

SOURCES AND EFFECTS OF IONIZING RADIATION

United Nations Scientific Committee on the Effects
of Atomic Radiation

UNSCEAR 1994 Report to the General Assembly,
with Scientific Annexes



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NOTE

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UNITED NATIONS SCIENTIFIC COMMITTEE
ON THE EFFECTS OF ATOMIC RADIATION

1994 REPORT

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

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INTRODUCTION

1. During the last few years the United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR)^a has undertaken a broad review of the sources and effects of ionizing radiation. Nine scientific annexes on particular subjects were issued in the UNSCEAR 1993 Report. Two further annexes have been completed, and these comprise the UNSCEAR 1994 Report. This is the twelfth substantive Report of the Committee, informing the General Assembly and the scientific and world community of its latest assessments^b. The two reports, 1993 and 1994, are complementary and provide a coherent summary of the Committee's findings and programme of work.

2. The present report and its scientific annexes were prepared between the thirty-eighth and forty-third sessions of the Committee. Serving as Chairman,

Vice-chairman and Rapporteur, respectively, at these sessions were: thirty-eighth and thirty-ninth sessions: K. Lokan (Australia), J. Maisin (Belgium) and E. Létourneau (Canada); fortieth and forty-first sessions: J. Maisin (Belgium), E. Létourneau (Canada) and L. Pinillos Ashton (Peru); forty-second and forty-third sessions: E. Létourneau (Canada), L. Pinillos Ashton (Peru) and G. Bengtsson (Sweden). The names of members of national delegations who attended the thirty-eighth to the forty-third sessions of the Committee are listed in Appendix I.

3. The scientific annexes of this report were developed at annual sessions of the Committee, based on working papers prepared by the secretariat. The Committee wishes to acknowledge the help and advice of a small group of consultants, appointed by the Secretary-General, who helped in the preparation of the material for this report. Their names are given in Appendix II. They were responsible for the preliminary reviews and evaluations of the technical information received by the Committee or available in the open scientific literature, on which rest the final deliberations of the Committee.

4. The sessions of the Committee held during the period under review were attended by representatives of the United Nations Environment Programme (UNEP), the World Health Organization (WHO), the International Atomic Energy Agency (IAEA), the International Commission on Radiological Protection (ICRP), the International Agency for Research on Cancer (IARC) and the International Commission on Radiation Units and Measurements (ICRU). The Committee wishes to acknowledge their contributions to the discussions.

5. In the present report, the Committee summarizes the main conclusions of the two scientific annexes, "Epidemiological studies of radiation carcinogenesis" and "Adaptive responses to radiation in cells and organisms". In addition, the Committee is reviewing the effects of radiation on the natural environment, and although the scientific annex has not yet been completed, a summary of this work in progress is given.

6. Following established practice, only the introductory part of the report is submitted to the General Assembly. The full UNSCEAR 1994 Report, including the scientific annexes, will be issued as a United Nations sales publication. This practice is intended to achieve a wider distribution of the findings for the benefit of the international scientific community. The Committee wishes to draw the attention of the General Assembly to the fact that the main text of the UNSCEAR 1994 Report is presented separately from its scientific annexes simply for the sake of convenience. It should be understood that the scientific data contained in the annexes are important because they form the basis for the conclusions of the report.

^a The United Nations Scientific Committee on the Effects of Atomic Radiation was established by the General Assembly at its tenth session, in 1955. Its terms of reference are set out in resolution 913 (X) of 3 December 1955. The Committee 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 was subsequently enlarged by the General Assembly in its resolution 3154 C (XXVIII) of 14 December 1973 to include the Federal Republic of Germany, Indonesia, Peru, Poland and the Sudan. By resolution 41/62 B of 3 December 1986, the General Assembly increased the membership of the Committee to a maximum of 21 members and invited China to become a member.

^b For the previous substantive reports of UNSCEAR to the General Assembly, see *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)*; *ibid.*, *Thirty-seventh Session, Supplement No. 45 (A/37/45)*; *ibid.*, *Forty-first Session, Supplement No. 16 (A/41/16)*; *ibid.*, *Forty-third Session, Supplement No. 45 (A/43/45)* and *ibid.*, *Forty-eighth Session, Supplement No. 46 (A/48/46)*. These documents are referred to as the 1958, 1962, 1964, 1966, 1969, 1972, 1977, 1982, 1986, 1988 and 1993 Reports, respectively. The 1972 Report with scientific annexes was published as *Ionizing Radiation: Levels and Effects, Volume I: Levels and Volume II: Effects* (United Nations publication, Sales No. E.72.IX.17 and 18). The 1977 Report with scientific annexes was published as *Sources and Effects of Ionizing Radiation* (United Nations publication, Sales No. E.77.IX.1). The 1982 Report with scientific annexes was published as *Ionizing Radiation: Sources and Biological Effects* (United Nations publication, Sales No. E.82.IX.8). The 1986 Report with scientific annexes was published as *Genetic and Somatic Effects of Ionizing Radiation* (United Nations publication, Sales No. E.86.IX.9). The 1988 Report with annexes was published as *Sources, Effects and Risks of Ionizing Radiation* (United Nations publication, Sales No. E.88.IX.7). The 1993 Report with scientific annexes was published as *Sources and Effects of Ionizing Radiation* (United Nations publication, Sales No. E.94.IX.2).

