

GENETIC AND SOMATIC EFFECTS OF IONIZING RADIATION

United Nations Scientific Committee on the Effects
of Atomic Radiation
1986 Report to the General Assembly, with annexes



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NOTE

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on the Effects of Atomic Radiation
to the General Assembly**

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INTRODUCTION

1. This is the ninth substantive report of the United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR)^a to the General Assembly.^b As anticipated in its 1982 report, UNSCEAR had been planning to conduct detailed studies on selected subjects, together with comprehensive assessments of the type normally issued. This report contains reviews of three special topics in the field of biological effects of ionizing radiation that are among those presently under consideration by the Committee: genetic effects of radiation (annex A), dose-response relationships for radiation-induced cancer (annex B), and biological effects of pre-natal irradiation (annex C).

2. The preparation of this report with its scientific annexes took place essentially from the thirty-first to the thirty-fifth sessions of the Committee, although the preparation of annex B started much earlier, its publication being delayed pending the dosimetric revision on the survivors of Hiroshima and Nagasaki. Most of the scientific work for this report was done at meetings of groups of specialists, which considered working papers prepared by the Secretariat that were modified and amended from one session to the next, according to the Committee's requests. The report itself was drafted at the thirty-fifth session. Mr. Z. Jaworowski (Poland), Mr. D. Beninson (Argentina) and Mr. T. Kumatori (Japan) served as Chairman, Vice-Chairman and Rapporteur, respectively, at the thirty-first session. The following members of the Committee acted in such capacities at subsequent sessions: Mr. D. Beninson (Argentina).

^aThe Committee was established by the General Assembly at its tenth session in 1955. Its terms of reference are set out in resolution 913 (X). It was originally composed of the following Member States: Argentina, Australia, Belgium, Brazil, Canada, Czechoslovakia, Egypt, France, India, Japan, Mexico, Sweden, Union of Soviet Socialist Republics, United Kingdom of Great Britain and Northern Ireland and United States of America. The membership of the Committee was subsequently enlarged by the General Assembly in its resolution 3154C (XXVIII) to include Germany, Federal Republic of, Indonesia, Peru, Poland and Sudan.

^bFor the previous substantive reports of the Committee, see *Official Reports 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)*; *ibid., Thirty-seventh Session, Supplement No. 45 (A/37/45)*. These documents will be referred to in this context as the 1958, 1962, 1964, 1966, 1969, 1972, 1977 and 1982 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). The 1982 report with appendices and scientific annexes appeared as: *Ionizing Radiation: Sources and Biological Effects* (United Nations publication, Sales No. E.82.IX.8).

Mr. T. Kumatori (Japan) and Mr. A. Hidayatalla (Sudan) at the thirty-second and thirty-third sessions; and Mr. T. Kumatori (Japan), Mr. A. Kaul (Federal Republic of Germany) and Mr. A. Hidayatalla (Sudan) at the thirty-fourth and thirty-fifth sessions. The names of those experts who attended the thirty-first to the thirty-fifth sessions of the Committee as official representatives or members of national delegations are listed in appendix I.

3. The Committee was assisted in the preparation of the report by a small scientific staff and by consultants appointed by the Secretary-General. That group, whose members are listed in appendix II, was responsible for the preliminary review and evaluation of the technical information received by the Committee or published in the open scientific literature. In approving the report, the Committee itself assumes full responsibility for its content; it wishes, however, to acknowledge the help and advice given by the group.

4. Representatives of the World Health Organization (WHO), the International Atomic Energy Agency (IAEA), the International Commission on Radiological Protection (ICRP) and the International Commission on Radiation Units and Measurements (ICRU) attended the sessions of the Committee held during the period under review. The Committee wishes to acknowledge their contribution to the discussion. Representatives of the United Nations Environment Programme (UNEP), to which the secretariat of the Committee is attached, were also present at all the sessions. The Committee would like to express its appreciation for the special attention and the support given to its activities by this organization.

5. The reports received by the Committee from States Members of the United Nations and members of the specialized agencies and of the IAEA, as well as from those agencies themselves, during the period from 27 March 1982 to 18 April 1986 are listed in Appendix III. Reports received before 27 March 1982 were listed in earlier reports of the Committee to the General Assembly. The information received officially by the Committee was supplemented by, and interpreted in the light of, other data available in the current scientific literature or, in some rare cases, from unpublished communications of individual scientists.

6. In the following, the Committee summarizes the main conclusions from the three specialized studies already mentioned, also in the light of previously released substantive documents.

7. Following past practice, only the main text of the report is submitted to the General Assembly, while

the full report, together with the scientific annexes mentioned above, will be issued as a United Nations sales publication. This practice is intended to achieve wider dissemination of the findings to the international scientific community, which makes use of the Committee's assessments as a source of independent and authoritative information. 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. It should be borne in mind that the scientific data given in the annexes are very important and form the basis for the main conclusions contained in this report.

I. GENETIC EFFECTS OF RADIATION

8. The Committee reviewed recent advances in various areas relevant to the evaluation of genetic radiation hazards in man. The most important areas are: the identification of the prevalence of naturally occurring monogenic, chromosomal and other disorders; the use of recombinant DNA technology for the analysis of human genetic material in normal individuals and in those with genetic disease; the relationships between gene mutations, chromosomal aberrations and cancer; the role of movable genetic elements in the production of spontaneous mutations and their implications for the estimates of the genetic risk; and other data directly or indirectly bearing on the quantification of genetic hazards and detriment in man. As a result of this extensive analysis, the Committee believes that the assessment of radiation-induced genetic risk contained in its 1982 report remains broadly valid.

9. The considerations that determined the choice of the major themes listed above can be briefly summarized as follows: (a) a precise knowledge of the prevalence of Mendelian and chromosomal disorders and those with a strong genetic predisposition constitutes an essential framework for perceiving the impact of such disorders in human populations and for placing the radiation risk estimates into perspective; (b) the advances in recombinant DNA technology that have occurred during the last few years have imparted a level of precision hitherto not possible to the study of the human genome for unravelling the action of specific genes in health and disease, including cancer, for analysing the mutation spectra and the nature of spontaneous and radiation-induced mutations and for formulating new approaches to the management of heritable disorders; (c) the recent convergence of ideas and techniques from viral oncology, cell genetics and molecular biology has resulted in major breakthroughs in knowledge on the molecular genetic basis of several spontaneously arising and mutagen-induced cancers; (d) the demonstration that there are movable genetic elements (mobile DNA sequences) in a number of species (and presumptive evidence for their occurrence in humans), and that a sizeable proportion of spontaneous mutations (in bacteria, yeast and drosophila) are due to these movable genetic sequences, is raising questions concerning the extent to which they may be causing spontaneous mutations in humans and whether there is a difference in nature between radiation-induced and spontaneous mutations; and (e) new data from human studies on detriment associated with certain spontaneously arising disorders of complex aetiology, as well as information from mammalian and other studies on genetic effects of radiation, illustrate the validity of the Committee's earlier views and conclusions.

10. New data on the prevalence of certain specific monogenic disorders in humans essentially confirm the Committee's earlier assessments. Likewise, a re-

analysis of data bearing on the contribution of chromosomal anomalies to spontaneous abortions and still births suggests that at least 40% of the spontaneous abortions that occur in the period from the fifth to the twenty-eighth week of gestation and about 6% of still births are associated with chromosomal anomalies. Recent results from cytogenetic surveys of new-borns carried out using banding methods show that the frequencies of spontaneously occurring reciprocal translocations and inversions are higher than those detected in studies in which banding methods were not used.

