amount of marrow shielded. The only long-term effect that appears to be affected by transplantation or shielding of haemopoietic cells is the induction of thymic lymphoma or of myelogenous leukaemia. These data, together with other findings [P3, S35, S36] may be viewed as evidence that marrow exhaustion does not contribute to natural aging or to radiation-induced life-span shortening.

312. The only generalization to be gained from the experiments where whole- and partial-body irradiation were compared is that partial-body exposure in the range of medium-to-low doses is less effective (both per unit dose and per integral dose) than whole-body irradiation for induction of life-span shortening. Experiments where doses of many Gy are given to sections of the body are clearly unsuitable for studies on the pathogenesis of life shortening, because under these conditions localized destructive lesions to the irradiated organs are decisive for survival or death of the animals. Data are unsuitable for other firm conclusions on the causes of death contributing to the loss of life-time. It appears however that inclusion of the kidneys in the irradiation field is a prerequisite for induction or acceleration of nephrosclerosis, a disease that in all strains of rodent tested and at doses of a few Gy largely contributes to life-span shortening. The tumour spectra and the pathogenesis of each tumour type are too variable for any meaningful generalization. In cases where leukaemia contributes substantially to the reduction of life, the lower incidence of this disease resulting from the shielding of the haemopoietic system [K12, K16, I2, C24] could explain the low efficacy of the partial-body irradiation in respect to life shortening.

IV. THE HUMAN DATA

A. INTRODUCTION

313. In this chapter the evidence for a non-specific life-shortening effect in the human species is discussed. The evidence available comes from three different sources of epidemiological studies: groups of people (radiologists, radiology technicians, physicians) exposed occupationally during their professional life; patients who have undergone radiation treatments for pathological conditions, mostly for tumour therapy or for control of ankylosing spondylitis; a large number of survivors of the A-bomb experience in Japan in 1945 and a few hundred people exposed in the Rongelap fallout accident in 1954. The data will be discussed separately, since the conditions of the exposure are different in the three groups and the characteristics of the sample size and of the epidemiological observations are also quite different.

314. The studies performed on humans are subject to a number of limitations, mostly related to the lack of any control over the variables in question. In general, the sample size is small for effects which have often a marginal incidence over the whole population studied. The life span study on the A-bomb survivors, numbering about 80 000 irradiated persons, is an exception. Often the time elapsed between irradiation and the epidemiological survey is insufficient to reveal effects which take a very long time to develop. In the case of radiotherapy patients there is the concomitant presence of an important disease which causes a decrease of survival completely unrelated to the radiation exposure and induces a prevalence of associated disabling conditions altering the spectrum and the time of occurrence of the causes of death expected in a normal population.

315. Finding suitable control groups to match the irradiated group is always a problem: the distribution of ages, the geographical location, the differences in the socio-economic status and in the living and working conditions between the control and the test sample are often quite large. When the effects to be studied are small the choice of an appropriate control group may often be decisive in order to assess their presence and magnitude. Although in many cases corrections can be applied to allow for obvious differences, a subtle difference may remain unrecognized and may thus alter to an unknown extent the interpretation of the data. In all cases differences in the composition of the control and the test sample, difficult to be recognized add variability to the data and uncertainty to the conclusions.

316. In retrospective studies the accuracy of the records is often a problem. For some groups (physicians, radiotherapy patients) the high standard of the medical care makes the records on causes of death very

useful and well documented. But in other instances records are poor and causes of death only approximately known. Uncertainties may apply only to some and not to all causes of death and the ability of the epidemiologist lies in identifying these sources of errors and properly allowing for them. Radiation dose records are mostly uncertain or unavailable; as in the case for occupational exposures where presumptive evidence must often be used instead of more precise statements of dose. In these cases no analysis of dose-response relationships are possible, but only contrasts of broad categories of exposed versus unexposed groups. At the other extreme, doses in the treatment volume are very well known for radiotherapy patients, but may not be easy to estimate for all tissues of importance outside the beam.

317. Radiation dose distribution in time is often unknown and variable within the ascertained or presumptive period of occupational exposure; the radiation beams are often of very low energy and therefore likely to be absorbed superficially; irradiation of the hands, arms or upper part of the body makes the sample of occupationally exposed individuals very inhomogeneous. And, in addition to the above-mentioned factors, the acute, fractionated or chronic conditions of the exposures make it difficult to compare the results of the various series. The interplay of all these variables would naturally call for multifactorial types of analysis, which however have not been specifically applied to the field of life shortening.

B. DATA FROM OCCUPATIONALLY EXPOSED PEOPLE

318. Following a number of papers where an increased rate of leukaemia in radiologists, as compared to other medical practitioners, had already been reported [M25, M26, U13], in 1947 Dublin and Spiegelman [D8] published some preliminary data on United States physicians during the period 1938–1942, showing essentially that physicians experienced the same longevity and mortality as a male test group of the same age in the United States. No evidence of diseases associated to radiation exposure was found in that study, but in a subsequent paper [D9] this research was extended to the mortality of medical specialists during the same period. Among 175 146 medical doctors listed in the American Medical Directory in 1940, 37 610 (or 21%) were classified as full-time specialists. During the five years covered by the study there were 12 419 doctors who died in the age group 35–47 and 2029 of these (or 16.3%) were medical specialists. The mortality ratio from all causes for specialists was 78%, taking the death rate of all physicians to be 100%. Radiologists were reported to have a mortality ratio of 0.90, dermatologists of 0.98, pathologists of 0.60. Radiologists showed a high rate of mortality from cancer and leukaemia and among 95 recorded deaths of radiologists leukaemias were higher than in any other speciality.

319. In 1956 Warren [W2] reported on 82 441 physicians dead during the period 1930–1954 inclusive. He found that physicians had a mortality rate about the same as that of the general adult population. In 1950 in the United States the average age at death for a male test group having reached 25 years of age was 65.6 years. Radiologists died on the average 5.2 years earlier than other non-exposed physicians, who died at 65.7 years. Also, the non-radiologists known to be exposed to radiation did show some life shortening (they lived on the average 63.7 years) although less than that of radiologists. Failla and McClement [F4] estimated that radiologists received an accumulated exposure that could vary from rather low values to about 1000 R, with a possible whole-body exposure of 500 R in 35 years of practice.

320. Warren [W2] found that deaths from leukaemia among physicians were 120 over the period 1950–1954, which rate was about three times that for the general adult population. During 1930–1954, 0.63% of the deaths from specified causes occurring among non-irradiated physicians were due to leukaemia, against a 2.33% among other specialists having had some contact with radiation and 3.65% of leukaemia deaths in radiologists. Also, the average age at death of physicians dying from leukaemia was 60 years, whereas radiologists with leukaemia died on average at 55.8 years. Not only radiologists and medical specialists exposed to some radiation had a shorter mean life span than other non-exposed doctors, but they seemed to die younger from practically every cause of death, neoplastic, degenerative, infectious or other stated or non-stated causes. This suggested that radiologists were subject to some factor lowering their resistance to disease and hastening aging. The fact that other specialists exposed to some radiation had mortality values intermediate between radiologists and non-exposed physicians was taken as a further evidence that such a common causative agent may be radiation.

321. In a subsequent paper Warren [W3] added two years to his previous series and compared the life span of radiology specialists (averaged over periods of 5 years) with the duration of life of the United States male population at large. He found that the mean age at death of radiologists before 1945 was less than 60 years, while after that date it increased progressively to approach by 1955 the average age at death of the general male population. This observation implied that during the period 1930–1955 there had been a lower rate of mortality of the radiologists as compared to the average male population, so that, in spite of a general tendency to an increased life span, the average age at death for the two populations compared had by the end of the period come very near.

322. Seltser and Sartwell [S37] examined the comparability of the groups in Warren's [W2] study, in order to see whether there might be other differences that could account for the apparent life shortening of the radiologists, compared to non-radiologist physicians. They tested the hypothesis that the observed differences might result from an unequal age distribution among the samples under comparison and found in effect that the age distribution of radiologists differed from that of the other physicians: radiology being a relatively new medical specialty, there were proportionately fewer radiologists in the older age groups where the mortality intensity was heavier. And when the expected age distribution at death was recalculated using data from 1940 and 1950, it was concluded that radiologists would in fact be expected to die at younger ages, just because there were proportionately fewer elderly radiologists. This finding raises some doubt on the comparison method adopted by Warren [W2]: it shows that the average age at death is in this particular case a misleading parameter, while comparison of age-specific death rates in the two groups would be a more reliable method of analysis. Seltser and Sartwell, however, did not prove that the exposure to radiation of radiologists had no effect on their life span.

323. Similar reservations about the method used by Warren [W2] were expressed by Lewis [L18] in a review on radiation-induced leukaemia. He pointed out after appropriate calculations that a difference of at least 6 years in excess in the life span of radiologists would be expected by comparison with other non-exposed physicians, solely on the basis of differences in the age distributions among the two samples compared. If this were true, radiologists might have had a slightly longer life span than other non-exposed doctors.

324. At approximately the same time the results were published of a survey on British radiologists by Court-Brown and Doll [C27]. The study concerned life expectation and cancer mortality among 1377 male radiologists, mostly diagnosticians, who had been members of specialist societies in Great Britain during 1897–1956. It proved impossible to assess the exposure to radiation of this group: it was simply assumed that the average dose received prior to 1921 (when the first recommendations on radiation protection were issued) was high, whereas the average exposure of those registered as specialists after that date had been likely to be within the limits recommended.

325. Mortality data were calculated from the population at risk at each age and in each year. The expected numbers of deaths were first estimated by assuming that mortality might be the same as for all men in England and Wales in the same age groups and over the same time period. Expected deaths were also calculated according to those expected in the upper social class or in the medical class as a whole, with some corrections concerning the relative mortality of people in various social groups aged 65 or more. By similar methods the number of deaths to be attributed to all types of cancer (appropriately corrected for occupation and social class) were obtained. All the data were kept separate for radiologists registering before or after 1921.

326. With regard to life expectation, the observed deaths were 463, fewer than expected on any of the assumptions mentioned, which would have been between 499 and 525. If deaths attributable to cancer were excluded, the relative differences between observed and expected cases became more marked and approached statistical significance. Thus, there was no evidence that occupational exposure to radiation caused a detectable non-specific shortening in the expectation of life. As to cancer mortality, a significant excess was found among radiologists entering practice before 1921, the excess being confined to tumours of the skin and pancreas (and possibly to leukaemia). No excess mortality from cancer was found in those entering radiology after 1921, although the time elapsed up to the completion of the study was insufficient to ensure that the cancer hazard had been totally expressed.

327. The study on British radiologists was recently updated by Smith and Doll [S59] to include observations up to the beginning of 1977, by which time about 55% of the 1338 persons had died. A reliable estimate of the dose received by these individuals proved impossible, but it was calculated that those entering the profession between 1920 and 1945 might have cumulated a whole-body dose of the order of 1 to 5 Gy. As in the previous study, the mortality of the radiologists was compared with that of all men in England and Wales, all men in the upper social class and all male medical practitioners. Radiologists entering the profession before 1921 had a 75% higher cancer death rate than other medical practitioners. Leukaemia, tumours of the pancreas, lung and skin were significantly elevated. The cancer death rate among those who had started the profession after 1920 was not significantly elevated. Data were not available to examine non-cancer mortality by individual causes. However, it was confirmed that the overall non-cancer death rate among radiologists was significantly lower in two out of three comparison groups than that of other classes under comparison. Thus, an extension by 20 years of the study provided no support for the concept of a non-specific life-span shortening.

328. Seltser and Sartwell [S38] returned again to the problem of mortality of radiologists of the United States, in comparison with other medical specialists. Their new study covered the period 1935–1958, during which the mortality experience of 33 616 members of several United States medical specialty Societies was analysed, in order to test the hypothesis of a possible increase in mortality due to occupational radiation exposure. The Societies were selected in such a way that their members had a postulated high (radiologists) intermediate (internists in general) or low (ophthalmologists and otorhinolaryngologists) rate of exposure to radiation. The mortality experience in these groups conformed to the above hypothesis and the median age at death was about 5 years greater among the lowest-exposure than the highest-exposure groups. The method followed for the comparison was to determine person-years of exposure, specific for age and calendar time, and to relate these to mortality. There were three periods along which comparisons were made: 1935–1944; 1945–1954 and 1955–1958.

329. Comparison of matched and paired subjects for low- and high-exposure groups were also carried out and they gave results consistent with those of group comparisons. The differences in mortality increased with age but decreased with calendar time for all except the oldest age classes. There was no excess mortality of radiologists in the 35–49 classes of age over the period 1945–1958, suggesting that by that time the hazards had been controlled. The increased risk of mortality was distributed over a number of assigned causes of death. In the Societies with a postulated high exposure mortality due to cancer, cardiovascular-renal diseases and all other causes combined was increased. Leukaemia showed the highest ratio of observed/expected deaths at all ages combined. In general, with the exception of leukaemia and other cancers, the mortality ratios were highest in the oldest groups of age. The excess of leukaemia and all cancers combined was greatest during the last working years and the excess in other causes during the post-retirement years.

330. From the above data Seltser and Sartwell [S38] inferred that occupational exposure to ionizing radiation on the part of radiologists had in the past produced a non-specific life-shortening effect. But the validity of this conclusion depends on the demonstration that the groups compared are similar in all respect, except for radiation exposure. The authors examined certain characteristics of the samples compared such as the geographic distribution of the groups, the region of residence, the size of the living communities, the birth-place: none of these comparisons revealed any difference among groups. Exclusion from the comparisons of the first five years after the members had joined the Societies, in an attempt to eliminate a possible selection due to persons with poor

health not joining the profession [C27], did not modify the conclusions. And the same was true for another possible cause of selection due to the unfit persons not entering the profession with the highest radiation risk. Factors known to affect the survivorship of other populations (smoking, diet, alcohol consumption, family longevity) could not be tested, but were not deemed to have caused significant differences among the population groups tested.

331. Seltser and Sartwell commented on the fact that the reduced survival (about 5 years) among radiologists for the years 1935–1944 was remarkably near to that obtained by Warren [W2]. This occurred in spite of the fact that the method used by this latter author (but not his conclusion) was criticized by Lewis [L18] and by the same Seltser and Sartwell [S37]. Whether Warren [W2] reached the right conclusion with the wrong method, or not, the results from his and from Seltser and Sartwell's study are in any case in good accordance.

332. The differences with respect to the negative findings of Court-Brown and Doll [C27] could first be explained, in the opinion of Seltser and Sartwell [S38], by the methods of analysis. The absence of a comparison between medical specialists in the British series would be a weakness, since specialist physicians have a more favourable survival experience than males in the general population, at least in the United States. Also, the numerical adequacy of the British data might be questionable, since with groups of the order of 1000 persons a life-shortening effect of as much as 10 years could go undetected, even if present. Other differences of substance may have regarded the more careful and earlier adoption of safety measures in the United Kingdom than in the United States; the fact that in the United Kingdom most radiological practice was carried out in hospitals and therefore much of the exposure might have been taken by radiology technicians and not by the specialists; the wider use of fluoroscopy than of radiography and also the greater number of films used per radiological examination in the United States than in the United Kingdom [V7]. It should be pointed out, however, that both the United Kingdom and the United States series agree in showing that since adoption of radiation protection limitations any hazard attributable to radiation can no longer be documented.

333. Two papers from Japan on a small group of radiology technicians were also reported. In the first one [K17] estimates of radiation injuries such as leukaemia, cancer of the skin and tumours of the inner organs were carried out but no mention was made of life-span shortening associated with the exposure of this group of people. The second paper [K18] reported that during the period 1933–1963 there were 52 radiology technicians dead in three Japanese prefectures. The corrected death rate corresponding to this number was significantly higher than that in the population at large employed in similar professions and aged over 15 years in 1955. There was some tendency of the death rate to increase with increasing occupational exposure, but no correlation with the age at which exposure first began. Except for skin cancer which was significantly higher, other causes of death were similar in this group as in the general population. Life expectancy in each age class was shorter than in male persons of comparable social and working conditions which were over 15 years of age in 1951 and 1952. A life-span shortening amounting to 6.6 years in the x-ray technicians was found, corresponding to an estimated loss of 0.92 d R^{-1}.

334. Another paper on the mortality of Japanese radiology technicians was made available to the Committee [S53]. During the period 1955–1965 the number of these technicians was estimated to be 74 721 and the observed number of deaths in this group was 91 (for male Japanese of the same age classes 325 were expected). Leukaemia deaths did not exceed the expected value, although the relative risk of leukaemia was an order of magnitude higher for people who had been employed for over 29 years. Seventeen deaths were registered in 1964 and 1965 (80 would have been expected for male Japanese of the same age classes) with an average age at death of 47.7 years (against 48.0 expected). The estimated exposure ranged from 9 to 37 R during the ten years of observation. Since there were no significant differences between observed and expected values, it should be concluded that radiation-induced life shortening was not proven in this population sample.

335. New data on the effects of ionizing radiation on radiologists were reported in 1966 by Warren and Lombard [W4]. The study comprised 5982 certified radiologists which were compared with all physicians of the United States in 1949–1951, with the male population of the United States aged over 25 years in 1950 and with a group of 3176 Massachusetts dentists. Although the number of certified radiologists increased more than three-fold from 1940 to 1960, their mean age did not change at all and remained between 46 and 47 years. The mean age at death of radiologists was 55.8 years in 1934–1939; 59.3 years in 1940–1949; 64.5 years in 1950–1959 and 70.1 years from 1960. The rate of this increase was higher than that of the general male population, so that, from 1960 on, the two curves expressing the increase in the average age at death versus time crossed with each other. The life shortening observed in preceding years could not be attributed to any one cause in particular, such as leukaemia, but was the aggregate of shorter life spans associated with many causes of death. Leukaemia had a higher risk (about 5 times) among radiologists than among the male population at large, but it occurred rarely and only after a number of years of occupational exposure. It was more common in radiologists than among the male population at large, but it occurred rarely and only after a number of years of occupational exposure. It was more common in radiologists after 40 years of age, but more common before 40 in the general population. In recent years the excess incidence of leukaemia in radiologists decreased. From the above findings Warren [W4] concluded that radiation protection measures had been effective in providing adequate safeguards for the radiology specialists.

336. Miller and Jablon [M27] searched for late radiation effects among men trained as radiographers in the United States Army during the Second World War. The mortality experience of this group of people (6560 persons in total) was compared over the period 1946–1963 with that of other groups trained by the Army as pharmacy (1522 persons) or medical laboratory technologists (5304 persons). It was difficult to ascertain the radiation dose but it was concluded from ancillary evidence, in the absence of more complete records, that they received substantially greater radiation than did patients exposed to x rays for diagnosis. Causes of death were investigated and in only 1 out of 16 possible comparisons between exposed and non-exposed groups there was a statistically significant difference of any interest in the present context. It referred to an excess of tumours of the respiratory tract

which was elevated among radiographers: however, the difference between expected and observed values was due in part to the low mortality rate from this cause of death in the control samples. No significant excess of leukaemia was found among the radiographers, but in a study of this size a two- to three-fold increase in the risk of leukaemia could have gone undetected. No information on life-span shortening was reported as such.

337. There was yet another report from Japan on the mortality and causes of death of radiology technicians during the period 1966–1972 [K19]. Among these technicians affiliated to the Japanese professional association there were during the above-mentioned period 134 deaths, a number much lower than expected, owing probably to some inadequacy of the survey. Out of these deaths, 6 were due to skin cancer and 2 to aplastic anaemia and these numbers were significantly higher than would be expected to occur among the population at large. Leukaemia was found in 5 cases, indicating no significant difference with the number expected. Concerning the average age at death, 52.7 years was the value found among radiology technicians, while the expected value would have been 48.6 years. A very recent evaluation of the doses absorbed by persons dying from neoplastic and non-neoplastic causes was reported [A17]. Statistical tests to investigate a possible relationship between dose and mortality showed no correlation for the majority of causes of death from malignant tumours and for the cancer versus non-cancer causes.

338. The mortality rates of United States radiologists in comparison with other medical specialists were re-examined by the Johns Hopkins University group [M28, M29] in two reports published in 1975 up to a total follow-up of 50 years. The comparison regarded male members of the Radiological Society of North America who were contrasted with fellows of the American College of Physicians and members of the American Academy of Ophthalmology and Otolaryngology. The information through 1954 available from the previous study by Seltser and Sartwell [S38] was updated for new members and decedents up to 1969. Deaths and causes of death were traced for 99.5% of the decedents. The persons under comparison were about 30 000 among all Societies for a total number of deaths of about 6500.

339. In the first paper [M28] the mortality rates from all causes were calculated by the life-table method of analysis with age- and time-adjustments of the death rates in such a way that cumulated rates could be compared within any 10 year cohort and across societies. No specific study of the influence of life style was included in this or the following [M29] study. Mortality from all causes depended on the decade of entry. During 1920–1939 death rates of radiologists were higher than those of any other specialist group for both cancer and non-cancer causes. The differential between the rates for radiologists and other specialists was lower in the 1930–1939 cohort and it disappeared in the 1940–1949 cohort. So did the graduation of death rate radiologists > internists > other specialists which was noticeable in earlier periods. Removing the deaths from cancers in the 1940–1949 cohort led to a disappearance of the difference between radiologists and non-radiologists noticed in earlier cohorts. The all-cancer mortality rates for radiologists were higher than those of other specialists up to the decade ending in 1949. The next decade had not aged sufficiently to show the expected peak of cancer mortality in the 60–64 years age group. It was pointed out that self-selection of the persons entering any one group and the life style after entering the specialty would have little influence on the data: thus, the presumed radiation exposure of the specialists under comparison would appear as the only reasonable way to explain the mortality differences and their trend over time.

340. In a companion paper [M29] the specific causes of death contributing to the excess risk of mortality in radiologists were examined. In the 1920–1929 cohort the radiology specialists, in addition to the previously-noted cancer mortality [M28], showed also the highest death rate for diabetes, cardiovascular-renal diseases, stroke, hypertension and suicide. After this early period radiologists ranged highest among other comparison groups only for cancer mortality. The excess of leukaemia observed in the 1920–1939 cohorts subsequently disappeared. During the same period, however, lymphoma mortality, particularly multiple myeloma, increased significantly in radiologists entering their profession in 1930–1949. Except for this latter finding, which was discussed in relation to possible effects of radiation on the immune system, the data reported confirmed and extended previous observations. The authors were aware of the peculiarity of their findings, as radiologists of the United States are the only human population where life-shortening effects of radiation, over and above those related to an excess tumour induction, have been observed. They specifically commented on this point and reaffirmed the validity of their observations. They also added [M28] that it may be premature to state conclusively that such an effect has disappeared in the 1940–1949 cohort, since relatively few persons in this cohort (193 out of 1011) had passed through the ages when mortality is higher: examination of an additional 5–10 years period might be required to determine whether such an effect has been reduced through a decrease of the occupational exposure.

341. More recently Polednak et al. [P4] reported on the mortality of a group of women employed in the dial-painting industry in the United States. A cohort of 634 subjects working in this industry during 1915–1929 was traced from employment lists. Mortality in these subjects was compared on the basis of death certificates with the general mortality rate of a comparable female test group. An increased death rate was observed in comparison with the expected rate in the exposed population (240 cases versus 188.5 expected).

342. Bone cancer (22 cases versus 0.3), cancer of non-specified sites (18 versus 2.6), cancer of the colon (10 versus 5) diseases of the blood and haemopoietic organs (4 against 1) and external causes (31 against 10.1) were also increased, as compared to the general population. Mortality from selected causes was also examined as a function of the year of first exposure, time period of observation and age at first exposure. The mortality ratios from all causes and all cancers in women exposed after 1925 were lower than in women exposed in 1915–1924, in good agreement with the fact that the work regulations for the dial painting industry came into operation at about that time. Large-scale measurements of radium burden on these women were begun in 1954 and an anlysis of the relationships of radium body burden to mortality was performed only on women alive in 1954 who had been measured at least once between 1954 and 1975. Only 360 women in the group were available for an analysis as a function of dose and therefore the comparison with respect to cause-specific

mortality was performed between two groups: subjects with a body burden lower than 1.8 MBq or those with a burden of 1.8 or more MBq. Mortality ratios from all causes higher than 1 were observed only in the groups with the higher body burdens (1.91). Among these, all malignant tumours, bone tumours and other unspecified neoplasms were also significantly elevated. Among women with less than 50 μCi body burden, tumours of the large intestine were the only significantly increased cause of death.

343. Another paper by Stehney et al. [S39] is more specifically concerned with the possible presence in this group of women of life shortening ascribable to causes other than bone sarcoma and carcinoma of the head sinuses. The study was performed by the life table method using comparable age- and time-specific mortality rates for females for the comparisons. There were 1235 women exposed before 1930: they were on average 20 years old at employment and about 44% of the persons in the group had died by the end of 1976. The observation times thus covered a period of between 45 and 60 years. Regarding death from all causes, 529 deaths before the age of 85 were observed versus 461 expected and the cumulative survival of the group was significantly less than expected, starting at 10 years after employment. When mortality rates for bone sarcoma and head carcinoma were subtracted from the mortality rate for all causes, there was no significant difference at the 5% level in the total population (455 cases observed against 460 expected) or at any of the time intervals considered. A correction for the effect of competing risks was also made on the data after exclusion of the radium-related tumours and the difference between observed and expected survival was similarly non-significant also under these conditions. When calculations on the expectation of life were performed at one year intervals from zero to 59 years after the first employment, differences between expected and observed mortality were again not apparent. The conclusion from this study is that when radium-tumour deaths are removed from the exposed sample the average survival is indistinguishable from that of the contemporary control group of the same age. Thus, to the precision obtainable with such a small sample size, only the radium-related tumours contributed significantly to life shortening of this population, with no evidence of non-specific effects.

344. The epidemiological data on uranium miners in Czechoslovakia [K25], the United States [A13] and Canada [G18] are discussed in Annex L in connection with the combined action of radiation and tobacco smoke on lung tumour appearance. The problem of life shortening has not been addressed specifically in published work on these series. However, to the extent that standardized mortality rates may indicate the prevalence of death mechanisms or causes, the data available can not be interpreted to show non-specific life shortening. The Hanford series [M31, G20] and the Portsmouth Naval Shipyard Series [R12] are similarly negative in respect to any such effect having been observed in the employees of a large atomic plant and of a nuclear shipyard.

C. DATA FROM RADIOTHERAPY PATIENTS

345. Doses administered to patients surviving radiotherapy are rather well known and may be taken as the independent variable against which any possible life shortening may be tested. The limitations with this group of people are due to partial-body exposure and to the possible effects of the disease initially requiring radiotherapy. The relevant data should thus be taken critically. Sørensen [S40] studied 184 patients treated for cancer of the uterine cervix in 1922–1929 in Denmark, surviving for at least 5 years after treatment and having been followed for the 20 years thereafter. Sørensen found that survival was not correlated with the stage of the disease at diagnosis. Each patient lost on average 3.5 years of life by comparison with the mortality experience of the female Danish population. This excess of deaths was exactly accounted for by patients who died during observation time for a recurrence of the neoplasia and there was no evidence that irradiation as such had decreased the survival rate of the patients without recurrence.

346. Newell [N11] attempted to establish some correlation between integral radiation dose and longevity in 217 women treated by radiotherapy at Stanford University in 1924–1947. The patients affected by cervical carcinoma in stages I and II had survived for 10 or more years after treatment. Radium treatment alone or radium in conjunction with x rays were used in the therapy. From the data Newell concluded that no life shortening attributable to radiation had occurred in the patients. The data were also evaluated independently by Kohn et al. [K20] who had access to the original records: their conclusion was the same.

347. A third series was reported by Kohn, Bailar and Zippin [K20, Z1] on about 500 cases of cervical carcinoma treated with x rays and/or radium obtained from two cancer registries in the United States. These women were treated prior to the age of 55 and survived at least 5 years after treatment. By the time of the last report about 38% of the women had died and this fact limited objectively the weight of the conclusions. The patients were grouped according to the stage of the disease at the time of treatment and according to the regional dose delivered. There was no evidence of radiation-induced life shortening. It was also reported that the incidence of leukaemia appeared in these patients to be lower than among patients treated for ankylosing spondylitis or for metropathia haemorrhagica.

348. Indirect information of a negative nature may be derived from a study of nearly 3000 children irradiated in infancy to shrink their allegedly enlarged thymus. These infants were followed in time and compared with about 5000 non-irradiated siblings. In spite of a four-fold increase in tumours, particularly of the thyroid, among the irradiated subjects, the report [H15] shows good agreement between observed and expected numbers of death. This indicates the absence of excess non-specific mortality, which may not in any case be surprising in view of the small portion of the body irradiated. The data of Peters et al. [P5] on 61 patients given local irradiation to suppress stomach hyperacidity after partial gastrectomy are inconclusive as to the presence of non-specific life shortening.

349. In 1965 Court-Brown and Doll [C28] reported on a sample of 14 554 persons (12 161 man and 2393 women) treated for ankylosing spondylitis with one or more courses of radiotherapy at various centres in the United Kingdom during 1935–1954. These patients had been followed for periods varying from 5 to 25 years up to the end of 1959 with reasonably good records of the

treatment; adequate follow-up information in 98% of the cases were available. The number of expected deaths in these patients if they had suffered only a normal mortality rate were computed from the numbers of person-years at risk for each sex, age group and calendar period and they were multiplied by the sex and age-specific mortality rates for each corresponding period. These calculations were performed for all causes of death, all cancers, the principal types of cancer and the respiratory diseases. The total death rate among the patients was about 1.8 times as high as the corresponding national death rate. When the various causes of death were analysed separately, the following observations were made.

350. In the test sample (by comparison with the general population) deaths attributable to arthritis and other forms of rheumatism were very high (about 100 times on average); deaths attributable to clinical conditions known to be associated with ankylosing spondylitis were on average 2.9 times more common; deaths from conditions attributable to irradiation (aplastic anaemia, leukaemia, cancers other than leukaemia) were about two times as common; deaths due to diseases from which the mortality could be similar to that of normal population had a prevalence of 1.3. This latter increase regarded all conditions examined and the total experience was sufficiently large for it to be highly significant. When mortality was examined as a function of the post-irradiation period, all causes of death other than cancer and aplastic anaemia were in a constant relationship to the expected mortality. In contrast, for leukaemia and aplastic anaemia mortality increased within the first 5 years of observation and then fell off; deaths from cancers of heavily-irradiated sites were increased approximately two-fold at 6–15 years after treatment. Many different types contributed to this excess, in a rough proportion to their natural incidence. Deaths from cancers originating in other lightly-irradiated tissues were not increased significantly.

351. The interesting observation in the present context is the increase in deaths due to non-specific causes and not grossly related to spondylitis or to irradiation. The authors [C28] pointed out a number of reasons that might account for this finding. Firstly, non-specific deaths might contain a small proportion of rare conditions related to spondylitis (lesions of the aortic valves, regional enteritis, proneness to accidents). Secondly, patients in this group carry other conditions known to be associated with spondylitis (amyloid degeneration, nephritis) that might decrease resistance to non-specific causes of death. Thirdly, the inaccuracy of the diagnoses at death, the possible effect of drugs and the use of imperfect death-rate values for the calculation of the expected numbers of deaths were discussed as other possible reasons. Finally, the constancy in time of the ratio between the number of deaths observed other than those presumably related to radiation over the expected number calculated from national mortality rates suggested that the above excess mortality was likely to be dependent on the spondylitis itself and unrelated to the form of the treatment.

352. The 1965 study of Court-Brown and Doll [C28] included many patients who had been treated with x rays more than once. This fact could complicate the interpretation of the late effects of the overall treatment, since subsequent irradiations may have contributed to the excess of death observed. A very recent study by Smith and Doll [S62] reports on about 14 000 patients with ankylosing spondylitis given a single course of x rays between 1935 and 1954. They were observed for an average follow-up time of 16.2 years, after a mean bone marrow dose of 3.47 Gy. The numbers of deaths expected by cause were estimated by multiplying the person-years at risk by the corresponding age- and sex-specific mortality rates for England and Wales. Mortality from all causes combined in the test sample was 66% greater than for members of the general population. Although the study was mainly concerned with cancer mortality, it did show that there was also a substantial excess of deaths from non-neoplastic conditions, which appeared to be associated with the spondylitis itself, rather than its treatment. However, the excess of deaths from leukaemia and cancers of the heavily irradiated sites in the test sample was attributable to radiation exposure. The authors concluded that, on the whole, the data did not support the suggestion that radiation could produce a non-specific effect of life shortening affecting death rates from causes other than cancer.