I. EPIDEMIOLOGICAL STUDIES OF RADIATION CARCINOGENESIS

7. The Committee has paid particular attention to the review of results of epidemiological studies of human populations exposed to ionizing radiation, since these form the main basis for quantifying the risks of radiation-induced cancer in man. Several study populations are available, including the survivors of the atomic bombings of Hiroshima and Nagasaki, patients exposed in medical procedures, those exposed occupationally and inhabitants of high natural background or contaminated areas, and these groups are the subject of continuing investigations.

8. Estimates of the risks of cancer caused by radiation exposure were derived in the UNSCEAR 1972, 1977 and 1988 Reports and discussed in the UNSCEAR 1993 Report. Although all information was considered, the primary estimates of risk were derived from results of the main study population, the survivors of the atomic bombings. An objective of the Committee's present review of this subject is to consider the large number of additional epidemiological studies now contributing quantitative information on the effects in humans of ionizing radiation and to evaluate comparative risk estimates.

9. Studies of disease in human populations must adhere strictly to epidemiological principles in order to achieve valid quantitative results. These include sound case ascertainment, an appropriate comparison group, sufficient follow-up, an accounting for confounding factors and well-characterized dosimetry. Such epidemiological studies are able to provide clear-cut evidence of risks for various sites of cancer, and also to evaluate the factors that modify risks, following high radiation doses. However, at low doses epidemiological studies are not able to detect and quantify statistically significant radiation effects.

A. EFFECTS OF EXTERNAL EXPOSURES

10. The Committee has examined the epidemiological studies that could be used to derive risk estimates from external, sparsely ionizing (low-LET) radiation exposures at high and low dose rates. The Committee has summarized the main features of these studies, including their strengths and limitations.

11. The primary study for the estimation of risk of cancer induction is the Life Span Study of survivors of the atomic bombings of Hiroshima and Nagasaki. The study, which began in 1950, comprises a large population of all ages and both sexes exposed to a range of doses at high dose rate. Data on cancer mortality and new data on cancer incidence are now available up to 1987. Since most of the original survivors are still living, many more years of follow-up will be necessary to determine the complete lifetime cancer occurrence in this population. Consequently, lifetime risk estimation requires projection beyond the period of observation.

12. Cancers for which statistically significant excess risks have been determined from the Life Span Study mortality data are leukaemia, breast, bladder, colon, liver, lung, oesophagus, ovary, multiple myeloma and stomach. The incidence data are broadly similar, but two of the sites, oesophagus and multiple myeloma, do not show significant risks. The incidence data are probably more definitive than the mortality data. Two additional sites, namely thyroid and skin, have significant excess incident cancers.

13. Studies of other radiation-exposed populations such as cervical cancer patients, ankylosing spondylitis and children treated for tinea capitis serve to clarify and generally support findings from the Life Span Study. Some also provide information on issues that cannot be addressed by the atomic bomb survivor data, such as the effects of low chronic doses, highly fractionated exposures and variability among populations. For some sites of cancer, including breast, leukaemia and thyroid, there are a number of very useful results from studies other than the Life Span Study. In general, there are no great disparities in risk estimates between the Life Span Study and the other studies.

14. Although the Committee has presented risk estimates for specific sites from results of many studies, general estimates of lifetime mortality risks for all cancers must still be derived from the Life Span Study. For this report the Committee has analysed the data from 1950 to 1987 and made projections to the full life-span of the population in several ways. Using the constant relative risk model allowing for sex and age at exposure (a more refined analysis than in the UNSCEAR 1988 Report), the estimates of lifetime risk of mortality following an exposure to 1 Sv (weighted dose) is 11% for solid tumours and 1% for leukaemia. Using alternative projection methods allowing for some decline in relative risk with time (as suggested by some epidemiological studies), lifetime risk estimates for solid tumours are 20%-40% lower. The constant relative risk estimates in the UNSCEAR 1988 Report were 10% for solid tumours and 1% for leukaemia at 1 Sv.

15. The Committee indicated in the UNSCEAR 1993 Report that risk estimates derived at high doses and high dose rates should be divided by a small factor to obtain the risk at low doses (<0.2 Sv). If a factor of 2 is used, the risk derived from the UNSCEAR 1988 Report would be 5% per Sv and from this report 6% per Sv for a constant relative risk projection. If alternative projection methods are used, however, the risk would be 4%-6% in the Japanese population (the applicability to other populations involves some additional uncertainty). Consequently, the use of a nominal value of 5% per Sv for mortality due to leukaemia and solid cancers from irradiation at low

doses for a population of all ages (4% per Sv for an adult working population) still seems valid to the Committee.

16. The effects of low-LET radiation delivered at low doses or low dose rates have been examined in studies of occupational, natural background and environmental exposures. Occupational studies offer the most promise of providing results that are statistically significant because they are based on large populations with a range of individual dose estimates and long periods of observation.