11. The frequencies of chromosomal anomalies in patients with mental retardation and multiple congenital anomalies vary from about 2.5% to 20% with a mean of about 12%. In sub-fertile males, the prevalence of such anomalies is an order of magnitude higher than in new-borns (6.0% versus 0.6%), but the frequencies of specific anomalies show considerable variation.

12. A substantial amount of information has now become available on fragile sites on human chromosomes. These are chromosomal regions exhibiting fragility (as evidenced by abnormal chromosomal configurations in metaphase preparations), which can be made visible under specific tissue culture conditions. The fragile site is always at exactly the same point on the chromosomes in all individuals or kindred, but is never seen in all cells examined. About 40 fragile sites are currently known, including one on the long arm of the X-chromosome. The latter is associated with X-linked mental retardation and is the most common genetically determined cause of mental handicap, next only to trisomy-21 (Down's syndrome). There are indications that certain fragile sites on chromosomes other than the X may predispose chromosomes to breakage. There is evidence, furthermore, that several non-random chromosomal changes involved in certain cancers have breakpoints that coincide with the fragile sites.

13. A systematic comparison of three studies of the estimated live-birth prevalences of congenital anomalies (a prospective study in the United States and two retrospective studies in British Columbia and in Hungary) shows that the prevalences vary from 8.5% in the United States to 6.0% in Hungary and to 4.3% in British Columbia. Among the reasons for the differences between those estimates are geographical and ethnic variations and differences in ascertainment efficiencies. Particularly noteworthy is the finding that musculoskeletal anomalies constitute about 50% of all congenital anomalies in Hungary, about 45% in the United States and about 30% in British Columbia. Anomalies of the integument constitute, furthermore, about 10% of the total in the United States, and about 1% in Hungary and British Columbia. The Committee

has used the live-birth prevalences from Hungary (6.0%) as a basis for making detriment estimates for spontaneously arising congenital anomalies.

14. Preliminary data suggest that the prevalence of other disorders with a strong genetic predisposition, which are disorders primarily of adulthood, may be at least about 60% in Hungary. Each of these disorders has a population prevalence of not less than 1 per 10,000. The values for the individual conditions in Hungary are well within the ranges reported for other countries. These conditions are both aetiologically and clinically heterogeneous. The estimated population prevalence of 60% is an order of magnitude higher than the 4.7% for British Columbia. It should, however, be stressed that: (a) since many individuals have more than one disorder, the actual proportion of the Hungarian population that suffers is probably less than 60% although still far more than the 4.7% in British Columbia; and (b) the value of 4.7% applies only to disorders appearing before the age of 21, whereas the value of 60% applies to those appearing up to age 70.

15. During the last few years, the application of recombinant DNA technology to the study of the human genome has revolutionized the field of human genetics. By using a variety of enzymes specifically active on the cells' genetic material, it has become possible to make direct analyses of normal and mutant genes. Several findings emerging from these studies have applications in the detection of carriers of serious genetic disorders, in pre-natal diagnosis and in the typing of tumours and lymphomas. Molecular approaches are increasingly being used to study mutation and DNA repair in mammalian cells.

16. Exciting advances have also been made during the last few years in understanding the genetic basis of cancer. Among these, the following deserve mention: (a) the discovery that mammalian and other genomes contain nucleotide sequences related to viral oncogenes (i.e. genes responsible for the production of tumours in a number of avian and mammalian species) and that these sequences, termed cellular proto-oncogenes, have oncogenic potential; (b) the identification of activated forms of proto-oncogenes in tumour cells and the discovery that such activations can occur through point mutations or specific chromosomal aberrations in which the breakpoint may involve the cellular oncogene itself; and (c) the probable participation of proto-oncogenes in the regulation of cell proliferation.

17. The conceptual foundations for dealing with movable genetic elements, one of the most active areas of current genetic research, were laid by McClintock over three decades ago. From genetic studies with maize, she postulated the existence of what are now called movable genetic elements. Such elements have since been discovered in a number of species, including bacteria, blue-green algae, yeast and drosophila. There are several lines of evidence suggesting that they are also present in mammalian (including human) genomes, and some of these have been characterized at the molecular level. In the organisms studied, these

transposable genetic elements have been shown to be capable of inducing chromosome breaks, duplications and a variety of other structural alterations, as well as gene mutations and changes in gene expression at many gene loci.

18. The finding that a sizeable proportion of spontaneous mutations in experimental organisms studied in this respect can be caused by movable genetic elements, and that the rate of transposition is either not affected or only minimally so by exposure to mutagens, could have implications for the evaluation of genetic radiation hazards. For instance, if the majority of spontaneous mutations in humans is a by-product of the dynamics of transposable genetic elements and if the nature of these spontaneous mutations differs from that of mutations induced by mutagens, the use of the doubling dose method in hazard evaluation may need to be re-examined. There is, however, no evidence at present for the thesis that a majority of spontaneous mutations in humans is due to movable genetic elements.

19. A number of recent studies on mammalian somatic cells have shed further light on the nature of the lesions in DNA that lead to chromosomal aberrations and the process of DNA repair associated with the formation of these aberrations. Particularly interesting are the new data obtained by the use of restriction endonucleases. These are enzymes that recognize specific sequences in the DNA and cleave them, producing fragments that are either blunt ended (both strands cleaved at the same position) or cohesive ended (each strand cleaved at a different position). Although the absolute frequencies of chromosomal aberrations were found to depend on the restriction enzyme used, those producing blunt-ended DNA breaks were much more efficient than those producing cohesive-ended breaks. Since these enzymes are known to produce only double-strand DNA breaks, these data provide further direct evidence that double-strand breaks in the DNA are the principal lesions involved in the production of chromosomal aberrations.

20. New data obtained on lymphocytes (white blood cells) of patients with chromosome instability syndromes show that, except in one case, the spontaneous rates of mutation relative to those of blood cells from normal individuals are higher by factors ranging from three to ten. The newly developed T-lymphocyte cloning technique has been successfully used in studies on radiation induction of 6-thioguanine mutants in human lymphocytes. The data show dose-dependent increases in mutation frequency and these frequencies are of the same order of magnitude as those determined in experiments with established fibroblast cell lines.

21. The results of an international collaborative study on the x-ray induction of chromosomal aberrations in human lymphocytes in vitro show that at low doses (from 0.004 to 0.3 grays) there is no increase in aberration yields up to 0.05 grays, beyond which the increase is linear with dose. Furthermore, according to the authors' analysis, the frequencies of all types of aberrations at 0.004 grays are significantly lower than the control values.

22. Data from direct cytological analysis of spermatozoa from normal human males have shown that the frequencies of chromosomal abnormalities in these cells vary between individuals (0-28%) with a mean of about 9.0%. Both numerical and structural anomalies have been found, the frequencies of the former in different individuals ranging from 0.6% to 5.0% and those of the latter from 1.5% to 15.8%. The frequencies of chromosomally abnormal spermatozoa in men who had undergone radiotherapy were higher (averaging over 20% but ranging from 6% to 67%, with a significant correlation between the frequencies of abnormal sperm and testicular dose) than before radiotherapy and were also higher than in non-irradiated men; again, both structural and numerical chromosomal anomalies were present.

23. The frequencies of spontaneously arising chromosomal anomalies in Chinese hamster oocytes and early zygotes have been determined using an improved chromosome preparation technique. The data suggest that the incidence of aneuploidy of maternal origin (2.1%) is three times higher than that of paternal origin and first division meiotic errors are about three times more frequent than second division errors.