D. DATA FROM A-BOMB SURVIVORS

353. The effect of radiation on aging and life shortening in an Oceanic population irradiated in 1954 was summarized in a report by Conard [C29]. A number of changes connected with aging was investigated and among them the opacification of the eye lens, the presence of chromosomal aberrations in perypheral lymphocytes, immuno-haematological and nephrosclerotic changes. Regarding life shortening in particular, the number of persons exposed was too small to allow any reliable assessment. The population under study includes in fact a control group and two irradiated groups of 334 persons in total, exposed to a maximum of 175 R from fission-product gamma radiation.

354. The study of the A-bomb survivors in Japan, is providing information on long-term radiation effects, including life shortening, that will eventually form the most extensive source of data on the human species. The earliest reports of the A-bomb series are particularly concerned with the description of the sample [B21] and with mortality from all causes [J5] and from specific causes up to 1960 [J6, A6].

355. The report covering the period up to 1966 [B22] was based on the T-65 dose estimates and included 16 356 deaths among about 109 000 people, comprising irradiated and control groups. When malignant neoplasms were excluded from the analysis, there was no evidence that radiation might aspecifically shorten life and the excess mortality of the irradiated sample could best be explained in terms of disease-specific effects, particularly leukaemogenesis and, more generally, cancerogenesis.

356. Mortality data from the Japanese sample up to 1970 [J7] allowed the following conclusions. Although late radiation effects on human mortality could to some degree resemble non-specific manifestation of accelerated aging, the most notable effect remained by far the induction of tumours and leukaemia. The authors could not conclude with certainty on the absence of an excess mortality, for example, from diseases of the circulatory system or from cerebrovascular conditions: but it appeared most unlikely, if there was indeed any excess, that it could approach the excess of tumour induction.

357. The problem of longevity in irradiated human populations with special reference to A-bomb survivors up to 1972 was reviewed by Anderson [A9]. He concluded that evidence for a tumour-independent shortening of life was equivocal and, in his opinion, this experience would be at variance with other reported experience in man. For this reason, judgement on the interpretation of the Japanese data should be reserved pending further evidence. However, from their review of thirty years experience with the A-bomb survivors [O2], Finch and Beebe [F1] could find no convincing evidence for a generalized increase in mortality from natural causes other than cancer, in contrast with the requirements of the hypothesis of accelerated aging.

358. A re-examination of the mortality experience of A-bomb survivors up to September 1974 was performed by Beebe, Land and Kato [B6]. The number of deaths from non-neoplastic diseases, whose increment could in principle be suggestive of a non-specific life shortening, was at the time about 14 000 among 82 000 survivors. In the irradiated sample, cerebrovascular diseases, other circulatory diseases and diseases of the digestive system showed no evidence of an increase. Deaths from diseases of blood or blood-forming organs were apparently increased, but difficulties with the diagnosis made this finding uncertain. All other non-neoplastic conditions were apparently unaffected.

359. When all diseases except tumours and diseases of the haemopoietic system were pooled together, their combination produced no further evidence of a relationship to radiation dose. Although the sample group in the Life Span Study could indeed be regarded as a highly selected group, there was no evidence that selection due to survival from early effects, as suggested by others [S41, R10], might have favourably influenced the subsequent mortality. It was concluded therefore that the views that ionizing radiation may cause premature aging in man or that the carcinogenic effect is only a part of a more general acceleration of aging find no support in the Japanese experience: radiation effects on long-term mortality do not appear diffuse but rather specific and focal and principally cancerogenic.

360. The latest available analyses of the mortality experience of Hiroshima and Nagasaki survivors should also be reported for completeness [B23, B24], although the information contained in them is essentially that discussed in Beebe, Land and Kato [B6]. These contributions showed that age-specific death rates for all non-tumorous causes (taken at 4-year intervals and adjusted for city and sex within each time period) separately calculated for the group receiving 0–0.09 Gy and that exposed to 1 + Gy were superimposable (see Figure XVII). This finding, as repeatedly pointed out, cannot be reconciled with the hypothesis

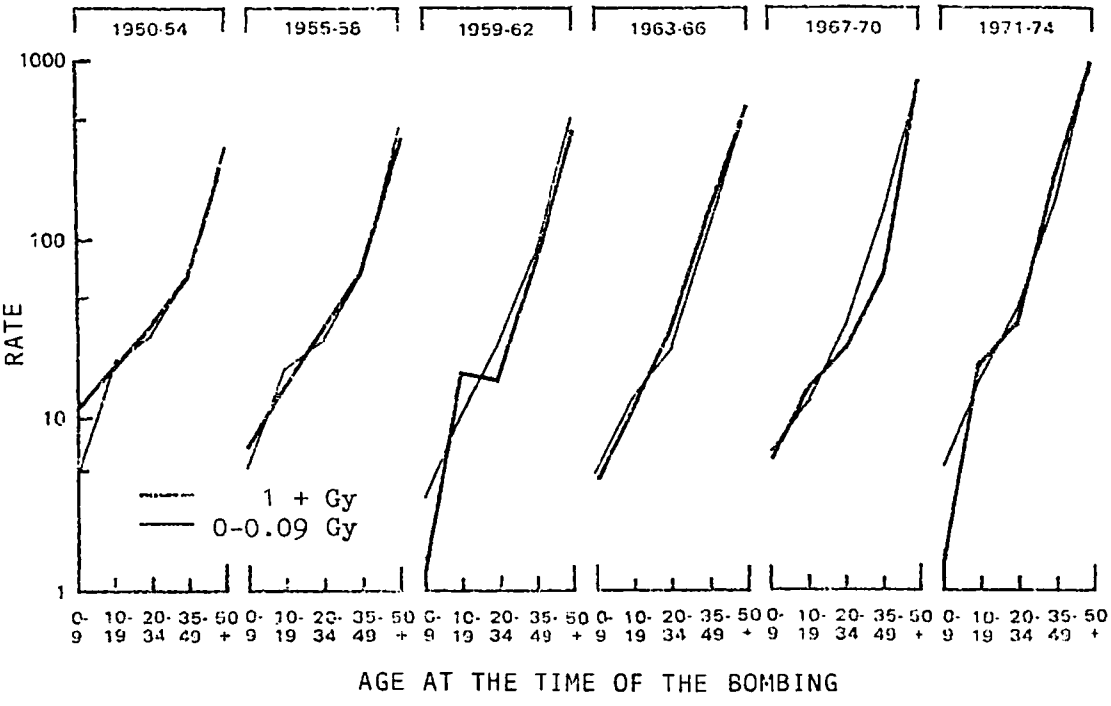


Figure XVII. Death rates (per 100 000 persons per year) from all diseases except neoplasms by age at the time of the bombing in Hiroshima and Nagasaki, during the period 1950–1974, plotted for each 4-year period separately for the group receiving 1 + Gy (heavy line) or 0–0.09 Gy (light line). The rates were adjusted for city and sex within time periods. Data from Beebe, Kato and Land [B24]

that radiation may accelerate natural aging, but rather shows that any life shortening present in the sample is associated with cancer induction. The results shown in Figure XVII did not change even when the observations were extended up to 1978 on the same cohort [K23]. The survival curve excluding deaths from malignant neoplasms for this cohort does not differ by dose over the whole period 1950–1978 [K23]. However, it is important to note that the most pronounced putative effects might be expected among the younger age groups where to date relatively few deaths from non-malignant causes have occurred.

361. The contrast between the Japanese data and the data on occupational exposure of radiologists of the United States and their mortality prior to 1950 was specifically discussed in the last publications [B23, B24], particularly in view of the most recent evidence of Matanoski [M28, M29]. It was pointed out that either the contrast groups in the occupational experience (radiologists against other medical specialists) were confounded by factors other than irradiation or that there are intrinsic differences in the nature of the radiation response between the Japanese survivors and the radiologists of the United States. Since the latter

hypothesis would be against a massive body of evidence collected on other mammals, one should logically be inclined to favour the first interpetation, particularly in view of the much more reliable experience from Japan, which is now based on about 20 000 deaths among about 80 000 A-bomb survivors.

362. Mention should also be made of an up-to-date report concerning the mortality experience of children exposed in utero to the A-bombs [K21]. There were 203 deaths among 1923 subjects during 1945–1976. The mortality ratio increased with dose in both cities. The increase was linear with dose in children dying within the first year of exposure, particularly within the first month; however, there was no increase between 1 and 9 years and only the suggestion of a further increase after 10 years of age. The excess mortality was significant only for children exposed during the third trimester of pregnancy, but loss of the embryos and foetuses might have been present in an unknown percentage of pregnancies before term. Regarding the causes of death, no information was available for 55 persons (out of a total of 203 deaths) most of whom died within one year after birth: loss of this information was due to the confusion in the official vital statistics reporting system which arose immediately after the war. The sample size is yet too small and too young for any conclusion about a possible excess death from non-specific causes.

E. CONCLUSIONS

363. The data on occupationally-exposed groups of workers do not lend themselves to complete dose-effect analysis and, in the absence of precise dose evaluations, conclusions must rely on comparisons between groups of exposed and non-exposed individuals. Under these circumstances, the homogeneity between the control and the test samples is critical because in many series the effects are marginal and their statistical significance may depend on the choice of controls.

364. The data on radiologists leave no doubt that particularly in the early days of radiology leukaemia and cancer were indeed induced in these persons. Observations in favour of this conclusion have been confirmed in all studies [D9, W2, W3, C27, S38, W4, M28, M29]. However, in some instances a higher incidence of neoplastic conditions was not accompanied by an increased death rate and shortening of life [D9, C27], while in others [W2, W3, S38, W4] there was a true loss of life amounting to 5 to 6 years, following exposure for the whole working life. Not all of this life shortening may be accounted for by leukaemia and cancer induction, and other non-neoplastic conditions contributed to it. Some of these may have been due to non-stochastic damage, such as skin necrosis, leading to death in the earlier series. There is no way to derive from the data, as there is no knowledge of dose, an approximate value of the life shortening per unit dose. There is unanimity in the conclusion that the induction of neoplastic conditions, accompanied or not by life shortening, has disappeared in more recent years, presumably after the adoption of radiation protection measures.

365. True shortening of life has only been reported in a series from the United States [W2,W3,W4,S38]. Reasons to justify the absence of life shortening among radiologists of the United Kingdom have indeed been given and the absence of effect could be accounted for by objective reasons and on methodological grounds. It has been pointed out that with samples of the order of 1000 persons prevalence ratios of the order of 2 to 3 for leukaemia and life-shortening effects of the order of 5 to 6 years can hardly be resolved. It should also be realized that induction of neoplasia is not necessarily linked to life shortening. Within the large limits of variation cited above an excess mortality ratio of 1.5 to 2.0 could be compensated by a lower rate of death from other causes, leaving the death ratio from all causes unchanged with respect to controls [S42].

366. In spite of the small sample size (about 1200 persons) the data on the mortality experience of dial painters convincingly showed that the only causes of death significantly contributing to the life-span shortening in these women are bone sarcoma and carcinoma of the head sinuses, tumours known to be specific risks for ^{226}Ra and ^{228}Ra exposure. To the precision possible with such sample size, therefore, non-specific mortality was not seen, in spite of the known presence of non-stochastic injury in these subjects, for example, in the bone. On the other hand, exposure under these conditions was localized and not extended to the whole body.

367. The experience on the radiology technologists, both from Japan and from the United States, is considerably more limited (and therefore much less significant) than that on radiology specialists. However, on the whole, it does not appear in contrast with the latter. Here again, induction of leukaemia and of some forms of cancer were often seen [K17, K18, M27, K19]; in one case life shortening was reported [K18], but not in others.

368. What may safely be concluded from the data on occupationally-exposed pioneer radiologists is that neoplastic diseases, particularly leukaemia and skin cancer, are real effect. Some life-span reduction may also have been present in these persons who were presumably exposed to high doses; however, this effect was reported unanimously to have disappeared in more recent years in radiology specialists entering their profession after the radiation protection rules have been in operation. If this conclusion is true, it should logically follow that within the range of doses recommended since that time (that is for exposure rates of 1 R per week as a maximum) no reduction of life span can be expected and any residual prevalence of leukaemia and tumour induction would be insufficient to cause a statistically detectable shortening of life.

369. In principle, radiotherapy patients have a number of favourable characteristics for epidemiological studies (knowledge of the dose, good standard of medical follow-up) which might counterbalance some negative aspects (small samples, death associated with the primary disease). In practice, the three small series available on women surviving radiotherapy for uterine cancer [S40, N11, Z1] have yielded negative answers in respect to life shortening. The size of these surveys is certainly inadequate for any firm conclusion, but a negative finding would not be unexpected under conditions where only a small fraction of the body was irradiated. It is known from animal experimentation that life shortening is less likely to be observed after partial-body exposure (see section III.D).

370. The experience on the ankylosing spondylitis patients [C28] does show at a first sight a small but significant prevalence of unspecific mortality. However, a thorough analysis of the causes of death,

discussion of the epidemiological evidence and consideration of the time-course of the excess mortality raise some doubt on the reality of this observation. On these grounds a dependence of the excess non-specific mortality on the spondylitis itself cannot be rejected. Thus, the survey seems inadequate to validate the existence of a radiation-induced non-specific shortening of life.

371. On the whole, therefore, the evidence coming from radiotherapy patients is negative for the presence of the life-shortening effect under discussion. Naturally, the weight to be attached to these data is relatively smaller than that applying to the surveys on occupationally-exposed people and much less than that carried by the studies on A-bomb survivors.

372. The incidence of leukaemia and various other malignant tumours is increased among the survivors of the A-bombs. These diseases are associated with a measure of life shortening and appear to account entirely for the observed shortening of life in the exposed groups, irrespective of dose. The absence of significant non-specific life shortening is important because this conclusion is based upon a large amount of data on person-years at risk. However, the limited experience in connection with the younger age groups where few deaths have occurred should be kept in mind in this regard.

373. The negativity of this survey is remarkable because the modality of the irradiation (acute, high dose rate) would be expected to produce a maximum of life shortening by comparison, for example, with the low dose rate occupational exposures. Also, the absolute amount of radiation absorbed over the whole body (of the order of 1 Gy or more, but for 90% of those exposed below 2 Gy) should also have produced a substantial life-shortening effect. But since there is no evidence to support the hypothesis that a selection of the early survivors might have favourably influenced the subsequent long-term mortality experience [R10], the conclusion must be accepted that up to the present time there is in this large sample of persons no evidence of a diffuse non-specific effect of life shortening. Any long-term effects are, on the contrary, very specific, focal and essentially cancerogenic.

374. In conclusion, the evidence concerning a non-specific radiation-induced life-shortening effect in man has been reviewed in the preceding paragraphs. This review has produced essentially negative answers, except for the pioneer radiologists of the United States. The data from this group of people are, however, in contrast with a massive body of data in experimental animals where such a non-specific effect, particularly at low-medium doses of radiation, cannot be substantiated. The data on the pioneer radiologists of the United States are in contrast with the much larger body of information on the A-bomb survivors. In the latter situation, the degree of life shortening observed can be accounted for by the increased prevalence of a variety of malignancies, although data on the survivorship of younger age groups are still limited. It may be noted in this connection that the early radiologists that experienced a degree of life shortening were exposed at a relatively early age.

375. Pending further evidence therefore, it should be concluded that radiation-induced life shortening in man is essentially due to the induction of specific neoplastic conditions. Non-specific effects on the life span, suggested in one instance, have not been proven beyond doubt: the weight of these data is therefore insufficient to modify the above conclusions.

V. GENERAL CONCLUSIONS

376. The Committee has reviewed in this Annex most of the existing data in animals and man on the subject of radiation-induced life span shortening and has considered the effect thereupon of the major physical and biological variables. The analysis of the Committee has been centred particularly around the possible existence of non-specific mechanisms of premature death, the dose levels at which these mechanisms might operate and their possible relationship to the physiological processes of aging. A non-specific life-shortening action and an aging effect of irradiation were claimed in earlier times on the basis of gross experimental observations of irradiated animals. The Committee believes, however, that a critical reappraisal of previous findings and the availability of more precise and significant new information have now made these concepts untenable.

377. The Committee has briefly reviewed the current concepts concerning natural aging and the possible mechanisms at the molecular, cellular, tissue and whole-body level that might be responsible for senescence. The Committee has also examined the interactions between such mechanisms and their expression in an animal population as statistical events causing the population's extinction in time. It has concluded that there are at present great difficulties in defining aging in ways other than by actuarial parameters and that it is impossible to decide whether the changes revealed by experimental observations in senescent animals are the causes of aging, effects of aging or indeed aging itself. The Committee has therefore decided to confine this Annex to the analysis of life shortening as such, pending further clarification of the notion of aging.

378. All available data consistently show that irradiated animals do experience on the average a shorter life span than their non-irradiated controls. However, the notion that such an effect may be due to the same spectrum of causes taking normal animals to death (although appearing earlier in time) may not be substantiated by experimental evidence. Thus, the idea of a non-specific effect of irradiation superimposable on physiological aging becomes conceptually improbable and logically unnecessary. This is particularly true at doses below the mean lethal dose where life shortening may be accounted for solely on the basis of radiation-induced tumour induction. Under these conditions life shortening becomes a compounded but very imprecise way of expressing by actuarial values the acceleration or higher incidence of tumour appearance in an irradiated animal population. However, at doses well in the lethal range a non-specific component of life shortening may become apparent, which may be substantiated by diffuse damage to the capillary blood vessels or to the connective tissues.

379. The Committee has reviewed and independently analysed the existing life-shortening data on mice submitted to a single acute dose of radiation of *both* high- and low-LET. While in each given experimental series the dose-effect relationships could be of many different forms, pooling many series resulted in an

apparently linear relationship for low-LET and an apparently convex upward relationship for fast neutron exposure. The different forms of the two relationships cannot be explained at present, but the fact that a linear function of dose may reasonably describe life shortening in a highly non-homogeneous population where different strains, ages and sexes are represented has interesting practical implications. Information on other mammalian species such as the rat, the hamster and the dog have also been examined in comparison with the mouse to which most data refer.

380. Single acute irradiation is undoubtedly an easy and efficient way to induce and study life shortening, but long-term irradiation at low doses is the most relevant exposure condition in practice. The existing data on rodents irradiated for the whole duration of their life was examined by the Committee as a function of the dose rate and of the total cumulated dose, for exposure to electromagnetic beams. The lower efficacy of the long-term as compared to the single-dose treatment has been confirmed for x and gamma rays. In the case of neutrons, long-term treatments have in some instances shown reduced life shortening compared with single doses and in others increased life shortening, particularly in more recent studies. Under long-term conditions of exposure phenomena of apparent life lengthening have been reported whose significance has also been discussed. The special case of chronic exposure to many injected, ingested or inhaled radionuclides has been studied but has revealed no life shortening in excess of that attributable to the induction of specific tumours caused by the various nuclides.

381. A variety of observations exist in experimental animals concerning the effect on life shortening induced by changes in the dose rate, dose fractionation and chronic exposure terminated before death of the animals. The Committee has reviewed this information and has concluded that all these treatments, but each to a variable degree, result in a level of life shortening which is intermediate between that of the acute and of the life-long treatments. Repair and repopulation mechanisms are operating under such circumstances. These mechanisms appear to depend markedly on dose and time parameters as well as on a large number of biological variables, following complex relationships.

382. A linear relationship for gamma rays, as suggested in paragraph 379 implies no dose rate dependence. Therefore fractionation of the dose or continuous irradiation at low dose rates should not reduce life shortening per unit dose. This however is at variance with the Committee's conclusions about the experimental observations (paragraphs 380 and 381). Thus a linear-quadratic relationship which can provide for the observed effects and which is equally likely according to the analysis in paragraph 95, might be preferable to a simple linear dose-response relationship. At low doses and dose rates the form of the response would be essentially linear in either case, but not with the same slope.

383. For neutrons, the convex upward shape of the dose-response relationship for single doses intrinsically implies an increased effect when the dose is fractionated or when low dose continuous irradiation is used. As has already been noted, the experimental results with neutrons have been mixed. In some cases, life shortening appeared to be reduced by lengthening the exposure, in other cases (particularly in more recent experiments) it is increased by fractionation. It is possible that real differences in dose-effect relationships for different tumour end-points do exist, and that these account for the complexities observed in the life shortening response for different strains or species.

384. The RBE of fast neutrons up to 14 MeV, as compared to low-LET radiation, has been assessed from published data and from the Committee's own analysis. For acute doses in the region of 0.01 Gy of neutrons, the RBE cannot be determined precisely. The predicted values could be about 10, but values as high as 50 might be possible, depending upon the assumed shape of the dose-response curves. Low-LET radiation appears to be about seven times less effective in studies with duration-of-life exposure than it is for single exposures. At low dose rates and duration-of-life exposure neutrons could be 20 to 40 times more effective than low-LET radiation.

385. The vast majority of the data reported on rodent and non-rodent species of mammals submitted to radiation of different types delivered at various dosages appeared, when appropriately analysed, to be consistent with the notion that life shortening after doses up to about the $LD_{50/30}$ can be accounted for essentially by an acceleration or an increased net incidence of tumours causing premature death. No data were found to clearly support the concept that radiation may advance in time or accelerate the appearance of diseases normally associated with senescence, without any change in the type and the relative incidence of these diseases.

386. The spectrum of radiation-induced diseases and the consequent life shortening depend largely on the specific physiological and pathological characteristics of the irradiated animals. The Committee has reviewed the evidence pertaining to the changes in life shortening seen in different species of animals. Such data had been obtained in the hope of constructing a scale of radiosensitivity values to aid in the extrapolation of findings from animals to man. The conclusions to be derived from such data may, however, hardly be taken as useful generalizations in view of the large differences pointed out above. Comparisons between strains of the same species, the mouse, have also been attempted and have revealed interesting regularities in the life-shortening response, in spite of the strain-related specificities. The formal genetic analysis of these findings is not yet sufficiently advanced to allow the identification of the common principles underlying the precocious death of animals through a variety of specific causes.

387. Extensive data led the Committee to conclude that the sex of the irradiated animals is also a significant variable affecting the susceptibility to life shortening: female animals are in general more sensitive than males, mostly owing to their higher rate of genital tract tumours and leukaemia in mice. As to the effect of age, irradiation in utero seems to produce usually less life shortening for a given dose than irradiation during the post-natal ages. Irradiation early in extra-uterine life also produces, all other conditions being equal, more life shortening than treatment in older ages. Physical conditions (temperature, stress), chemical treatments (oxygen, radioprotective substances) and partial-body irradiation have been studied in respect to their influence on life shortening. The presence and the extent of these effects have been assessed by the Committee.

388. Data derived from irradiation of human subjects were the object of special attention in this Annex. They were obtained through epidemiological investigations carried out on persons exposed in the course of their professional life (radiology specialists or technicians, dial painting workers), on patients treated with radiation for various pathological conditions (tumours, ankylosing spondylitis) or on survivors of the atomic explosions in Japan. The Committee has investigated the reliability of the different series from the point of view of exposure conditions, dose assessment, methodology of study and significance of the conclusions.

389. With regard to occupational exposure, it has repeatedly been shown that a component of life shortening observed in radiology specialists exposed in the United States during the early days of clinical radiology cannot be accounted for solely on the basis of tumour induction. Such a component has apparently disappeared at about the time when radiation protection recommendations limiting exposure to less than 1 R per week came into practice. Analogous investigations carried out on a group of British radiologists were unable to reveal such an effect. Numerous other studies conducted on radiology technicians or on dial painters (these latter series carry less weight due to the smaller size of the groups) were also negative for the presence of non-specific life shortening. The Committee therefore concluded that the existence of such an effect is doubtful under the conditions of the above studies or, more conservatively, that exposures to 1 R per week or less does not cause any detectable non-specific shortening of life in man.

390. With regard to medical exposure, investigations on patients treated with localized radiotherapy for cancer of the uterus did not reveal any life-shortening effect. A survey on spondylitis patients was inadequate to validate the presence of life shortening associated to the radiation treatment rather than to the disease itself requiring radiotherapy. Although the importance to be attached to these conclusions is limited by the modality of the treatment (partial-body) the conditions are also, in general, against the notion of non-specific life shortening.

391. The epidemiological series in man which carries by far the highest degree of significance and reliability for the numerosity and the accuracy of the observations is that on the A-bomb victims. For the last thirty years and up to the present stage of the observations this series has indisputably shown that there is no evidence of life shortening that could not have been explained by an increased appearance of leukaemia and solid tumours.

392. In essence, the review of the Committee has been unable to substantiate in experimental animals and in man a non-specific effect of life shortening below the mean lethal dose. While the presence of such an effect cannot be excluded for higher doses, there is no firm evidence that diffuse non-specific mechanisms causing premature death in the irradiated animals may be operating at the low doses and dose rates of significance to the radiation protection of man. On the contrary, long-term radiation effects are very specific and essentially cancerogenic under these conditions. In the light of present data, a higher incidence of tumours fully explains the life shortening seen in the irradiated populations.

VI. RESEARCH NEEDS

393. Given the above conclusions, the Committee believes that experimental research specifically designed to analyse the physical and biological variables affecting radiation-induced life shortening only should not be assigned high priority. It is, however, advisable that the collection of data on life span might proceed in parallel with other experiments planned for different purposes, in particular for the study of induction of neoplasia. Specific recommendations as to the general strategy and the detailed topics to be followed in this field have been issued in previous reports of the Committee. In order that the best use might be made of data on life span shortening obtained in the course of long-term experiments, these data should be collected and analysed according to methodological needs repeatedly discussed in the preceding text.

394. For the actuarial analysis of the data, use of the following methodologies is recommended:

(a) Analysis of mean and median ages at death and survival times following standard statistics, both as absolute parameters and relatively to the control values;
(b) Analysis of the extinction curves of the irradiated versus the control population;
(c) Analysis of age-specific mortality rates in irradiated and control groups;
(d) Corrections of the life-shortening data to account for the effects of competing diseases by methods which have been shown to enhance the capacity to discriminate between specific and non-specific causes of death;
(e) The use of multifactorial models in the analysis of complex physical, physiological and pathological interactions.

395. Attention has been repeatedly drawn to the fact that in order to assess specificity or non-specificity of life shortening detailed clinical surveillance during life and pathological examination of the animals at death is necessary. Although the assessment of causes of death is difficult in animals, it is essential if the data to be gathered are to be of the most use. Serial sacrifice experiments, whether included in life-span studies or not, would be particularly valuable to investigate the evolution in time of the diseases contributing to premature death. Attention should also be drawn to the renewed importance of interspecies extrapolation, not only for life shortening but for tumour induction as well, because of the lack of human information for some types of radiation, including neutrons. In this regard experiments in species intermediate in life span between mouse and man are of special importance. Questions of particular interest at this time relate to the sensitivity of embryos to life shortening and to tumour induction among the different species.

396. The Committee's recommendation for a low priority to be assigned to research solely on radiation-induced life shortening derives from the opinion that such an effect may be explained at low doses and dose rates by tumour induction, with addition, at higher dose rates, of specific non-stochastic effects described in Annex J. It is perfectly compatible with the well established fact that gaps still exist in knowledge of the life-shortening effects of radiation in mammals. The

Committee has identified many areas which could profitably be explored among which are:

(a) The analysis of physical and biological factors contributing to the life-shortening effect in complex regimes of long-term irradiation;
(b) The analysis of the causes leading to an apparent life lengthening for irradiation at low doses and dose rates and the influence of biological variability or repair phenomena thereupon;
(c) The problem of RBE, particularly at low doses and dose rates, of radiations of different qualities;
(d) The dose levels at which non-stochastic effects as well as tumour induction might become of importance in the causation of death after whole or partial-body irradiation;
(e) The extent and mechanisms of life shortening after pre-natal irradiation;
(f) The influence of modifying factors, including radiosensitizing and radioprotective treatments;
(g) The role played by the different pathological conditions in determining the form of the dose-effect relationship for life-shortening;
(h) The comparison of life-shortening effects in different species.

397. The Committee believes that the collection of data about the effect of radiation in causing or contributing to deaths in men should continue to be given the highest priority. This applies not only to the series on the atomic bomb victims which will undoubtedly be followed with care, but to all other groups and particularly to those undergoing occupational exposure and to patients treated by radiation for benign diseases and for cancers with a good prognosis. The final conclusions drawn from such data will be of immediate relevance to the knowledge and prevention of radiation effects in the human species. This recommendation is made since further knowledge is needed regarding deaths from non-stochastic damage, in addition to cancer induction, at as wide a range as possible of both dose and dose rate.

398. The loss of life expectancy by affected individuals in whom a tumour has been induced by radiation is an important factor in risk estimation. It involves a knowledge of the frequency of induction of each tumour, the average latent period and the average age of the population at risk. The lost time per affected individual can then be used as a basis for comparison of hazards between occupations involving exposure to ionizing radiation and, for example, lost time due to accidents (fatal and non-fatal) in a range of industries [14]. These estimates can also be used to derive an average loss of life span for the entire population at risk from a given average dose. It would be useful to have direct estimates of the life shortening per unit dose for populations such as the Japanese survivors, when these are feasible.

Table 1

Life shortening after single acute whole-body x- or gamma-ray treatments

Species and strain	Sex	Radiation	Percentage life lost per Gy or per 100 R	Range of percentage shortening	Days lost per Gy or per 100 R	Form of curve g/	Ref.
Mouse							
10 strains	M	98 kVp x	4.2	?	15	linear	[G2]
BAF1	M	80 kVp x	4.2 a/	30.2	24	?	[G3]
	M	135 kVp x	4.9 a/	30.4	29	?	
	M	250 kVp x	4.6 a/	27.2	27	?	
	F	80 kVp x	6.7 a/	39.2	35	?	
	F	135 kVp x	5.2 a/	32.1	34	?	
	F	250 kVp x	6.7 a/	39.2	43	?	
CAF1	F	250 kVp x	3.2-6.3	19	21-42	convex upward?	[K7]
Swiss	F	250 kVp x	4.7	0-30	19	linear	[S17]
CF1	F	gamma from weapon	2.6	8-37	25	linear	[S18]
	M	x rays	7.8-10.9	11-31	?	convex upward?	[B8]
LAF1	M	gamma	5.0 b/	3-45	37 c/	concave	[U5]
	F	from weapon	6.3 b/	10-51	47 c/	upward	
6 strains	M	200 kVp x d/	4.1	23.2	28	concave	[G4]
	F		5.4	30.6	81	upward	
SAS/4	M+F	15 MeV x	5.4	5-44	40	linear	[L1]
RF/J	F	250 kVp x	9.1	36.5	45	linear?	[S19]
RF	F	60-Co gamma	4.7	28-85	25	linear	[S21]
RF/Un	M	250 kVp x	-	3-31	56-3	convex	[U7]
	F	60-Co gamma	-	5-29	15-2	upward	
C57BL/6L	F	300 kVp x	4.1 e/	3-32	23 e/	convex	[Y1]
A/J	F	300 kVp x	5.9 e/	7-38	29 e/	upward	[Y1]
RF	F	300 kVp x	7.7 e/	6-32	75	convex upward	[C12]
LAF1	M+F	60-Co gamma	2.5 e/	7-29	15	concave upward	[G5]
B6CF1	M	60-Co gamma	5.3	5-42	45	linear	[A7]
	F		5.3	6-43	48	linear	
(C57BLxC3H)	M	250 kVp x	2.5	0-9	22	linear?	[C13]
BALB/c	M	250 kVp x	7.3	0-66	54	linear?	[M8]
C57BL	M	250 kVp x	9.8	0-48	68	linear?	[M8]
RFM	F	137-Cs gamma	9.6 e/	0-38		complex	[S44]
	M		6.7 e/	0-20		linear?	
BALB/c	F	137-Cs gamma	7.0 e/	0-14	39 e/	linear?	[S44]
B6CF1	M	60-Co gamma	5.1 e/	0-40	42 e/	linear	[T4]
	F		5.2 e/	0-45	43 e/	linear	
Rat							
Wistar	M	250 kVp x	4.2-4.9	7-29	35-41	linear?	[H5]
	F		2.8-4.0	4-24	15-22	linear	
	F	250 kVp x f/	0.4	39	28	?	[L3]
Dog							
Beagle	F	250 kVp x	6.7	3-24	284	linear?	[A2]

a/ Data derived on the hypothesis of linearity from experiments at the LD_{50} level.
b/ Figures obtained at the LD_{50} level.
c/ Figures derived from Grahn and Sacher [G1].
d/ Average for all strains.
e/ Data derived on the hypothesis of linearity.
f/ Data derived from a single exposure of 100 R given under 5 % oxygen.
g/ As given by the authors.