17. The most comprehensive occupational study to date involves nuclear workers in the United Kingdom. This study reports a significant excess risk for leukaemia and a positive, but non-significant excess for all cancers as a group. A smaller study carried out in the United States found non-significant deficits of cases among exposed workers. In a combined analysis of these two studies, the results of which were statistically non-significant, there was excess incidence of leukaemia and all cancers, which were about half the estimates for the atomic bomb survivors. Initial findings in studies of workers in the atomic energy programme of the former Soviet Union with exposures of the order of several sievert accumulated over several years show clear excesses of cancer in the highest dose groups broadly consistent with the levels of risk seen in the survivors of the atomic bombings.

18. Comparisons of cancer incidence in areas of high and low natural radiation background have been undertaken in China, France, Japan, Sweden, United Kingdom and United States. None, including the largest, that in China, has produced statistically significant associations.

19. Populations exposed to environmental releases of radionuclides have provided little information on risk. However, one circumstance of special interest concerns releases of fission products into the Techa River in the former Soviet Union during 1948-1951. In the 28,000 people studied there was some evidence of an excess of leukaemia not inconsistent with results derivable from the study of the survivors of the atomic bombings.

B. EFFECTS OF INTERNAL EXPOSURES

20. Of the radionuclides emitting low-LET radiation that may enter the body, iodine-131 is the most important, since it is used to diagnose thyroid conditions and to treat hyperthyroidism and thyroid carcinoma. Environmental exposures to iodine-131 from fallout and from accidents at nuclear installations have also occurred. Iodine-131 appears to be less effective than external radiation in causing thyroid cancer, perhaps by a factor of 3-5. More studies are needed to clarify the possibly greater risks in children than in adults, as indicated by external radiation exposure. The Committee is aware of reports of thyroid cancer incidence in locally exposed individuals following the Chernobyl accident and intends to examine this issue in a future report.

21. More densely ionizing (high-LET) radiation exposures result from alpha-particle-emitting radionuclides, such as radon and its decay products and radium and thorium used in medical and industrial applications. High-LET radiation is more effective in causing damage in tissue than low-LET radiation. Alpha-radiation is not very penetrating, however, so exposures occur only when the radionuclides in air, food or water are taken into the body. The Committee has examined the few epidemiological studies that can provide risk estimates.

22. Radon is an important source of exposure of the public in houses and other buildings. The risk of lung cancer caused from exposure to radon is derived from studies of miners of uranium and other minerals. There is no consistent evidence that radon causes cancer in tissues other than the lung. The excess incidence of lung cancer from radon is concentrated in the period 5-14 years after exposure and decreases with time. The risks for low and protracted exposures are likely to be more appropriate for applying to exposure levels experienced by the public. The numerous studies of residential radon exposure have so far contributed little to radon risk estimation, mainly because of their low statistical power. Important issues that must be addressed include the impact of confounding factors such as smoking and arsenic-containing dusts in mines.

23. Estimates of carcinogenic risk in bone and liver have been derived from exposures to alpha-emitting radionuclides: radium-224 in the case of bone and Thorotrast, a thorium-based x-ray contrast agent, in the case of liver.

24. Long-lived radium-226 and radium-228 at high levels have caused bone sarcomas and carcinomas of the paranasal sinuses in radium dial painters, and the risk extends over the long periods in which these radionuclides are lodged in bone. Precise risk estimates have not been derived. No excess cancers were identified in workers exposed to small amounts of plutonium or to uranium dusts. Workers exposed in Russia to a combination of external radiation and plutonium did have excess lung cancers at the higher exposure levels.

C. OTHER RELEVANT STUDIES

25. In the last decade there were many studies of the incidence of leukaemia near nuclear installations in the United Kingdom following the identification of several leukaemia clusters. One report suggested paternal exposure as a cause. However, in the light of more recent reports it is unlikely that any of these clusters or excesses are due either to environmental radiation or to paternal exposure. A possible explanation is that the excesses are due to the spread of infection that occurs when populations from urban and rural areas mix. No such pattern of clusters was found in subsequent studies around nuclear installations in Canada, France, Germany and the United States.

26. Initial excesses in leukaemia were observed following a single nuclear test explosion in the United States and, following that, explosions carried out by the United Kingdom, but the observation seems to be due in the first case to chance and in the second case to an unusually low incidence in controls for the British participants in the tests and to unusual latencies in the cohort of New Zealand participants. No clear effect is evident.

II. ADAPTIVE RESPONSES TO RADIATION IN CELLS AND ORGANISMS

28. The scientific community has been aware for many years of the possibility that low doses of radiation may result in changes in cells and organisms, which reflects an ability to adapt to the effects of radiation.

29. It has been suggested in recent years that conventional estimates of the risks of stochastic effects of low doses of ionizing radiation may have been overstated because no allowance was made for the process referred to as adaptation. This is the name given to the possibility that a small prior dose of radiation may condition cells in such a way as to stimulate cellular repair processes and thus reduce either the natural incidence of malignant conditions or the likelihood of excess malignancy being produced by radiation.

30. There is substantial evidence that the number of radiation-induced chromosomal aberrations and mutations can be reduced by a small prior conditioning dose in proliferating mammalian cells *in vitro* and *in vivo*. It seems likely that this effect is linked to an increased capacity for DNA repair. While it has been observed under specified and clearly defined conditions, it has not been seen with all cell systems.