24. Further data on the x-ray induction of non-disjunction in young and old female mice have become available. In one set of experiments, the frequencies of eggs having more than the haploid number of chromosomes (hyperhaploidy) were higher in old (1.5%) than in young (0.2%) non-irradiated mice. After x irradiation, the frequencies of hyperhaploid eggs from both young and old mice showed a linear relationship with dose, but there were no differences between the young and old mice in this regard. In another set of experiments with young female mice and eggs, sampled at various intervals after irradiation, significant and greater-than-linear increases in hyperhaploidy were found, as the eggs sampled at shorter intervals after irradiation were found to be less sensitive than those sampled at other time intervals. In a further set of experiments, it was shown that the use of gonadotropin to induce ovulation had no effect on the sensitivity of the oocytes to the radiation induction of either numerical or structural anomalies.

25. Further genetic evidence on the x-ray induction of heritable reciprocal translocations in male mice (following spermatogonial irradiation) has been obtained. This shows that there is a dose-dependent increase in frequency up to 6 grays, the average rate being $(3.9 \pm 0.3) \times 10^{-3}$ per gray. The frequencies of translocations after 1.5 grays are consistent with expectations based on cytogenetic studies, whereas at higher exposures the frequencies appear to be lower than expected, in line with previous findings.

26. A comparison of the cytogenetic data on the x- or gamma-ray induction of reciprocal translocations in a number of non-human primate species (including the data reviewed in the 1982 report) show that the spermatogonia of one marmoset species, *Callithrix jacchus*, have a sensitivity similar to that of the Rhesus monkey. However, both these species are much less

sensitive than another marmoset, *Saguinus fuscicollis*. The crab-eating monkey, *Macaca fascicularis*, is intermediate between Rhesus monkey and *Callithrix jacchus*, and *Saguinus fuscicollis*, which was studied over 10 years ago. Changes in technique may be partly responsible for these differences. The recently studied crab-eating monkey, *Macaca fascicularis*, is about twice as sensitive as the Rhesus monkey to acute irradiation, but the most recent data suggest that the former species may be less sensitive to chronic gamma irradiation.

27. Data on the induction by x rays of congenital anomalies in the offspring of irradiated mice show that the incidence of these anomalies (detected by in utero examination) is significantly higher following irradiation of post-meiotic germ cells in males. The frequencies of these anomalies also tended to rise after spermatogonial exposure.

28. Further data have become available on the radiation induction of heritable tumours in mice. Spermatids in males and maturing oocytes in females seem to be the most sensitive stages for the induction of genetic changes that lead to tumours in the progeny; spermatogonia are also affected. The pattern of transmission of these tumours is consistent with a dominant mode of inheritance and a penetrance of about 40%; they also have a low expressivity.

29. In order to estimate the radiation risks associated with the induction of reciprocal translocations in human germ cells, model studies using x-irradiated blood lymphocytes and fibroblasts have been carried out. The location of the translocation break points, lengths of segments involved etc., were determined in banded chromosome preparations. The information so derived was used: (a) to inquire into the minimum possible imbalance that each of these translocations will generate, should they occur in germ cells; and (b) to compare these estimates with those available from studies reported in the literature of cases of partial monosomies and trisomies (i.e. loss or addition, respectively, of small chromosome segments). The main conclusion was that about two fifths of these translocations could generate viable imbalances in terms of abnormal progeny. More data are required before these figures can be used within the framework of risk assessment.

30. On the basis of limited data then available on the incidence of unbalanced structural rearrangements in new-borns and in spontaneous abortuses, the Committee estimated in its 1972 report that about 6% of all human conceptions with a structurally unbalanced chromosome complement could result in live births with congenital anomalies. This value was also used in the Committee's 1977 and 1982 reports. Recently, the Committee's attention was drawn to an error in these calculations, which when corrected gave a value of 3.5%. However, a further re-calculation using the more extensive data currently available led to a revised estimate of 9% of imbalanced products of balanced reciprocal translocations surviving to birth and resulting in congenitally malformed children.

31. In its 1982 report, the Committee estimated that the risk for the irradiation of males from the induction of dominant mutations (leading to genetic disease in the first generation progeny) lies in the range of one to two cases of affected individuals per million live-borns per milligray of sparsely ionizing, low-dose-rate, irradiation; the rough estimate of risk for the irradiation of females under similar conditions was 0-1 case per million live births. These estimates were based on the induction of dominant skeletal and cataract mutations in mice. New information from radiation-induced reduction of litter size in mice following exposure of parental males to x or gamma rays suggests the induction of genetic changes having dominant effects in the first generation and manifesting after birth at a stage earlier than that under scrutiny in the skeletal and cataract studies. The rate of induction of these changes appears to be about one half of that mentioned above for males. It seems probable that in the human species these lethals would act at some stage in early life.

32. In its 1977 and 1982 reports, the Committee estimated that the risk from the induction of autosomal recessive mutations (i.e. mutations in genes located on chromosomes other than the X) leading to recessive genetic disease was negligible, and it made no further attempts to quantify this risk. A recent study has shown that it is possible to provide a quantitative estimate for this class of disorders. These calculations, based on a combination of data from observations on human populations and from mouse experiments, show that a one-time exposure to a dose on the order of 1 milligray of sparsely ionizing, low-dose-rate, irradiation of the parental generation is not associated with any risk of induced recessive genetic disease in the first generation, thus confirming the earlier conclusion of the Committee. However, in the following ten generations, such an exposure may result in about one extra case per million live-borns by the tenth generation.

33. In 1982, the risk associated with the induction of structural chromosomal aberrations (predominantly reciprocal translocations) in males and females was estimated to lie between 0.03 and 1, and 0 and 0.3 cases, per million, respectively, of congenitally abnormal children per milligray of sparsely ionizing, low-dose-rate, irradiation. Using all the currently available data on primates, the Committee now estimates that the expected number of congenitally abnormal children ranges from 0.1 to 1.5, and 0 to 0.5, following irradiation of males and females, respectively (all rates expressed per million live births per milligray).

34. The risk estimates discussed so far are arrived at by using the so-called direct methods and pertain to effects expected in the first generation following a one-time radiation exposure of the parents. In contrast, the doubling dose method is primarily used to quantify risks under conditions of continuous radiation exposure. With this method, the expected risks are related to, and expressed as a fraction of, the spontaneous prevalence of Mendelian and chromosomal disorders as well as those of a more complex

aetiology. The Committee sees no reason for any alteration of its 1982 estimates for autosomal dominant, X-linked and chromosomal disorders. These estimates are briefly recapitulated in the following (all estimates per milligray of continuous sparsely ionizing, low-dose-rate, irradiation of the parental generation and on a population of one million live births): (a) autosomal dominant and X-linked disorders, 10 cases of affected individuals at equilibrium and 1-2 cases in the first generation; and (b) chromosomal disorders (mainly those arising as a consequence of unbalanced structural anomalies), 0.4 case at equilibrium and 0.3 case in the first generation. In these calculations, the spontaneous prevalence figures assumed are: 1.0% dominant and X-linked disorders; 0.25% autosomal recessive; and 0.3% chromosomal disorders. The doubling dose was, furthermore, assumed to be 1 gray.

35. New data on congenital anomalies and other disorders of complex aetiology suggest that their spontaneous prevalence (especially of the latter) is higher than the estimates considered in the 1982 report (see paragraphs 13-14). This difference is mainly due to the inclusion of data on individuals up to 70 years of age in the recent studies, whereas an earlier one only contained data on individuals up to 21 years of age (the estimates from the latter were used in the 1977 and 1982 reports). Considerable uncertainties still remain on the following problems: (a) whether the doubling dose estimate of 1 gray (this is based on mouse data on clear-cut genetic end-points such as specific locus mutations, dominant visibles and reciprocal translocations) is valid for disorders of complex aetiology; and (b) whether the estimate of 5% mutational component used in the 1977 and 1982 reports is realistic for these disorders. In the absence of further information, particularly on the mechanisms of maintenance of these disorders in the population, and thus a basis for predicting a possible radiation-induced increase in their prevalence, the Committee is not in a position to provide risk estimates for these disorders.