Table 2

Life shortening after single acute whole-body neutron treatments

Species and strain	Sex	Radiation	Percentage life lost per Gy or per 100 R	Range of percentage shortening	Days lost per Gy or per 100 R	Form of curve c/	Ref.
Mouse							
Swiss	F	thermal column	4.7	0-30	19	linear	[S17]
CF1	F	weapon neutrons	4.7	8-30	37	linear	[S18]
LAF1	M	weapon	6.7	9-23	79	concave	[U5]
	F	neutrons	15.6	9-39	6	upward	
CF1	F	fission neutrons	22 a/	9-45	6	linear?	[V1]
RF/Un	M	1 Mev	9.0-18.0	19-28	21-6	convex	[U7]
	F	neutrons	8.4-14.9	33-47	11-3	upward	
	F	14 MeV neutrons	6.7 a/	9-26	40	convex upward	[D1]
BC6F1	M	fission	35.9 b/	7-26	300- 90	convex	[A7]
	F	neutrons		9-31	390-110	upward	
RFM	F	fission	45-77	4-25	-	convex	[U8]
		neutrons	42-70	0-20	-	upward	
B6CF1	M	fission	-	0-25	-	convex	[T4]
	F	neutrons	-	0-31	-	upward	
Rat	M	fission neutrons	10 a/	22	-	?	[K8] [K9]
Guinea-pig	M	fission neutrons	12 a/	12-16	~ 100	?	[K8] [K9]

a/ Estimate derived from a first-approximate assumption of linearity.
b/ Estimate derived from data at the smallest dose of 0.2 Gy.
c/ As given by the authors.

Table 3

Approximate scales of sensitivity of various animal species for the life-shortening effects of irradiation

Irradiation condition	Approximate sensitivity			Refs.
	More sensitive		More resistant	
Chronic x-irradiation	Monkey	Rat, dog and mouse about equal	Rabbit	[B11]
Acute x- or γ-irradiation		Rat and mouse about equal		[U1]
Chronic γ-irradiation	Man	Guinea-pig, rat, dog and mouse about equal		[G1] [S23]
Chronic γ-irradiation	Guinea-pig	Man, dog and mouse about equal		[G6]
Chronic γ-irradiation		Dog and mouse about equal		[N7]
Chronic γ-irradiation	Goat	Mouse		[H9]

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ANNEX L

Biological effects of radiation in combination with other physical, chemical or biological agents

CONTENTS

Introduction

1. In man's living and working environments situations are often encountered in which different ambient factors of a physical, chemical or biological nature could conceivably combine with ionizing radiation in giving rise to undesirable effects. In this paper for the first time the Committee considers the combined action of radiation with potentially important environmental conditions. Since this paper concentrates on radiation in environmental circumstances, three important areas of combined action between radiation and chemical agents are not considered here. The first concerns the combined action of chemical agents (both chemotherapeutic compounds and sensitizers of various kinds) to enhance radiation effects in clinical radiotherapy [B28, D24, D25, H28, H29]. The second results from the restriction of this paper to radiation effects combined with agents which affect carcinogenesis, not therefore including combined effects in mutagenesis. This area may be considered by the Committee in the future. The third area not treated in detail in this paper is the effects of a combination of protective agents with acute radiation exposure [A12] because this subject is of only minor importance in estimation or modification of risk.

2. There is a great scarcity of systematic data on which an analysis of combined effects can be based, in

spite of the large number of reports where combined actions were tested and interactions claimed. Thus, this Annex must be somewhat different from others in which a large body of literature data is reviewed and systematically analysed. This Annex will be instead more hypothetical and will attempt to suggest definitions, to identify suitable methods of analysis, to select from a large amount of diffuse information the conditions and the data of importance for further consideration and to provide suggestions for future research.

3. The following review of experimental or epidemiological data should be simply taken as an illustration of some theoretical analyses using examples from the literature. These considerations point, on the one hand, to the very preliminary character of this Annex and, on the other hand, express a word of caution against hasty conclusions in view of the present state of knowledge and the large variety of situations encountered.

4. There are many instances of possible combined actions in which different agents may interact with ionizing radiation. Among the physical agents, for example, temperature should be considered. It is well known that ambient temperature in different environments may vary within a range of about 70°C although control mechanisms allow man to survive under the most extreme conditions. It is also known, however, that small changes in the temperature of cells may result in striking changes of cell survival upon irradiation. These changes are presently being investigated for their potential in cancer therapy [C1, F2, D16]. Ultraviolet light, itself carcinogenic, sound, ultrasound and vibrations are present in many living and working environments and may give rise to combined actions. The same can be said for static electromagnetic fields, and high-frequency or very high frequency (microwaves) electromagnetic radiation.

5. Man-made (xenobiotic) chemicals in the environment are a major concern for toxicologists. According to some estimates [M2] the number of identified molecules is now more than four million and every year a few hundred thousand new items are added to the list. There are some tens of thousand chemicals in common use in modern societies, not including pesticides, pharmaceuticals and food additives. The so-called "energy related pollutants" are also to be considered in this category. They include the oxydes of carbon and nitrogen, sulfur compounds, polycyclic hydrocarbons and some others. Among them 3,4-benzo(a)pyrene (BP) is frequently used as an index of polycyclic hydrocarbons with cancerogenic properties [S2]. Its yearly production is estimated to be approximately 5000 t [S31]. The time course of its production may be followed, for example, by lake sediment analysis [H11]. The concentration of BP in the air of large industrial cities may reach values of 100 ng/m^3 [B10]. BP is also one of the many chemical constituents of tobacco smoke and may be considered of importance for some sections of the population occupationally exposed to radiation. The circulation of BP and of other polycyclic aromatic compounds in the environment has been studied extensively [S2, S31].

6. The list of chemicals whose action might combine with that of radiation in the environment is very extensive. Special attention should be given to situations of practical interest where the chemical agents themselves have carcinogenic properties [H21]. For example, many industrial effluents contain trace elements such as arsenic, nickel or chromium. These substances may produce carcinogenic or mutagenic effects [T7]. The same is true for dust and fibres. Dust is a very common and widespread industrial emission and a component of many occupational environments. It has been reported that dust or fly ash from power stations may have carcinogenic properties [K9] or may serve as carriers of trace metals, radioactive nuclides or polycyclic aromatic hydrocarbons [B22]. In mines mineral dust may combine with the organic products of diesel exhausts and with radioactive radon and thoron daughters [C16]. Asbestos fibres are also often a significant component of occupational and home environments which may include ionizing radiation.

7. High levels of mutagenic chemicals have been reported in many types of food [S32]. Broiled meat and fish contain mutagenic compounds arising from the pyrolysis of proteins and aminoacids. Mutagens and co-mutagens have also been reported in derivatives of vegetable foods, such as caffeine. As mutagenicity often correlates well with carcinogenicity, the above substances may be considered potential carcinogens, both alone or in combination with radiation. According to some estimates [H2] up to 20–50% of spontaneously occurring human tumours can be attributed to diet. Some pharmaceutical substances are also known for their carcinogenic potential: depending on their use and diffusion they could also be considered as candidates for combined actions.

8. Among biological agents, viruses may be regarded as environmental factors likely to interact with radiation. It is well known that some viruses have an important role in the aetiology of some radiation-induced animal tumours as specific agents. There is a possibility that specific agents of a similar nature may be involved in the induction of tumours in the human species and non-specific associations or combined actions, even though on a purely speculative basis, may be visualized. Natural hormones could also be viewed as a special case of interaction in view of the well-known dependence on the hormone level of some forms of radiation-induced tumours in experimental animals.

9. There are two ways of carrying out an analysis of combined actions. The first is to search for any possible effect, whatever its practical significance or quantitative value might be. The second is to concentrate on those effects that may be of importance for the assessment of risk in man. The first approach is that to be followed in the present preliminary analysis. The present practice in radiation protection is that of assuming sensitivity values across the population which apply to all groups, e.g., to males and females of all ages. This practice does not deny the existence of real changes in the susceptibility between various classes of people, but recognizes the convenience that for practical purposes a single average value of the risk is desirable and sufficient.

10. In acknowledging the merits of this approach, the Committee wishes to emphasize that unless the effects to be validated as synergistic or antagonistic are extremely important (i.e., unless they might lead to changes of at least an order of magnitude in the risk estimates) and unless they also applied to substantial fractions of the population at large, they presumably may not be of relevance in assessing risk estimates in man. The above consideration applies to the estimation of risks for radiation protection purposes. It does not contradict the fact that if some synergistic or antagonistic effects can be identified under specific exposure

conditions of occupational or medical relevance, appropriate actions should be taken to change such conditions. Under such circumstances, however, the problem would not be any longer one of radiation protection philosophy, but rather one of practical occupational medicine. It would not involve basic changes in the approach to such matters but specific remedial local actions.

11. Radiation effects with particular regard to carcinogenic and to genetic and developmental consequences of irradiation were considered by the Committee in its 1977 report [U1]. Non-stochastic effects of whole- or partial-body irradiation (Annexes K and J, respectively) and genetic effects (Annex I) are also discussed in this report. When reviewing such a broad field as that of combined actions, no effects should be excluded from consideration at whatever level (subcellular, cellular, tissue, organ, whole-body) they may be manifested. This is particularly true in view of the heterogeneity of the data available and of the fact that understanding of combined effects will eventually require knowledge of the mechanisms involved. That is why effects other than those mentioned above will be discussed in this Annex. However, the main emphasis will be on stochastic effects. Where possible, epidemiological data will be considered, even though studies of this sort are rare and often statistically inconclusive.

12. Each of the possible interacting agents may act alone in producing biological effects or may only be active in conjunction with other factors, particularly radiation. Exposure to any of these agents may be acute, subacute or chronic, within a wide range of doses and dosages. The pattern of exposure may also play a role, as the contemporaneous action of the various agents or the order of their sequence and the intervals between treatments may conceivably affect the quality or the degree of the effect. Of all possible situations of combined actions the Committee chose to particularly investigate conditions where long-term exposure to low levels of the agents on large human populations may apply, because these conditions may possibly affect radiation risk estimates in man.

13. The combined action of several agents is not a new problem in medicine. As early as 1928 Loewe [L1] quantitatively reviewed the approaches to the assessment of the action of combined drugs. So-called "isobolic diagrams" were proposed in this regard. This Annex will consider this approach in detail, as well as other approaches extensively used by toxicologists [M1, T1]. Some of these ideas were adapted specifically for the needs of the Annex and illustrative material has also been derived and modified for the same purpose.

14. Nomenclature in the analysis of combined actions was a problem that was recognized very early [L1]. In order to simplify the discussion to follow, it is appropriate to provide some clear definitions and terminology. Two classes of combined effects will be considered. In the first class, both ionizing radiation and the other agent (or agents) produce the effect under discussion. The second class includes the combinations where ionizing radiation produces an effect whose nature or amount may be modified by the other agent which by itself is inactive. This classification is only made as a convenient approximation.

15. For the first class of interaction there are three types of combined actions. When the end-effect of the combined action equals the sum of effects of the two agents acting independently, the resulting situation is one of "additivity". If additivity does not apply, then there are two possibilities. When the effect of the combined action exceeds the sum of the effects produced separately by the agents, the situation is one of "synergism". Finally, when the combined action results in an effect which is less than expected from the sum of the action of the interacting agents, the situation is termed "antagonism". The precise meaning of the "sum of effects" will be expanded further in chapter I. The notion of summation of effects pre-supposes the existence of a quantity which may be meaningfully added.

16. The concept of additivity cannot be extended to the second class of combinations since radiation is here the only agent capable of producing an effect. Under these circumstances the comparison is usually between doses of radiation producing the same amount of effect in the absence or in the presence of the modifying agent. If, for a certain degree of effect, the dose of radiation required is greater in the presence of the modifying agent, the resulting action is termed "protection". Conversely, when the dose of radiation is less for the same degree of effect in the presence of a modifying agent, "sensitization" occurs.

17. The above classification is not an absolute one. For example, sensitizing substances which have been assumed to be inactive, may be able to produce some effect at high exposure levels. Also, if one considers carcinogenesis as an effect, promoters may be viewed as a special case of sensitizers and many promoters may show initiating properties. The low environmental levels of the interacting agents are mainly those of interest in this Annex. At these levels the threshold-type dose-response curves of the sensitizers and promoters may render their contribution negligible or zero. A unified approach to both classes of interaction in terms of interaction coefficient and more precise quantitative definitions of the concepts introduced in the above paragraphs will be developed in chapter I.

18. For exposure of the public the most significant man-made source of irradiation is for diagnostic medical purposes where the yearly dose equivalents may be up to the order of a few millisievert (mSv) (see Annex G). Sources of occupational exposure are much more varied and may range from exposure to radon in mines to x rays generated by electronic appliances. The yearly occupational exposure according to ICRP recommendations should not exceed 50 mSv [I1]. Average yearly exposures to natural sources of radiation are between 2 and 3 mSv (see Annex B). The actual occupational exposure in industry has average values of about 5 mSv (see Annex H). Thus the other physical, chemical or biological environmental agents would combine with ionizing radiation at levels of the latter of 1–10 mSv per year. These levels are usually referred to as low doses.

19. It is sometimes held that in view of the ubiquitous nature of background radiation all experimental or epidemiological studies on the toxicity, carcinogenicity or mutagenicity of chemicals or other agents are automatically performed to account for the concomitant radiation risk. All the relevant risk assessments would therefore be in essence assessments of combined action [S1]. This may be too broad a generalization for the following reasons. Firstly, the actual levels of exposure to ionizing radiation may be orders of magnitude higher than those cited in the preceding

paragraph, and the levels of the other agents orders of magnitude lower than those at which experimental risk assessments were performed. In view of the non-linearity of the dose-response relationships for most chemical agents, extrapolation of the risk assessments between such widely different situations would be unwarranted. On the other hand, some chemicals which are ineffective in producing detrimental changes when acting alone, may instead provide a significant modification of the radiation action, as in the case of carcinogenic promoting substances. Animal experiments are usually carried out at levels of exposure to chemical or other agents which are much higher than those found in the environment, which weakens the basis for extrapolation. Under such conditions of great uncertainty the best course of action is to reserve any judgement and to investigate the facts.

20. In summary, the scope of this Annex is:

(a) To review possible quantitative approaches to the assessment of the combined action of radiation and other environmental conditions, based on the concepts of additivity, synergism, antagonism, sensitization and protection;

(b) To explore whether and to what extent concepts in other fields of the biological sciences may be applied to the special case of interaction with radiations, particularly at very low doses of the combining agents;

(c) To consider experimental results on the combined action of radiation and other conditions, in order to elucidate possible mechanisms of action that may allow generalizations and extrapolations;

(d) To review existing epidemiological data on subgroups of populations living or working under the action of radiation and other environmental toxic agents;

(e) To identify possible areas for useful research in the field of combined effects.

I. MODES OF INTERACTION

A. GENERAL APPROACH

21. When examining the concept of combined action it is useful to start with the definition of a quantity referred to here as "exposure", X, which may apply to any environmental agent [L3, L4]. Exposure is the independent variable in exposure-effect relationships. Without exposure to the agent there can be no effect over the spontaneous level and with increasing exposure the effect appears to follow some kind of functional "exposure-response" relationship. This generalized concept of exposure is different from the notion of exposure in radiation physics (see Annex A). In the case of ionizing radiation the absorbed dose, D, is used instead of the exposure and "dose-response" relationships are established to functionally relate the energy absorbed by the irradiated object with the response observed. If radiation quality must be taken into account, the quantity defined as dose equivalent, H, may be used in place of the generalized concept of exposure, X.

22. The definition of exposure (or dose), X, is more difficult in the case of other agents [L3]. Often this notion includes the product of some intensive quantity (e.g., energy flux per unit area per unit time) multiplied by an extensive quantity (e.g., the time during which the agent acts on the biological system). It has been proposed in the case of chemical compounds [E1] to define exposure as the number of primary chemical events leading to the final effect, but at present the nature of such events is only known in rare cases and their quantification exceptional. The concentration of an agent may often meaningfully be taken as the intensive quantity, multiplied by time as the extensive one. The notion of exposure is by definition extensive and in the case of a chemical substance it could be represented by the formula

$$X = \int_0^t C(t)\,dt \qquad (1)$$

Obviously, to give exposure some biological meaning, the concentration of the agent, C(t), should be expressed at the level of the target biological structure, but this is often impossible. A useful type of exposure characterization such as the pharmacological dose (the quantity of the chemical introduced per unit weight of the organism) does not provide such information. In these cases special assumptions concerning the intake, retention, metabolism and excretion of the agent under investigation must be made [L3, W4].

23. Even the relatively simple case of a chemical acting on a culture of cells in vitro may require special consideration of the kinetics of the substances involved and of the different forms of their possible transformation [W4]. One may, for example, consider a scheme whereby a chemical A is converted into intermediate B which is in turn transformed into a cell-bound moiety C leading to the observed effect:

$$A \rightarrow B \rightarrow C \rightarrow$$

Clearly the concentration of C is the quantity to be used in equation (1) to express the exposure. It often happens, however, that the only information available is on the chemical A, the most readily measurable quantity, and this information may not be directly proportional to the values for C. Thus, there might be apparent absence of effect, in spite of a high concentration of A, on account of absence of moiety C, at least at the beginning of exposure.

24. Thus, the metabolic activation of chemicals into active forms is of great interest [M19, S33]. Chemical carcinogens are known to be subject to complex processes of enzymatic reactions in vivo. The chemical compound introduced into the body may be considered as a pre-carcinogen which, through various reaction pathways, will eventually produce proximate and ultimate carcinogenic derivatives. From a purely chemical point of view, one of the important generalizations of the recent years is that the ultimate forms of chemical carcinogens are usually electrophilic (i.e., electron-deficient) reactants. Many specialized examples of such processes are considered in the above mentioned reviews [M19, S33].

25. In some cases the binding of chemicals with cell constituents may be monitored by the use of radioactive labels. Examples of such studies in vitro with two derivatives of nitrosourea were provided in [W4]. Experiments in vivo are also available [E1, W9, P8] in which correlations are established between the administered doses of the compounds, the amount of bound moieties and the biological effects. These studies help clarify the concepts of administered versus active doses of the compounds.

26. If the exposure, X, to a given interacting agent (or to several agents) may be satisfactorily defined, the

definition of the effect, Y, should be considered. There are different ways of expressing in quantitative terms the response of a biological object. Y may be, for example, the fraction of cells showing loss of a specific function or the fraction of exposed animals affected by a given mutation or carrying a given type of tumour. In such cases Y describes the probability of induction of that given effect as a result of the exposure X. In other cases Y may describe the degree of a given effect: for example, the weight loss of an exposed animal, the mean number of tumours per animal, changes in various haematological indices. Graded effects may sometimes be reduced to probabilistic quantities by appropriate analysis, but this is not always the case and it may represent a limitation.

27. The simplest functional relationship between exposure and response, $Y = F(X)$, is the linear one:

$$Y = Y_0 + kX \qquad (2)$$

Here the term Y_0 accounts for the effect produced in the absence of exposure or of any other known cause in an apparently spontaneous fashion. The coefficient k defines the sensitivity of the biological system to the agent. When the separate action of each agent is described by equation (2), then the increment of response of the system to each agent may be written as

$$\Delta Y = Y - Y_0 = kX \qquad (3)$$

If one assumes that the increments of response to one agent are independent of the presence of the other interacting agent, the increment of response for the simultaneous action will equal the sum of increments ΔY_1, ΔY_2

$$\Delta Y = k_1X_1 + k_2X_2 \qquad (4)$$

This is the situation of additivity.

28. However, the experimental value of ΔY in case of a combined action can be higher or lower than the ΔY expected from equation (4). If $\Delta Y_{obs} > \Delta Y_{exp}$ the situation is defined as synergism. If $\Delta Y_{obs} < \Delta Y_{exp}$ the situation is one of antagonism. As a measure of the deviation of the experimental results from additivity one may introduce an interaction factor

$$\omega = \Delta Y_{obs}/\Delta Y_{exp} \qquad (5)$$

The value of $\omega = 1$ will correspond to additivity, $\omega > 1$ to synergism and $\omega < 1$ to antagonism.

29. The above concepts may be represented in a graphical form as in Figure I. Here a given level of response Y* is chosen, which level may be obtained by the action of each agent separately (X_1^* or X_2^*, respectively) or by the combined action of both agents at variable exposures X_1 or X_2. If additivity is operating and equation (4) is applicable, all points (X_1, X_2) producing the level of response Y* must lie on the middle diagonal line of Figure I. This line is called the isobolic line and the diagram is called isobolic diagram [L1]. The scale of Figure I is chosen in such a way that the co-ordinate value equals 1 for each agent acting separately, that is. $X_1/X_1^* = 1$ and $X_2/X_2^* = 1$.

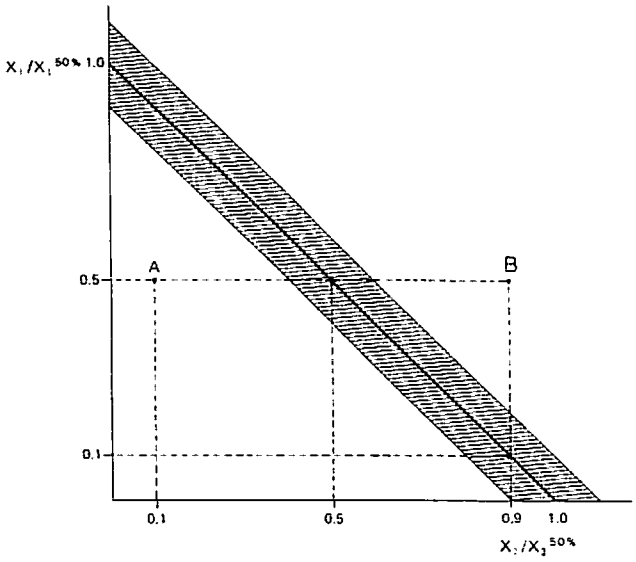

Figure I. Isobolic diagram in case of linear additive response to the action of two agents

30. The isobolic line in Figure I describes an ideal case of additivity, but all experimental exposure-response relationships are affected by errors. In real situations therefore the line of additivity expands to an area of additivity, such as that covered by the horizontal shading lines in the same figure. If the exposure-response relationships for the agents acting separately are linear, the type of interaction may be defined by simple graphical procedures. For a given level of effect, Y*, several levels of exposure to both agents are tested: if the experimental points (X_1, X_2) fall into the area of additivity, the interaction will be regarded as additive. If the points fall to the left of the area of additivity, the interaction will be one of synergism; and, conversely, one will be dealing with an antagonistic interaction when the experimental points are found on the right-hand side of the area. In Figure I the experimental point A would be regarded as confirming synergism, experimental point B as confirming an antagonistic interaction.

31. As an example of the application of this analysis, the experiments of Murthy et al. [M3] on diploid yeast BZ34 may be of interest. The cells were irradiated by ^{210}Po alpha particles or by ^{60}Co gamma rays separately or in combination. The end-point studied was reversion to arginine independence. Linear dose-response relationships were found for both radiations given separately with slopes of 25.5 ± 2.6 and 10.9 ± 0.4 reversions per 10^6 survivors per Gy applying to the alpha and to the gamma radiation, respectively. In the case of combined simultaneous treatment with both radiations (25% of the dose was by alpha radiation at 0.5 Gy/min and 75% by gamma radiation at 1.54 Gy/min) the slope of the regression line changed to 17.7 ± 0.9 reversions per 10^6 survivors per Gy. The results may be interpreted by an isobolic diagram, as in Figure II. For the level of reversion Y* = 180 rev/10^6 survivors the dose of ^{60}Co gamma would be 15 Gy and that of ^{210}Po alpha 6.4 Gy. The dashed lines parallel to the isobolic line in Figure II establish the 95% confidence limits. If one plots the points corresponding to the same level of reversions for the two agents combined, one finds the point denoted A which lies clearly to the left of the area of additivity. It is concluded that synergistic interaction of the two agents applies in this case. This is an example of isobolic diagram analysis in its most simple form.

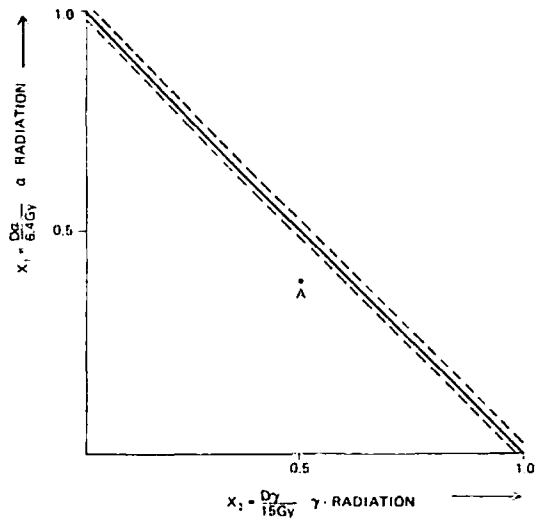

Figure II. Isobolic diagram for reversion of yeast to prototrophy (Y = 180 rev/10^6 survivors) under the action of alpha radiation from polonium-210 and gamma rays from cobalt-60 [M3]

32. In the above example the mutation frequencies could be meaningfully added because their increase with dose was linear. The same procedure is not applicable when the effects change as exponential or sigmoid functions of the dose, unless the dose-response relationships may be converted to linear or quasi-linear functions.

33. The process of additon itself may be performed in two ways. The first, takes the response to the dose A from the survival curve A and adds it arithmetically to the response to dose B from survival curve B. Both doses are counted from the origin of the co-ordinates. Loewe [L1] designates this type of addition as heteroaddition. A second process of addition, called isoaddition, is also possible. Let us assume that agent A is applied before agent B (Figure III b, e, h). Figure IIIa shows the

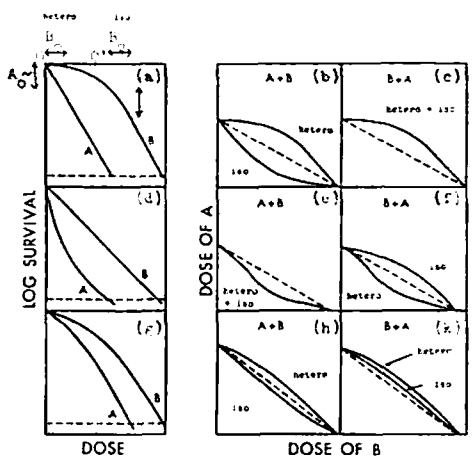

Figure III. Examples of hetero- and iso-addition for agents A and B in case of different dose-effect curves and different order of treatment by the agents [R7]

case when the dose A_o is given before B_o. In the case of heteroaddition the dose B_o would be counted from the origin of the co-ordinates. In the case of isoaddition, on the contrary, the latter dose would be counted from point O', corresponding to the survival level on curve B to which the biological system is brought by the action of agent A. It is easily appreciated that for isoaddition the response to B_o will be much greater than in the case of heteroaddition. This is the reason why the isobolic lines of iso- and hetero-addition are so different in Figure IIIb.

34. The area between two isobolic lines may be called the envelope of additivity [S3]. As a result of different sequencing of the agents this envelope may reduce to a line [R7], as shown in Figure IIIc. This occurs when one of the two interacting agents produces an exponential response. Other examples (Figure III d, e, f, g, h, k) show how the form of the response curves and their relative curvature define the form of the envelopes of additivity and the influence of a different sequence of the agents.

35. The above considerations may be generalized to any type of exposure-response relationship. Since any a priori judgement about the type of addition (iso- or hetero-addition) is impossible, both possibilities should be accounted for. The practical usefulness of the envelope of additivity lies in the fact that if the experimental points fall within the envelope, additivity is to be expected. When they fall to the left (point A in Figure IV) synergism is operating; and, conversely,

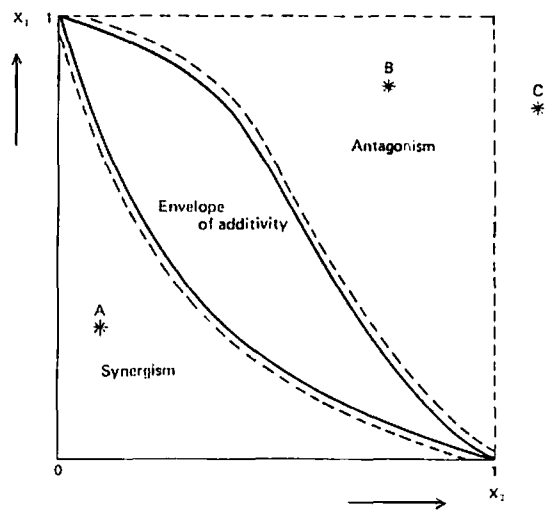

Figure IV. Envelope of additivity and areas of synergism and antagonism

antagonism will be operating if they fall to the right (point B in Figure IV). Enlargement of the envelope due to experimental errors is also shown in the same Figure IV. Attention should be drawn to the fact that although in principle the area of antagonism extends from the upper right-hand border of the additivity envelope to infinity, the straight dashed lines in the figure define the area beyond which the administration of one agent requires application of the other at levels greater than its single exposure level for the same effect. Point C in Figure IV lies in such an area where exposure X_1 requires an exposure X_2 greater than unity.

36. Discussion has so far been limited to the class of interaction where both agents may produce the effect under study. A large number of agents are however known in radiation biology which may modify the radiation response of the system without being themselves active in determining the effect. These modifying agents are called radioprotectors or radiosensitizers, without regard to their mechanism of action [M10]. The same approach as that used in the preceding paragraphs for the assessment of the interaction type may also be generalized to the modifiers. However,

since only radiation dose-response relationships are considered here, a specific approach to sensitization and protection may be developed.

37. Oxygen is one of the most important modifying agents [D1]. Its action is extremely general at all levels of biological organization in the sense that macromolecular, cellular and tissue systems irradiated under oxygen show an enhanced effect compared to that resulting from the same dose delivered under anoxia. This enhanced effect is often expressed as an oxygen enhancement ratio (OER) defined as

$$OER = D_{(non\text{-}oxygenated)}/D_{(oxygenated)} \quad (6)$$

expressing the ratio of doses D under anoxia and under oxygen to obtain a given level of effect. Other similar quantities may be used for the description of the effect of different modifiers. For example, the thermal enhancement ratio (TER) in the case of the combined action of radiation and heat, is:

$$TER = D_{(standard\ temperature)}/D_{(enhanced\ temperature)} \quad (7)$$

or the dose reduction factor (DRF) for radioprotectors

$$DRF = D_{(protector)}/D_{(no\ protector)} \quad (8)$$

For radiosensitizers, the factor in common use is the dose modifying factor (DMF)

$$DMF = D_{(no\ sensitizer)}/D_{(sensitizer)} \quad (9)$$

This quantity defined for a particular level of response is often referred to as enhancement ratio (ER) or sensitizer enhancement ratio (SER) or dose modifying ratio (DMR).

38. Also for modifying agents one may define the increment of effect in the presence of radiation alone, ΔY, and the increment in the presence of the modifier ΔY_M. The concept of an interaction factor may also be introduced, as follows

$$\omega = \Delta Y_M/\Delta Y \quad (10)$$

When linear relationships apply both in the absence and in the presence of the modifier, the value of the interaction factor ω will coincide with the value of the dose modifying factor (DMF). In Figure V the line

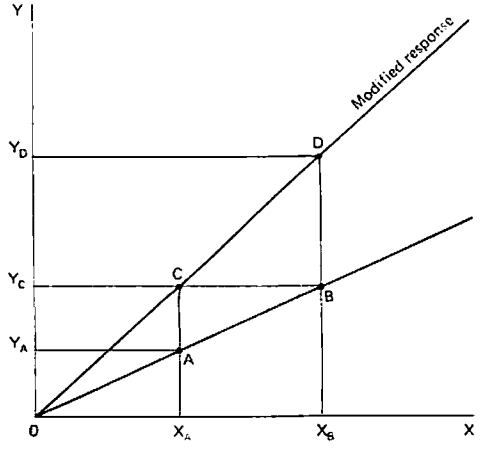

Figure V. Linear exposure-response relationships in the absence (OAB) and in the presence (OCD) of a sensitizing agent

OAB is the response in the absence of the modifier and the line OCD the response in the presence of a sensitizer. In this particular case

$$\omega = Y_C/Y_A \quad (11)$$

and

$$DMF = X_B/X_A \quad (12)$$

However, as the ratio Y_C/Y_A is equal to X_B/X_A both definitions coincide. In this special case of linearity the values of ω and of DMF will be independent of the level of exposure, because the straight line is fully defined by only one parameter (the slope at 0 exposure or the response at any specific exposure). In geometrical terms, the ratio Y_D/Y_C in Figure V is the same as Y_C/Y_A.