31. There is increasing evidence that cellular repair mechanisms are stimulated after radiation-induced damage. It has to be resolved whether these are related to increased DNA repair. Whatever the mechanisms, they seem able to act not only on the lesions induced by ionizing radiation but also on at least a portion of the lesions induced by

27. People with certain recessive hereditary diseases, such as ataxia-telangiectasia and retinoblastoma, are known to be sensitive to radiation exposure and are more likely to develop second cancers if treated with radiation. There are indications that those who do not have the disease but are genetic carriers may also be more sensitive than normal individuals to cancer induction, possibly by radiation exposure, but studies so far are not definitive.

some other toxic agents. There appears to be similar overlap in regard to the type of DNA damage that induces adaptive response.

32. It remains doubtful whether the immune system plays any role in these processes. In the UNSCEAR 1993 Report, Annex E, "Mechanisms of radiation oncogenesis", the Committee concluded that the immune system may not have a significant influence on radiation carcinogenesis after low doses. In this Report, Annex B, "Adaptive responses to radiation in cells and organisms", that conclusion is not altered, although some transient effects on the immune system have been identified.

33. Extensive data from animal experiments and limited human data provide no evidence to support the view that the adaptive response in cells decreases the incidence of late effects such as cancer induction in humans after low doses. However, further experimental studies should be conducted.

34. As to the biological plausibility of a radiation-induced adaptive response, it is recognized that the effectiveness of DNA repair in mammalian cells is not absolute. The mechanisms of adaptation are likely to coexist with the mechanisms induced by low doses that may result in malignant transformations. An important question, therefore, is to judge the balance between stimulated cellular repair and residual damage. The Committee hopes that more data will become available and stresses that at this stage it would be premature to draw conclusions for radiological protection purposes.

III. EFFECTS OF RADIATION ON THE NATURAL ENVIRONMENT

35. All living organisms are exposed to radiation from natural sources (cosmic rays and the natural radionuclides present in all components of the terrestrial and aquatic environments) and from local, regional and global contamination arising from human activities.

36. The Committee has not previously attempted to review the effects of radiation on plants and animals in the

environment. There is, however, a substantial body of information that can form the basis for such a review. The accumulation of radionuclides in plants and animals in the environment has been considered, particularly from the viewpoint of their transfer through food chains leading to man but also in terms of basic physiology. These data may be developed to provide estimates of the possible concomitant radiation exposure.

37. Previous reports of the Committee have presented summaries of the extensive laboratory studies of the effects of radiation on a variety of animals. In addition, data on radiation effects have been obtained from use of large, sealed sources of gamma rays in the environment and from investigations of the effects, actual or potential, in contaminated areas. Together, these data may be used to assess the relative radiosensitivities of a wide range of organisms and the

effects of radiation exposure on those individual attributes (mortality, fertility, fecundity etc.) that are essential for the maintenance of healthy natural populations.

38. The Committee is in the process of reviewing these data and intends to provide a scientific assessment of the impact of increased radiation exposure on the natural environment in a future report.

*Appendix I*MEMBERS OF NATIONAL DELEGATIONS
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^a At the thirty-eighth and thirty-ninth sessions: Federal Republic of Germany.

^b At the thirty-eighth, thirty-ninth and fortieth sessions: Union of Soviet Socialist Republics.

^c At the thirty-eighth, thirty-ninth, fortieth and forty-first sessions: Czechoslovakia.

*Appendix II*SCIENTIFIC STAFF AND CONSULTANTS COOPERATING
WITH THE COMMITTEE IN THE PREPARATION OF THIS REPORT

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Scientific Annexes

ANNEX A

Epidemiological studies of radiation carcinogenesis

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INTRODUCTION

1. The results of epidemiological investigations form the main basis for quantifying the risks of cancer induction in man following exposure to ionizing radiation. Many such studies have been completed and published and many others are in progress to evaluate the effects of irradiation in groups of individuals exposed inadvertently as a result of conditions in the workplace, at home or in the environment or because of atomic detonations or intentionally for purposes of diagnosing or treating diseases.

2. In the UNSCEAR 1988 Report [U2] the results of epidemiological studies were examined to derive estimates of the risk of cancer induction from exposures to ionizing radiation. The estimates were based primarily on the extended follow-up with revised dosimetry of the life span study of survivors of the atomic bombings of Hiroshima and Nagasaki. The risk estimates for cancer referred specifically to the Japanese population exposed to absorbed doses of the order of 1 Gy of uniform whole-body low-

LET radiation at high dose rate. The results of other studies were used primarily to support the principal results derived from the life span study.

3. In this Annex further review of epidemiological studies of radiation carcinogenesis is provided. One objective is to review the risk estimates in the UNSCEAR 1988 Report and assess their validity in the light of new information on all epidemiological sources. Further studies of the survivors of the atomic bombings in Japan provide new information on cancer incidence, mortality, dose-response relationships, the effects of exposure in childhood and the appropriateness of various models of radiation risk for use in risk projection. A large number of additional epidemiological studies are contributing quantitative or otherwise useful information on the effects of both high- and low-LET ionizing radiation in human populations. They include studies of patients exposed to radiation for diagnostic or therapeutic purposes, studies of workers

occupationally exposed in the nuclear industry, studies of populations exposed to terrestrial gamma rays at varying levels and to other environmental exposures, studies of individuals exposed to radon in homes and other buildings, and studies of the effects of local and global fallout from atmospheric tests of nuclear weapons.