36. The Committee continued to focus attention on detriment (handicap, years of life lost, years of handicapped life) associated with spontaneously arising genetic and partially genetic disorders, with the hope of eventually formulating an adequate framework to view the increases in such detriment at the individual and societal levels as a result of radiation exposures. Some limited information from the follow-up of children with sex chromosomal anomalies and autosomal balanced structural rearrangements shows: (a) that no individual with sex chromosomal anomalies has had any serious mental retardation; and (b) that balanced structural rearrangements are probably not as harmful as previous reports (based on cytogenetic studies of mentally retarded individuals and inmates of penitentiaries) have implied.

37. The results of a study on the estimation of detriment associated with spontaneously arising congenital anomalies in humans have been published. In this study, the authors used the live-birth prevalence

values derived in Hungary for these anomalies (about 60,000 per million live births) to estimate detriment in terms of years of life lost, years of potentially impaired life and years of actually impaired life. For the period and the population for which these estimates apply, the mean life expectancy is 70 years. Calculations show that, with a total prevalence of 60,000 per million live births (i.e. 60,000 individuals per million affected with one or another type of isolated or multiple congenital anomalies), about 480,000 years of life are lost, 2.0-3.7 million years of life are potentially impaired and, of the latter, 450,000 years of life are actually impaired per million live births.

38. In terms of the average number of years of life lost (an index of detriment at the individual level), the central nervous system anomalies cause the greatest amount of detriment (55 years), followed by anomalies of the respiratory and cardiovascular systems and chromosomal anomalies (about 25 years for each of these) and others. Anomalies of the ear, face and neck (including cleft lip, with or without cleft palate), of genital organs and of the musculo-skeletal system have a small or negligible effect in this regard.

However, when the ranking is done according to the total number of years of life lost (an index of detriment at the population level), anomalies of the cardiovascular system are associated with the highest amount of detriment (about 180,000 years per million live births), followed by those of the central nervous system (about 120,000 years per million live births), of the alimentary system (43,000 years per million live births) and others.

39. One possible crude way of expressing detriment is in terms of the number of years of actually impaired life. Expressed in this way, anomalies of the cardiovascular system are associated with the greatest amount of detriment (98,000 years per million live births), followed by those involving the genital organs (72,000 years per million live births), chromosomal anomalies (56,000 years per million live births) and others.

40. On the basis of the above analysis, a comparison of the detriment caused by congenital anomalies with that caused by monogenic disorders (the latter is discussed in the 1982 UNSCEAR report) reveals that detriment is much higher for congenital anomalies.

II. DOSE-RESPONSE RELATIONSHIPS FOR RADIATION-INDUCED CANCER

41. The Committee examined the nature of the dose-response relationships for a variety of cellular and sub-cellular radiobiological effects *in vitro* and *in vivo*. Under a number of simplifying assumptions, the quantitative information derived was used to fit various models of radiation action to cancer induction data in experimental animals and in humans, in an attempt to predict the possible shape of the dose-induction curves for cancer, at low doses and dose rates that, although most interesting for practical purposes, cannot be studied directly. These procedures enabled the Committee to suggest the most probable form that the relationships for several types of cancer would take under these conditions and the type of bias that might affect the estimates of risk coefficients at low doses and dose rates, if one or the other model should apply. This exercise is seen as an important preliminary step towards a re-evaluation of the risk estimates for radiation-induced cancer, which the Committee is planning to release in the near future.

42. In order to estimate the risk coefficient, i.e. the frequency, of radiation-induced cancer or the relative increase of tumour frequency per unit dose over the natural incidence at low doses and dose rates, two types of information are required: firstly, empirical data on the incidence of various forms of malignancy at relatively high doses where observations have actually been made; and, secondly, a knowledge of the form of the relationships linking the incidence of cancers with the radiation dose. Such data would allow predictions to be made of the cancer incidence at doses, and perhaps also at dose rates, very much lower than those at which direct observations are available in humans.

43. When the incidence of a given tumour in exposed animal or human populations is followed as a function of increasing dose, several findings are apparent. At relatively low doses (about 0.1 gray of sparsely ionizing radiation), only seldom (and then mostly in controlled animal experiments) can a statistically significant increase of cancer or leukaemia be shown. At higher doses (from a few to several grays, with considerable differences between different tumours), the incidence of such malignancies may be shown statistically to exceed the level observed in non-exposed control populations, the excess increasing as some function of the dose. At still higher doses (many grays) the incidence gradually starts to fall off, owing to cell killing. Dose-response relationships of this type, passing through a maximum at some intermediate dose, are often found in experimental animals.

44. The usual interpretation of such a shape postulates the concurrent presence of two different phenomena: (a) a dose-related increase of the proportion of normal

cells that are transformed into malignant ones; and (b) a dose-related decrease of the probability that such cells may survive the radiation exposure. Both of these phenomena are normally operating in the region of doses where data are available, but to a different degree for various doses and different types of cancer. With this interpretation, some of the cells that would otherwise show transformation are killed, so that the fraction actually seen as transformed is reduced at high doses. What happens at the low doses, where direct information is lacking, may only be inferred from a combination of empirical data and theoretical assumptions, linked together into some models of radiation action.

45. The models referred to are simplified semi-quantitative representations of complex biological phenomena. Present knowledge of the mechanisms of carcinogenesis, including radiation carcinogenesis, is not adequate to design comprehensive models accounting for all physical and biological factors known to influence the induction of cancer. To avoid some of the complications involved, the Committee suggests that the range of doses over which extrapolations may meaningfully be performed should be limited to low and intermediate doses, below about 2 grays of sparsely ionizing radiation. Under these conditions, it seems likely that no serious distortions would result from non-stochastic radiation effects, which are observed when doses exceed fairly high thresholds, characteristic for each tissue and each effect.

46. The formulation and analysis of models of radiation carcinogenesis must rely on a few basic assumptions, as follows:

- (a) The observed dose-response relationships for clinically visible tumours *in vivo* approximately reflect the relationship between dose and cancer initiation at the cellular level, despite host reactions and the effect of latency, which may modify this relationship to some degree. This assumption is based on the overall similarity of the dose-response curves for cancer induction with those of various other cellular effects of radiation. The Committee postulates this concept simply as a working hypothesis;
- (b) Cancer initiation is believed to be a uni-cellular process occurring at random in single cells. This is also a working hypothesis that has not yet definitely been proved. However, evidence to the contrary, i.e. that cancer initiation takes place in several cells, is less convincing, although some limited evidence supports the idea. The uni-cellular theory of cancer induction is compatible with the notion that some, still ill-defined, influences resulting from irradiation of neigh-

bouring cells or other organs may modify the probability that an initiated cell will develop into an overt malignancy. Firm biological evidence in favour of this last notion is very fragmentary;

- (c) The absence of a dose threshold for induction is characteristic of many, if not all, tumours. For some animal tumours (e.g. tumours of the ovary or thymic lymphoma of the mouse), threshold-type dose-response relationships are observed. In other cases (e.g. tumours of the skin), cancer is only induced with great difficulty, i.e. after high doses of radiation. In still others (i.e. epidermoid lung cancer in humans), the data are unclear, owing perhaps to a short follow-up of the patients. In spite of these exceptions, however, the absence of a threshold dose is assumed by the Committee as a working hypothesis for the moment;
- (d) The susceptibility of an irradiated animal or human population to tumour induction is assumed to follow a bell-shaped distribution. Although genetic predispositions to the development of some forms of malignancy are well documented, efforts to show that such phenomena apply also to radiation-induced human cancer have not been successful so far. Therefore, pending further studies, the same distribution of susceptibilities to the induction of cancer in irradiated and non-irradiated populations is also provisionally accepted as a working proposition.