39. The circumstances differ of course in cases of non-linear exposure-response relationships that would most probably apply to the vast majority of the situations in practice. Figure VI illustrates one such case where the

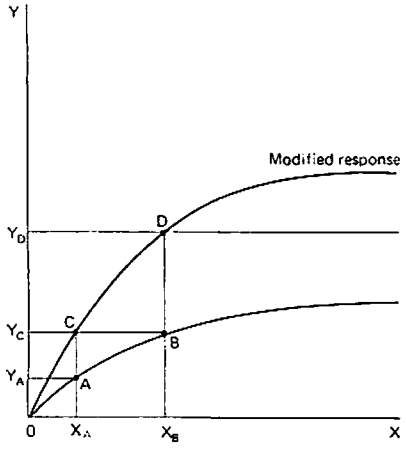

Figure VI. Non-linear exposure-response relationships in the absence (OAB) and in the presence (OCD) of a modifying agent

ratio Y_C/Y_A is not any longer equal to, but is actually much smaller than the ratio X_B/X_A. At exposure level X_B the definition of an enhancement ratio is meaningless because the line through point D parallel to the abscissa will never cross the other response curve OAB, but an interaction factor for a modified response as defined in equation (10) may still be applied. However, the value of ω will depend on the level of exposure or response.

40. The situation is further complicated when the application of a modifier significantly changes the general form of the dose-response relationship. In such cases the use of ω, that is the use of an enhancement ratio in terms of increment of effects, may not be applicable. The solution requires specifically defining a suitable quantitative measure of the modifying effect under the conditions applying to the experimental situation.

41. The concepts and approaches outlined so far are quite sufficient for a discussion of the available scientific literature on the interaction of different agents with radiation. When possible, in the text to follow the concepts of interaction factor and envelope of additivity on isobolic diagrams will be applied. However, further refinements and generalizations of the concepts outlined may be of some value, as in the

two following sections. These sections may however be omitted without significant detriment to the understanding of the experimental material reviewed in the chapters to follow.

B. SURFACE OF RESPONSE AND ISOBOLIC DIAGRAMS

42. The methodology of assessment of effects in combined exposures outlined by Loewe [L1, L5] allows a much broader approach to the problem. If, for the sake of clarity, one assumes only two interacting agents, the response to agent 1 is given by the function $F_1(X_1)$ and that to agent 2 by the function $F_2(X_2)$. The simultaneous action of the two agents will result in some new function $F(X_1,X_2)$. The functions $F_1(X_1)$ and $F_2(X_2)$ describe the response on a plane; the new function $F(X_1,X_2)$ describes the response in a three-dimensional space. This new function is called the surface of response. It may be used for any number of agents, and in these cases it will be described in multi-dimensional space. The concept of a surface of response makes the approach to the assessment of interaction geometrically clear. In this case the comparison is drawn between the surface obtained as a result of addition of responses to single agents (surface of additivity) and the surface of response for the function $F(X_1,X_2)$.

43. Let the functions $F_1(X_1)$ and $F_2(X_2)$ be linear with a simple law of addition operating for simultaneous action. Then one obtains the surface of response (and the surface of additivity at the same time) as the inclined plane in Figure VII. Cross-sections of this

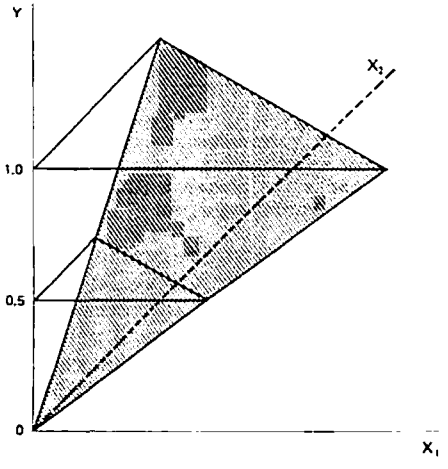

Figure VII. Surface of response in case of linearity and additivity for the combined action of two agents

plane at different levels of response (in Figure VII at Y = 0.5 and at Y = 1.0) will always produce straight lines which are isobolic lines in the sense of Figure I. By choosing the scales of the coordinate along the X_1 and X_2 axes it is possible to adjust the angle of the cross section line with the coordinate plane so as to make it equal to 45°.

44. The linearity of the functions $F_1(X_1)$ and $F_2(X_2)$ is however by no means a necessary condition for obtaining linear isobolic diagrams. The case of S-shaped functions is considered in Figure VIII. The two functions are represented by the curves in the co-ordinate planes YOX_1 and YOX_2. The surface of additivity (i.e., the dotted surface in Figure VIII) has now also a changing curvature similar to that of a tense sail, but horizontal planes at levels of response Y = 0.5 and Y = 1.0 still transect this surface by straight lines, so that

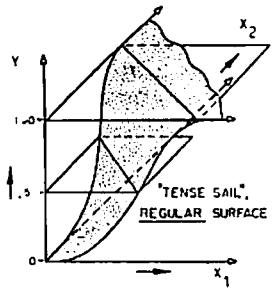

Figure VIII. Surface of response in case of additivity for curvilinear functions

again the isobolic diagrams are of the same type as in Figure I. According to this graphical representation, synergistic interaction is expressed by a deviation from the surface of additive response nearer to the OY axis. The new synergistic surface of response is presented in Figure IX and it resembles an inflated sail. The cross-

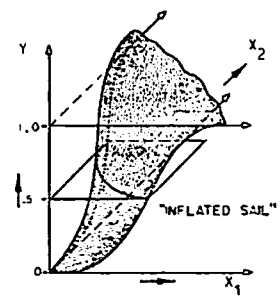

Figure IX. Synergistic surface of response

section of this surface by a horizontal plane at the level of effect Y = 0.5, for example, produces a curve which is the isobolic diagram of a synergistic interaction. The case of antagonism is exemplified in Figure X, where

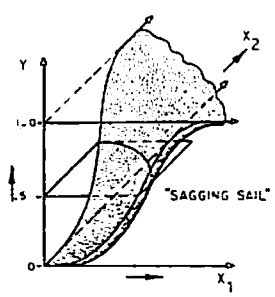

Figure X. Antagonistic surface of response

the antagonistic surface of response is further removed from the OY axis, in the form of a sagging sail. Transection of this surface by an ordinate plane (Y = 0.5) results in a curve with a concavity towards the origin of the co-ordinates, i.e., a curvature in the opposite direction than that of the synergistic action.

45. The above interactions may be represented by the isobolic diagrams of Figure XI, where the isobolic lines are the cross sections by a horizontal plane at the level of effect Y = 0.5 of the three surfaces of response in Figures VIII, IX and X. Such comparisons can be made at any level of effect, but in the case of agents present in the environment the levels would generally be low. It is therefore of interest to examine the shape of the

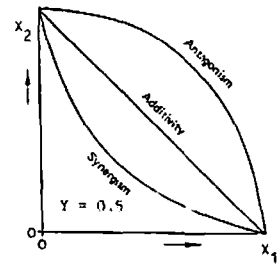

Figure XI. Isobolic diagrams obtained as the cross sections of surfaces of response in Figures VIII, IX, X at the level Y = 0.5

surfaces of response around the origin of the co-ordinate axes. It is not uncommon that the form of the surfaces might go from a synergistic type to an additive type in the region of low effects. At different levels of effect the interaction might even change from the synergistic to the antagonistic type, or vice versa.

46. Changing situations of this sort are illustrated in Figure XII, where the form of the surface of response is

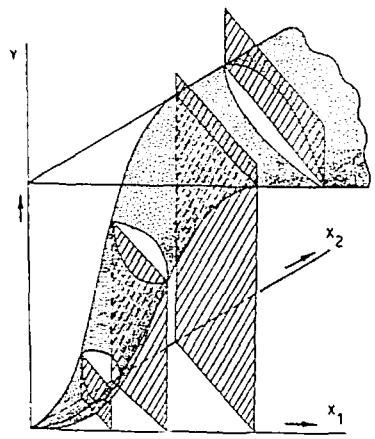

Figure XII. Cross sections of the surface of response by 45° vertical planes

made clearer through other types of cross sections. In the case shown the planes transacting the surface are diagonal, parallel to the Y axis and with an angle of 45° with respect to the X_1 and X_2 co-ordinate axes. The areas of the planes transacted by the surface and covered by the dashed lines show the extent of the difference between the real surface and an ideal surface of regular additivity. The plane nearest to the origin shows a strong antagonistic interaction, but the further the transacting plane is removed from the origin, the less important becomes the antagonism; until, at very high levels of exposure, the interaction becomes synergistic. Cross sections of this type can also help in assessing the mode of interaction and are called "interaction diagrams".

47. In Figure XII the levels of exposure are limited by the vertical planes chosen, but the levels of response may change. Such changes of response which depend on the relative contribution of X_1 and X_2 form the interaction diagram as shown in Figure XIII. The lower curve in Figure XIII shows the line of interaction (antagonistic interaction) resulting from the transaction of the surface of response by the vertical plane nearest to the origin of the co-ordinates in Figure XII. The case

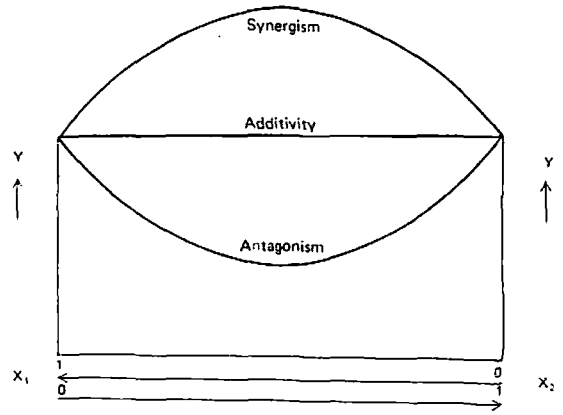

Figure XIII. Interaction diagrams in cases of additivity, synergism and antagonism

of additivity is represented by the line parallel to the exposure axis, while the case of synergism is described by the curve with upper convexity. Again, the line of additivity divides the space into two portions: an upper one, where interaction is synergistic and a lower one with an inhibitive type of effect. In essence, this method of analysis relies on the comparison between two surfaces: the actual surface of response and the surface corresponding to the presumed additivity of the effects of the two agents given separately. If the real surface of response is higher than additive, there is synergism. Antagonism would operate in the opposite case.

48. Construction of the surface of additivity is a prerequisite for all comparisons. It has however been discussed already that the addition of responses in complex biological systems represents a problem in itself because the results of iso- or hetero-addition depend on the sequence of the interacting agents. Adding to these uncertainties the experimental errors, turn the surface of additivity into a shell of additivity, corresponding to the envelope of additivity of the bi-dimensional representations. Although the actual comparisons should always be performed in relation to a shell of additivity, it is often more convenient to use the two-dimensional representations under the form of isobolic diagrams (or interaction diagrams). Elaborate methods of analysis have been developed for the interaction of several agents [C21].

49. When all the above assumptions have been dealt with, the comparison of the experimental data with the ideal case of additivity is straightforward conceptually and technically simple. For a given combination of exposures (X_1, X_2) the interaction factor ω may be calculated as the ratio of the actual ordinate of response to the ordinate of the additivity surface in the point (X_1, X_2). To this end interaction diagrams are particularly convenient. In Figure XIII the interaction factor ω for the combination X_1, X_2 as in point D will be equal to the ratio AD/BD in the case of synergism and to the ratio CD/BD in the case of antagonism. When iso- or hetero-addition give different outcomes, they should be used instead of the segment BD, and the upper and lower values of ω will be obtained, ω_u and ω_l, respectively

C. PROBABILISTIC ASSESSMENT OF THE INTERACTION

50. As any biological end-point which is expressed at a sufficiently high level of complexity may be viewed as the final outcome of a long chain of intercorrelated

events, it appears quite natural and wholly justified to express any end-effect by the probability, P, that it may occur. The dependence of this probability on the absorbed radiation dose may sometimes be one of direct proportionality but in most instances, and particularly for the most complex effects, the relationship may be more complex. Essentially the same can be said about the effects of other physical and chemical agents.

51. In probabilistic terms, if two agents act simultaneously on a biological system, one possible assumption is that the two agents act independently, which allows comparison of the results of the joint actions with the presumed outcome of the two agents acting independently. In some respects, this notion is similar to that of heteroaddition, with the difference that the probabilistic approach is conceptually much broader. The discussion to follow will again be limited to the simple case of two agents acting simultaneously but may in principle be extended to any number of agents.

52. The Committee agrees that the most important effects of radiation in man are carcinogenesis and mutagenesis, effects that are described by the ICRP [11] as stochastic in the sense that their probability of occurrence increases linearly with dose and without threshold; their severity is independent of dose; and no causal relationship with radiation exposure can empirically be established for any given case. It is well known that these effects do occur even in the absence of artificial irradiation with a frequency which is much higher than would be expected if they were induced only by natural background radiation. For the purpose of the present analysis, they may thus be viewed as stochastic derangements of physiological processes to which a probability of occurrence P_0 could be attributed.

53. If one assumes that the exposure X_1 to an agent causes a probability P_1 of a given effect, t, the overall probability that this same effect can be observed, taking into account the spontaneous level P_0 and assuming that P_0 and P_1 are independent is:

$$P_{t1} = P_0 + P_1 - P_0 P_1 \tag{13}$$

Since in biological experiments control and test groups are run concurrently, the following formulae may also be convenient:

$$P_{01} = P_{t1} - P_0 \tag{14}$$

$$R_1 = P_{t1}/P_0 \tag{15}$$

They show the absolute and relative increase of the probability to observe the given end-effect following exposure X_1. A similar set of equations can also be written for a hypothetical second agent:

$$P_{t2} = P_0 + P_2 - P_0 P_2 \tag{16}$$

$$P_{o2} = P_{t2} - P_0 \tag{17}$$

$$R_2 = P_{t2}/P_0 \tag{18}$$

54. When the action of the two agents is combined, the expected probability of observing the overall effect P_{et} may again be calculated on the hypothesis of independent action:

$$P_{et} = P_0 + P_1 + P_2 - P_0P_1 - P_0P_2 - P_1P_2 - P_0P_1P_2 \tag{19}$$

The absolute and relative increases in probability of observing the effect as a result of the joint action of the two agents will accordingly be:

$$\Delta P_{exp} = P_{et} - P_0 \tag{20}$$

and

$$R_{exp} = P_{et}/P_0 \tag{21}$$

55. When an experiment is performed on the combined action of two agents, the observed total probability of effect, P_{ot}, will in general be different from the expected probability P_{et}. One of the possible definitions of the interaction factor ω might be simply the ratio between the actual and the expected probabilities, P_{ot}/P_{et}. It is easy to see, however, that if this definition is adopted the value of the ratio will depend critically on the absolute value of P_0. When the effect under study has a high spontaneous level of occurrence, the interaction factor ω may be about 1 despite the observed absolute deviation between the experimental values and the expected value based on the hypothesis of independence. On this ground, another definition of the interaction factor, ω, is preferred, as follows

$$\omega = \Delta P_{obs}/\Delta P_{exp} \tag{22}$$

where

$$\Delta P_{obs} = P_{ot} - P_0 \tag{23}$$

The two definitions of the interaction factor will naturally coincide if $P_0 = 0$. The probabilistic definition of ω in equation (22) coincides in essence with the definition of interaction factor in equation (5).

56. The denominator of equation (22) is calculated on the basis of the independence of action of the two agents (equation (19)). Equation (20) may be rewritten by using equations (14) and (17):

$$\Delta P_{exp} = P_{o1} + P_{o2} - \frac{P_{o1}\,P_{o2}}{1 - P_0} \tag{24}$$

Accordingly, the equation for the interaction factor will assume the following form

$$\omega = (P_{ot} - P_0) \Big/ \left(P_{o1} + P_{o2} - \frac{P_{o1}\,P_{o2}}{1 - P_0}\right) \tag{25}$$

If P_{o1} and P_{o2} are small, the above equation reduces to

$$\omega = (P_{ot} - P_0)/(P_{o1} + P_{o2}) \tag{26}$$

or, changing the probabilities to the corresponding ratios for $P_0 \neq 0$, according to equations (15) and (18)

$$\omega = (R_{obs} - 1)/(R_1 + R_2 - 2) \tag{27}$$

where

$$R_{obs} = P_{ot}/P_0 \tag{28}$$

57. To give an example of such a type of treatment, the experiment on diploid yeast irradiated with alpha and gamma radiation [M3] and analysed by the method of the isobolic diagram (see section I.A.), may now be recalculated to obtain the interaction factor. For a dose of 9 Gy of mixed irradiation (25% alpha and 75% gamma) the level of reversion will be 180 per 10^6 survivors, corresponding to a $P_{ot} = 18\ 10^{-5}$. The spontaneous level of reversion $P_0 = 2\ 10^{-5}$. If one knows the alpha and gamma doses and the slopes of their regression lines, one may calculate P_{o1} and P_{o2} to be $5.7\ 10^{-5}$ and $7.4\ 10^{-5}$, respectively. The last term in equation (25) is negligible and one may use equation (26)

$$\omega = \frac{P_{ot} - P_0}{P_{o1} + P_{o2}} = \frac{18\ 10^{-5} - 2\ 10^{-5}}{5{\cdot}7\ 10^{-5} + 7{\cdot}4\ 10^{-5}} = 1.22 \qquad (29)$$

The fact that ω is greater than unity suggests a synergistic interaction.

58. The question arises of establishing errors and limits of confidence for the interaction factor. The theory of error transfer may be applied to this end. The value of ω as defined in equation (22) may be considered as the ratio of two stochastic quantities ΔP_{obs} and ΔP_{exp}. The mean value of this ratio is

$$\overline{\omega} = \frac{\overline{\Delta P}_{obs}}{\overline{\Delta P}_{exp}} \qquad (30)$$

The error matrix for $\overline{\Delta P}_{obs}$ and $\overline{\Delta P}_{exp}$ will be

$$\begin{bmatrix} S^2(\overline{\Delta P}_{obs}) & S(\overline{\Delta P}_{obs})\, S(\overline{\Delta P}_{exp})\, q_{12} \\ S(\overline{\Delta P}_{obs})\, S(\overline{\Delta P}_{exp})\, q_{12} & S^2(\overline{\Delta P}_{exp}) \end{bmatrix} \qquad (31)$$

where S is a symbol representing the mean quadratic error and q_{12} is the correlation coefficient. The mean quadratic error of $\overline{\omega}$ will be in this case

$$S^R(\overline{\omega}) = \frac{(\overline{\Delta P}_{obs})^2}{(\overline{\Delta P}_{exp})^2}\left[\frac{S^2(\overline{\Delta P}_{obs})}{(\overline{\Delta P}_{obs})^2} + \frac{S^2(\overline{\Delta P}_{exp})}{(\overline{\Delta P}_{exp})^2} - 2q_{12}\frac{S(\overline{\Delta P}_{obs})\, S(\overline{\Delta P}_{exp})}{\overline{\Delta P}_{obs}\,\overline{\Delta P}_{exp}}\right] \qquad (32)$$

If the distribution of $\overline{\Delta P}_{obs}$ and $\overline{\Delta P}_{exp}$ is normal and $\overline{\Delta P}_{exp}/S(\overline{\Delta P}_{exp}) > 5$, then the distribution of $\overline{\omega}$ should also be approximately Gaussian.

59. The same problem of assessing an error to $\overline{\omega}$ was considered by Rothman [R1] for the case of epidemiological investigations and he used the same definition of the interaction factor. If a log-Gaussian sampling distribution is assumed, an estimator of ω referring to a large sample interval may be written as

$$\omega_l = \exp\left[\ln\overline{\omega} - k_\alpha S(\ln\overline{\omega})\right]$$
$$\omega_u = \exp\left[\ln\overline{\omega} + k_\alpha S(\ln\overline{\omega})\right] \qquad (33)$$

where k_α is the abscissa value for a given level of significance α. The methods for the calculation of $S(\ln\overline{\omega})$ for cohort studies and case-control studies have also been given in [R1].

60. To illustrate further, the confidence limits for the experiment on yeast considered above [M3] in paragraphs 31 and 57 may now be calculated. In the example $\overline{\Delta P}_{obs} = 16\ 10^{-5}$ and $\overline{\Delta P}_{exp} = 13\ 10^{-1}$; $s(\overline{\Delta P}_{obs}) = 0.8\ 10^{-5}$; $S(\overline{\Delta P}_{exp}) = 0.9\ 10^{-5}$. In case of a synergistic interaction there cannot be a negative correlation between $\overline{\Delta P}_{obs}$ and $\overline{\Delta P}_{exp}$; equation (32) may therefore be used without the third term within brackets as an upper estimate of $S^2(\overline{\omega})$. Fitting the above values to the equation, $S^2(\overline{\omega}) = 0.01$ and $S(\overline{\omega}) = \pm 0.1$. The estimated value is therefore $\overline{\omega} = 1.22 \pm 0.10$ and, for 95% confidence limits, $\omega_l = 1.02$ and $\omega_u = 1.42$.

61. For complex biological systems a possible situation of isoaddition should be kept in mind. In probabilistic terms this means that if the action of agent 1 takes the system to probability level P^*_{o1}, then P_{o2} will depend not only on the level of exposure X_2 but also on the value of P^*_{o1}. Therefore P_{o2} becomes a conditional probability $P_{o2}(X_2/P^*_{o1})$. The same is true for a reversed order of application of the agents. In this situation different conditional probabilities depending on the sequence of the agents and on the levels of exposure should be used in equation (24). This will give finally upper and lower limits for ΔP_{exp}. Corresponding upper and lower limits for the interaction factor ω may be calculated as

$$\omega_u = \Delta P_{obs}/\Delta P^l_{exp} \qquad (34)$$

and

$$\omega_l = \Delta P_{obs}/\Delta P^u_{exp} \qquad (35)$$

These limits will be further extended by the presence of experimental errors.

D. THEORY AND PRACTICE

62. Before proceeding further to the analysis of some experimental and epidemiological data, it is necessary to discuss briefly the applicability of the concepts reviewed in the preceding section to situations involving complex biological effects. In doing so, it will immediately be realized that even problems which may appear of minor and mostly speculative importance in the analysis of the action of a single agent, are likely to become very difficult to disentangle when various agents are combined, giving rise to much uncertainty in the assessment of the type of interaction that might apply.

63. The definition of an effect is hardly ever a problem in radiation biology. The conditions under which the effect is manifested, its degree of expression or its probability of occurrence may usually be described with sufficient precision. What may be less easy to define is the dose-effect relationship at all levels of exposure, particularly at the low ones. When two agents are combined, depending on the form of the respective exposure-response relationships, more or less effect might be obtained at a given exposure regime than might be predicted on fragmentary knowledge of the relevant relationships. This points to the need to establish with sufficient precision through appropriate controls not only the response to be expected at the exposure levels of interest for the particular experiment, but to obtain a full dose-response curve for both agents under study. The ultimate aim is to establish experimentally the surface of response corresponding to the full

range of both agents. However, if the number of experimental points to establish a given exposure response curve with one agent is N, to establish the whole surface of response with the same number of experimental points in a given sequence of administration requires N^2 experimental points. Reversing the order of administration will in turn double the number of experimental points to $2N^2$. Such an increase in the size of the experiments is often not feasible and complete series of the type envisaged are almost never reported or conducted.

64. The definition of the level at which a supposed synergistic or inhibiting action may take place is extremely important in the analysis of such actions. Here the need for operational definitions of practical significance and the need of resolving mechanisms in biological experiments may often be at variance or even incompatible. If, for example, one takes a very complex biological short-term end-point, such as the death of an animal (but the loss of reproductive integrity of a cell may be sufficiently complex, depending on the level at which the mechanisms of action may be resolved), exposure to any toxic agent in sufficient amounts could produce such an effect. This of course will happen at times and with mechanisms differing from one agent to another and mostly specific to each agent. The combined application of two agents may in principle produce apparently antagonistic or synergistic effects when some of the pathways of action of the two agents happen to interfere with each other. But at this level of complexity, even though the end-point might be of practical significance, the real existence of combined actions may be difficult to assess. Only when the mechanisms of action of the two agents are reasonably well defined will there be any merit in making use of the concepts of synergism or antagonism, in order to avoid misuse of the terms. Within this framework it may also be discussed how the presence of one may enhance the detectability of another interacting agent, when both produce the same effect.

65. Confusion of iso- with hetero-addition could result in the false identification of synergism. For example, one could visualize two agents, both toxic to the bone marrow and both inducing leukopaenia with a very curvilinear relationship to exposure, as is usually the case. It is easy to imagine that the action of the combined treatments might produce more effect than expected by the same doses of the two agents separately, simply because of the curvilinearity of the relationships and of the isoadditive character of the combined effect. It is also easy to understand that death of the animals might ensue at levels of the combined agents which are much below those of the two agents acting separately. If leukopaenia and death were the end-points of reference, in the absence of any other information one might be tempted to think of a synergistic action. Yet, to call such an effect synergistic would be unjustified because isoaddition would be operating in this case. Clearly, without knowledge of the whole range of responses, it would be impossible to clarify the issue. It should be realized that too often the cases of synergism claimed in the literature have been insufficiently analysed in this respect and there is ground to doubt that they might stand up to more refined investigations.

66. As to long-term effects, it is usually thought that tumour induction is a sufficiently well-defined phenomenon to be taken as an end-point, as though all tumours have the same aetiology and pathogenesis and there are not great variations in the incidence of various tumours between species, strains and experiments. This assumption is imprecise when different doses of the same agent are administered, because expressing the response as overall tumour induction may mask important effects on some tumour classes. The assumption is however particularly dangerous in studies of combined actions because under these conditions changes in the tumour spectrum would certainly be expected. It is essential therefore that the end-point of the studies be specific and extremely well defined. The same reasoning applies to the genetic and developmental effects.

67. Changes in the state of the biological system may be brought about by sequential treatment. For example, a large body of evidence on mammalian cells indicates that dose fractionation in radiobiology is a difficult subject to investigate. Usually the first dose produces partial synchrony of the irradiated population, so that the response of the surviving cells to the second dose fraction is altered with respect to that of a non-exposed undisturbed population. It would be very easy but totally unjustified to think of antagonistic or synergistic effects in the absence of information on the survival curve of the overall population and of its constituent sub-populations and in the absence of data on the amount and time sequence of synchrony induced by the first treatment. There is every reason to believe that such cases may occur also in respect to other chemical treatments and it should in fact be pointed out that treatments with chemicals (BUdR, hydroxyurea, for example) are often used to obtain experimentally synchronized cell populations. The amount of information available in respect to such effects by the various agents discussed in the following parts of this Annex is lacking or extremely limited. Efforts to clarify the situations occurring in practice through experimental analysis might help to avoid misconceptions.

68. Another point calling for great caution concerns the time parameters of the combined action. Two types of treatment may be visualized, contemporaneous and sequential. Partial overlapping and fractionation of the exposure to each of the agents could increase the complexity of the temporal patterns of exposure. Contemporaneity of the treatment time does not necessarily imply a simultaneous action at the level of the target structures. For example, in the case of chemical or pharmacological substances, variable time for metabolic processing of the agents might be required and it would temporally displace the action on the biological structures of interest. If hetero-addition is assumed to operate, administration of one agent before another, or vice versa, should not in principle lead to a change in the end-result. But, on the other hand, if reversing the order of administration does produce a change (qualitative or quantitative) of the response, the conclusion should not necessarily be drawn that some interaction differing from additivity applies. This all points to the relativity of the definitions and to the difficulties of translating into sensible biological terms the precise statements of the theory.

69. There are biological effects for which the timing and the sequence of the actions is all-important. According to one hypothesis, for example, tumour induction may be regarded as the result of two independent phenomena, initiation and promotion. Initiation is visualized as a fast irreversible process

acting on normal cells and conferring upon them the character of neoplastic ones. It precedes promotion but without the latter could not result in a growing tumour. Promotion, which on the other hand is ineffective if not preceded by initiation, takes place during fairly long times and may be reversible. Many agents share the properties of initiators and promoters in different degrees at different doses. Thus, reversing the order or altering the time pattern of administration of two carcinogenic agents is bound to produce changes in the qualitative or quantitative expression of their final action. This should be kept in mind when designing experiments on combined action.

70. The issues discussed in the preceding paragraph are further complicated by the fact that the time for tumour appearance is important, as is the final tumour yield. The rate of appearance of tumours in time (once this rate is referred to a given tumour type and is corrected for competing risks) is an important parameter since, in principle, it is related to the promotive action of a treatment; while the final tumour incidence is related to the initiation action. When agents possessing both properties are administered in combined experiments the precise nature of the interaction and its influence on the combined end-point would not normally be resolved without detailed information of the mechanisms involved.

71. The decisive importance of the temporal pattern of exposure to ionizing radiation vis-à-vis practically all biological end-points is documented for a variety of biological effects in the specialized sections of the previous report (see Annexes H, I, J of [U1]) and in Annexes I, J and K of the present report. In general, fractionation or protraction of the exposure lead to a decrease of the final effect, although in some cases deviations from this general pattern are reported [H19]. It is not unreasonable to expect that changes in the yield of effect may also occur by altering the pattern of exposure to other agents interplaying with radiation, so that the final effect of the combined treatment cannot be predicted, particularly in the region of the low doses which are of major concern in the present context. Precise information about the temporal distribution of the exposure is therefore required in evaluating the combined effects.

72. In conclusion, the notions of synergism, additivity and antagonism which may be defined in theory and evaluated by appropriate statistical analyses, are seen to lose some of their clarity when confronted with the complexity of biological organization and the variability of experimental conditions. They may, on the other hand, acquire important practical connotations. Normally the assessment of combined actions requires clear understanding of the nature of the biological effect under study; precise knowledge of the pattern of its manifestation in time for the combining agents; reasonable definition of the exposure-effect relationships for each of the interacting agents, particularly when effects must be analysed over a range of exposures; control experiments to check for the applicability of the effect to different conditions of exposure. Without the detailed information described above, such notions will probably remain confined to the realm of theory and the subject of disbelief or overestimation, as the case might be. Only studies of mechanisms might eventually solve these uncertainties.

II. PHYSICAL AGENTS

A. COMBINATIONS OF VARIOUS TYPES OF IONIZING RADIATION

73. The simplest type of interaction, where most of the reservations raised in the preceding sections do not apply due to the similarity of the underlying mechanisms, is that between two different types of ionizing radiation. Mixtures of high- and low-LET radiations have repeatedly been tested for the presence of synergistic or inhibiting effects due to the combination of two beams, since current understanding of radiation action is not sufficiently advanced to allow prediction of possible interactions. In other studies external irradiation was combined with internal or the effects of mixtures of radionuclides were tested.

74. Studies on the combined action of fast neutrons, heavy ions and x rays were stimulated by possible radiotherapeutical applications [N2, N4, N5, B16, D13, F5]. Interaction of sublethal reparable lesions produced by neutrons and x rays was shown in experiments where x-irradiation was delivered at different intervals after neutrons [N4]. The actual survival curves of cells in vitro lay between those to be expected on the basis of iso- and hetero-addition. Similar experiments with results in the same direction were performed with neon ions [N5]. Cells irradiated with ions, incubated for three hours and then exposed to x rays showed a partial restoration of the shoulder of the survival curve. However, the results of Durand and Olive [D13] are in disagreement with those reported above because they showed no recovery after combinations of neutron-neutron, x ray-neutron and neutron-x-rays. It should be pointed out that these experiments were not confirmed. A theoretical description of the interaction of high- and low-LET radiation based on the theory of dual radiation action was provided by Zaider and Rossi [Z3]. Within the frame of definitions accepted in this report their interaction would be confined to the envelope of additivity.

75. Some insight into the nature of the underlying processes may be provided by studies of repair. When tested at the tissue level, the rate of recovery from sublethal damage appeared to be independent of the radiation causing it [H12]. It was suggested that recovery from sublethal damage does apply to the low-LET component of the damage, whatever the radiation producing this damage [G3, H13]. Naturally, in the case of neutrons which cause relatively more lethal than sublethal damage the final effect will not be clearly determined until one of the two components, the sublethal, has been repaired at sufficiently long fractionation times [H15]. Further evidence shows [H14, F3] that tissues treated with neutrons or with x rays to similar levels of biological damage and then submitted to an x ray course appear to be more radiosensitive when neutrons had been delivered in the conditioning treatment. Thus, the presence of different components in the LET spectrum and the presence of different types of damage to be repaired (sublethal, potentially lethal) each with characteristic time parameters make the picture rather complex.