4. Although it has been well established that radiation exposure after high doses causes an increased risk of cancer in many organs, there remain many important questions about the effects of high-dose and high-dose-rate exposure compared to the effects of low-dose chronic exposures; variation in risk with age at exposure, individual sensitivity and ethnicity, including transferral of risk from one population to another; changes in dose response with time since exposure; and the joint effects of radiation and other agents. As epidemiological data accumulate, it is possible to carry out more detailed investigations of these issues. Recent findings are reviewed in this Annex.

5. The data available from epidemiological studies allow estimates of radiation risk to be calculated. While it would be desirable to make joint analyses of all these data, differences in quality and lack of sufficient information in many of the studies present great difficulties. The Committee has, however, attempted to make a comparative study of risk estimates for specific types of cancer that can be separately derived from the various studies. The types or sites of cancer considered here include those for which data are available from one or more studies involving reasonably large populations with quantitative individual or population average dose estimates. These risk estimates should be interpreted cautiously because of differences between the various study populations, but they nevertheless provide a rough guide to the degree of consistency among the various studies. As an aid in the interpretation of the risk estimates derived here, descriptions are provided of the nature of the various populations considered and of the strengths and limitations of these studies.

I. METHODOLOGICAL CONSIDERATIONS

A. THE ROLE AND LIMITATIONS OF EPIDEMIOLOGY

6. Among the biological effects of concern when human beings are exposed to low doses of ionizing radiation, the most important long-term effect is the possible induction of cancer. Much can be learned about the nature of the cancer-induction process from laboratory experiments in cellular systems and animals. Even some insights into the mechanism of induction may be obtained in this way. Nevertheless, until now the most potent method of studying radiation-induced cancer is the epidemiological study of exposed human populations. Only epidemiology is able to describe the types of cancer induced in humans, their frequency as a function of dose and time after exposure and the many factors, such as age and sex, that modify their expression. Furthermore, only epidemiology is able to quantify these responses and, as a result, derive estimates of the risks of cancer induction as a function of dose. As successful as epidemiology has been in contributing to a broad understanding of radiation-induced tumours in humans and the quantitative risks of the process, it has some inherent limitations. When the dose is high, epidemiological studies have identified clear-cut responses, and risk estimates for many types of cancer have been derived and their dependencies on other factors explored. However, when the dose is low and the effect to be detected is very small compared with the natural occurrence of cancer in the irradiated population, quantification of the risks is very difficult and perhaps impossible. Additional strengths and weaknesses of epidemiology will be discussed further below.

7. Epidemiological studies can provide valuable information about the applicability to humans of dose response and other information suggested by data obtained in experimental systems. Although epidemiology is not intrinsically expected to contribute much to the overall knowledge of radiobiological mechanisms, the many parameters that epidemiology has established as modifying and influencing cancer induction must nevertheless be taken into account in any theory of the mechanisms of action of radiation-induced cancer. Radiation epidemiology has already contributed to general theories of carcinogenesis, as, for example, in breast cancer, where epidemiological studies have shown that at young ages the female breast is especially vulnerable to environmental insult.

8. Some information on the carcinogenic effects of radiation exposure is provided by clinical trials, but most epidemiological studies of radiation effects are inherently observational in nature. That is, they are arranged by circumstance rather than as a result of experimental design. This means that the conditions of exposure, the study population and the allocation of individuals to the various exposure levels are outside the control of the research worker. In fact, the exposures are often determined for reasons quite unconnected with the objectives of a particular epidemiological study. In the case of exposure to ionizing radiation, exposures occur, for example, as a result of the geographic location of an individual at a particular time (in studies of the survivors of the atomic bombings in Japan); the place of residence and type of dwelling (in studies of the effects of domestic exposure to radon and of exposure to terrestrial gamma-radiation);

occupation (in studies of radium dial painters, uranium miners, tin miners and workers in the nuclear industry); medical treatment of disease (in studies of patients with ankylosing spondylitis or cervical cancer); or simply prevalent medical fashion (in studies of children who received radiotherapy for a supposedly enlarged thymus and children whose mothers were given x-ray examinations during pregnancy).

9. The characteristics of epidemiological studies have the following consequences:

- (a) the effects of interest cannot always be studied directly or with the desired precision;
- (b) randomization procedures can rarely be used to ensure the absence of undesirable systematic differences between those exposed at different levels;
- (c) studies cannot usually be repeated at the command of the investigator.

The observations that can be made are limited to the effects of exposures that have actually occurred. For example, while the effect of radon exposure on lung cancer incidence in the general population is of great interest, current risk estimates are determined only in studies of miners with occupational exposures to radon and its decay products. These populations consist of males who were between the ages of 18 and 65 at the time of exposure, and the conditions under which the exposures were received differ markedly from those in which general population exposures are received. In addition, there are often systematic differences between those exposed at different levels and the general population; appropriate comparison populations are therefore important. For example, in the thyrotoxicosis study carried out in the United States [S2], an excess of leukaemia was observed when rates for patients treated with ^{131}I were compared to rates for the general population. However, a non-exposed group of thyrotoxicosis patients was found to have leukaemia risks comparable to the patients treated with ^{131}I .