47. On the above assumptions, it is possible to infer likely shapes for the dose-response relationships of radiation-induced cancer. Such inferences rely on the analysis of various other radiation effects observed at the cellular level. These effects involve the cells' genetic material, which is also thought to be the primary target for cancer initiation. The production of mutations and chromosomal aberrations in somatic and germinal cells and the oncogenic transformation in vitro of mammalian cell lines are examples of such effects. If cancer induction in vivo involves mechanisms similar to, or related to, those underlying the effects listed above, it is expected that all these phenomena will respond similarly with respect to changes in dose, dose rate and fractionation. As such similarities have actually been observed, it may be possible to extrapolate the shape of dose-response relationships between the effects mentioned above and the phenomenon of cancer induction.

48. Three basic non-threshold models of radiation action as a function of dose have been reviewed with respect to such cellular effects and to cancer initiation: the linear, the linear-quadratic and the pure quadratic models. Notwithstanding some exceptions, these may provide a general envelope for the dose-response curves of a variety of radiation-induced end-points at the cellular level, as well as for tumour induction in experimental animals and human populations.

49. The vast majority of dose-response curves for induction of point mutations and chromosomal aberrations by sparsely ionizing x rays and gamma rays can be described by a linear-quadratic model. For the

same end-points, when cell killing is accounted for, a linear model usually applies to densely ionizing radiations, such as alpha particles or neutrons. As a rule, for a number of chromosomal structural abnormalities, curvilinearity (upward concavity) is observed for sparsely ionizing radiation. For the same effects and a wide range of doses, linearity prevails for densely ionizing particles. Linearity of the dose-response for somatic mutations and terminal chromosomal deletions has been found in some cell lines, even for sparsely ionizing radiation, although this is rare.

50. Approximate estimates of proportionality constants linking the chromosomal effects with the dose or its square may be obtained experimentally; they allow the frequency of such effects to be predicted at low doses and dose rates from observations at higher doses. For cancer induction, however, only fragmentary information supports the notion that similar quantitative relationships with the dose might apply. The Committee has estimated that, if the risk of tumour induction at 1 or 2 grays of sparsely ionizing radiation (at high dose rate) were extrapolated linearly down to zero dose, this procedure would overestimate the risk by a factor of up to five in typical situations.

51. Over the last few years, much information on radiation-induced oncogenic transformation of mammalian cells has become available. The cancerous nature of the transformed cells is shown by the fact that after transformation in vitro they are able to form malignant tumours upon transplantation back into animals, under appropriate conditions. Transformation in vitro is therefore regarded as a model, albeit a simplified one, of radiation carcinogenesis at the cellular level. Cells exposed in vitro to sparsely ionizing radiation 24 hours after seeding are transformed according to complex kinetics that cannot be fitted to models used for other cellular effects, such as cell killing. Moreover, fractionation of the dose (below 1.5 grays total) has in some instances appeared to enhance transformation, which is contrary to what would be predicted by a linear-quadratic model; in other instances, however, it has clearly not enhanced transformation.

52. Further research is needed to reconcile such conflicting observations on the nature of the response after fractionation at low doses. Several experiments indicate that anomalous results can arise from atypical conditions of cellular growth soon after establishment of the culture. In fact, irradiation of non-dividing cells or cells under exponential growth conditions (which are thought to be more representative of an asynchronously dividing cell population in vivo) produces results that are compatible with those obtained for other cellular effects; thus, for example, high-dose-rate gamma irradiation results in a greater frequency of transformation than low-dose-rate exposure.

53. There are indications that, when cells are irradiated with neutrons, low dose rates or dose fractionation may increase the rate of transformation, even at low doses. However, whereas some observations on tumour induction in experimental animals clearly support these findings, others do not. In other experiments,

enhanced transformation by neutron fractionation or protraction was seen only at intermediate and high doses. In view of the paucity of such data and of the uncertainties involved, further research is needed before enhancement of cancer induction by neutron fractionation and protraction (relative to single or high-dose-rate exposure) can be accepted for the purposes of risk assessment. Such a possibility should, however, be kept in mind, even though the theoretical basis to explain these phenomena is uncertain at present.

54. Recent experimental findings on radiation-induced tumours in experimental animals have not substantially changed the main conclusions reached in annex I of the 1977 UNSCEAR report. Most data support the notion that dose-response relationships for x rays and gamma rays tend to be curvilinear and concave upward at low doses. Under these conditions, tumour induction is dose-rate dependent, in that a reduction of the dose rate, or fractionation, reduces the tumour yield. A linear extrapolation of the risk from high doses delivered at high rates to zero dose would thus, as a rule, overestimate the real risk at low doses and dose rates. However, in one experimental mammary tumour system (matched by epidemiological data on human breast cancer), irradiation with x rays and gamma rays produced a linear dose response with little fractionation and dose-rate dependence.

55. For densely ionizing neutron irradiation, tumour induction in animals follows in general a very nearly linear curve at the lower end of the dose scale and shows little dependence on dose rate. In some cases, however, enhancement upon fractionation (and possibly protraction) has been noted. Above about 0.1 gray, the curve tends to become concave downward, markedly so in some cases. Under these conditions, a linear extrapolation of the risk down from intermediate or high doses and dose rates would involve a variable degree of underestimation.

56. The Committee reviewed existing data on dose-response relationships for radiation-induced tumours in man. This whole matter must be treated with caution because, at present, observations are very fragmentary, those for neutrons totally absent, and definitive data for atomic bomb survivors at Hiroshima and Nagasaki are still not available. For example, dose-response data for sparsely ionizing radiation have not been reported for lung and bone tumours, while data for densely ionizing radiation have not been reported for thyroid and mammary cancer. For sparsely ionizing radiation, the data available in some cases (lung, thyroid and breast) are consistent with linear or linear-quadratic models. For breast cancer, linearity may, however, predominate, as the incidence is little affected by dose fractionation. The linearity of the response for lung cancer after exposure to alpha particles from radon daughters does not contradict the above statement, because the dose-squared component with alpha particles is minimal. Some doubts still remain, however, as to osteosarcoma induced by bone-seeking alpha- or beta-emitting radionuclides. Thus, in spite of the fragmentary character of the data from humans, a general picture is emerging from which several tentative conclusions can be derived.

57. For sparsely ionizing radiation, linear extrapolation downwards from about 2 grays would not overestimate the risk of breast and possibly thyroid cancer, would slightly overestimate the risk of leukaemia, and would definitely overestimate the risk of bone sarcoma. A lack of direct evidence does not permit any assessment to be made of the magnitude of the overestimate for lung cancer.

58. For densely ionizing radiation, the risk of lung cancer from accumulated exposures to radon decay products at low dose rates from dose levels roughly corresponding to 20-50 sieverts would neither be overestimated nor underestimated by linear extrapolation to very low doses. However, extrapolation from observations made at higher cumulative exposures might result in a significant underestimation owing to observed flattening (saturation) of the dose-response curve in this region. It should be stressed that the absolute risk coefficients derived for male miners, of whom a high proportion are smokers, should not be applied to the general public without due corrections for various factors (intensity of smoking, lung ventilation rate, presence of other contaminating pollutants etc.) that are thought to increase the risk in miners.

59. The incidence of bone sarcoma after alpha-particle internal irradiation by long-lived bone-seeking radionuclides is distorted by the existence of a pronounced inverse relationship between accumulated dose and latent period, resulting in an apparent threshold at low doses. If this is a correct explanation for the upward concavity of the dose-response relationship, a linear extrapolation from a mean skeletal dose of a few tens of grays down to the milligray region would grossly overestimate the risk.