76. New studies on combined radiation treatments were reported on Chinese hamster cells in culture irradiated first by neon ions (LET = 180 keV/μm) and subsequently by 225 kVp x rays. Cell survival was the end-point analysed [N9, N10, N11]. The results for the three levels of survival presented in Figure XIV show

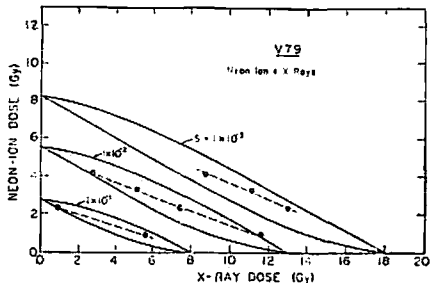

Figure XIV. Isobolic diagrams at three levels of survival for Chinese hamster V79 cells after irradiation with neon ions followed by x rays [N10]

that the experimental points fall in the middle of an envelope of additivity formed by application of hetero-addition (upper curve) and isoaddition (lower curve). When the order of application is reversed (Figure XV)

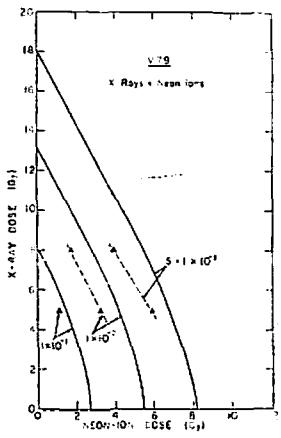

Figure XV. Isobolic diagrams at three levels of survival for Chinese hamster V79 cells after irradiation with x rays followed by neon ions [N10]

the envelope of additivity is reduced to a line, a situation illustrated earlier in Figure III c and e. Under these circumstances one would conclude for the presence of synergism, if not for the fact that the actual levels of survival do not change after the two sequences of treatment. This apparent paradox is explained by the fact that radiation may be considered to be synergistic with itself when survival is not exponential with dose.

77. The above examples suggest that in cases where the sequence of treatments does not change the final outcome, the isobolic diagrams should be constructed with the order of treatment that gives the greatest possible area of the envelope of additivity. As to the interaction of ions and x rays, this does not appear in general to exceed the isoaddition limits (interaction of x rays with itself) and only in few experiments true synergism may be suspected. Further work on the mechanisms at the cell kinetics and molecular level could clarify the precise conditions of the interactions.

78. Moskalev et al. [M21], modelling the effects of nuclear fallout, gave ^{131}I orally (0.3 kBq/g) to rats and irradiated them at the same time externally with gamma ($\sim$ 6 Gy) or beta (surface dose $\sim$24 Gy) radiation. Other animals were only irradiated externally. Lethality at 90 days was about five times lower in the combined treatment group, which was attributed to changes in the hormonal state in the course of acute radiation sickness. Other studies were also reported on the yield of mammary tumours in rats following ^{131}I and external irradiation with x or gamma rays [M22]. For low iodine exposure (0.04–0.08 kBq/g body weight) an increased yield of tumours was seen in the combined treatment group; for high iodine exposure the reverse was true. Other experiments [V4, V5] tested tumorigenesis in rats with ^{131}I (3.7 kBq/g) and external thyroid irradiation (up to 3 Gy). No significant effects of the combination were reported. The interaction in these cases is attributed to hormonal disturbances, about which more data will be provided in chapter IV. Luz et al. [L14] reported on an enhanced osteosarcoma induction in mice by the joint action of two radionuclides, a short-lived alpha-emitter (^{227}Th at 190 kBq/kg) and a beta emitter (^{227}Ac at 1.9 kBq/kg). A higher than additive osteosarcoma incidence was reported at 700 days post-exposure, amounting to interaction factors of about 1.7 in terms of final tumour incidence and of about 1.3 in terms of the time for 50% tumour appearance, as compared to the effects of the two doses given individually. The authors attributed the interaction to the stimulation of osteogenic cell division due to the protracted action of the low level ^{227}Th formed from ^{227}Ac or to the continuing activation of a virus by the same cause. It is clear however that without kinetic studies and accurate physical dosimetry at the level of the sensitive bone cells it would be difficult to validate the phenomenon as belonging to the class of synergistic effects.

B. UV AND IONIZING RADIATION

79. The combined action of UV and ionizing radiation has been examined repeatedly in various experimental systems of micro-organisms [H10, Y4]. The experiments of Haynes in E. coli B/r [H10] may be examined as a good quantitative example. Pre-irradiation of the bacteria with different UV exposures increases the final slope of the x ray survival curve. Changing the sequence of the agents leads to a disappearance of the synergistic interaction, but only if the cells are irradiated in rich medium. If cells are irradiated in buffer the order of irradiation is not so important. This suggests that post-irradiation events may affect the interaction mechanisms. Many experimental data point to these events in relation to repair mechanisms [M24]. It appears that the repair of single-strand DNA breaks induced by x rays may be inhibited by prior UV irradiation. For some recent reviews of DNA repair mechanisms and their genetic control see references [D10, M23, S34].

80. Experiments are also available on mammalian cells in culture [H16]. Synchronized Chinese hamster cells were irradiated in mid-S phase with fixed doses of UV and then exposed to graded doses of x rays (case I); alternatively, fixed doses of x rays were followed by graded doses of UV (case II). In case I the resultant survival curve may be obtained by isoaddition showing that, despite the different nature of the molecular lesions, the damage by UV is fully additive with that of x rays. The UV survival curves in case II are higher than the theoretical curves obtained by isoaddition, but lower than those obtained by hetero-addition. The size of the shoulder on the combined action curves in case II is less than that of the pure UV survival curve. Thus, the damage produced by x-ray pre-irradiation is only partially additive with the subsequent UV damage. In mammalian cells, according to these data, the situation

of survival additivity seems to prevail. These data have been analysed by others [L28] according to the molecular theory of cell survival.

81. Transformation of mammalian cells in vitro is also a relevant end-point. DiPaolo and Donovan [D17] tested the morphological transformation of Syrian hamster cells with UV and x rays. Irradiation by UV alone (254 nm) gave a yield of transformants linearly increasing with dose. X-irradiation produced no transformation at all. X-irradiation (2.5 Gy) followed by UV (1.5 J/m^2) at 24, 48 or 72 hours resulted in a greatly increased yield of transformants. An interaction factor of 3, 11 and 2.2 may be calculated at the above time intervals, showing the interaction to be very time dependent. Increasing the UV dose to 3 J/m^2 led to a decrease of the 48-hour interaction factor, thus showing its dose dependence. The relevant biological mechanisms remain unclear owing to the lack of understanding of the phenomenon of transformation.

82. A synergistic interaction of UV and x rays was found by Holmberg and Jonasson [H22] for chromosomal aberrations in human lymphocytes. G_0 cells were irradiated first by 254 nm UV (5 – 10 J/m^2) and then by scalar doses of 260 kVp x rays (1.25–2.0 Gy). UV alone gave a very small yield of dicentrics; UV followed by x rays doubled the yield of x rays alone. The interval between the treatments was less than half of a minute. Reversing the order of administration did not change the interaction factor of about 2. When phytohaemoagglutinin-stimulated cells entering stage G_1 were used in the same experiments no synergism was observed [H23].

83. Experiments with chronic exposure to UV light of different spectral composition and parallel chronic or acute exposure to ionizing radiation were also reported. They involved complex biological end-points such as LD_{50} or life span. Galanin et al. [G2] studied in mice and guinea-pigs the haemopoietic functions and the life span under conditions of combined chronic irradiation by UV and gamma rays (dose rate 0.5 Gy/day). The experiments showed that animals receiving the combined treatment lived longer and had haematological values closer to normal than controls receiving only the gamma treatment. Acute damage was also influenced in the same favourable way by the combination of chronic UV irradiation with lethal and sublethal doses of gamma radiation [L15]. In experiments by Yatzula [Y3] on rats the treatment by UV preceded or was made concurrently with x-irradiation or internal irradiation by ^{32}P. Again, a decrease in the $LD_{50/30}$ was seen after the joint treatment. Animals under combined irradiation had a better recovery of the body weight and showed less severe skin reactions. Physiological adaptation mechanisms could be invoked to explain such effects.

84. A comparison of the carcinogenic action on rat skin of UV and ionizing radiation, was made by Burns and Albert [B11]. The predominant tumor type observed following UV irradiation was a keratoacanthoma; after electron irradiation epidermal tumours were mostly seen. The yield of keratoacanthoma in rats irradiated at four weeks of age by different doses of ionizing radiation up to 30 Gy and then exposed for different periods to high and low fluences of UV was not influenced by the ionizing radiation dose and depended primarily on UV exposure. Absence of interaction was also seen in the case of epithelial skin tumours. Only one UV treatment schedule (high-fluence, 25.2 10^4 J/m^2, from 5 to 16 weeks of age) enhanced the yield of epithelial tumours for lower doses (5.5 and 11 Gy) but not for higher doses of electrons (17 Gy). However, some of this increase was also observed in the zero-dose group and neither of these increases was statistically significant at $P = 0.05$. The absence of oncogenic interaction between the two radiations is a particularly good illustration of the fact that there may be a difference in the targets specific to the two radiations.

85. The examples reviewed in this section illustrate several important points. They show that the type of interaction depends on the biological end-point studied, on the level of exposure of the agents applied, on the order of their administration, on the stage of cell cycle, state of growth of the cells, etc. Under these circumstances it is not surprising that no general conclusion about the character of the UV and ionizing radiation interaction may be drawn.

C. ELECTROMAGNETIC AND IONIZING RADIATION

1. Experimental data

86. Many industrial, scientific, military and domestic appliances produce microwaves, electromagnetic radiation having frequencies of from approximately 10 to 10^5 MHz. In some cases the same apparatus may produce very soft x radiation, as well as microwaves; in other instances ionizing radiation from other sources may be present in an occupational environment together with microwaves. The assessment of a possible combined action of these two agents is very difficult because exposure parameters for microwaves equivalent to the absorbed dose of ionizing radiation are absent [B23]. Even such a simple characteristic as the density of energy flux (DEF) is lacking in some experimental work. The quantitative expression and the underlying mechanisms of effects are far from clear. Differing views have been expressed on the nature of these mechanisms. Some authors consider the effects of microwaves to result from the dielectric heating of the tissues [M13]; others place the main importance on specific actions of the microwaves, particularly on the central nervous system [P9, G4]. A combination of these views has also been considered [B12].

87. In several early experiments [P18, M14, T3] the changes induced in the lethal action of radiation by microwaves were studied. The results consistently showed an antagonistic type of interaction on the lethality induced by ionizing radiation following pretreatment of rats [P18], dogs [M14] and mice [T3] with microwaves. Later, interaction in the sense of additivity was reported for the same biological end-point [B13]. In more recent experiments Davydov et al. [D14] studied the lethality to mice after high exposure rates of microwaves prior to acute gamma irradiation. Curves of the Rashevsky type describing the relationship between mean survival time and radiation dose were reported, and a shift to shorter survival times after combined treatment was observed. The animals were irradiated for 10 consecutive days with microwaves at a frequency of 2400 MHz with density of energy flux (DEF) 10, 20, 40 and 100 mW/cm^2, and exposure times of 40, 20, 10 and 4 minutes, respectively. It is interesting to point out that the degree of interaction was highest for DEF = 100 mW/cm^2 and depended rather on the intensive factor (DEF) than on the extensive one (energy admin-

istered). An approximately linear decrease in the $LD_{50/30}$ with increasing DEF was observed. Extrapolation of this relationship to zero gamma dose would give a DEF value of about 325 mW/cm². The authors argue that at this level of DEF death might be brought about by microwave irradiation alone. If so, this would imply additivity of the two agents for a very complex end-point.

88. The state of the haemopoietic system of the animals in the course of the microwave pre-treatment described above was studied by Tichontchuk [T4] after 31 day irradiation at 100 mW/cm². Gamma radiation at 4 Gy was given after the last microwave treatment. The haematological parameters that were followed in the course of these experiments included the weight of spleen and thymus, and the number of cells in the circulating blood. An inhibitory action of the microwave irradiation alone on the haemopoietic system was noted, with a pronounced leukopaenia. The subsequent gamma treatment added further injury to the blood-forming organs, which could explain the additive type of interaction observed in [D14]. It is however fair to point out that other data on an inhibitory interaction of the same two agents have been reported in the literature [L19, F4, R8].

89. Rotkovska and Vacek [R8] exposed mice under conditions similar to those in [D14]. Lethality following low-LET radiation was again the experimental end-point tested. A definite decrease of lethality was observed if the mice were exposed after the x-ray treatment for five minutes to microwaves (2450 MHz, 1000 mW/cm²). Animals treated with microwaves showed also an increased number of haemopoietic stem-cells surviving and increased values of erythro- and myelo-poiesis. Differences of these results from those in [D14] could possibly be due to the reverse order of application of the interacting agents. A more recent paper by Rotkovska et al. [R14] provided further details of the therapeutic effect of microwaves on short-term mouse survival following whole-body x-irradiation and attributed the antagonistic effect of the two agents to an increased survival of the stem cells in the bone marrow.

90. For the purpose of the present document most interesting are the studies where clearly non-thermal, down to environmental, levels of microwaves were tested. Sakovskaya et al. [S25, S26] modelled in the animal a situation of chronic irradiation by microwaves and low-energy x rays. Female mice were irradiated in 31 or in 82 sessions, each delivered every second day and including 20 minutes microwave irradiation at DEF 2.5 and 5.0 mW/cm², and x irradiation (effective energy 10 keV) up to doses of 0.15 or 0.3 Gy. The end-points studied comprised body weight and weight of several organs (i); number of mice producing litters (ii); fertility (iii); weight of the litters at one month of age (iv); fraction of bone-marrow cells carrying chromosomal aberrations (v); lysozyme content of the blood serum (vi). Control groups and groups irradiated with only microwaves or x rays were also included in the experiments.

91. Statistically significant ($P < 0.05$) changes of the control values were obtained for the end-points (ii), (iii), (v) and (vi). A decrease of the lysozyme content of blood serum was observed, approximately to the same degree, for both the experimental groups irradiated with microwaves alone or with x rays alone. In the group receiving the combined irradiation the decrease of the enzyme was slightly greater, but the corresponding point on an isobolic diagram would fall into an envelope of additivity. For the chromosomal aberrations again an increased yield was seen in the groups receiving the separate treatment and again to approximately the same extent. The group under combined treatment showed a slightly higher incidence of aberrations, but the corresponding experimental points were not outside the envelope of additivity. Microwaves alone seemed to show a slight stimulating action on the fertility of the mice and on the fraction of mice producing litters; but in the combined treatment group a decrease of both end-points was observed. An additive type of interaction would appear more likely to apply in general to these experiments.

2. Epidemiological evidence

92. The combination of ionizing radiation and high- or low-frequency electromagnetic radiation is characteristic for a number of occupational environments in electronic and radiotechnical plants. Increased ambient temperature, constant electric or magnetic fields, sound pollution and vibration may also be part of these environments [O2]. Wolfovskaya et al. [W3] studied the health of female workers employed in assembling, testing and vacuum pumping of high-voltage electronic equipment. They were exposed to electromagnetic fields of different frequencies (electric field strength 600–2500 V/m and magnetic field strength 50–320 a/m) and to x irradiation at dose rates of up to 25 μGy/hour. The effects studied included frequency of functional disturbances of the nervous system, blood pressure, dysmenorrhoea, changes in the sedimentation rate of erythrocytes, thrombo- and leuko-cytopenia. It was claimed that the important determinant of the symptoms was x irradiation. However, a high percentage of disturbances of the nervous system found among these workers was attributed to microwave exposure. The nature of the end-points, their variability between groups and the lack of any precise dosimetry and statistical analysis make it difficult to validate such conclusions.

93. Similar comments may be made with respect to other epidemiological studies on the clinical effects of combined exposure to microwaves and ionizing radiation. A survey was reported of workers testing microwave generators [B9]. Four groups of people (200 subjects in total) were included in the survey: two groups worked under combined exposure to microwaves and ionizing radiation; one was exposed to microwaves only and the last one was the non-exposed control. A group exposed to gamma radiation alone was not included in the study. Asthenia and migraine were characteristic complaints in all exposed groups. For the first two of them the symptoms were 20–50% more frequent than for the third group and between 2 and 2.5 times more frequent than in the fourth. Dysfunctions of the autonomic nervous system were 2 times more common in the groups with combined exposure than in the third group and 3–4 times higher than in controls. The combined action of ionizing radiation and microwaves was also investigated in workers by Lysina [L17] but loosely defined conditions of exposure render any judgement of the type of interaction impossible.

D. SUBOPTIMAL TEMPERATURE AND IONIZING RADIATION

1. High temperature

94. Broad quantitative studies on the effect of heat on cells and the interaction between heat and ionizing radiation started in the 1960s, stimulated by the possible application in the treatment of cancer. Several conferences and symposia have by now taken place on this subject [C17, C18, P12, D20] and good reviews are available [D18, F2]. A full discussion of this subject is beyond the scope of this Annex, which will only briefly cover the most basic aspects. Heat alone may damage mammalian cells and tissues at temperatures of 42°C given for a sufficiently long time [F8]. Thermal inactivation curves as a function of the temperature or of the treatment time at a given temperature may be produced, having characteristics similar to those of the radiation inactivation curves. There are reasons to consider that the target for cell killing by heat may be plasma membranes [D18] but other targets such as lysosomal membranes or macromolecules cannot be excluded.

95. Treatment of cell cultures with heat increases their sensitivity to radiation in the sense that the final slope of the x ray survival curves becomes steeper after pre-heating [F8]. Thermal enhancement ratios as defined by equation (7) may be used to quantify the effect and for different cell lines the values of this ratio seem to correlate well with the sensitivity of the cells to heat [R9]. After pre-heating for 1 hour at 42.5°C the TER may reach values higher than 2 [R9]. These values seem to increase for irradiation at low dose rates [B24] because recovery from sublethal damage is sharply reduced by treatment with heat [L18]. A delay of rejoining of strand breaks in DNA [C19] and inhibition of DNA synthesis, including repair synthesis [S37], were observed after heat treatment. The targets for enhancement of radiation sensitivity by heat are different from the targets for simple heat inactivation and include all the repair systems and the chromatin [W10, D18, D26, S49].

96. The temporal pattern of treatment is very important for the synergistic interaction of radiation and heat [S35, D19, S36, O3]. Maximum interaction is usually observed with the simultaneous presence of the two agents and it declines as the interval between treatments increases. Figure XVI [F2] illustrates the time course of the decay of heat potentiation of x-ray damage in a variety of normal mammalian tissues for hyperthermia given either before or after irradiation.

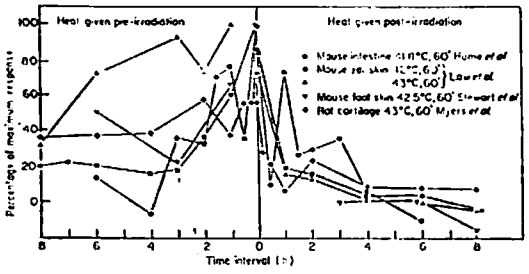

Figure XVI. The time course of the decay of heat potentiation of x-ray damage in normal tissues for hyperthermia given at different times before or after irradiation. The tissue responses are normalized to the percentage of the maximum response which occurs, for each curve, at the shortest time intervals. Data from [F2]

97. Data on the life span of animals irradiated for the duration of their life under conditions of high environmental temperature are reviewed in Annex K. A study with pre-implantation mouse embryos exposed in vitro to 39°C immediately after x irradiation [V8] showed a great increase in the number of micronuclei in the cultured cells, indicating an enhanced chromosomal damage after combined treatment.

98. For animals, and for mammals in particular, it is difficult to foresee under what conditions a direct sensitizing action of high temperature in the environment might come about, since normally healthy mammals maintain a fine regulation of their body temperature. However, Dobrovolsky [D11] reported experiments on rats where the effects of chronic irradiation due to the daily intake of ^{35}S (0.55 MBq/kg), ^{45}Ca (1.3 and 2.8 MBq/kg) and ^{32}P (0.37 MBq/kg) in the course of a year were studied in combination with daily exposure for two hours to a temperature of 40°C. Survival, body weight, fertility (mean number of litters per female), haematological parameters and histology of the ovaries were the end-points studied. During the first period of treatment the changes characteristic of a chronic radiation injury appeared to be aggravated by the combined treatments. During the second half of the treatment, however, the combination of irradiation and high temperature appeared to increase and accelerate repair processes. Fertility of the female animals depended on the mating time, but in general the combined action group had enhanced fertility in comparison with the control groups [D12].

99. Epidemiological investigations of combined actions were made on workers at metallurgical plants who were exposed to ionizing radiation and also received periodically high temperature exposure [M12]. Primary functional disturbances of the nervous system were seen with higher frequency in this group as compared to other groups of workers. People having a shorter occupational history were reported to show vascular dysfunctions attributable to dystonicity of the autonomic nervous system. For longer occupational times asthenia also accompanied the above symptoms in a higher percentage of workers. Owing to the obvious difficulties in the quantification of such subjective symptoms any judgement about this type of interaction should be reserved.

2. Low temperature

100. Cold-blooded animals are good experimental material for studies of the influence of low temperature on radiation sensitivity. Much relevant information was published in a specialized symposium [R10]. In very general terms, regeneration of tissues [H24], lethality after fractionated irradiation [E7] and recovery from radiation injury in self-renewing tissues [E8, E9] in fish are considerably inhibited when the animals are kept at suboptimal temperatures. A detailed discussion of these data is beyond the scope of this report which is essentially centred on mammalian systems and on end-points of practical importance for man.

101. Trujillo et al. [T5] reported that RF/Un female mice showed a linear decrease of their ability to withstand a standard cold stress (6°C – 7°C for 14 days), as a function of increasing age. Mice exposed to protracted ^{60}Co gamma exposures at 0.5 Gy/day and then allowed to recover for 90 days showed a similar linear decrease with increasing radiation exposure in

their ability to survive the same stress. This radiation induced effect was considered similar to life shortening through natural aging and was estimated to be equivalent to 9.3 days/Gy. Other data on the combined effect of duration of life irradiation in animals under conditions of low ambient temperature are discussed in Annex K.

102. In experiments by Gambino et al. [G5] rats were irradiated whole-body or on the adrenals only with a standard exposure of 5 Gy and then were exposed for 3 hours daily to 0°C. Reduced longevity, growth retardation, cataract, greying of the fur, and induction of tumours were the long-term effects seen in animals that had been whole-body irradiated, while animals irradiated only on the adrenals did not show such phenomena. The treatment at low temperature did not modify the incidence of these effects, with the exception of a slight reduction of the accelerated onset of tumours seen in whole-body irradiated animals. Since the treatment with low temperature as such gave rise to a reduction of the life span and to differential effects in the incidence of inflammatory and neoplastic conditions, the experiments are not easily interpreted [H17].

103. In many of the experiments described the temperature could not act as such, but as a condition producing physiological adaptive changes. Some information on the influence of miscellaneous physical treatments (permanent or transitory high altitude, high or low ambient temperature, mechanical damage, severe metabolic or physical stress) in respect to tumour induction in animals were already reviewed by the Committee in its 1977 report (Annex I) [U1]. The findings were on the whole negative. When interaction effects were reported they were not very large and explanations in terms of physiological adaptation mechanisms to the exposure conditions could readily be produced. In respect to life shortening, which at the low doses and dose rates of interest in radiation protection is mostly associated with tumour induction, some data are reported in Annex K. They concern low and high environmental temperature and specific and non-specific stress. Here again, the effects reported were marginal and often of antagonistic character, i.e., leading to an increased life span by the joint treatments. These effects could be explained on the ground that suboptimal living conditions frequently act by decreasing, rather than by enhancing, the susceptibility of the animals to the effects of radiation. However, even though the impression is in favour of the lack of positive synergistic evidence, the data are few, the effects unspecific and the underlying mechanisms obscure so that no definitive statement can be made.

E. MAGNETIC FIELDS AND ULTRASOUND

104. A fairly extensive body of literature exists on the effects of magnetic fields in biological systems [P14] but studies of their combined action with radiation are relatively few. A review is to be found in [N6]. This problem may conceivably be of practical significance for workers in thermonuclear fusion devices. It should also be recalled that the use of transversal magnetic fields to improve the dose distribution of high-energy electrons in radiation therapy has recently been envisaged.

105. Sikov [S38] tested various combinations of high-intensity magnetic fields with gamma-irradiation in mice. Of the various end-points considered (lethality, developmental changes, biochemical effects) only two appeared to be susceptible to the action of magnetic fields applied alone (2 to 4 10^8 Tesla, T): audiogenic seizure and the level of tryptophan pyrrolase in liver. In both cases radiation alone had little effect and the results of the combined treatments could be attributed to the action of the magnetic field. A decrease in the slope of the probit line of mortality (gamma rays, 5.8, 7.5, 8.6 and 10 Gy) without change of the LD_{50} value following the contemporaneous exposure to the 4 10^8T field indicated a decrease of spectrum of radiosensitivity values induced by the joint treatment. Fields of 2 10^8 T were inactive to this end.

106. Although some indications of synergism were reported for biochemical indices following localized liver irradiation [W11], experiments on the survival of cell cultures in vitro were negative in this respect [R11, N6]. Uniform magnetic fields of 1.4 10^7 T in combination with radiation produced no changes in the form of the survival curves of cells in vitro or in the pattern of recovery from sublethal damage, as compared with radiation alone [R11]. Higher intensities of the magnetic field (2 10^8 T) or non-uniform fields were also without effect for similar end-points in other experiments [N6]. There is therefore on the basis of presently available evidence little ground to expect an enhancement of the effects of radiation by the joint application with magnetic fields.

107. Ultrasound is widely used for diagnostic and therapeutic purposes, as well as in many industrial appliances. Some experiments considered its possible interaction with ionizing radiation. Harkanyi et al. [H18] irradiated mice by ultrasound (800 kHz, exposures of 0.1, 0.5 and 1.0 W/cm^2) followed two hours later by 0.5 Gy of x rays. Single-treatment groups were also set up at the same time. The yield of chromosomal aberrations in the bone marrow of the animals was taken as the end-point. None of the ultrasound exposures produced any significant increase over the spontaneous level, while the effect of the ionizing radiation dose was easily assessed. No change in this level of effect was found in the group of mice undergoing the combined treatment.

F. DUSTS AND FIBRES

108. For many industrial environments the combination of radiation exposure and exposure to dusts is quite usual, as, for example, in mining, metallurgical industries, power plants and construction works. Many dusts and fibres have been shown to be carcinogenic or pathogenic by themselves. Direct experiments on mammals about the action of dusts are available [C3, C16, K9, P2, P10, P11]; concerning fibres, asbestos and other minerals have been given particular attention [W12, B25]. Since dusts may be soluble or insoluble, according to the different types of materials, studies of their combined action with radiation could be covered under the chemical or under the physical section, respectively. In the first instance the chemical compounds dissolved from dust particles would be the actual agents taking place in any combined action; in the latter the size and the distribution of the dust particles would be the parameters of relevance.

109. Panov et al. [P10] studied the respiratory and renal systems of rats after intra-tracheal instillation of a neutral ^{210}Po solution (37 kBq/rat) and quartz dust (50 mg in saline suspension). Lung fibrosis was found to be

more pronounced in the combined treatment group. Malignant tumours of the respiratory tract were also said to be observed more frequently in this group, although no precise description of all the histological and statistical aspects of these tumours was presented in the work. Similarly, in kidneys glomerulo-tubular lesions were found more often in the group under the combined action of the two agents.

110. Ponomareva et al. [P11, P2] used different types of mineral dust with admixture of highly active thorium oxide. Rats were made to inhale or were instilled intratracheally for periods of time up to one year. The chronic action of these agents gave rise to inflammatory lung processes and to fibrosis. Tumours of the lung were also observed after 1.5 to 2 years. When an additional chronic whole-body irradiation course was given to the animals (gamma rays, 20 mGy/day, total dose 2.5 Gy) the lung tumour yield was increased by a factor of two, in comparison with the group under combined treatment and a group receiving external irradiation only. There were no experiments performed to define the specific role of dust in combination with internal or external radiation treatment. The data obtained from the group combining internal irradiation and dust were used to standardize conditions of occupational exposure including a combination of these agents [B15].

111. Experiments on the combined action of internal alpha irradiation ($^{239}PuO_2$) and chrysotile asbestos fibres (mean fibre length 1–10 μm) were performed by Sanders [S12, S24, S13]. Insoluble particles were administered to rats by intra-tracheal instillation. Animals receiving only the PuO_2 had a more homogeneous distribution of plutonium particles in the lung, while the combination of treatments led to a concentration of the radioactive particles within the asbestos-induced scars in the peribronchiolar regions of the lung. In groups receiving plutonium alone the pulmonary retention half-time of the nuclide was about 200 days; in the combined-treatment group it was 450 days. Correspondingly, the cumulative absorbed doses to the lung two years after instillation were 4 and 12 Gy. The incidence of pulmonary carcinoma was 4.5% in rats given the asbestos, 32% in rats receiving plutonium alone and 21% in the combined-treatment group. Thus, per Gy of absorbed dose, the incidence was about four times greater in the plutonium group than in the combined-treatment group. An explanation for the finding could be that by a reduction of the number of epithelial cells receiving alpha dose a reduction of the resulting yield of tumours could come about. In another series [S12] the two agents were injected intra-abdominally. The agents both tended to concentrate in the fibrous adhesions of the peritoneum and the omentum, inducing sarcomas and mesotheliomas to a final incidence which was not appreciably different from an expected sum of effects.

112. Lafuma et al. [L16] reported preliminary results of experiments with rats where internal or external irradiation were combined with intrapleural injection of crysotile asbestos. In a first series 8 rats were exposed to 3000 WLM (see definition of WLM in Annex D) of radon-222 over 1 month and they received about 70 days after the beginning of exposure, 2 mg of crysotile in suspension intra-pleurally. As in the case of previous experiments with radon inhalation [L8] a very small proportion of animals developed lung tumours after radiation exposure and no mesotheliomas were observed at all. Exposure to crysotile only resulted in a very low incidence of mesotheliomas. However, the combined treatment led to the appearance of lung cancer in all rats, 7 of them being mesotheliomas. A clear synergism is here obtained. The same type of results was obtained in a second experimental series where whole-body mixed gamma-neutron reactor irradiation was given (2.3 Gy of 0.5 MeV neutrons with a gamma component of 0.75 Gy). The animals were injected with the same amount of crysotile 125 days after the radiation exposure. The results on lung tumor induction are given in Table 1 and show that, in addition to an increase in total tumours, mesotheliomas only appear in the irradiated group given crysotile intrapleurally. These preliminary data should be confirmed in larger experiments.

113. Sanders et al. [S22] studied the effects of beryllium oxide aerosol inhalation in combination with plutonium oxide aerosol on more than 600 rats. Aerosol particles were of micron and submicron sizes. Exposures up to initial alveolar depositions of 1 to 91 μg beryllium and 0.15 to 6.7 kBq of ^{239}Pu were performed. The results obtained by the two agents given separately and by their combination (beryllium aerosol being introduced prior to plutonium aerosol) as total incidence of pulmonary tumours show that the changes in lung tumour incidence due to the combination of the agents were insignificant. This in spite of the fact that the alveolar clearance of plutonium was decreased by exposure to beryllium and the translocation of plutonium to the thoracic nodes was increased.

III. CHEMICAL AGENTS

A. INORGANIC COMPOUNDS

114. Changes in the physical and chemical characteristics of the water matrix of biological systems may bring about changes in radiosensitivity. Chinese hamster cells were exposed to media containing deuterium oxide (D_2O) following ^{60}Co gamma irradiation and cell survival was scored as the end-point [B17]. Under these conditions the cell response to radiation was greatly enhanced. Depending on the concentration and the treatment time of D_2O, dose modification factors of up to 4.5 could be found. Pre-irradiation incubation had, on the contrary, a very slight effect on the radiation response. The sensitizing effect of D_2O depended clearly on the conditions of cell metabolism, since it was influenced by the type of media and by the temperature. It was found that the radiation damage capable of interacting with the deuterium oxide was repaired by the cells when they were kept for three hours at 37°C in the growth medium and split-dose experiments suggested that the sublethal damage repair capacity was reduced in the presence of D_2O. The heat sensitivity of the cells was unaffected by D_2O and the enhancement of radiation response induced by heat was also independent of the presence of D_2O.