10. Because investigators lack control over many important aspects of epidemiological studies, observed associations between exposure and subsequent disease can be distorted by the presence of factors associated with the exposure and with the disease in the individuals studied. Thus, an important aspect of the design and analysis of any epidemiological study is to identify and eliminate such distortions. Factors such as age, sex and ethnicity are important, easily measured determinants of disease that should be taken into account in virtually every study worthy of serious consideration. Other factors, such as cigarette smoking, socio-economic status and employment history, are quantifiable in principle if accurate records are available or if interviews can be carried out with each study participant. When such information is obtained after the exposure or disease diagnosis, special care must be taken to ensure that the ascertainment is of equal quality for exposed and unexposed individuals or for cases and controls.

11. A common study design in radiation epidemiology is the cohort study. In a cohort study, a fixed, well-defined group of individuals not known to be suffering from the disease, or diseases, of interest is enrolled and followed forward in time. Information is collected on deaths from, and if possible, incidences of the diseases of interest in the enrolled population. Because the diseases of interest are often rare and the effects of exposure relatively small and because there is a need to determine how risks vary with sex, age at exposure, time or other factors, epidemiological cohort studies of radiation effects need to include thousands or even tens of thousands of individuals in the study group, and follow-up must continue for years or decades. Although prospective follow-up data are available in many cases, most cohort studies were begun with a retrospective review of historical data such as employment or medical treatment records. The size of a cohort study and, for a retrospective cohort study, its timing usually preclude personal contact between the investigators and individual cohort members. Thus, individual data on other than a few basic items are rarely available. An important element in the design of cohort studies is to ensure that the relationship between disease rates and the exposure is not distorted by unmeasured factors.

12. It is not possible at present to determine if a specific cancer was caused by radiation, although there are encouraging indications that advances in molecular biology will allow such a determination [T16, U1]. Therefore, the extent of radiation-induced cancer in a cohort must be inferred by comparing similar groups with different levels of exposure. In cohort studies this may involve the comparison of exposed and unexposed groups or, ideally, groups receiving a range of exposures. In many studies of radiation effects it is not possible to include an unexposed control group; therefore, inferences are based on comparison of the observed number of cases to an expected number derived from national or regional rates. While these rates are usually readily available for mortality, they are much less often available for cancer incidence. Thus, an internal comparison group is especially important for studies of radiation-induced cancer incidence, as illustrated by the thyrotoxicosis study mentioned above. When national or regional rates must be used, it is desirable to investigate, if possible, the validity of the comparison. This was done in the British ankylosing spondylitis study by identifying and following up roughly 1,000 individuals with the disease who were not treated with radiation [S21]. When internal controls are available, national rates may still be useful as a check on the validity of the control group and on the stability of inferences about dose effects. This has been done in some analyses of data on survivors of the atomic bombings in Japan [P13, P23].

13. When it is not possible or practicable to conduct a cohort study, case-control studies can provide valuable information on radiation effects. The strength of a case-control study lies in its ability to make effective use of

data on relatively small numbers of cases and controls. In this type of study, information is collected both on individuals who have already developed the disease and on disease-free controls. Controls are usually individually matched to the cases with regard to age, sex and other relevant factors. Case-control studies are often constructed from within previously defined cohorts in order to allow the use of more detailed data than could be obtained for the full cohort. In a case-control study, inference is based on a comparison of the level of various factors, e.g. radiation dose, in the cases and controls. The validity of a case-control study depends on the extent to which the controls are truly representative of the population from which the cases were drawn. This is not always easy to achieve. Case-control studies are appropriate for gaining insights into several areas in radiation epidemiology. Examples include the assessment of the effect of radon exposure in the home on lung cancer risk among people with different smoking habits [B37, P30, S5] and of the interactions of radiation and other risk factors for breast cancer in the survivors of the atomic bombings in Japan [L16] and cervical cancer patients [B20, B21].

14. An important consequence of the observational nature of epidemiology is that considerable caution must be exercised before assuming that the relationship between a disease and some environmental or occupational exposure is a causal one. Once the requirements for high quality data and appropriate analysis have been satisfied, criteria for evaluating causality include the following: the strength of the association between the disease end-point and the presumed causative factor; the consistency of data from a variety of studies; the existence of a dose-response gradient; and experimental evidence that similar effects can be produced in the laboratory. In the context of radiation, a good example is given by lung cancer and occupational exposure to radon [C6]. In the late nineteenth and early twentieth centuries, radon concentrations in the mines of central Europe were high, and it was eventually established that approximately 50% of the miners died from lung cancer [M14]. Elevated risks of lung cancer were later seen in a variety of other mining populations exposed to high concentrations of radon, including miners of iron ore in Sweden and Britain, fluorspar miners in Canada and uranium miners in Canada and the United States. A very recent analysis of 11 underground miner studies indicates that of almost 2,700 lung cancers found among 68,000 miners, fully 40% are attributable to radon exposure during the miners' working lives [L21]. Also, some of the more detailed studies have demonstrated a strong dose-response relationship, and similar results in laboratory studies on rats and dogs have been available since the 1970s. Doubts about the causality of the relation are reduced by the observation that miners in other types of mines, such as coal or nickel miners, which would have been equally dusty but where levels of radon are not increased, have been shown to have little or no increase in the risk of lung cancer or possibly even a decrease [A4,

G12, M14, M16]. Despite these findings, the role of dusty conditions in the mines and especially the presence of arsenic are not yet fully understood [C21, L17].