60. No data on the induction of breast cancer and leukaemia in humans by densely ionizing radiations are available at present and therefore no direct inferences can be made about risk extrapolation to the low-dose domain. On the basis of general knowledge, if the risk at intermediate doses could be derived from data on sparsely ionizing radiation (suitably corrected for the greater effectiveness of the densely ionizing particles), a linear extrapolation down to low doses might either underestimate or correctly estimate the real risk in these cases.

61. For radiation-induced cancers of other organs, only data on experimental animals are available. For sparsely ionizing radiations, upward concave curvilinear dose-response relationships with pronounced dose-rate and fractionation effects are usually found. If similar curves apply to cancers in humans, a linear extrapolation of risk coefficients (obtained at the intermediate dose region after acute irradiation) to the low dose and low dose rates would very likely overestimate the real risk, possibly by a factor of up to five. For densely ionizing radiation, should relevant values become available, a linear extrapolation from high to intermediate doses would probably underestimate the risk.

62. Upon close inspection of the data, some regularities seem to emerge that may indirectly help in assessing the character of dose-response relationships

in humans. A similarity in the shape of the relationships was noted between humans and experimental animals for tumours of several organs for which reasonably good information exists: mammary and thyroid cancer (sparsely ionizing radiations) and lung and bone cancers (densely ionizing radiations). Should

this pattern be confirmed, knowledge derived from epidemiological studies in humans at intermediate or high doses, and from the shape of the dose-response relationships in several animal species, would make it possible to assess the bias introduced by linear extrapolation of the risk coefficients to low doses.

III. BIOLOGICAL EFFECTS OF PRE-NATAL IRRADIATION

63. The Committee reviewed the following: modern knowledge of developmental events, particularly in the brain of mammalian embryos and fetuses; recent data on effects induced by irradiation of animals in utero; and findings concerning children exposed to radiation in the mother's womb during the atomic bombings at Hiroshima and Nagasaki. These, and a large body of older data, were used to derive quantitative estimates of risk for a number of radiation effects in utero, such as the induction of death, malformations, severe mental retardation and cancer. For the small doses and dose rates of radiation likely to be encountered in practice, the risk is judged to be relatively small in comparison with the natural incidence of congenital anomalies in non-irradiated individuals.

64. The consequences of pre-natal radiation exposure have attracted much attention since the last review of this subject by the Committee in 1977. New information from experimental animals irradiated in utero, recent findings of human embryology (particularly in the central nervous system) and a review of dosimetric and clinical data on children exposed before birth during the atomic explosions of Hiroshima and Nagasaki, called for a new study of this subject. There was also a need for a detailed re-assessment of effects such as the induction of malignancies following irradiation in utero, which had not been covered in depth in the 1977 report.

65. The Committee had already identified and described the main consequences of pre-natal exposure in mammals and had roughly classified them as follows: (a) lethal effects, induced by relatively small doses before or immediately after implantation of the embryo into the uterine wall, or induced after increasingly higher doses during all stages of intra-uterine development, to be expressed either before or after birth; (b) malformations, characteristic of the period of major organogenesis when the main body structures are formed, and especially of the most active phase of cell multiplication in the relevant structures; (c) growth disturbances without malformations induced at all stages of development, but particularly in the latter part of pregnancy; and (d) miscellaneous effects on various body structures and functions. The Committee had concluded, on the basis of considerable experimental evidence available at that time, that killing of cells, mainly through the induction of chromosomal aberrations, was the common mechanism underlying all these effects; any differences were particularly related to the time during development when the radiation insult was applied.

66. It should be realized that congenital anomalies arise in all animal species even in the absence of any radiation beyond that received from natural sources. Human malformations may be classified, according to their cause, into: those that can be traced back to the

mutation of single genes (representing about 6% of all malformations scored at birth); those originating from the incorrect interplay of numerous genetic factors (about 50%); those due to the presence of chromosomal anomalies (about 5%); and those caused by some known environmental teratologic agents (about 6%). There is no apparent cause for about one third of all malformations. The incidence of congenital anomalies depends to a large extent on the time at which they are scored. If a level of about 6% incidence of malformed babies at birth (birth prevalence) is taken as an average value for the human species, a higher value applies to embryos and fetuses before birth, because the malformed new-borns are only the carriers of the relatively milder forms, which are compatible with life. Some malformations disappear after birth, although more become evident that are not scored at birth. Thus, the global incidence of malformations roughly doubles if grown-up children, rather than new-born babies, are examined. The global incidence figures are, however, highly dependent on a large variety of factors and so are the figures pertaining to the various classes of malformations. Any assessment of the radiation's effectiveness in inducing damage in utero must be viewed against this natural level of inborn defects and its variable expression.

67. The Committee reviewed much information derived from human specimens and experiments in non-human primates, establishing to an increasing degree of detail and precision the developmental events that are important for their radiobiological consequences. Morphological embryology is gradually providing an accurate description of the stages in embryonic human growth, in good agreement with the results of non-invasive clinical measurements. The newest findings are increasingly pointing to the cerebral cortex as an extremely sensitive structure in human development, particularly (but not exclusively) in early pre-natal life, from the eighth to the fifteenth week after fertilization. At the same time, the microscopic study of the brain cortex is providing a very detailed picture of the cellular events leading to the formation of this structure as development proceeds. Such morphological analyses are integrated by biochemical studies, which help to provide an overall description of the structure and function of the developing brain.

68. These studies show the formation of the cerebral cortex as a carefully programmed and unique sequence of events in which cell division, migration and maturation are taking place concomitantly. Numerical, spatial and temporal relationships between various types of cells must be maintained with a high degree of precision in order for the brain cortex to be correctly assembled and its function normally developed. Disruption of this programme of cellular and tissue phenomena by radiation, coupled with the

limited capacity for repair of neurons, the functional brain cells, may cause irreversible damage. Whether radiation impinges on the reproductive capacity of the primitive brain cells, interferes with the orderly migration to their ultimate position in the cortex, or inhibits establishment of the appropriate cellular connection, the net result of the radiation insult is manifested in a loss of cerebral, particularly mental, function. This is the picture, albeit very schematic, emerging from the available data. However, the morphological and functional complexity of the developing brain cortex defies any simple interpretation of radiation effects, on the basis of the criteria applying to other self-renewing tissues of the body.

69. Pre-natal development of mammals in utero may be roughly divided into three periods: the pre-implantation, extending from fertilization to settling of the embryo into the uterine wall; the major organogenesis, characterized by the formation of the main body structures; and the fetal period, during which growth of the structures already formed takes place. There is a very large variability in the relative duration of these periods between animal species, as well as in the total duration of intra-uterine life. Also, at any given stage of development, the state of differentiation or maturation of any one structure, with respect to all the others, varies considerably in different species.

70. There have been no new findings in humans on the effects of radiation during the pre-implantation phase, owing presumably to the difficulties of obtaining information during this stage. In animals, however, many new data have been produced by analyses in vitro and in vivo. These data have mainly confirmed the special sensitivity of the pre-implantation embryo to killing and a decreasing sensitivity with increasing developmental complexity, with ample oscillations of the responses as a function of time, particularly during the earliest phases of embryonic development. In the rodent, doses on the order of one-tenth of a gray or less have been reported to increase mortality significantly for irradiation during pre-implantation.

71. For irradiation during the phase of major organogenesis, new data on experimental animals have added details to the previously known picture, but have not substantially altered its main features. At this stage, malformative effects emerge as the most prominent consequences of irradiation, sometimes accompanied by growth disturbances of various structures or of the whole body. The presence of maximum sensitivity periods at the time of the main differentiation of the various structures results in a marked time dependence for the appearance of various types of malformation. Some malformations, particularly those of the skeleton, have been very well studied as a function of dose, generally confirming a curvilinear trend; others, especially those of the central nervous system, have been carefully analysed in terms of cellular events and reactions leading to their formation.