115. Some natural mineral components of the diet may change the radiation response of the animals [K10]. Rats were kept on diets with low (50 mg/d Ca and 0.2 mg/d F) or high (150 mg/d Ca and 3 mg/d F) content of calcium and fluorine and after 5 weeks of such diet were given radioactive ^{90}Sr. As a result of the combined treatments the haemopoietic system of the first group of animals was more severely damaged and their mean life span shortened by 50–70 days, as

compared with the group with high Ca and F in the diet. The protective action of the high Ca and F diet is achieved at intakes of the two minerals not higher than the upper limits of physiological intake for humans. Similar results were obtained if external gamma irradiation was added to the internal ^{90}Sr irradiation. In other experiments rats were subjected only to gamma irradiation and to diet changes. In all cases the survival at short term and the life span proved to be higher in groups with high calcium and fluorine intakes.

116. The different trace metals found in the air, food and water of some parts of the industrialized world [T7] may alone induce adverse health effects, including malignancies and teratological effects, at sufficiently high concentrations. They may also conceivably combine with the action of ionizing radiation at the background level or under special conditions of exposure. The universal spread of these metallic contaminants make studies of their possible combined action particularly important. Data on the combined action of silver ions and radiation in bacterial systems (spore or vegetative stage) have been provided by Richmond and Powers [R12] and Held and Powers [H25].

117. Lead chloride ($PbCl_2$) in concentrations of 0.1 and 1 $\mu g/cm^3$ was studied in combination with radiation (doses of approximately 1 Gy) for its ability to induce various effects in vitro on embryonic systems [S15]. The number of nucleated cells per mouse embryo, the labelling and mitotic indices and the number of micronuclei per cell were among the effects scored. At both concentrations a synergistic increase of the micronuclei was found, accompanied by an inhibition of embryonic development. For cadmium, the combined effects with radiation were found to be additive in the same system [M26]. Lead was studied by Kudrizkaya [K3] for its capacity to damage spermatogenesis in the mouse. Exposure was given chronically over a period of about six months up to cumulated concentrations of 0.3 mg/g of lead chloride and 81 kBq/g of ^{90}Sr, administered in drinking water. Testis weight or the number of spermatocytes were unaffected by lead alone, while ^{90}Sr significantly decreased the control values of both end-points. Combination of the treatments produced a final effect which was lower than that caused by radiation alone, an antagonistic type of interaction. Lappenbush [L25] injected adult male rats with cadmium chloride (125 to 250 mg) intraperitoneally for 30 days twice per week and subsequently irradiated them with x rays. The 60-day survival was unaffected by doses of the contaminant lower than 125 µg. The radiation $LD_{50/30}$ was found to decrease linearly with increasing exposure to cadmium. The numbers of red and white cells in the peripheral blood were affected by the combined treatment in a complex way.

118. Platinum (cis-dichloro-bis platinum, DBCP) and radiation affected the survival of ovarian-derived Chinese hamster cells in culture according to a synergistic type of interation [C8]. Chromatide aberrations were also induced in higher percentages. In order to observe synergism the chemical had to be administered between four hours before and two hours after irradiation. Two or three days elapsing between the chemical and the radiation treatment abolished the interaction. The synergistic effect was considered to result from radiation-induced single-strand breaks in the DNA which occurred in linear proportion to dose, opposite to a single platinum complex intra-strand cross-link which occurred linearly with respect to platinum concentration. The combination of the two lesions led to lethality. A simple mathematical model to describe the experimental data was developed.

119. The nitrocompounds, especially the oxides, are rather common pollutants of the air. Sensitization of anoxic bacterial spores was reported when they were irradiated in NO_2-saturated water [P15]. A study is available in mammals [K4] where inhaled plutonium-239 under the form of plutonium pentacarbonate ammonium (69 kBq/kg of lung tissue) was administered to rats, after which the animals were also made to inhale nitrogen oxide (0.09 mg/l) or chlorine (0.05 mg/l) for 15 minutes. After the combined treatments the incidence of lung cancer was almost doubled as compared with the irradiation treatment alone. Tumours were multifocal and different types of tumours were seen in the combined than in the single treatment. Pneumosclerosis was also enhanced in the combined treatment group.

120. Occupational situations where exposure to ionizing radiation may be accompanied by exposure to other detrimental chemicals should not be uncommon in industrial practice, but epidemiological data in this field are very rare. In one case observations were carried out on workers exposed to gamma rays for industrial radiography and also to vapours of hydrofluoric acid (HF) [S21]. The changes investigated (levels of T-lymphocytes, C-reactive protein and auto-antibodies) were mainly immunological. The group under the combined influence of radiation and the toxic chemical was reported to have lower levels of T-lymphocytes and higher levels of C-reactive protein and auto-antibodies than the groups exposed to only one of the agents.

B. ORGANIC RADIOSENSITIZING COMPOUNDS

121. The present section includes what is essentially a review of substances which may enhance the radiation response of biological systems, and are called radiosensitizers. Compounds inhibiting the radiation response are called radioprotectors. In many cases these substances were specifically developed for their protective or sensitizing properties. The study of radioprotective chemicals has been strongly pursued [R2, M7, M29, B29]. More recently, the application of such compounds in clinical tumour therapy has been discussed [Y7]. Also, a new field has grown and is still rapidly expanding, that of the radiosensitizing compounds [M10, R6], whose potential in clinical radiotherapy is being tested.

122. The relevant data will be reviewed briefly because it seems unlikely that situations will arise in which these substances may pose significant problems of public or occupational health. For a review of biological effects, mostly lethal, of the combined action of acute irradiation with other common industrial poisons (at high toxic levels) the reader is referred to Tiunov et al. [T2]. Annexes J and I of the 1977 report [U1] reviewed the action of radioprotective and radiosensitizing chemicals in respect to the production of embryonic and foetal damage by radiation and of tumour induction, respectively. The available information on the action of chemical radioprotective drugs for life-shortening effects in animals is reviewed in Annex K of this report.

123. Several classifications of radiosensitizing substances have been proposed [M10, P16, S39], based on their mechanisms of action. Keeping in mind that in some cases the molecular mechanisms are still unknown and that some agents may act through more than one mechanism, one classification may be as follows: 1. Agents modifying the primary radiation chemical processes, including (a) electroaffinic agents and (b) iodine compounds; 2. Agents interacting with DNA metabolism (DNA-base analogues); 3. Antibiotics and other agents interfering with repair processes (see section III C); 4. Agents reacting with nucleophilic groups (SH groups); 5. Other radiosensitizing agents.

124. The best known example of the first class of agents is oxygen whose level in biological systems at the time of irradiation greatly influences the yield of radiation effects. A massive body of literature exists on the action of oxygen and the interested reader is referred to [A11, P1]. A large number of electroaffinic compounds or hypoxic cell sensitizers is also known but their detailed discussion is beyond the scope of this Annex. Such compounds may contain one of the following chemical groups: the carbonyl (CO), the aldehyde (CHO), the nitro (NO_2), the cyano (CN) groups, homo- and hetero-cyclic rings. Stable free radicals are also electro-affinic agents. The radiosensitive properties of such compounds are manifest when they are present in biological systems at the time of irradiation or if they are irradiated separately and then immediately added to the biological system.

125. The same is true of the iodine compounds which may also change the concentration of radiation-induced free radicals. If cells are exposed to irradiated iodoacetamide within milliseconds after irradiation cell killing takes place, which is not observed if irradiated cells are exposed to non-irradiated iodoacetamide, thus showing the role in sensitization of short-lived transient compounds [D9]. Radiosensitization takes place also with other iodine compounds: iodide, iodoacetic acid, iodopropionic acid, methyliodide, p-iodophenol, iodobenzoic acid and others. Reactions with -SH groups may account for part of the sensitizing effect of some of these compounds [M7].

126. Attention has recently been given to the radiosensitizing properties of iodine contrast media used in radiodiagnostics [S43, N7, A2, M25]. Sensitizing effects on bacterial killing were first reported [S43] and then an increased yield of chromosomal aberrations in peripheral lymphoctyes of children undergoing x-ray angiocardiography with contrast media [A2, N7]. It has also been reported that sensitization of mammalian cell killing by iodine compounds would occur for x but not for gamma rays [M25]. These data are explained by the difference in doses due to photoelectric effect in the case of x rays. An accurate physical dosimetry should clarify this issue.

127. Quinones are unsaturated carbonyl compounds with conjugated structures and electron affinic properties. Several quinones and their derivatives have been found to sensitize bacterial and yeast cells under oxygenated and anoxic conditions [A4, M11, S16, S17]. It has been postulated that the sensitization of E.coli B/r by vitamin K5 is mediated by radiolytically produced hydroxyl radicals [S16]. Diphenylquinone was found to enhance the action of radiation in mice [A4]. In some bacterial systems under anoxia the value of DMF could be about 3 (10^{-3} M indanetrion monohydrate [B7]) or even 4 (100 ppm vitamin K5, [S16]). Newly synthesized isoindole quinones showed promising characteristics when tested in vivo on soft tissue sarcomas transplanted into mice [C13].

128. Electroaffinic compounds containing nitro groups can specifically increase the radiosensitivity of anoxic cells, leaving that of oxygenated cells unchanged or even decreased. These properties would be advantageous for tumour radiotherapy [A5, D8, H4, H8, P17, Y5]. The radiosensitiziation by mizonidazole was proved to occur for hypoxic mammalian cells in vitro and in vivo [A12]. Under aerobic conditions no sensitizing effect of the compound at any stage of the cell cycle was observed [P17] and under anoxia the strongest effect occurred in middle-S. Toxicity of the agent under anoxia requires low exposures to the agent.

129. Yuhas and Li [Y5] studied the effects of the compound at a concentration of 6 mM in combination with the radioprotective compound cysteine (8 mM) on mammalian cells in culture, showing protection under conditions of oxygenated irradiation and sensitization under anoxia. Hall et al. [H8] tested eight different nitro compounds: for all of them the DMF was an increasing function of the concentration and for some it reached a value of about 3.5, equalling the average value of the OER in the cells tested. In general, 2-nitroimidazoles were more effective sensitizers than 5-nitroimidazoles. Other nitrocompounds, the nitrofurans, may be even more effective, specifically under anoxia [R3, R6]. Sensitization by nitrocompounds was greater when they were administered prior to irradiation [D8]. Radiosensitizing properties were also described for nitrogen-containing stable free radicals such as triacetone-amide-N-oxyl (TAN) [E5, B21] and 2,2,6,6,-tetramethyl-4-piperidinol-N-oxyl (TMPN) [P6].

130. DNA base analogues belong to the second class of radiosensitizers. Extensive studies were made especially on halogenated DNA base analogues such as 5-fluorouracyl (5-FU), 5-bromouracyl (5-BU) or 5-bromo-2-deoxyuridine (5-BUdR) [K13]. Significant enhancement of killing was shown for viruses, bacterial and mammalian cells [S18]. Some attempts for a clinical application of these substances have also been reported. For a review of the relevant studies see [M7, M10].

131. The third class of radiosensitizers will be considered in section III.C. Here various substances capable of modifying the biochemical cellular processes should be mentioned, belonging to classes 4 and 5. Several organic chemicals capable of enhancing radiation damage share the property of being -SH reactive. Since -SH compounds are known to be radioprotectors, the correlation has been investigated between the ability to bind -SH groups and the capacity to sensitize the cells to the action of radiation. Bruce et al. [B8] found that the capacity to sensitize was well correlated to the amount of p-hydroxymercuribenzoate bound to cells.

132. Sensitization of anoxic cells is an important goal for tumour radiotherapy [A13, R6]. Radiosensitization of bacterial cells under anoxia by N-ethyl-maleimide (NEM) was shown as early as 1960 by Bridges [B6]. Other data on bacterial and mammalian cells are also available [L12, M18, K11]. A DMF of 1.5 with human cells in vitro irradiated with x rays was reported by Klimek [K11]. The known property of NEM to bind -SH groups led to the hypothesis [L12] that NEM could bind the free non-protein -SH groups, thus preventing DNA repair through donation of hydrogen from these

groups. Other experiments by Klimek and Zemanova [K12] showed that under concentrations of NEM too low to inhibit DNA synthesis a high proportion of the original free thiol groups was still present, thus implying other mechanisms for NEM sensitization. However, the role of intracellular thiol groups would also be supported by experiments of Sinclair on oxygenated [S40] and anoxic [K17] Chinese hamster cells exposed to NEM and radiation. Repair of lethal damage is inhibited by the presence of NEM but the mechanisms of such an inhibition are still unknown.

133. Another organic compound that may produce cytological changes is carbon tetrachloride (CCl_4). Its administration to animals induces, for example, liver cell proliferation [A6] similar to that induced by partial hepatectomy. Cole and Nowell [C20] examined the effect of CCl_4 on the induction of hepatomas in fast neutron irradiated mice with doses of 1.7 to 3.1 Gy. At various times after irradiation some animals received the compound subcutaneously. Sixty-one percent of animals receiving the combined treatment developed hepatomas, as compared to 19% of the mice irradiated only. Since CCl_4 alone produced no hepatomas, the interaction factor is approximately 3. Histologically the tumours were similar in both groups but tumours of larger size were more frequent in the combined modalities group. The authors concluded for a promoting effect of CCl_4 in liver cancerogenesis. Procaine hydrochloride, a local anaesthetic acting on cell membranes, has been shown to sensitize bacterial and mammalian cells to the action of radiation [S19, S20].

134. Alkylating agents may react with DNA bases and thus directly influence the radiosensitivity of cells. The alkylating agent spirohydantoin mustard (SHM) was tested in combination with x-irradiation on brain tumour cells in vitro [D15]. The enhancement of cell killing was greatest when the cells were irradiated four hours before the drug treatment. The doses ranged from zero to 20 Gy and the subsequent chemical treatment with SHM lasted one hour at concentrations of 0, 2, 3, 4 and 5 μg/ml. The results were normalized and the corresponding isobolic diagrams were built. At levels of cell killing down to 10% a synergistic interaction was apparent, although for lower levels of survival down to 0.1% the interaction turned into an additive one. This and another paper [D2] by the same authors are some of the rare examples where the analysis of the interaction type was carried out according to the approach outlined in chapter I of this Annex, involving the use of isobolic diagrams.

135. The same brain tumor cells cultured in vitro were exposed for one hour to 1, 3, 5, 7.5 μg/ml of 1,3-bis(chloroethyl)-1-nitrosourea (BCNU), followed 15 hours later by a series of x-ray doses of up to 20 Gy [D2]. Survival curves for the x rays alone, the BCNU alone and for the combination of both agents were obtained and on their basis isobolic diagrams for survival levels of 1, 2 and 3 log cell kill were constructed as in Figure XVII. The figure shows the experimental points for the combined treatment connected with a dashed line; all the points except one fall into the envelope of additivity applying at each survival level. The point at the lowest level of survival (7.5 μg/ml of BCNU, 4 Gy of x rays) falls outside the respective envelope, although the displacement is not so great that it might not be explained by experimental uncertainties.

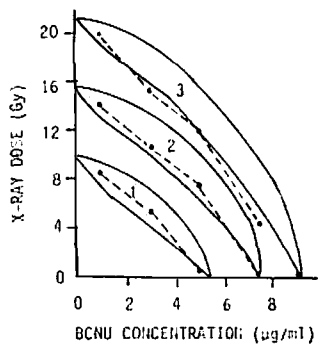

Figure XVII. Isobolic diagram for the combined action of BCNU and x rays on 9L rat brain tumour cells [D2]

136. The scope of this brief overview of chemicals capable of modifying radiation sensitivity is simply that of illustrating the very wide range of processes whose alteration may in turn lead to a synergistic or antagonistic interaction in irradiated biological systems. The data reviewed are as such of little relevance for the main scope of this Annex, because the doses of radiation used are usually very high (up to several Gy, depending on the susceptibility of the systems tested) and the concentrations of the chemicals often toxic. It is however appropriate that they should be mentioned because the processes governing different aspects of cell radiosensitivity might also be relevant at lower levels of exposure. No practical situation where the above mechanisms would be significant can currently be envisaged at the low doses of interest for the purpose of the present Annex.

C. CARCINOGENIC CHEMICALS

137. Organic substances which are known to have carcinogenic properties should be discussed separately. Some, such as the alkylating agents, have already been mentioned in section III. B. Carcinogenic agents are usually divided roughly into initiators and promoters, following the two-stage theory of carcinogenesis [B18]. It is known however that such a subdivision is not rigid because many agents share the properties of both classes. In combination experiments it may be expected that the final tumour yield may depend on the properties of the interacting agents, as well as on the order and time pattern of their administration. A potent initiator followed by an active promoter might be expected to give the highest carcinogenic response and reversal of their order of administration a drastic reduction of this response. Another important trait is the spectrum of the tumours induced, as some agents may be extremely specific in this respect and their interaction with radiation might change this selectivity.

138. Precise quantitative data were provided by DiPaolo et al. [D21, D17, D22] and Kennedy et al. [K14] on the morphological transformation of mammalian cells in culture in regard to the interaction between ionizing radiation and the carcinogen benzo(a)pyrene or the promoting agent phorbol ester. The experiments elucidated the dose-time relationships for an effect of special significance for practical purposes, showing enhancement factors of up to 9 fold, depending on the conditions of exposure and on the doses of the agents interacting. This series of experiments also attempted to elucidate the mechanisms of interaction. For the same biological end-point, the

promoter 12-0-tetradecanoylphorbol-13-acetate (TPA) administered after x-ray or neutron irradiation to C3H/10 T 1/2 cells in culture was shown to act synergistically, with complex relationships as a function of the radiation type and dose [H27].

139. A study showing an increased yield of leukaemia in mice pre-irradiated with x rays and subsequently treated with methylcholanthrene was published by Furth and Boom [F9]. An increased yield of leukaemia in mice induced by x rays, methylcholanthrene or oestrogens was also shown by Kawamoto et al. [K6] when the animals were simultaneously treated by urethan. After Berenblum investigated the interaction of x rays and urethan in mouse leukaemogenesis in great detail and showed that the order of administration of the combined agents was of decisive importance [B2, B26] many other authors reported enhancement of leukaemia under the same agents [D4, L22, V6, G1] particularly in young animals [B1, L23] where enhancement is especially pronounced. This may be on account of differences in the drug distribution or catabolism as a function of age [C2]. Data have also been reported for croton oil [I2], myleran [U5] and novoembicyn [A8] in conjunction with radiation.

140. Combined treatments of pre-implantation mouse embryos in vitro with x rays or phenols (which are promoting and mutagenic chemicals in some test systems) showed that the effects were, at most, additive [M30]. Schmahl and Kriegel irradiated mouse embryos in utero at 11–13 days p.c. (1 Gy at each time) and injected the pregnant mothers at 17 days p.c. with 0.5 mM/kg of ethylnitrosourea [S42]. Tumour development was followed post-natally up to 18 months. Results from this series are shown in Table 2, with the interaction factor calculated according to equation (5). If one considers total tumours as the end-effect, interaction appears to be antagonistic ($\omega = 0.44$). If one takes each category of tumours separately, one may conclude for at least one clear case of synergism and one of antagonism for leukaemia and hepatomas, respectively. This appears to be a good example of a change in the tumour spectrum brought about by the combined treatment. However, for more definitive statements exposure-response curves within a broader range of values for both the single and the combined actions would be required.

141. Much work has been carried out on the skin, the tissue where the two-stage mechanism of carcinogenesis was originally identified [B18] and can be more easily tested. Electrons or UV light in association with other carcinogens usually result in a higher yield of tumours than any of the agents administered alone. This applies to methylcholanthrene [C14] and to 7,12-dimethylbenz(a)anthracene (DMBA) [E6, S28]. However, a recent report [B19] on this latter substance in association with 0.8 MeV electrons (5–25 Gy) in respect to carcinogenesis of rat skin showed that the tumour yields were approximately equal to the sum of the yields induced by the separate treatments, so that prior irradiation did not appear to alter the susceptibility of rat skin to DMBA carcinogenesis.

142. The case of 4-nitroquinoline-1-oxide (4NQO) has been particularly well analysed. When applied in combination after beta rays from ^{90}Sr-^{90}Y (both agents at doses that did not separately induce tumours) it appeared to have a synergistic effect for skin tumour induction in mice. Reversing the order of administration of the treatments led to a much smaller yield of tumours by about an order of magnitude [H5]. When the interval between beta irradiation and subsequent chemical treatment was made to vary between 11 and 408 d, the tumour induction rate was found to be almost at the same level for all treatment times, indicating that the latent carcinogenic change induced by skin irradiation may persist for a very long time and remain available for subsequent interaction with the 4NQO [H6]. Finally, caffeine was found to further increase the incidence of malignant tumours in mouse skin when painted after beta rays and 4NQO treatment [H7].

143. Croton oil, a typical promoter of skin neoplasia from which TPA is extracted, gives uncertain results when combined with radiation: enhanced effects with UV [E2] and electrons [S29] or absence of any enhancement [G6, B20] have in fact been reported. It may be said in very general terms that the concepts of initiation and promotion may be verified on the skin also in the case of drug-radiation interactions. However, the results of combined treatments on the skin could also be interpreted on different grounds and some of the previously mentioned experiments [H5, E2, E6] would in fact be regarded by others [N3] as clear examples of co-carcinogenesis by chemical and physical agents.

144. The situation with respect to other tumours or to systemic leukaemogenesis is definitely more difficult to interpret. In the case of the lung, urethane (which specifically induces adenomas in mice) has been used in association with x rays at various doses and dosages. A reduction in the incidence of tumours (both as percentage incidence and as tumours/animals) has been obtained in one experimental series [F6]: cell killing by the high radiation dose in the urethane-induced tumours was held responsible for the effect. Recalculation of these data by others [L21] led however to a different interpretation. Additive effects of radiation and urethane were reported in another series, and the final outcome of the treatments was deemed to depend on two competing phenomena, cell killing and cell transformation, whereby, depending on the dose of the two agents, any effect may become possible. Immunological phenomena might also interfere in this case to make the picture very complex [C15].

145. Procarbazine (PCB), a drug used frequently in the treatment of the Hodgkin's disease, is a known carcinogen in experimental animals since it gives rise to pulmonary adenoma and leukaemia in mice, mammary tumours in rats and acute myelogenous leukaemia in primates. Hybrid (BALB/c × DBA/2) F_1 mice were given this drug and ionizing radiation at different times to test for possible synergistic effects [A7]. Single-treatment groups received 300 mg/kg PCB weekly for four weeks, a dose effective for induction of pulmonary adenoma and leukaemia; or 0.6 Gy/d of 300 kVp x rays for five d, a dose which did not result in tumours of the lung. Combined-treatment groups received radiation three days or three weeks before PCB or PCB three days before irradiation at the above dosages. The experiments were terminated within 12 weeks with killing of the surviving animals. Pulmonary adenomas in mice receiving both agents were significantly increased over the level of induction by PCB alone. Thymomas were also increased significantly in the animals given the drug three days before or after irradiation. The authors concluded for a synergistic effect of the combination and hypothesized that an increase of the normal tendency of mice to develop pulmonary adenoma

would be at the origin of the interaction. Immunosuppression combined with direct cellular damage might also be responsible for the effect.

146. Among studies where combinations of chemical carcinogens and radiation were tested, the experiments of Metivier [M6] regarded the action of PuO_2 given by inhalation, in combination with benzo(a)pyrene (BP) or dimethylnitrosamine (DMNA), compounds which are widespread environmental pollutants. Both carcinogens were given after the exposure to the PuO_2: BP (2 × 5 mg) was administered intra-tracheally in association with haematite 2–3 weeks after the nuclide; DMNA (2 or 20 ppm) was given orally, added to the drinking water. Tumours of the lung and of other sites, histological types of tumours, invasiveness and survival time were the principal end-points investigated.

147. BP alone led to a small increase of tumour incidence above the control level. PuO_2 (0.63 kBq) produced similarly a slightly increased incidence. Both agents combined produced an appreciable increase in the number of tumours with an increased invasiveness. Survival time reflected closely the results on tumour incidence, being essentially unchanged for the two agents given alone and practically halved by their combination. At least on qualitative grounds, a synergistic interaction was operating in these experiments, the latency period of the tumours in the combined treatment group being evidently shorter. For higher levels of PuO_2 (6.3 kBq) a synergistic action might also be present, but its expression (particularly with regard to survival time) is much less clear. In the case of DMNA no synergistic action with respect to alpha radiation alone was found. At high concentrations (20 ppm) the latter drug produced a subacute intoxication and no synergistic effect. It was reported however that inhalation of PuO_2 in association with DMNA did result in an increased tendency of liver tumours to metastasize into the lungs.

148. In the experiments of Little et al. [L10] the interaction between benzo(a)pyrene (BP) and alpha radiation of ^{210}Po, was examined. The experiments were performed on hamsters and the two agents were administered by intratracheal instillation, absorbed on haematite particles or dissolved into physiological saline. In a first series of experiments the two agents were administered simultaneously in 15 weekly instillations (0.3 mg BP + 0.2 kBq ^{210}Po/treatment). Under these conditions the results were compatible with an additive interaction of the two agents.

149. In a second series of experiments BP was given 15–18 weeks after the administration of a single dose of 1.5 kBq ^{210}Po. While BP alone (2.4 mg in eight weekly instillations of 0.3 mg) or ^{210}Po alone produced practically no lung tumours, the combinations of both agents resulted in a clear synergistic effect, with 17% of the animals developing frank tumours of the lung. Physiological saline and gelatine were mostly used as carriers. When the administration of BP preceded the ^{210}Po treatment no increase of tumour induction was seen. It is remarkable that when the second treatment consisted of saline alone, without BP, a sharp increase of the tumour yield was seen, compared to the ^{210}Po treatment alone. The instillation of isotonic saline could act as a non-specific stimulus to cell proliferation [L11] and subsequent experimental work [L24] appeared to lend support to this hypothesis. Autoradiographic experiments showed that after treatment by BP or by saline the epithelial cells of the hamster lung undergo a wave of mitoses. This enhanced proliferation would be essential for the expression of the radiation-transformed cells.

150. A biochemical approach to the study of mechanisms of interaction between radiation and chemicals in the case of lung tumour induction was followed by Queval and Beaumatin [Q1]. These authors studied the correlation between the capacity by various substances of inducing pulmonary enzymes and their ability to shorten the latency period of the lung tumours in rats, following inhalation of radon daughters. The research established that compounds such as benzoflavone, methylcholanthrene and benzopyrene are highly effective in enzyme induction and capable, at the same time, to shorten the latent period of tumour appearance.

151. Large experimental series were carried out on the combined effects of radiation and inhalation of uranium ore dust and diesel oil exhaust fumes at the Pacific Northwest Laboratory [C16]. The experiments on hamsters involved about 600 animals non-exposed or exposed to radon and radon daughters, uranium ore dust and diesel engine exhaust, alone or in various combinations. Squamous cell carcinomas developed in only a few of the animals exposed to radiation and they were always preceded by a squamous metaplasia of the alveolar epithelium. In general, however, the hamster lung was found to be rather refractory to the malignant transformation and did not even develop lesions that could be classified as pre-cancerous when exposed to levels of the above agents which were regarded as realistic for life exposure regimes. Thus, the hamster lung under these conditions may not be a useful model for pulmonary cancerogenesis in man.

152. Knizhnikov et al. [K9] modelled another case of industrial exposure by a combination of shistose ash, benzo(a)pyrene and ^{210}Po. The mice were exposed to ash alone, ash with BP or with ^{210}Po, and to the triple combination of the agents together. The yield of lung tumours and their latency period were studied and at the levels used the yield was reported to increase from 35% (ash only) to 61% (triple combination). The latency period decreased in the same two groups from 300 to 200 days. An interaction factor may be calculated from these data of about 1.3, indicating some synergistic interaction. Other control groups were included in this series.

153. The intragastric administration of 3-methylcholanthrene followed by x rays [S30] or fission neutrons [S4] produced no more than additive effects for induction of mammary adenocarcinoma. However, the same chemical applied locally on the brain, in association with beta irradiation resulted in an antagonism which was proportional to radiation dose [M15].

154. There are many different experiments concerning a variety of other tumours. X rays alone or in combination with benzo(a)pyrene produced the same incidence of neoplasia [K7]. Dibutylnitrosamine (DBNA) or 4-ethylsulphonyl-naphtalene-1-sulphonamide (ENS) combined with x rays showed no effect on tumours of the urinary bladder but a reduction of the mammary tumour incidence [F7]. A synergistic action on the production of liver and gastric carcinoma by fission neutrons in combination with N,N'-2,7-fluorenylenebisacetamide (2,7-FAA) was reported, but no interaction for intestinal tumours was found [V7].

Localized x-irradiation in association with the same drug administered in the diet accelerated the induction of hepatomas [N1] and similar effects were reported with the association of x rays and o-aminoazotoluene [K8] and of ^{144}Ce and dimetylaminoazobenzene (DBA) [M16]. Experiments on additive carcinogenic effects of 9,10-dimethyl-1,2-benzanthracene or 1,2,5,6-dibenzanthracene in association with chronic internal irradiation from ^{90}Sr were also reported [Z1, Z2].

155. The mutagenic substance N-methyl-N'-nitro-N-nitrosoguanidine (MNNG) was tested in combination with whole-body fission neutron irradiation for its carcinogenic properties on the gastrointestinal tract of rats. A high incidence of gastric and duodenal carcinomas was found after the MNNG treatment but the neutrons did not produce any tumour. Combining the two treatments did not change the effect of MNNG [V3]. Survival and tumour induction were tested in three strains of rat following x-irradiation in association with urethane. In spite of some interesting differences observed between strains, the overall effect of the joint treatment was not greater than the sum of the separate effects at the dosage level studied [M17].

156. In work by Sanders [S12], besides the combined action of $^{239}PuO_2$ and asbestos, the combined action of $^{239}PuO_2$ with benzo(a)pyrene was also studied, both agents being administered intra-peritoneally. The action of BP alone produced mostly abdominal sarcomas. The combination of BP and 13.3 kBq of $^{239}PuO_2$ resulted in an approximately additive yield of sarcomas. Other tumours which are characteristic of the plutonium action were also produced. The administration of BP increased the translocation of plutonium to liver and lung, which points to the need that possible metabolic effects leading to different dose patterns in various organs upon the joint administration of two substances should be taken into account when discussing the results of combined actions.

157. In conclusion, it appears that the evidence reviewed is very conflicting. The number of substances tested is large and the amount of information relating to each of them very little. The pathogenesis of the tumour systems tested is complex and the conceptual distinctions between induction and promotion cannot be held in many instances. In some cases the application of chemicals after irradiation may enhance the tumour yield by comparison with the opposite order of application. In other cases, the association of treatments may actually decrease rather than enhance the induction of neoplasia when the toxicity of the combined agents outweighs their additive carcinogenic properties [U2]. No definite conclusions with respect to any class of tumours may therefore be drawn before the dose, the dosage schedule, the order of administration and modalities of the combined treatments are properly and thoroughly explored, which is very rarely the case in the contributions that have been reviewed.

D. THE SPECIAL CASE OF TOBACCO SMOKE

1. General

158. Tobacco smoking is a widespread habit of many human populations in spite of a well documented association between smoking and lung tumour incidence. The relationship between annual death rate from this cause and number of cigarettes smoked per day is reported to be linear with slope of about 10^{-4} [D5, D23] and with incidences of lung cancer rising from about 0.07 10^{-3} per year in non-smoking males to 3 10^{-3} per year for male persons smoking 35 or more cigarettes per day. The chemical composition of tobacco smoke is very complex and includes more than 1000 identified compounds [S9], a number of which are aromatic hydrocarbons that have been shown to act as carcinogens. Smoke and tobacco tar also contain a number of tumour promoting and co-carcinogenic agents.

159. The two-stage nature of the carcinogenic action of tobacco smoke was shown by a classical experiment on mouse skin by van Duuren et al. [V1]. The initiator, 1,2-dimethylbenz(a)anthracene (DMBA) acted in this case as an initiator and cigarette smoke condensate (CSC) as the promoter. Five weekly applications of CSC after a single application of DMBA greatly increased the rate of tumour appearance, by shifting the latency period from 450 d (for DMBA alone) to approximately 100 d. The initiating action of the tar components is relatively low compared to that of DMBA. In this particular case the initiator was a chemical substance, but any other carcinogenic agent, ionizing radiation in particular, could be effective in combination with the promoters contained in the smoke concentrate. This point was proven experimentally by McGregor [M27, M28] who treated rat skin with beta radiation and subsequently applied CSC. Rats treated with CSC only produced no tumours. A two- to three-fold increase in the numbers of skin tumours was observed in the groups under combined action, as compared with the animals exposed to beta radiation alone. It should, however, be realized that only few agents can be considered as pure initiators or promoters, the rule being that many carcinogenic agents have the properties of both classes of substances and sometimes to various degrees, according to the different animal models tested.