15. Radiation exposures of the general population usually involve low doses delivered gradually over time. For example, in the UNSCEAR 1993 Report [U1], it was estimated that the average annual effective dose to adults from all natural sources of radiation is about 2 mSv and that the proportion of people receiving an annual effective dose in excess of 10 mSv is very low. Interest in assessing the effects of radiation for the purposes of radiological protection therefore centres on the effects of exposures to a few millisievert per year. The vast sample sizes that would be required for direct study of the effects of such exposures were discussed by Land [L7] and by Goss [G24]. That it is difficult for epidemiological studies to provide definitive results in such circumstances becomes evident.

16. The ability of radiation to act as a carcinogen in most organs and tissues of the body has been well established by studies at much higher doses (for example, of about 1 Sv or more, often delivered at a high dose rate) and in which the exposure has increased cancer morbidity rates by 40%-50% or more, i.e. studies in which the relative risk is about 1.5. As the results of numerous studies discussed in this Annex illustrate, epidemiological studies can detect and quantify effects of this magnitude and provide useful information on the factors that affect them, including sex and age at exposure. However, if a study is to address lower dose exposures (0.1 Sv or less), and if it is assumed that the response is linear in dose, the increase in cancer risks would be only 5% or less, i.e. the relative risk would be 1.05 or less. To have a reasonable probability of detecting a risk (i.e. statistical power) of this magnitude, an epidemiological study would require thousands or even hundreds of thousands of cases of the disease of interest among exposed subjects. Even if it were feasible to assemble cohorts (or case series) large enough to detect such low-dose effects, it would be difficult to interpret any findings because other undetected small differences between the control and exposed populations would easily mask existing effects or induce spurious effects of this size. In view of the lack of power of most studies to detect low-dose effects, it should be recognized that the failure of a particular study to demonstrate an effect (positive or negative) at low doses is not necessarily an indication that such effects do not exist. Furthermore, the fact that epidemiological studies lack the power to detect the small effects that might be seen at low doses does not mean that they provide no information on low-dose effects. Such studies can often provide upper limits for the magnitude of the risk. Also, it is important to note that epidemiological studies have been quite successful in detecting the effects of radiation exposure in sensitive subgroups of the population, e.g. prenatal exposure to x rays with exposures of about 0.01 Gy and childhood thyroid cancer at doses of roughly 0.1 Gy.

17. The term "statistical power" is relevant to the issue of significant results from radiation studies, especially low-dose studies. Statistical power depends on the sample size, the length of follow-up, the method of analysis and the average dose to which the group is exposed. The follow-up must extend for a substantial period beyond the latency period, which is the time between the exposure and the occurrence of disease. When doses are low (<0.2 Sv), the sample size must be very large in order to detect a small effect, as noted above [G24, L7].

18. It would seem that, for the foreseeable future, the important questions in epidemiology — the effect of fractionated low-dose exposures, the temporal pattern of the effect in a population, the relative magnitude of the effect among those exposed at different ages and the joint effect of radiation and other agents — must continue to be evaluated from studies on effects at high doses, with supporting laboratory experiments to guide the extrapolation from high to low doses. Nevertheless, it is essential that human populations exposed at lower doses be monitored to ensure that extrapolation from the results of studies on effects at high doses has not given risk estimates that are inappropriate. The most suitable groups for study in this way are those in which some individuals have exposures higher than those received by most members of the public from natural radiation or common diagnostic medical procedures. Examples of such groups include radiation workers and people living in areas with high indoor radon concentrations. Studies of the geographical variation in mortality with exposure to sources such as terrestrial gamma-radiation and radon are in principle also important. However, in practice it is difficult to interpret such studies owing to problems in obtaining adequate exposure data and in allowing for socio-economic and other factors that may influence disease rates to a greater extent than the variation in radiation exposures.

19. The interpretation of results from studies of populations exposed to low levels of radiation presents many problems. Inevitably, the studies will tend to be negative in the sense that major potential effects, such as the association between exposure and leukaemia rates may not reach statistical significance. However, they may still be of great value in so far as they provide upper bounds to the risk in situations of practical interest. Also, if several similar studies can be carried out, as is at present happening with studies of radiation workers and residential radon exposures, it may be possible to combine results, making it easier to quantify an effect.