72. Contrary to what is observed in experimental animals, radiation-induced malformations of body structures other than the central nervous system are

uncommon in humans. The Committee has discussed the reasons for such a difference. Beyond any explanation, however, the discrepancies between different species must be taken as a warning against indiscriminate attempts to project findings across species, without due consideration of the embryological characteristics of each species: short of this, any extrapolations, particularly the quantitative ones, would be unwarranted.

73. Radiation-induced damage to the central nervous system in humans is first observed at the conventionally assumed end of organogenesis (eight weeks post-fertilization) and extends well into the fetal period (up to 25 weeks). A re-examination of the dosimetric and clinical findings in individuals irradiated in utero at the time of the atomic explosions in Japan has allowed an important step forward to be made in the analysis of effects and the establishment of a risk estimate in man. At the same time, morphological and biochemical studies on human samples have established a clear-cut correlation between the time of maximum sensitivity of the brain structures and the time of most intense division and migration of the neurons in the brain cortex, thus extending to man a concept found to be valid for experimental animals.

74. A study of about 1600 children exposed in utero at Hiroshima and Nagasaki to various doses and at various developmental stages has confirmed that about 30 of them have shown clinically severe mental retardation, an incidence far higher than would normally be expected. When the occurrence of this condition was studied as a function of developmental stage at the time of the bombing, it was found that mental retardation was not observed before 8 weeks from conception, was at a maximum between 8 and 15 weeks when neuronal proliferation in the cortex is most active, and then was somewhat lower between 16 and 25 weeks, when the supporting tissues in the brain develop and connections between neuronal cells are established. The incidence of mental retardation as a function of dose is reported to be apparently linear without threshold at 8-15 weeks, with a risk coefficient of 0.4 per gray. The incidence is about four times lower at 16-25 weeks. There is an indication that, in addition to these extreme mental handicaps, other less prominent functional brain deficits might be present in children irradiated in utero, and it is expected that this cohort will eventually yield more useful information. While some aspects of these findings may not yet be explained on available radiobiological knowledge, there is no doubt as to their overall interest, particularly with respect to the quantification of the attendant risk.

75. A variety of effects have been documented in the experimental animal following irradiation during the fetal stages, including effects on the haemopoietic system, the liver and the kidney, all occurring, however, after fairly high radiation doses. The effects on the developing gonads have been particularly well documented, both morphologically and functionally. There appears to be at present little correspondence between the cellular and functional damage as a function of dose, but doses of a few tenths of a gray as

a minimum are necessary to produce fertility changes in various animal species.

76. Data on effects in utero following the uptake of radioactive substances by the mother and their passage to the developing fetus are very fragmentary, particularly in view of the many variables that may influence the dose eventually delivered to the conceptus. Among the most important variables, the following should be mentioned: the physical and chemical characteristics of the radionuclides; the route and schedule of administration; and the kinetics of transfer and metabolism in the mother, through the placenta and into the fetus. Only for some nuclides of practical importance (tritium, plutonium, iodine) is the amount of information slightly more extensive, but there is clearly a need to enlarge the data base in a systematic way to other nuclides and to investigate an adequate range of concentrations and tissue doses.

77. A number of physical and chemical factors have been reported that appear to modify the response of the developing mammals, but here again the information is insufficient for broad generalizations. Among the physical factors, both the type and energy of the radiation, with values of the relative biological effectiveness (RBE) on the order of five for neutrons at intermediate doses, have been examined in some detail. Fractionation and protraction of the dose have also been investigated for both sparsely and densely ionizing radiations and have consistently produced a reduced effect in comparison with singly administered doses. The picture emerging from these data is sketchy, however, and leaves conspicuous gaps in our knowledge. Among the chemical factors, oxygen and a variety of radio-protective and radio-sensitizing drugs have been proved (at least qualitatively) to have modifying effects in developing tissues similar to those seen in adult tissues. There have also been some scattered results from combined treatments of radiation with other agents, although much more systematic work would be required to substantiate some claims, particularly those of synergistically active treatments.

78. The Committee has reviewed in some depth the data available on the induction of tumours in animals irradiated pre-natally, in an attempt to compare their susceptibility with that of animals irradiated after birth. Such comparisons are rendered particularly difficult, however, owing to variations in species, strain and sex, the lack of extended time- and dose-response analyses, and the interplay of various biological end-points. In the Committee's opinion, the available evidence fails to substantiate the existence of a higher susceptibility to radiation-induced carcinogenesis of animals in utero, and points, on the contrary, to a lower susceptibility. Differences in

tumour types arising in animals irradiated before or after birth are probably the most consistent finding in the work analysed, a finding that is not unexpected in view of the different developmental stages of the animals at irradiation.

79. In humans, evidence on tumour induction by pre-natal irradiation comes essentially from two major sources: firstly, children that survived in utero irradiation at Hiroshima and Nagasaki, and that have continued to show no evidence of excess cancer in the studies conducted so far; secondly, two large retrospective studies of children exposed in utero for medical reasons. The latter children have consistently shown an excess of tumour and leukaemia cases over the first 10-15 years of their post-natal life, to a level roughly 50% above the natural incidence for the low (but not very well known) doses involved. Correction of the data for a number of social and medical factors that might have distorted the association between irradiation and incidence of tumours in those children was insufficient to cancel the correlation entirely. The Committee has reviewed and discussed several inconsistencies between the experimental and the human findings, as well as between the epidemiological findings themselves.

80. Beyond the existence of the association itself, which appears to be sufficiently well established, the most significant issue in this respect concerns the causality of the pre-natal radiation treatment in increasing the post-natal incidence of leukaemia and cancer. The Committee believes that the important consideration in these matters is the existence of the association. Denying the causal relationships on the basis of the overall inconsistency of the experimental and epidemiological findings would mean emphasizing scientific considerations over the practical need of allowing for any possible risk. The Committee has therefore decided to accept provisionally the causal nature of the association for practical purposes, while emphasizing that this is simply on account of prudence and not on any firmly established scientific grounds.

81. At the end of its review, the Committee attempted to derive quantitative risk estimates for a number of radiation-induced effects in utero (mortality, induction of malformations, mental retardation, tumours and leukaemia) and to attribute the risk to the periods of pregnancy over which it applies. Under a number of qualifying assumptions, it is possible to conclude that, for the small doses likely to be encountered in practice, the overall risk is relatively small (no more than 0.002 for the live-born at 0.01 gray) in relation to the natural incidence of malformations in non-irradiated individuals, which is on the order of 0.06 in the human species.