2. Experimental data

160. Various examples of interaction between radiation and tobacco smoke have been reported in animals [C5, C6, C16]. In experiments by Chameaud et al. [C5, C6] rats were exposed to radon inhalation in special chambers. They developed respiratory cancers as a function of exposure and exposure rate, starting from a control background incidence of practically zero. Similarities could be shown histologically between these tumours and human lung tumours. Inhalation of cigarette smoke in these animals did not result in malignant transformation of the respiratory cells but only in benign lesions of the bronchial epithelium and lung parenchyma [C7]. In interaction experiments the exposures to radon daughters was chosen to be 100, 500 and 4000 WLM, because it was shown in previous tests that the incidence of lung cancers of respectively 1–2, 5–10 and 30–40% would result from them [L8]. Cigarette smoke inhalation was carried out under standardized conditions for periods of 15 min ten times per day, four days per week, for one year. No change in the animals' life span was seen after this treatment. An elaborate classification of the pathology was set up to follow the spread of tumours at death.

161. For the highest radiation exposure (4000 WLM) the incidence of lung cancer was 34% and it increased to 68% in animals also exposed to smoke. At 500 WLM,

7% and 28% were the corresponding figures and at 100 WLM, 0% and 3.3%. Since smoking was without effect, equation (22) in a simplified form may be used to analyse the data. Accordingly, the values of the interaction factors for the above groups are 2, 4 and ∞. Pathologically, tumours appeared to be more advanced in animals receiving the combined treatments, indicating that neoplastic lesions developed earlier in these animals. Microscopically, the same tumour histotypes were found in the irradiated group and in the group with combined exposure. The authors pointed out the similarity between these findings and those in uranium miners and proposed their rat tumour system as a good model system for the human situation [C7, L8].

162. Another interesting aspect of the laboratory experiments with rats which is in accordance with some results from epidemiological studies on uranium miners is the complex dependence of the lung tumour yield in the animals on the exposure rate and on the level of exposure. Human data strongly suggest that lung cancer may be produced more efficiently at low than at high exposure rates [L6, K1], in the sense that per unit dose higher incidences of tumours are produced at low than at high dose levels. It should be pointed out that low doses are usually obtained at low dose rates. In the experiments of a French laboratory the incidence of lung cancer in the rat per 10^6 WLM changed from over 200 at cumulative exposures of around 175 WLM to 46 at 8000 WLM [L8].

163. The above mentioned French group investigated in further experiments the temporal aspects of a combined treatment in rats of radon daughters and tobacco smoke, by reversing the order of administration of radiation and tobacco smoke with respect to the previously cited experiments [C7, C8]. In this case radon exposure followed exposure to smoke [L9], without any enhancement of carcinogenesis. This observation is in keeping with the notion that tobacco smoke has a promoting action. It was not possible to examine the relationship between the level of exposure to smoke and tumour incidence, since higher levels of exposure led to a toxic action of some tobacco constituents and, on the other hand, lower exposures required an excessive number of animals for statistical validation of the data.

164. The effect of grading the exposure to tobacco smoke may to some extent be studied by the use of chemicals which are constitutents of tobacco smoke or tar, although it should be kept in mind that in this case the mechanism of action could be rather different. Morin et al. [M5] examined the effect of inhaled radon daughters in combination with the I.P. administration (25 mg/kg/week for 13 weeks) of benzo-5, 6-flavone (BF), a substance which is not in itself a carcinogen. Treatment with BF was started at three months after the end of radon exposure at 6000 WLM during about two months. One hundred percent of the animals developed lung tumours (multifocal, invasive epidermoid type with a latency period of 3 months), as compared with an expected 50% within 15 months after radiation exposure given alone. When BF administration was started 16 months after radon exposure, no difference was seen with respect to the group receiving only radon. This was taken as evidence that the promoting action of BF was exerted during the period of latency of the radon induced malignancies.

165. Grading the exposure to BF (25, 9, 3 mg/kg/week) and to radon daughters (6000, 3000, 500 and 100 WLM) gave 12 possible combination groups [L9]. Preliminary data showed that the reduction of the latent period was dependent on the product of the parameters characterizing exposure to each agent, as though a lower dose of one could be compensated by a higher exposure to the other in a multiplicative manner. Such a dependence resembles to some extent the "relative risk model" proposed by Lundin et al. [L6] to account for epidemiological data in uranium miners.

166. Modelling of chronic inhalation of radon daughters and tobacco smoke simultaneously was carried out on experimental animals at the Battelle Northwest Laboratories [C16]. The temporal aspect of the administration of the combining agents differed from the experiments of the French group already reviewed [C5, C6], where exposure to smoke followed the radon treatment. The experiments comprised seventy beagle dogs: twenty of them were exposed to radon, uranium ore dust and cigarette smoke; twenty to smoke only; and twenty to radon plus uranium ore dust. The other animals served as the controls. Exposure to tobacco smoke was performed through special masks during several daily sessions.

167. Animals that developed lung tumours had in general cumulative exposures to radiation in excess of 13 000 WLM. This dose level is about two orders of magnitude higher than that reported to cause lung cancer in man. The possibility was therefore considered that the longer life span of the human species might allow more tumours to appear while, for the same tumour incidence, much of the exposure in dogs would be "wasted", i.e., ineffective in producing additional tumours. Differences in histotype between human and dog respiratory neoplasms were also noted. Cigarette smoke had a reducing effect on the radiation lung cancers (2 cases out of 20 animals) as compared to animals non-exposed to smoke (8/20). It was suggested —but in the absence of direct experimental evidence— that smoke through an increased production of mucus might result in a lower dose of radiation to the target cells; alternatively, smoke might stimulate mucociliary clearance. Changes in the lung that were associated to tobacco smoke were emphysema, chronic bronchitis and bronchiolitis, lung fibrosis. The antagonistic effect of tobacco smoke on lung tumors induced by radon daughters was confirmed in a very recent report of these experiments [C22].

168. It may thus be concluded that reasonable dose-response relationships for lung tumour induction in experimental animals may be obtained for exposure to ionizing radiation. The separate effects of tobacco smoke may also be studied, but testing their combined action poses serious problems. The temporal sequence of administration is very important; there are probably differences in target cells with respect to the two agents; there may be other unknown factors complicating the picture; the mechanisms of induction have not been sufficiently clarified. It may be tentatively proposed that a common feature of many experiments in animals (and of some epidemiological series in man) is a promoting action of the smoke (or some of its constituents), leading to a shortening of the latency in tumour appearance. Whether this might be due to a non-specific stimulating action on the proliferation of the respiratory epithelia or to a specific effect of some smoke constituents is impossible to say at present.

3. Epidemiological evidence

169. Uranium miners are exposed to radon and radon daughters. They represent the first occupational group on which extensive epidemiological surveys were made of the effects of radiation in combination with tobacco smoke. The exposure levels for this group of workers are usually expressed in WLM: for the equivalence of this operational unit with other radiation units, see Annex D. In an epidemiological survey [L2] 3414 miners exposed to up to 10^4 WLM from the year 1950 were followed up to September 1967. Against 251 deaths expected during this interval of time, 398 deaths were actually observed, the main causes for the excess being violent deaths (120 observed versus 51 expected) and malignant tumours of the respiratory tract occurring ten or more years after beginning of work in the uranium mines (62 observed versus 10 expected). The time relationship and the increase in cancer mortality as a function of radiation exposure indicate a causal relationship between the two variables.

170. Information about the smoking habits of the miners were collected during the survey and also in an annual census of uranium miners which was started in 1963. Standardized mortality ratios of lung cancer by smoking categories [H3] were used for calculation of the expected death rate for respiratory cancer. The reference population was a random sample of adult males from the United States and the ten expected cases mentioned above were calculated according to these data. It was found instead that the cases expected would be 16 for the same total population of 3414 miners if the lung tumour incidence among males of four Colorado plateau states in the United States would be taken as the reference control. Table 3 shows the distribution of observed and expected respiratory cancer deaths between smokers and non-smokers. The increase in the number of cancer cases is attributable to irradiation by inhaled radon daughters. The relative excess of risk between smokers and non-smokers is the same (3.9 against 4.0 for the two categories, respectively). If one calculates the increase in cancer incidence due to irradiation per person year at risk, one finds $1.7\ 10^{-3}$ for smokers and $1.7\ 10^{-4}$ for non-smokers, the difference being attributed by some to a 10-fold synergistic increase of the risk for the smoking miners.

171. A more accurate analysis shows however that this could be a misleading argument. It should be realized that the statistical significance to be attached to the number of tumours observed in the non-smoking group is very low, owing to the small number of cases observed. The estimate of the probability of tumour induction obtained from this number is therefore affected by a large error. A statement such as the preceding one of a ten-fold increase in risk in the smoking population, would be equivalent to using for the assessment of the interaction factor the formula

$$\omega = (P_{o1} - P_{11}) / P_{o2} \qquad (36)$$

where the signs 1 and 2 refer to smoking and radiation, respectively. In fact, this formula cannot be used under the circumstances, because of the mentioned low statistical significance of the term P_{o2} (the probability of respiratory cancer death in the non-smokers) and of the absence of the term P_{o1} from the numerator and denominator.

172. According to the reasoning presented in chapter I of this Annex, when P_{o1} and P_{o2} are small, one calculates the interaction factor ω by the formula

$$\omega = \frac{P_{o1} - P_0}{P_{o1} + P_{o2}} \qquad (37)$$

Table 4 shows the results of separately analyzing the data for the period 1950–1967 [L2] (A: top line) and for the last four years of the same period, 1964–1967 [A1] (B: bottom line). As may be expected, risk estimates based on the most recent period of observation are higher, excluding re-evaluated estimates of spontaneous risk and risk of smoking. The interaction factors are however close enough to each other and indicate a synergistic interaction. In view of the low statistical significance of the results, other indirect evidence may be of great value.

173. Archer and collaborators [A1, A3, L6] point out some of this evidence. In a larger group of uranium miners 207 lung cancers were identified; all of these individuals except three were cigarette smokers [A1]. Since it is known that 71% of miners are smoking, it is clear that in the above group smokers are over-represented. Another observation relates to the age at diagnosis: in the 207 people mentioned, 17 stopped smoking eight or more years before diagnosis; 16 stopped between four and eight years; 19 smoked less than 15 cigarettes/day (light smokers). Controls were chosen to match as closely as possible the exposed individuals in relation to age at the start of mining, cumulative radiation exposure, years of hard rock non-uranium mining. All of them smoked 20 or more cigarettes per day and none stopped smoking more than one year before diagnosis. The comparison showed that non-smokers or those who stopped smoking eight or more years before developing lung tumours had a mean age at diagnosis three years greater than smoking controls. Light smokers differed from controls by a year and a half, and those who stopped smoking between four and eight years before diagnosis differed from controls by less than one year. The results support the hypothesis that cigarette smoking acts in these miners as a promoting agent [V1] by decreasing the length of the latent period. These conclusions were strongly supported by an update of the earlier uranium miners mortality studies in the United States [A3]. The incidences of lung cancer between different categories of smokers are shown in Figure XVIII [A3].

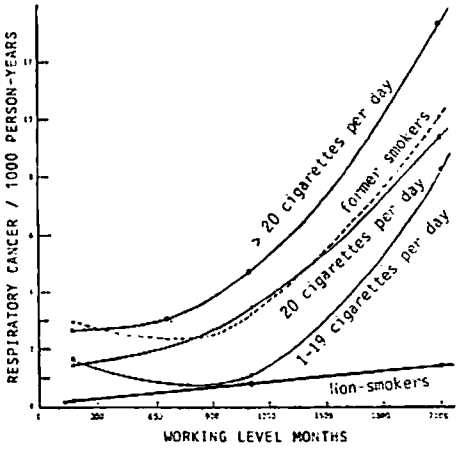

Figure XVIII. Mortality from respiratory cancer as related to radon daughter exposure in different smoking groups [A3]

174. High rates of lung cancer in smoking persons are also observed in workers of industries that use known carcinogenic substances such as chromates [O1, L7] and asbestos [S10]. In addition, among persons developing lung cancers in the same groups of workers, smokers were over-represented. These data may be taken to show a non-specific promotive influence of tobacco smoking. At the present time there is by no means a full understanding of these mechanisms in smoking individuals. It could be that tobacco smoke contains enough initiators and promoters to give the observed yield of respiratory cancer. Alternatively, in case of smoking acting apparently alone, some environmental factors may provide the initiating stimulus and the role of smoking might be essentially promotive. The chemical composition of smoke itself might even not be the decisive factor in the promoting action of this agent. As shown by experiments of Little et al. [L10] reviewed previously, the irritation of the respiratory epithelia by non-specific physical or chemical agents (instillation of saline solutions, for example) could have a promoting effect.

175. It could of course be debated if promotion as such is an effect to be included under the general heading of synergistic. Two extreme situations may be visualized in this respect. There could be, on the one hand, a forward displacement in time of the tumours appearing, but with a final yield of tumours not different from the situation in which promotion is not operating. Alternatively, a continuously increasing rate of tumour appearance might take place, leading finally to an incidence higher than that in the absence of promotion. A variety of intermediate situations could also operate between these two extremes. Clearly, if the final tumour incidence would be taken as the reference end-point, the first of the two situations depicted would not come under the definition of synergism, while the latter would. But if instead, more correctly, the length of tumour-free life lost is taken to be the reference parameter and it is assumed that smoking alone could cause cancer, both situations, as well as all the intermediate ones, would be rightly described as synergistic interactions.

176. In their 1979 paper Lundin et al. [L6] gave a more elaborate quantitative treatment of respiratory cancer death in uranium miners. A log-normal distribution of the time elapsed from exposure to diagnosis based on other experimental and theoretical evidence [M4] was assumed to apply. It was also assumed that this distribution would have a standard deviation of 0.17609 in log t units, where t is the number of years elapsed after the beginning of exposure. The choice of the standard deviation was rather arbitrary and, according to criteria developed in reference [M4], somewhat below the range expected usually. The parameter describing exposure (when the risk from earlier was added to that of later exposures) was the Eff WLM (k) for the year k, defined as

$$\text{Eff WLM (k)} = \sum_{j} w\,(k - j)\ \text{WLM (j)} \qquad (38)$$

where $0<j<k$; w(k–j) is the proportion of the area under the log-normal distribution density curve which is bounded by the interval from (k – j – 1/2) years to (k – j + 1/2) years; and WLM(j) is the exposure in WLM during the year j.

177. Two alternative hypotheses were examined: that the increase in absolute risk might be proportional to radiation exposure, in which case the risk increase would be independent of the rate associated with cigarette smoking, aging or other environmental factors (a); that the increase in relative risk may be proportional to radiation exposure (b). In this case the increase in risk should be proportional to that risk which would have affected the miners in the absence of radiation. The analysis of both models was carried out based on the form of the temporal distribution of the respiratory cancer deaths.

178. Three temporal parameters were used, namely, the age of the miners, the calendar year and the years after the beginning of exposure. Computations were as follows: (a) for the absolute risk hypothesis

$$n_x = \alpha_A\, X_{rad} \qquad (39)$$

where X_{rad} = av (Eff WLM_x). In the above formula n_x is the predicted excess of lung cancer deaths among miners in stratum x and the av (Eff WLM_x) is averaged over all the person-years at risk in the stratum; (b) for the relative risk hypothesis

$$n_x = \alpha_R\, E_x\, X_{rad} \qquad (40)$$

in which n_x is proportional to the product of the expected number of lung cancers E_x in the stratum, multiplied by the exposure X_{rad}. The symbols α_A and α_R in the above equations are coefficients applying to the two situations postulated. The sum of $n_x + E_x$ gives the total predicted number of lung tumours for each particular set of parameters.

179. Calculations were made of the number of deaths according to the age category and with assumptions of mean latency times of 5, 10 and 15 years. The relative risk model gives results which are closer to observations and latency times of 10 to 15 years fit the data best. One of the parameters which is most strongly influencing the expected number E_x is the smoking category (Table 5). It may be assumed that E_x is proportional to smoking exposure X_{sm}. Then the predicted excess of respiratory tumour deaths will be proportional to both smoke and radiation exposure as

$$n_x \simeq X_{rad}\, X_{sm} \qquad (41)$$

The probability of developing lung cancer per person per year is shown in Table 5 for four smoking categories. The last column of the table gives the corresponding interaction factors and shows that the highest value is for former smokers and the lowest for heavy smokers, ω being intermediate for light smokers. This result comes about through an insufficient increase in P_{ot} by comparison with P_{tt} for heavy smokers, an observation which contradicts the previous conclusion about the applicability of the relative risk model. The authors interpret this observation as evidence against a possible "synergism" defined as an increase in the total radiation risk of lung tumour development. Such a risk they consider to be approximately the same for all categories of smokers and somewhat higher than for non-smokers. They classify the observed increase in the lung tumour death as promotion. However, as already discussed before, there is good ground to describe it as synergism (see paragraph 175).

180. Lundin et al. [L6] do not exclude the possibility that for longer time intervals the yield of lung tumours in non-smokers might be the same as that of the smokers exposed to radon daughters. One preliminary

report on lung cancer in Swedish iron miners seems to support this possibility [R15]. In an other epidemiological study of metal and iron-ore miners in Sweden carried out by Axelson and Sundell [A9] the risk for the non-smokers was claimed to be higher. However, the size of the groups analysed was rather small and the statistical significance of the observed effects correspondingly low. Also, the methodology of the case-control study was not fully described in the publication [A9] and it raises some questions in the form presented.

181. Long latency time for lung cancer and the incidence dependence on the dose rate could also obscure the final picture. Uncertainties in the distribution of miners between exposure categories could lead to distortions in the estimates of risk. The lower risk of the American uranium miners could be justified to some degree by their possible misclassification into higher exposure categories [S11, K1]. It should also be mentioned that for these miners the observation time elapsed from the beginning of work in the uranium mines is not much longer than 20–30 years, which might be insufficient for the development of lung cancer among non-smoking individuals. Another important factor could be the exposure rate which was lower for the Swedish than for the miners in the United States. It has already been mentioned that lower exposure rates may bring about a higher total yield of potential tumours. Different exposure rates can be met in epidemiological studies with Czechoslovak [S11, K1] and Canadian [H20] miners.

182. Enhanced mortality for chronic respiratory diseases other than cancer resulting in pulmonary insufficiency (pneumoconiosis, pulmonary fibrosis, emphysema) and for acute conditions (pneumonia, asthma) could also be the result of combined radiation and tobacco smoke exposure [A3]. An increase in the rate of mortality from these diseases for uranium miners in the United States was clearly observed which might be related to radiation exposure. It is interesting to note that the rate is highest for light smokers, so that at high exposure levels mortality is twice as high as for heavy smokers. Some possible interaction between radiation and smoke is also evident for these diseases but, at this point, the contribution of other ambient conditions like siliceous dust or diesel fumes should also be considered, for which data are very scarce.

183. The epidemiological data discussed point to a synergistic interaction between tobacco smoke and radiation exposure in the sense discussed under paragraph 175. Non-specific effects induced by some component of tobacco smoke could be responsible for the results described. Thus, changes in the production of mucus, a slower rate of clearance of radioactive particles by the ciliary action and metaplasia of the epithelia might result in a higher dose delivered to the target cells in smokers than in non-smokers. Against this general proposition is however the observation that promotion by tobacco smoke is still found when smoke is applied long after radiation exposure. Clearly, these questions cannot be settled now with the limited information available. Quantitation of the degree of synergism is also impossible with the necessary degree of precision and significance, owing to the low number of tumours observed, particularly among the non-smoking individuals, and to the complex temporal pattern of lung cancer development.

E. OTHER DRUGS

184. It may appear somewhat artificial to separate in this section substances which are utilized for their pharmacological properties in clinical medicine from other organic substances mostly developed for their radiosensitizing actions. The separation may be made on the ground that interaction with radiation may be incidental in the former case but is pursued as a specific goal in the latter. In spite of a widespread and increasing use of many drugs in modern societies, it is difficult to visualize situations where the combined effects of any of them with radiation may pose significant problems in public health. The cases of interaction in the treatment of specific diseases where the combined use of radiation and drugs might increase the risk of undesirable effects on the patient may be more important. However, in most of the work reviewed radiation doses were very high and, irrespective of the nature of the interaction (synergistic or antagonistic), extrapolating the findings to lower levels may be very difficult or impossible in view of the modification of the form of the dose-effect relationships that might occur at low doses.

185. Antibiotics are widely used in clinical medicine and some of them are also used in combination with radiation for cancer chemotherapy [P3, P4, P5, P16]. Among them, actinomycin D was shown to have a synergistic interaction with radiation on Chinese hamster cells in culture. Elkind et al. [E3] related this effect to the ability of the drug to impair recovery of sublethal damage, as shown by a reduction of the shoulder of the survival curves at low doses (2–5 10^{-3} μg/ml). Ten-fold higher doses given before irradiation increased the exponential slope of the survival curves. Time was also an important parameter in these experiments because no synergism was observed with treatments by actinomycin later than 10–12 h post-irradiation or when the drug was applied more than six hours before irradiation [E4].

186. The molecular basis for the action of actinomycin D on cells is due to its proven ability to bind to DNA and thus to create a steric hindrance to the synthesis of RNA. Interesting studies on the combined action of this drug and of another drug, cordycepin, were reported on two cell lines in culture by Robertson et al. [R13]. For actinomycin D interaction factors of 1.2 and 1.3 in the two cell lines were reported with x rays. The survival parameters affected were both the exponential slope and the shoulder of the survival curve, but mostly the former. With cordycepin the interaction factors were 1.1 and 2.2, respectively, and the main parameter affected was the extrapolation number. The nature of the differences described led the authors to some hypothesis on their molecular basis.

187. Actinomycin D was also tested in preimplantation mouse embryos in tissue culture for its combined effect with radiation [S15]. The concentration of the drug was here several orders of magnitude lower (10^{-4} μg/ml) than in previously reported experiments by Robertson [R13] and the drug alone was ineffective at these concentrations in retarding the development of the embryos to the blastocyst stage. Combining the drug with tritiated water led to a higher effect than that of tritiated water alone, with interaction factors between 2 and 4, depending on the tritium concentration in the culture medium. The lower values were observed at the highest concentrations. This observation could be explained by the more effective inhibition of the repair

processes at low radiation doses. A re-analysis of these data in terms of isobolic diagrams [S48] showed that the results of combined treatment fell clearly outside of the envelope of additivity in the direction of synergism. The possibility that the shape of the dose-response relationships may be changed by the combined treatments has been discussed in this context [S39]. Other experiments showing a radiosensitizing action of actinomycin D have also been reported [M7].

188. In humans, Wara et al. [W2] studied the effect of actinomycin D on the induction of radiation pneumonitis occurring 1–3 months after the irradiation of lung metastases in 41 patients. Doses of the order of 7.7 Gy were necessary to elicit pneumonitis in 5% of the patients and these doses were reduced to 5.5 Gy (DMF = 1.4) when an actinomycin treatment was given along with radiation. Similar DMF were obtained for radiation-induced intestinal injury, oesophageal lethality and pulmonary lethality in LAF_1 mice treated with this drug at the same time [P5]. The values of the DMF obtained for a variety of chemotherapeutic drugs in the above experimental series are given in Table 6 and a detailed review of experimental and therapeutic findings related to this topic has been written by Phillips and Fu [P3]. In patients treated for erythema of the skin d'Angio et al. [D6] reported a DMF of 3.4 by combining x irradiation and actinomycin D.

189. Dritschilo et al. [D7] investigated the mechanisms of the combined action with radiation of actinomycin D and adriamycin. Non-toxic levels of actinomycin and minimally toxic levels of adriamycin produced suppression of potentially lethal damage repair in plateau-phase Chinese hamster cells in culture. For actinomycin this suppression persisted as long as the drug was present in the culture medium, but as soon as it was removed prompt repair took place. This suggested that suppression did not act through fixation of injury to a non-repairable state. Adriamycin was different because cells exposed to it could eventually proceed to repair potentially lethal injury even in the presence of the drug, after an initial delay of the repair processes.

190. Redpath et al. [R4] studied the effect of combining adriamycin (2 or 1 mg/kg, 5 daily fractions) and x irradiation (10 Gy/fraction, 5 daily fractions) on mouse tissues. Enhancement of damage was seen for lung and foot skin damage, when the interval between the beginning of the radiation and of the drug course was within two to seven days. In another series the radiation sensitivity was studied after the single dose of 1 mg/kg intraperitoneally. No effect was found in this case. Experiments were performed in the same laboratory on the radiosensitivity of ICR male mice irradiated whole-body with fast neutrons (mean energy 25 MeV) or photons (6 MeV), in combination with a single dose of adriamycin (10 mg/kg) [C9]. The $LD_{50/6}$ for photons was reduced from 13 to 10 Gy; that of neutrons from 5.6 to 4.3 Gy. The RBE for gut damage was unaltered by the addition of adriamycin. The data indicated that for drug administration 16 hours before or after the radiation exposure the interaction will be the same.

191. A cell cycle dependence of the synergistic interaction of a drug with radiation was shown for dihydroxyanthraquinone (DHAQ), a potential cancer chemotherapeutic agent similar to adriamycin and actinomycin D [K5]. The survival of x-irradiated Chinese hamster cells in combination with different exposures to DHAQ was the end-point of this study. DHAQ had a toxicity which was more pronounced during the early phases of the cell cycle. After combined treatment a synergistic effect was noted for cells in the S phase, but in all other phases of the cycle additivity prevailed. In asynchronous populations DHAQ enhanced the radiation-induced cell lethality primarily by increasing the slope of the radiation dose-survival curve.

192. Lucanthone (Miracyl D) has long been used in the treatment of schistosomiasis. The drug has a heterocyclic ring structure resembling that of actinomycin D. A synergistic type of interaction of this drug with ionizing radiation has been shown for HeLa cells. This effect decreased with the time lag allowed between radiation and the treatment with lucanthone [B4]. The same publication refers also to increased 30-day lethality in mice given 4 Gy of total body radiation and a simultaneous injection of 180 mg/kg of the drug.

193. The influence of lucanthone in combination with x-irradiation was also studied on V-79 cells and on spheroids [D3]. The treatment of asynchronous cells with 5 μg/ml of the drug led to a progressive decrease in the proportion of cells in G_1 and to an accumulation of S-phase cells. The toxicity of the drug was noted only during this latter phase of the cell cycle. In general, the survival of the single cells after the combined treatment was lower, owing to a reduced capacity of the cells to accumulate and repair sublethal damage. For equal levels of drug toxicity, the radiation-modifying effect of the drug was greater in the spheroids, pointing to a larger interaction in the system which has greater capacity for accumulation and repair of the sublethal radiation damage.

194. Lucanthone has also been shown to be active in respect to induction of developmental defects in mice. Pregnant animals (8 days p.c.) were given 70 mg/kg of the drug and treated one hour later with 0.5 Gy of x-radiation. The treatment resulted in a distinct synergistic increase of the eye abnormalities of the embryos [M8]. The above studies were further developed with a decrease of the x-ray dose down to 0.01 Gy [M9]. Pregnant mice of the strains F/A and NMRI were irradiated at eight days p.c. with 140 kVp x rays, with or without treatment with lucanthone. The foetuses were observed 4–5 d after irradiation for the presence of macro- and microscopic developmental defects (post-implantation loss, growth retardation, eye abnormalties, exencephaly, cleft palate and limb defects). There was a strain specificity with respect to the sensitivity to lucanthone given alone, the NMRI mice being more susceptible to lower doses of the drug. A dose of 0.01 Gy was reported to produce a statistically significant increase of the abnormalities and combination of the two treatments gave rise to a synergistic interaction. Some strain specificity was also found for the combined effects, because the F/A mice were more susceptible to the joint action. Higher doses of radiation (0.5 Gy) producing an approximately 4-fold increase of the control abnormalities were also reported to produce synergism. Other data on the enhancement of radiation effects by antibiotics (ledermycin, reverine) were also reported [M9].

195. Bleomycin was reported to potentiate the radiation damage in rat brain tumour cells of the line 9L [H9]. The drug enhanced cell lethality mostly through an increase of the slope of the radiation dose-survival curve, its D_o decreasing from 3.7 to 2.1 Gy in

the presence of the drug. There was also a more modest decrease in the capacity for accumulation of sublethal damage, shown by a decrease of the D_q from 3.2 Gy in the absence to 2.9 Gy in the presence of the drug. This was evidence for an inhibition of repair of the sublethal radiation damage. Other authors observed an additive effect of bleomycin and x rays with small doses of the antibiotic and a synergistic action with high doses [B30].

196. In experiments by Lin et al. [L20] Chinese hamster cells in culture were treated with the drug diethyldithiocarbamate (DDC), a substance that has been shown to inhibit the enzyme superoxide dismutase responsible for eliminating the O_2^- radical from the cells. The killing effect of the drug depended on its concentration and exposure time. Eight to ten days of incubation at concentrations of 10^{-9} M produced no changes; while 10^{-4} M was a definitely toxic level. DDC-treated cells later undergoing gamma irradiation survived less well than cells treated with the same doses of the two agents separately. The drug also significantly enhanced the heat sensitivity of the cells.

197. Antimalarial drugs such as quinacrine and chloroquine or their derivatives are now also used for diseases requiring long-lasting treatments such as rheumatoid arthritis. Sensitization by these drugs in combination with radiation was shown on a variety of systems. E.coli K-12 rec$^+$ incubated after irradiation with quinacrine up to 0.4 mM showed a killing increase [F1]. Chinese hamster cells [V2] as well as tumour cells in vitro [K2] were also reported to show similar effects. In vivo Utley et al. [U3] showed a distinct effect on skin sensitivity, as judged by the hair loss in irradiated rats treated intraperitoneally with daily doses of hydrochloroquine (52 mg/kg) for one week prior to irradiation. A case of skin sensitization in a woman who had been taking hydroxychloroquine daily (200–600 mg/day) for years prior to and during radiotherapy for a breast tumour was reported in the same paper.

198. Enhancement of x-ray induced cell killing by caffeine treatment for 16–20 hours post-irradiation was shown on a number of rodent and human cells in culture. The effect was brought about by concentrations of the drug causing less than 15% killing. It consisted mainly in a removal of the shoulder of the survival curve, without much alteration of its slope. The findings indicated the existence in mammalian cells of processes of repair of radiation damage that are inhibited by exposure to the drug [W5]. Enhancement of the killing effect of single doses of ^{60}Co by caffeine was also confirmed on human and hamster cells in culture at concentrations of 2.0 – 2.5 mM in the culture medium for two days after irradiation [S23]. In split-dose experiments exposure to caffeine of the cells for 4 hours between dose fractions did not result in any effect and it was therefore concluded that the sensitization by caffeine was brought about through a modification of expression of the potentially lethal, rather than of the sublethal, damage. The possible role of caffeine as a sensitizer of the single-hit potentially lethal damage was further confirmed experimentally and through an analysis of the existing literature [S27].

199. The sensitization by caffeine on x-irradiated HeLa cells was found to depend on the drug concentration [T6]. At post-irradiation levels of caffeine of 1 mM a synergistic effect was observed mainly on cells in the G_2 phase, irrespective of where in the cell cycle they had been irradiated. Increasing the caffeine level to a range of 7 to 10 mM brought about not only a higher response of the G_2 cells, but also some response of the G_1 cells. Treatment at higher concentrations resulted in dose-survival curves having smaller shoulders and steeper terminal slopes. It is interesting to point out that the shapes of the time-survival curves measured for the G_1 and G_2 cells differed. The authors interpreted this difference to reflect two operationally distinct modes of interaction with the drug.

IV. BIOLOGICAL AGENTS

A. GENERAL

200. Many biological conditions may influence the state of health of a human population. Viral and bacterial infections, eating habits and the state of nutrition, the conditions of living and working, the use of biologically active substances or drugs are known to affect to various degrees the incidence and pattern of diseases in humans and therefore to alter the actuarial characteristics of populations. There seems to be little hard evidence that conditions adversely influencing the survival and disease incidence could also substantially change man's sensitivity with respect to late radiation effects. This notion cannot however be dismissed or excluded because the complex pathogenesis of the effects of major interest in human radiation biology (tumour induction, genetic changes, developmental abnormalities) leaves scope for combined actions in both directions.

201. The Committee wishes to stress that the above general notion is much easier to be entertained academically than to be experimentally demonstrated. The agents that may be considered as possible candidates for interaction with radiation are very many and diversified; their influence, already in the absence of radiation, is often little known in respect to the effects described above; and the data available are fragmentary. Therefore, to attempt a systematic discussion is almost impossible. In spite of such limitations, the Committee has decided to gather the available evidence on the effects of hormones and the effects of infections. Reference to existing epidemiological studies will also be made.

B. HORMONES

202. The influence of hormones on the radiation sensitivity of human populations with respect to cancer induction can be predicted on the general notion that many experimental and human tumours are known to be variously susceptible to the action of hormones. Mammary gland, prostate and thyroid tumours are very hormone-dependent, while for other malignancies a certain degree of dependency may be postulated, for example, on the notion of a different susceptibility between sexes or on the effect of castration. As to the practical significance of a combined action of hormones and radiation, changes of the hormonal state take place during physiological conditions (menarche, pregnancy, menopause, stress). Treatment of many diseases requires prolonged use of hormonal preparations and an increasingly large part of the female population use hormonal treatments (essentially oestrogens) for contraceptive purposes. Oestrogens are also contained in commercially available cosmetic preparations and some drugs used rather extensively (derivatives of Rauwolfia, phenothiazine, chlorinated

hydrocarbons) have hormonomimetic activities. Finally, hormones themselves could be to some degree carcinogenic [C4]. There appears to be therefore sufficient ground for some analysis of their combined actions with ionizing radiations.

203. Much general evidence about tumour induction in animals has been discussed in the 1977 report of the Committee, Annex I [U1]. It was concluded that various radiation-induced tumours are differently affected by the animals' hormonal balance during the course of the carcinogenic process. The effects reported seemed to be tumour-, strain- and sex-specific and it appeared likely that the mechanisms of action (which are at present almost unknown at the molecular or even at the cellular level) might have been very different under the various conditions tested. Annex K to this report contains some discussion of the influence of the animal's sex on the life shortening action of ionizing radiation. This appears mainly as a higher susceptibility to sex-specific tumours, particularly the mammary neoplasms and the tumours of the genital tract in the female.

204. Segaloff and Maxfield [S7] studied specifically the influence of oestrogens on mammary carcinogenesis in the rat. Pellets containing 5 mg diethylstilbestrol (DES) and 15 mg cholesterol were implanted subcutaneously into 8-week old A × C rats. The animals were hysterectomized to prevent fatal oestrogen-induced uterine infections. X-radiation was delivered only to the left mammary chain by shielding the opposite one. Spontaneous mammary tumours in this strain of rat are essentially nil. Radiation alone (about 8 Gy) produced only a small number of tumours (1.1 per chain at risk) appearing late (median 80 weeks at the appearance of the first tumour). DES alone gave 1.7 tumours per chain with median appearance times of 33 weeks. Combined treatments resulted in an earlier appearance of the tumours (26 weeks) and in an increased incidence (5.6 tumours/chain). Even a crude estimate based on final incidence would lead to an interaction factor ω of the order of 2, an estimate which (apart from its unknown statistical value) fails to take account of the appearance time which is shortened by the hormonal treatment.

205. Shellabarger et al. [S8] irradiated with 0.43 MeV neutrons rats of the strain A × C in doses of 0.096 Gy. The carcinogenic response to irradiation was insignificant (3 adenocarcinomas in 33 rats); DES, on the other hand, produced some effect (182/25 rats). Combining the treatments led to an earlier appearance of tumours in much greater number (842/35 rats). There were therefore strong indications of a synergistic interaction and a crude estimation of ω is in the range of about 3. However, on Sprague-Dawley rats the same combined treatment produced a negligible incidence of tumours (2/31 rats) in comparison with the action of radiation alone (11/31 rats). DES in this case had no synergistic but rather an antagonistic effect. The experiment is a good example that, depending on the strain used, the same type of treatment may give rise to antagonistic or synergistic actions.

206. Most recent experiments by the same group [H26] confirmed the effect of DES and showed, in addition, a synergistic action of 17-ethinyl-estradiol (EE2) in rats. The complex of these data would imply that the synergistic interaction is not with the hormones examined but rather with their oestrogenic activity. In other studies by Segaloff and Pettigrew [S5] graded doses of radiation of 0.5, 1.5 and 4.5 Gy were used. Radiation given alone increased the incidence of benign tumours in proportion to dose, but the increase of malignant tumours did not follow a statistically significant proportionality and resulted in a rather low number. Combining radiation and DES produced a synergistic interaction at 0.5 Gy ($\omega \simeq 1.4$), but the increase in tumour incidence was most pronounced at 1.5 Gy (crude $\omega = 2.0$) and somewhat less at 4.5 Gy (crude $\omega = 1.6$). The combined treatment led to an earlier tumour development.

207. The role of prolactin in combination with radiation and with the chemical carcinogen N-nitroso-N-buthylurea was studied by Yokoro et al. [Y2] in W/Fu rats. Prolactin was produced by grafting a mammotropic pituitary tumour. Prolactin alone was ineffective in inducing mammary tumours. After doses of 2 Gy of x rays two fibroadenomas were seen among 27 animals with mean appearance times of about 6 months. Prolactin in combination with irradiation accelerated tumour appearance and induced tumours in 60% of the animals at the dose of 2 Gy. There were statistically significant differences in the tumour incidence between animals receiving 0.5 or 2.0 Gy and a similar synergistic interaction of prolactin and radiation was also found in respect to 14 MeV neutrons. Two interesting observations were made in these experiments. First, delaying the pituitary graft as long as seven months after irradiation still produced an enhanced effect, showing that the transforming lesions induced by radiation could remain available for hormonal interaction for a very long time. Secondly, most of the tumours produced by the interaction were adenocarcinomas, while most of the spontaneously occurring ones in this strain of rat are late appearing fibroadenomas.

208. In a more recent study by the same laboratory [Y6] fission neutrons (2 MeV mean energy) mixed with gamma rays were given to W/Fu rats. Only 2% of the animals developed mammary tumours after irradiation alone (up to 0.2 Gy) but 42% did when prolactin was given shortly after irradiation by grafting the prolactin-secreting pituitary tumour. Delaying the prolactin treatment up to 12 months produced 24% tumours, which observation supports the one previously reported [Y2]. A similar synergistic interaction of diethylstilbestrol (DES) and neutron irradiation in the production of mammary, pituitary and hepatic tumours was observed in castrated male W/Fu rats [S41].

209. The above results suggested to Yokoro [Y2] that in the previous studies the synergism between DES and radiation [S5, S7] could act via an increased production of prolactin. At the same time, Shellabarger [S6] was able to show that A × C rats (in which interaction with hormones was found) carried prolactin-secreting pituitary tumours; on the contrary, the Sprague-Dawley rats which did not show any synergism between radiation and DES carried no such tumours. In recent experiments by the group of Shellabarger [S44, H26] on A × C rats a strong dependence was shown between the interaction factor and the dose of DES and radiation. The dependence on the DES dose appeared to be mediated via the oestrogenic stimulation of prolactin secretion. The higher and the earlier the levels of prolactin in plasma, the greater was the yield of individual and multiple mammary adenocarcinomas.

210. Another oestrogenic hormone (polyestradiol phosphate) and a corticosteroid (methyl-prednisolone) were tested in combination with internal irradiation by

Nilsson et al. [N8] on CBA mice. Three doses of ^{90}Sr (0.925, 1.850 and 7.400 kBq/g) were applied, which led to a maximum of 2% animals with pituitary tumours. Polyestradiol alone produced 10% of such tumours. Combining the treatments resulted in 44 and 37% of animals with tumours, for the first and the second dose of ^{90}Sr, respectively, an increase corresponding to an interaction factor of approximately 4. Combined treatment also led to a decrease of the tumour induction time with respect to the groups given the radionuclide alone, close to that of the animals receiving only the hormone. Prednisolone in combination with radiation was ineffective in increasing the incidence or decreasing the induction time in comparison with groups receiving strontium alone.

211. Modelling of situations in animals that may operate in women taking contraceptive oestrogens was undertaken in the Netherlands [B3, B5]. The complete outline of these experiments calls for three different strains of rat (Sprague-Dawley, Wistar Wag/Rij, Brown Norway); four types of radiation (300 kV x rays and 0.5, 4 and 15 MeV neutrons); a range of different doses (from 0.1 to 2 Gy, according to the radiation employed); and various types of female animals (intact or hysterectomized, respectively with or without hestradiol-17-beta). The results of this series are still incomplete, but some preliminary conclusions may be drawn. For WAG/Rij rats the proportion of animals surviving without tumours abruptly decreased starting from nine months of age after irradiation with 4 Gy x rays and hormonal treatment. For animals receiving only irradiation or hormonal treatment a 50% decrease was observed after 22 months. The total yield of tumours for the combined treatment group was also higher. Considerable differences in the susceptibility to tumour induction were found between strains. Brown Norway rats having the lowest spontaneous incidence of mammary tumours had an intermediate susceptibility to the radiation-induced ones. Pathological data showed that malignant tumours were relatively rare in the Brown Norway and in the Sprague-Dawley strains, but were instead quite common in the Wag/Rij rats, amounting in the latter strain to nearly one-half of all tumours. A synergistic interaction of radiation with the oestrogen treatment was manifested not only through an increased proportion of rats with malignant tumours (from 0.43 to 0.83 in the Wag/Rij rats) but also through an increased absolute incidence of neoplasia in Wag/Rij and Sprague-Dawley rats. The minimum latency period in untreated control animals could be in excess of 22 months; in irradiated animals without hormones this period decreased to 10–12 months and a decreased latency in the hormone-treated rats in comparison with untreated groups was observed as a rule. The synergistic action of the hestradiol-17-beta is of the same type as the interaction between radiation and DES.

212. Kennedy and Weichselbaum [K15] reported a synergistic interaction between cortisone and x rays for transformation of C3H 10 T 1/2 cells in culture. The end-point scored is of great significance since it relates to tumour induction in vivo and the synergistic effect was statistically significant at $P < 0.001$. However, the transformation mechanisms in this particular cell line are still little understood [K16] and it is not possible to quantitate the results in terms of transformation frequency per surviving cell. It seems thus more prudent to test for effects in vivo before accepting the conclusions as generally valid.

213. Although the most informative data on the subject of combined action of radiations and hormones can only come from epidemiological surveys, data in this area are only indirect. It is known for breast cancer induction that age at exposure is a major determinant in all series available [T8, B27, S47]. Taken together, the data suggest that when the most profound hormonal changes occur (menarche, menopause) the risk per unit dose deviates most significantly from the mean risk for the whole life.

C. INFECTIOUS AGENTS

1. Viral infections

214. Viruses have a very important role in the pathogenesis of some radiation-induced experimental tumours like the thymic lymphoma, the myeloid leukaemia and the osteogenic tumours of different strains of mice. The Committee has reviewed the relevant evidence in Annex I of its 1977 report. It is difficult in fact in many instances to separate the action of the virus from that of radiation, because the interplay of the biological and of the physical factors is in these cases so intimate that it would not be possible to elicit the effect without the presence of the two agents combined. To think of a synergistic effect under the circumstances would be inappropriate because none of the agents alone may be active for the specific end-point. Moreover, the vertical transmission of the viruses through successive animal generations makes it a normal constituent of their genome, which is exactly the reason why some tumours are specific to some strains.

215. Radiation enhancement of in vitro cell transformation by viruses has long been reported [P13, S45]. An example was given of a combined treatment of Wistar/Furth rats with radiation and Gross mouse leukaemia virus [Y1]. Animals aged 7–8 weeks were intraperitoneally inoculated with a standard dose of virus (0.4 ml of leukaemic filtrate) and none of the 15 animals injected developed leukaemia. Whole-body x-irradiation (four doses of 1.5 Gy given at five days interval) produced also no tumours in 12 irradiated animals. The combination of both treatments gave rise to more than 50% leukaemias in 20 treated animals. In view of the lack of effects by the separate treatments, the interaction factor would in this particular case be equal to infinity. It was suggested that radiation might have acted through a modification of the physiological state of the target cells by rendering them susceptible to the action of the virus or through a modification of the immunological response of the host.

2. Bacterial infections

216. Environmental conditions have often been reported to influence the induction of specific tumour types in irradiated animals through their action on the microflora. It is conceivable that the response to any carcinogenic stimulus, including radiation, may interfere with expression of the carcinogenic damage by modifying the number, susceptibility or turnover rate of the target cells or by altering the immunological response against transformed cells. The most extreme conditions under which to test such hypotheses are provided by the study of germ-free as opposed to gnotobiotic or conventional animals.

217. Following irradiation of RF/Un mice myeloid leukaemia is decreased in the absence of microbial flora [W6], an effect which has been attributed to the reduced myelopoietic cell proliferation in germ-free animals [W7, W8]. Radiation-induced lymphatic leukaemia is, on the contrary, unaltered by germ-free conditions in many other strains of mice [P7, W1, W6]. Gnotobiotic and conventional animals show no qualitative differences with regard to virus particles found with the electron microscope [P7]. Induction of other solid tumours in irradiated mice gives variable results [A10, W7] and radiation-induced malignant or benign tumours are unaffected in germ-free rats. Thus, the data essentially show that the pathogenesis of radiation-induced cancer is similar in conventionally reared or in gnotobiotic animals. It should be concluded that the microbial flora as such has only a minor role in the development of haemopoietic neoplasms, perhaps via a modification of the immune system.

V. CONCLUSIONS

218. The interaction between ionizing radiation and other agents represents a field of great potential importance in view of the ubiquitous nature of radiation and of the many situations of interaction that might occur in modern life with a variety of physical, chemical or biological agents. Yet, it is very difficult to define and substantiate the notion of interaction with even a moderate degree of refinement. Many reports have claimed some kind of interaction but comprehensive analysis does not show a sufficiently good conceptual basis for the nature of the interactions. There is a lack of systematic treatment of any given case, particularly with regard to the mechanisms of action. There is further a need to apply existing methodologies of analysis from other fields of the biological sciences to the study of these problems.

219. The Committee has carried out a preliminary analysis of the combined actions in the radiobiological field, centered mainly around situations that may possibly be of importance for risk assessments in man and may therefore reflect on the present foundations of radiation protection. Available information on tumour induction, genetic defects and developmental effects was therefore scrutinized in the course of this analysis for any evidence of combined actions. The conditions of long-term exposure to low levels of the interacting agents were reviewed in detail, although in most of the reports the levels of exposure were much higher than the environmental. Where possible, the accent was on the results of epidemiological studies in humans, although the bulk of the information relates to animals.

220. The Committee proposes that two types of interaction may be considered. The first is one where both the ionizing radiation and the other interacting agent(s) are capable of producing some effect. Additivity, synergism and antagonism are the three possible conditions of interaction. The second type of combined action is that between ionizing radiation and other agents which are, when given alone, inactive. Protection or sensitization are the terms that apply in these cases, when reduction or enhancement, respectively, of the radiation effect are the end-results of the interactions. Such classification is not an absolute one because the doses of the interacting agents and the types of effect may influence profoundly the nature and degree of the interaction.

221. The concepts of exposure, dose and response may be applied to the special case of the combined action with ionizing radiation. The existing methodologies of analysis (isobolic diagram, envelope of additivity, surface of response) allow the assessment, at least on a semi-quantitative basis, of the results of combined treatments. These analyses may be further extended to generalized probabilistic treatments of the experimental results, taking into account the variability of the biological systems under study and leading to a more quantitative and satisfactory description of the interaction factors.

222. The applicability of these rather abstract notions to practical situations, particularly in the presence of complex biological effects, has been discussed. The need to define the effects with precision and to explore the full exposure-response ranges to all agents, acting separately or jointly, is a necessary prerequisite to meaningful studies. Also, pitfalls have been identified which may simulate conditions of interaction. In relation to important biological end-points such as the induction of tumours, the need to combine pathological and actuarial observations for a complete description of the phenomena has been underlined.

223. The temporal pattern of the exposure (contemporaneous or sequential, chronic or acute, single or fractionated) as well as the order of administration appear of decisive importance in respect to the production of a given type or degree of effect and have also been examined in the Annex. All these conditions relate to practical situations, even though they may tend to blur the clearly defined notions of additivity, synergism and antagonism. A detailed knowledge of the nature of the effects, their relationships to time and to the full range of doses of the interacting agents, including the zero-dose condition, is important. In many papers these basic conditions were imperfectly described. In other cases, the statistical significance of the results was too low for a complete assessment of interaction. Thus, the present conclusions should only be considered as preliminary.

224. An instance of interaction could be that between two different types of ionizing radiation, usually a combination of high- and low-LET radiation. Uncertainties exist as to the degree of interaction, owing to the essentially unknown nature of the primary radiation lesions and their repair systems. Even in cases where the yield of effect per unit dose of the two radiations differs by an order of magnitude, the interaction is within the limits of hetero- and iso-additivity. The study of the combined action of UV and ionizing radiation may be very valuable for the analysis of primary lesions and repair mechanisms. Experiments on survival of mammalian cells point to simple additivity. The important practical case of skin cancer induction, when tested in the animal, produced no evidence of interaction.

225. Examples of synergistic effects have apparently been reported in workers exposed jointly to ionizing radiation and microwaves in the radiotechnical industry. Functional disturbances of the nervous system and subjective symptoms of discomfort were mainly found in these workers. The nature of the symptoms, the difficulties of their quantification, the frequently uncontrollable conditions of exposure and the unsatisfactory dosimetry, the incomplete statistical evaluation, are all reasons for which these reports should be regarded with some reservation.

226. The combined action of suboptimal temperatures and radiation has given evidence of interaction in both directions, synergistic or antagonistic, depending perhaps on the type of effect, order of administration and level of exposure to the interacting agents. It would not be expected that any such effect would normally play any important role in higher animals, in view of their highly developed system of body temperature regulation. High altitude, metabolic or physical stress, mechanical damage, magnetic fields and ultrasound were also considered for a possible interaction with radiation: the results were variable but there was no evidence of significant synergistic interaction. In all these fields the data are very few, the effects non-specific and the mechanisms too obscure to allow any definitive statement.

227. The combined action of radiation, given internally or externally, with various types of dust shows under repeated testing, particularly with regard to tumour induction in the respiratory system, synergistic, additive or antagonistic effects. Considering the uncertainties and limitations of the data, the synergistic effect of the combined treatment did not exceed a factor of about two and the inhibitory effects a factor of about four, compared to situations where radiation was administered alone.

228. A variety of inorganic chemical compounds containing lead, silver, cadmium, calcium, beryllium, platinum, chlorine and fluorine, were also tested in experimental animals in conjunction with radiation for their carcinogenic, developmental or generally toxic properties. The results were once more extremely variable. In many cases the experience was so superficial, the effects so varied and the biological systems so different that no conclusions could be offered. Some of these interactions may be of significance in working situations and could profitably be explored further.

229. In this review, radioprotective and radiosensitizing substances were not examined in detail, since conditions relevant to the exposure of the population were the main object of the Annex. High levels of radiation and nearly toxic levels of these substances have been used in the relevant studies. A great variety of underlying mechanisms, complex relationships to the dose, to the radiation type, to the presence of oxygen were described for these chemical compounds. Since these substances are only utilized in the clinical field, none of them would be expected to pose significant problems of public or occupational health.

230. The possible combined action of radiation with compounds known for their carcinogenic properties has been the object of special attention. The substances examined include many initiators and promoters but the systematic information collected for each one of these substances is very incomplete. The evidence reviewed is conflicting and no final statement may be offered in regard to any substance or to any class of tumours before the dose, the schedule of administration and the treatment modalities are analysed to a greater depth, which is seldom the case in the experiments available.

231. Regarding benzo(a)pyrene and dimethylnitrosamine, two compounds having a widespread diffusion in the environment, experiments on lung tumour induction provided some evidence of a synergistic interaction (expressed mostly through a shorter latency time) for the former, but not for the latter substance. Fairly elaborate experiments in the hamster on the combined effect of radiation, uranium ore dust and diesel oil exhaust fumes yielded no evidence of synergistic effects, but the animal tested could be rather refractory to lung tumour induction. These studies should be extended in view of their practical implications.

232. Experimental data in animals and epidemiological experience on occupationally exposed human populations is available concerning the combined action of radiation and tobacco smoke. Tumours and inflammatory diseases of the respiratory system have been studied in this respect. In humans it appears that smoke may act by shortening the time of appearance of the radiation-induced lung tumours. It is not yet clear if such an action may be the result of promotion by some component of the tobacco smoke or due to a non-specific effect of the smoke on the respiratory epithelia. The experience in animals is still insufficient for a firm conclusion.

233. The precise evaluation of an interaction factor in humans critically depends on the length of the observation period as well as on the age structure and exposure history of the populations under study. It is impossible to say if the displacement in time of the tumour appearance will eventually result in an increased final yield of tumours in the smoking as compared to the non-smoking irradiated population. However, even if the final incidence of tumours between smoking and non-smoking irradiated individuals were the same, the effect should still be regarded as a synergistic one, since it would effectively lead to a reduction of the tumour-free life of the smokers developing tumours. This appears to be the only well documented case of a synergistic interaction in humans and in this sense it is a special case.

234. Antibiotics and other drugs were also considered for their possible interaction with radiation. Variable degrees of synergistic interaction were described for effects ranging from cell survival in vitro to tumour induction in animals. The relevance of these findings to individuals outside the clinical field is however difficult to evaluate, particularly in view of the limited diffusion of these substances in the general environment and of the high doses usually involved in the above interactions.

235. Possible cases of interactions with biological agents which were considered included those with hormones and with infectious agents. Regarding hormones, there is evidence that a variety of tumours of the experimental animal may be sensitive to their action. Diethylstilbestrol and oestradiol-17-beta were shown to have synergistic interaction for the production of mammary tumours in various strains of rat, with interaction factors in the range of 1.5 to 4. This type of synergism is also expressed through a shortening of the time for tumour induction. There is a large variability between strains, such that the same treatment schedule could produce potentiation in some strains and inhibition in others. There is also variability in relation to the tumour type. Epidemiological information in the human species is scanty and only indirect.

236. It is difficult for many animal tumours which are known to have a viral etiology (thymic lymphoma, myeloid leukaemia, osteogenic tumours) to consider their induction as the result of a synergistic interaction,

because the effect could not be elicited in the absence of either the virus or radiation. There is also no evidence that bacterial infection may play a major role in combination with ionizing radiation in modifying the yield of tumors.

237. For humans in environmental circumstances the Committee has been unable to document any clear case of synergistic interaction between radiation and other agents, which could lead to substantial modifications of the risk estimates for significant sections of the population. Presumably this is due to the fact that most of the agents likely to act synergistically with radiation, as judged by the results of animal experiments, are not found in sufficient concentration in nature. A specific exception is the case of tobacco smoke, which raises essentially problems of industrial hygiene in some working environments. Further research in the field of the combined effects is desirable because this area of study is still in an early stage of development and could profitably be pursued in a systematic way.

VI. RESEARCH NEEDS

238. An eminently practical research need is that of modelling experimentally situations encountered in living or working environments to test for undesirable effects. A second important and more basic research need is the identification of interaction mechanisms. The first need is essentially descriptive, the second essentially interpretative and both may interrelate to mutual advantage. There is also a third research need for the monitoring of possible effects in human populations by epidemiological studies. This latter is the most valuable for risk estimates in man.

239. Experiments of the first type are usually to study in experimental animals situations of practical interest for humans. It should be recalled that results obtained in a given animal species are not easily extrapolated to other species. In designing these experiments, exposure levels should be kept as similar as possible to the modelled situation. In combined action work, the assumption that effects showing at a given dose may exist to a lower degree at lower doses may not be true. Numerous examples of changes in the interaction with changing dose levels of the combining agents exist. The order and rate of administration of the agents should ideally mimic the real situation, although this may be impossible for chronic exposures of interest in practice. Long-term chronic rather than acute end-points should be focused upon. Tumour induction, effects on pre- and post-natal development after exposure in utero and genetic effects are the most significant classes of radiobiological end-points for further studies.

240. In the more basic studies, frequently involving experiments at the cellular and sub-cellular levels, there is considerably more latitude for research because the range of end-points is wider and the experiments financially less demanding. Good planning requires the careful choice of experimental end-points and of exposure level.

241. Epidemiological studies should have high priority under the existing circumstances. The inherent lack of control over many of the exposure variables should be compensated by the best possible definition of the exposure conditions, by the quantitation of the responses and by adequate statistical treatment of the observations. A conceptual and practical distinction should be made between interactions of relevance under special working environments involving possible problems of occupational medicine and large-scale exposure situations which could change risk estimates and could pose therefore more difficult problems of public health.

242. The use of a standardized nomenclature in the field of combined effects is highly desirable, because too often misconceptions are made possible by inaccurate terminology.

243. Considering the main technical requirements for experimental investigation of combined effects:

(a) Efforts should be made to report biological data as some function of the exposures in the target structures. For radiation, this problem is relatively simple and studies of energy deposition are reasonably advanced. In other cases (physical agents) this may simply require development of better dosimetric techniques and apparatus, but in most cases (particularly for chemical substances) it will imply detailed studies of the intake, metabolism, concentration and excretion of the interacting substances when a direct measure of their concentration at the level of the target structures is not possible;

(b) There is a need to define clearly and specifically the effects to be studied, especially when they are complex ones. For example, overall tumour induction may not in itself be a sufficient indication of a combined action because, even in the absence of significant changes in the overall interaction factor, changes in the spectrum of different tumour classes could take place. In the case of tumours it is important to study the rate of appearance, together with the final incidence, because shifts of the occurrence in time might reveal synergistic actions which would not be apparent otherwise. Also, actuarial and pathological observations should be combined and data corrections for competing risks should be applied;

(c) The variable "time" in the combined actions should be given proper attention, in the sense that contemporaneous and sequential treatments and reversal in the order of application should be examined. These studies are particularly important when the agents under examination have initiating or promoting characteristics and the sequence of their action is therefore decisive. Fractionated and chronic treatments could also be profitably examined, depending on the specific model situation and on the time characteristics of the agents combining;

(d) It is essential that appropriate methodologies of analysis of the interactions be used to avoid mistakes in the interpretation or inaccurate reports of the data. It is only through such objective analyses that precise statements and quantitative evaluations may be drawn. There is, more specifically, a need to refer any given interaction to conditions of iso- and hetero-addition;

(e) Appropriate control series should be set up to test exposure-reponse curves not only around the exposure levels of interest for the particular experiment but also for an extended range of exposures, including the zero values. Different combinations of exposures of the interacting agents should also be tested;

(f) It is important that the nature of the interaction should be as much as possible resolved through an analysis of the effects at various levels of

biological complexity, from the population level, through the whole-body, tissue, cellular and molecular levels. These studies allow generalizations and avoid misrepresentations of the interaction.

244. The specific areas of work identified by the Committee as particularly important for their basic or practical implications are:

(a) At the molecular and chromosomal levels, studies on the interaction of chemical, physical and viral agents on constitutive and induced processes related to DNA replication and repair of radiation damage (in simple as well as complex organisms) and relevant to the understanding of the mechanism of mutagenesis and to the estimations of genetic risks to man. These studies should concentrate whenever possible on low doses of radiation and of exposure to other agents and be correlated to relevant biological end-points like gene mutations and chromosome abnormalities as well as to cell differentiation (e.g., the immune system, developing organisms) or carcinogenesis;

(b) Studies of the interaction of different types of radiation, particularly for end-points which are of significance for practical purposes;

(c) At the systemic and whole-body level studies of combinations of tobacco smoke, fibres and dusts, organic and inorganic carcinogens and pollutants with radiation would be of great value;

(d) In human populations, further surveys of smoking and non-smoking workers professionally exposed to internal lung irradiations should be pursued. Under special working conditions the study of interaction of radiation with chemicals and microwaves would also be appropriate;

(e) For the population at large, the possible interaction of hormones and radiation, particularly in human females, should be tested, provided suitable groups might be identified. The increasingly widespread use of contraceptive hormones is of particular importance.

(f) Studies of combined effects in the treatment of patients (for cancer and other diseases) by combined treatment with radiation and chemotherapy and hormones, leading to carcinogenesis and to non-stochastic effects which may be "recalled".

Table 1

Lung tumours following neutron irradiation and crysotile treatment
[L16]

Group	Number of rats	Number of rats with lung tumours	
		Carcinomas	Mesotheliomas
Irradiated	20	1	0
Irradiated + Crysotile	9	4	3

Table 2

Effects on tumour development of prenatal exposure of mice to x rays and ethylnitrosourea (ENU) or to either treatment alone
[S42]

Type of tumour	Number of affected animals a/				Interaction factor ω (when applicable)
	x-irradiation (3 x 1 Gy)	ENU treatment (0.5 mMl/kg)	x rays + ENU	Control	
Leukaemia	3 (5.3)	3 (2.4)	10 (12.6)	2 (2.3)	3.4
Lung tumours	8 (14.3)	22 (17.8)	6 (7.6)	11 (12.8)	
Hepatomas	2 (3.5)	6 (4.9)	2 (2.5)	1 (1.1)	0.23
Pancreatic adenomas	0 (0)	1 (0.8)	2 (2.5)	0 (0)	
Intestinal tumours	0 (0)	2 (1.6)	0 (0)	0 (0)	
Ovarian tumours	6 (7.0)	0 (0)	10 (11.2)	0 (0)	1.6
Total tumour incidence	19 (33.9)	34 (27.6)	30 (38.0)	14 (16.6)	0.44
Tumour multiplicity (affected organs per animal)	1.0	1.0	1.5	1.0	
Number of tumours standardized	34	28	57	17	1.1

a/ The percentage of affected animals is shown in parentheses.

Table 3

Respiratory cancer deaths (RCD) in Colorado plateau uranium miners in relation to smoking [L2]

Smoking category	Person-years at risk (PYR)	Observed RCD (O)	Expected RCD (E)	O/E	$\frac{O-E}{PYR}$
Smokers	26392	60	15.5	3.9	$1.7\ 10^{-3}$
Non-smokers	9047	2	0.5	4.0	$1.7\ 10^{-4}$

Table 4

Interaction factors and probabilities ($\times 10^{-4}$) of respiratory cancer deaths per one person-year at risk for single and combined action of smoking and irradiation

Data base	Spontaneous	Smoking		Irradiation		Combined action			
	P_0	P_{t1}	$P_{o1} = P_{t1} - P_0$	P_{t2}	$P_{o2} = P_{t2} - P_0$	P_{ot}	$\Delta P_{obs} = P_{ot} - P_0$	$\Delta P_{exp} = P_{o1} + P_{o2}$	$\omega = \frac{\Delta P_{obs}}{\Delta P_{exp}}$
A	0.6	5.9	5.3	2.2	1.6	23	22	6.9	3.2
B	1.1	4.4	3.3	7.1	6.0	42.2	41.1	9.3	4.4

A: Derived from the 1950-1967 data base [L2].
B: Derived from the 1964-1967 data base [A1].

Table 5

Interaction factors and probabilities ($\times 10^{-4}$) of respiratory cancer deaths per one person-year at risk for uranium miners of different smoking categories [L6]

	Spontaneous	Smoking		Irradiation		Combined action			
	P_0	P_{t1}	$P_{o1} = P_{t1} - P_0$	P_{t2}	$P_{o2} = P_{t2} - P_0$	P_{ot}	$\Delta P_{obs} = P_{ot} - P_0$	$\Delta P_{exp} = P_{o1} + P_{o2}$	$\omega = \frac{\Delta P_{obs}}{\Delta P_{exp}}$
A	1.7	1.7	0	6.5	4.8				1
B	1.9	2.6	0.7			42.1	40.2	5.5	7.3
C	1.3	7.0	5.7			41.0	39.7	10.5	3.8
D	1.1	27.7	26.6			51.2	50.1	31.4	1.6

A: Non-smokers.
B: Former smokers.
C: Light smokers.
D: Heavy smokers.

Table 6

Dose modifying factors (DMF) for combined treatment by some chemotherapeutic drugs and radiation [P5]

Drug	Drug dose mg/kg	Dose modifying factor (DMF)		
		Intestine injury	Oesophageal lethality (from $LD_{50/28}$)	Pulmonary lethality (from $LD_{50/160}$)
Actinomycin D	0.75	1.3	1.6	1.6
Adriamycin	15	1.7	-	-
BCNU	8.25	1.1	0.9	0.74
Bleomycin	3	1.1	1.14	0.98
Cyclophosphamide	75	1.0	0.86	1.3
Hydroxyurea	500			1.03
Vincristine	0.5			1.18
Prednisolone	10			0.84

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