Appendix I

LIST OF MEMBERS OF NATIONAL DELEGATIONS

List of experts attending the thirty-first to the thirty-fifth sessions
as official representatives or members of national delegations

ARGENTINA

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

AUSTRALIA

K.H. Lokan (Representative)

BELGIUM

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

BRAZIL

L.R. Caldas (Representative), E. Penna Franca (Representative)

CANADA

E.G. Letourneau (Representative), A.M. Marko (Representative),
W.R. Bush, G.C. Butler, D.K. Myers

CZECHOSLOVAKIA

M. Klímek (Representative)

EGYPT

S. El-Din Hashish (Representative), M. El-Kharadly

FRANCE

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

GERMANY, FEDERAL REPUBLIC OF

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

INDIA

K. Sundaram (Representative)

INDONESIA

A. Baiquni (Representative), M. Ridwan (Representative),
O. Iskandar (Representative)

JAPAN

T. Kumatori (Representative), J. Inaba, R. Ichikawa,
Y. Kameyama, A. Kasai, A. Yamato

MEXICO

J.R. Ortiz Magaña (Representative)

PERU

M. Zaharia (Representative), L.V. Pinillos Ashton (Representative)

POLAND

Z. Jaworowski (Representative)

SUDAN

A. Hidayatalla (Representative), A.A. Yousif

SWEDEN

B. Lindell (Representative), K. Edvarson, L.-E. Holm,
K.G. Lüning, S. Mattsson, J.O. Snihs, J. Valentin,
G. Walinder

UNION OF SOVIET SOCIALIST REPUBLICS

L.A. Ilyin (Representative), A. Guskova (Representative),
E. Golubkin, D.F. Khokhlova, A.A. Moiseev, Yu.I. Moskalev,
V. Pavlinov, O. Pavlovsky, V.V. Redkin, V.A. Shevchenko

UNITED KINGDOM OF GREAT BRITAIN
AND NORTHERN IRELAND

J. Dunster (Representative), J.H. Edwards, K.E. Halnan,
P.S. Harper, A. Searle

UNITED STATES OF AMERICA

R.D. Moseley (Representative), R.E. Anderson, R. Baker,
C. Edington, J.H. Harley, H.H. Rossi, W.L. Russell,
P.B. Selby, W.K. Sinclair, J.W. Thiessen, H.O. Wyckoff

Appendix II

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

A. Czeizel
A.M. Kellerer
J. Liniecki
K. Sankaranarayanan
G. Silini
F.D. Sowby

Appendix III

LIST OF REPORTS RECEIVED BY THE COMMITTEE

1. Listed below are reports received by the Committee from Governments between 11 November 1982 and 14 April 1986.
2. Reports received by the Committee before 11 November 1982 were listed in earlier reports of the Committee to the General Assembly.

| <i>Document No.</i> | <i>Country</i> | <i>Title</i> |
|----------------------|--|--|
| A/AC.82/G/L. 1673 | Czechoslovakia | The values of strontium-90 concentration in vertebrae |
| 1674 | Union of Soviet Socialist Republics | Ingestion of global strontium-90 and caesium-137 with the food ration of the population of the Soviet Union 1976-1979 |
| 1675 | Germany, Federal Republic of | Environmental radioactivity and radiation levels—annual report 1979 |
| 1676 | United Kingdom of Great Britain and Northern Ireland | Radioactive fallout in air and rain: results to the end of 1981 |
| 1677 | United Kingdom of Great Britain and Northern Ireland | Environmental radioactivity surveillance programme: results for the UK for 1981 |
| 1678 | Switzerland | 25th report of the Federal Commission on radioactivity for the year 1981 |
| 1679 | Union of Soviet Socialist Republics | Combined effects of radionuclides and external irradiation on the organism of rats |
| 1680 | Union of Soviet Socialist Republics | Studies on the radiation health in the Russian Soviet Socialist Republic (RSFSR) following the stratospheric fallout of strontium-90 and caesium-137 1963-1978 |
| 1681 | Union of Soviet Socialist Republics | Calculations of microdosimetry characteristics for heavy charged particles with energy levels of 2-10 MeV/nucleon |
| 1682 | Czechoslovakia | The values of stable strontium in vertebrae, femoral diaphyses, and their ratio in different age groups (1970-1973) |
| 1683 | Germany, Federal Republic of | Environmental radioactivity and radiation levels—annual report 1980 |
| 1684 | Union of Soviet Socialist Republics | Combined effects of radiation and chemical factors |
| 1685 | France | Surveillance de la radioactivité en 1981 |
| 1686 | Belgium | Radioactivity measured at Mol 1980 |
| 1687 | United States of America | Environmental Measurements Laboratory: Environmental report, 1 May 1982 |
| 1688 | United States of America | Environmental Measurements Laboratory: Worldwide deposition of strontium-90 through 1981 |
| 1689 | United Kingdom of Great Britain and Northern Ireland | Radioactive fallout in air and rain: results to the end of 1982 |
| 1690 | New Zealand | Environmental Radioactivity Annual Report 1982 |
| 1691 | Czechoslovakia | Lung cancer in exposed human populations and dose-effect relationship—July 1983 |

| <i>Document No.</i> | <i>Country</i> | <i>Title</i> |
|---------------------|--|--|
| 1692 | United Kingdom of Great Britain and Northern Ireland | Environmental radioactivity surveillance programme: results for the UK for 1982 |
| 1693 | Union of Soviet Socialist Republics | Brief results of a study into the combined effect of ionizing radiation and other environmental factors in the Ukrainian SSR |
| 1694 | Union of Soviet Socialist Republics | Relative biological effectiveness of protons and heavy ions |
| 1695 | Union of Soviet Socialist Republics | Study of the vertical migrations of radionuclides in the bottom deposits and soil of a body of water with no through current |
| 1696 | United States of America | Environmental Measurements Laboratory: Graphic presentation of strontium-90 fallout data 1954-1982 |
| 1697 | Switzerland | 26th report of the Federal Commission on radioactivity for the year 1982 |
| 1698 | France | Surveillance de la radioactivité en 1982 |
| 1699 | Union of Soviet Socialist Republics | Mechanisms of the competitive effect of iron on the exchange processes of plutonium-239 in the organism |
| 1700 | New Zealand | Environmental Radioactivity Annual Report 1983 |
| 1701 | United States of America | Strontium-90 in the U.S. diet, 1982 |
| 1702 | United States of America | Worldwide deposition of strontium-90 through 1982 |
| 1703 | Japan | Radioactivity Survey Data in Japan, Number 65, June 1983 |
| 1704 | Switzerland | 27th report of the Federal Commission on radioactivity for the year 1983 |
| 1705 | United Kingdom of Great Britain and Northern Ireland | Environmental radioactivity surveillance programme: results for the UK for 1983 |
| 1706 | United Kingdom of Great Britain and Northern Ireland | The radiation exposure of the UK population—1984 review |
| 1707 | United States of America | The high altitude sampling program: radioactivity in the stratosphere |
| 1708 | Germany, Federal Republic of | Environmental radioactivity and radiation levels in the years 1981/82 |
| 1709 | United States of America | Strontium-90 in the human bone in the US, 1982 |
| 1710 | United States of America | Annual report of the surface air sampling program (EML-440) |
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| 1714 | Union of Soviet Socialist Republics | Radiation doses of workers using radio-isotope devices in industry |
| 1715 | Union of Soviet Socialist Republics | Justification of assessments of the carcinogenic risk associated with low-dose radiation |
| 1716 | Union of Soviet Socialist Republics | Assessment of the possibility of using an iron preparation for optimal monitoring of the plutonium-239 content in the human body |
| 1717 | Union of Soviet Socialist Republics | Radiation loads from pharmaceutical preparations marked by radioactive iodine isotopes |

| <i>Document No.</i> | <i>Country</i> | <i>Title</i> |
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| 1718 | Union of Soviet Socialist Republics | The effect of differences in the radiosensitivity of cells in certain persons to the accuracy of the extrapolation of dose ratios to low-dose values |
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| 1724 | Union of Soviet Socialist Republics | The influence of non-radiation factors on the kinetics of radioactive iodine metabolism in the thyroid |
| 1725 | Union of Soviet Socialist Republics | Some problems of biological effects under the combined action of nitrogen oxides, their metabolites and radiation |
| 1726 | United States of America | Occupational exposure to ionizing radiation in the United States—a comprehensive review for the year 1980 and a summary of trends for the years 1960-1985 |
| 1727 | United States of America | Environmental Measurements Laboratory: Worldwide deposition of strontium-90 through 1983 |
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| 1730 | Japan | Radioactivity Survey Data in Japan, Number 70, September 1984 |
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