20. There is still another consequence of studying populations exposed to low levels of radiation: if a large number of significance tests are carried out, some findings will reach nominal statistical significance purely by chance. To minimize the difficulties of interpretation in such situations, it is important to clearly specify which of the many hypotheses tested were of special interest a

priori and which were singled out after the event. For example, in 1982 Smith and Doll [S13] reported a large, statistically significant standardized mortality ratio (SMR) for tumours of the central nervous system other than those of the brain among British patients who received radiotherapy for ankylosing spondylitis. With additional follow-up, however, the magnitude of this risk estimate decreased markedly, and the statistical significance of the effect disappeared [D5]. Similarly, earlier analyses reported statistically significant increased risks of multiple myeloma in survivors of the atomic bombings [S7] and in workers at the Hanford plant [G20]. However, in the life span study incidence data [P33] in which roughly 50% more cases are reviewed, evidence for increased myeloma risks in the cohort is weak and, in any case, the risk is likely to be much smaller than suggested in the earlier reports. A recent report on the Hanford workers [G16] reports lower risks that are no longer statistically significant.

21. The above discussion is formulated largely in terms of mortality and thus ignores the fact that some radiation-induced cancers are not fatal. The difference between incidence and mortality is sometimes small, as, for example, in cancers at sites such as the stomach, liver or pancreas or in adult leukaemia, which have low (<20%) relative survival rates. (The relative survival rate is the ratio of the probability of surviving for a fixed period, usually five years, after diagnosis to the survival probability in the general population [J6].) However, mortality data cannot be expected to provide complete or reliable risk estimates for sites with high relative survival rates, since such cancers are unlikely to be listed as the cause of death. Examples of cancers that have relative survival rates greater than 50% include thyroid, melanoma and non-melanoma skin cancers, female breast, uterine corpus, prostate and urinary bladder [M29]. The issue of incidence versus mortality is further complicated by the fact that survival rates vary widely from country to country (see Table 1) and by the fact that they vary with time within single countries for many reasons, including improvements in medical therapy (see, for example, [H30]).

22. Since many countries do not have general population cancer registries and radiation-exposed populations are not usually included in existing cancer registries, it is difficult to carry out incidence studies of radiation effects. However, despite the difficulties a number of important incidence studies are now available. These include the registry-based cervical cancer cohort and case-control studies [B12, B21], survey-based studies of breast cancer among women exposed to radiation for the treatment or diagnosis of various medical conditions [B1, B18, B31, M19, S9], analyses of breast cancer and, most recently, a series of general analyses of cancer-registry-based incidence data on the survivors of the atomic bombings in Japan [P33, T15]. As has been noted by Hoel and Dinse [H29], it is possible to construct models for cancer incidence at some sites by combining data on mortality

following radiation exposure with case-fatality data. However, these methods appear to be of limited utility as they require data on the time from diagnosis to death.

23. Doll and Peto [D19] discussed other issues related to the strengths and weaknesses of epidemiological studies. By the nature of epidemiological studies, the contribution of any single study, however excellent, is much more limited than that of an experimental study. Firm conclusions can be drawn only when a number of studies carried out in different circumstances provide similar results. Accordingly, it is especially important in this field to carry out critical reviews of all the relevant studies from time to time, and to attempt to integrate the available information into a meaningful composite.

B. QUALITY OF DATA

24. Careful attention to data quality is important in the conduct, interpretation and comparison of epidemiological studies. There are many factors that can affect the quality of the data in studies of populations exposed to radiation. These include incomplete follow-up or exposure-related differences in the completeness of follow-up; recall bias in the ascertainment of exposure information; and comparability of the exposed and control groups. In addition, when moving beyond simple ascertainment of the existence of an effect to more precise quantitative descriptions of the effect, there must be a good understanding of the nature and quality of the dosimetric data. In comparing the results of different studies or in applying risks from one population to another, in addition to all these factors that might affect the data quality, it is necessary to consider carefully other factors, such as the comparability of the populations under consideration with respect to age, sex, ethnicity, smoking, diet and possible specific demographic factors.

25. In cohort studies it is essential either to ensure that the follow-up is virtually complete and that all relevant occurrences of disease in the enrolled population have been identified or to understand the nature of incomplete follow-up and adjust for it. It is particularly important to obtain and make use of information on migration or loss to follow-up. Obtaining complete follow-up is generally much easier for mortality data than for incidence data. For example, in Japan the compulsory system of family registration (*koseki*) makes it possible to obtain death certificates for virtually all deceased members of the atomic bomb survivor cohort, while cancer incidence data are generally available only for survivors who reside in the areas covered by the Hiroshima and Nagasaki tumour registries at the time of diagnosis. In mortality analyses, *koseki* information on emigration from Japan is available and is used to identify people who are lost to follow-up. As will be described later, special measures were taken to allow for the effects of migration in analyses of the data on cancer incidence in the survivors of the atomic bomb-

ings. In some places (e.g. the Nordic countries), long-standing national cancer incidence registries exist, and cancer ascertainment is facilitated by record linkage procedures based on personal identification numbers.

26. Even when good sources of follow-up data are available, one must be concerned about the quality of the data and their interpretation. For example, the general underreporting of cancer on death certificates, which may be age-dependent, means that although reasonable estimates can be made of relative risks, absolute risks are underestimated from death certificate diagnoses. In site-specific analyses, especially those based on death certificates, the misclassification of cancer types on the death certificate (mainly underreporting of cancer) can also affect risk estimates. Sposto et al. [S66] investigated the impact of cancer/non-cancer misclassification and found that after allowing for cancer recorded as non-cancer and *vice versa*, cancer risk estimates from the life span study should be increased by more than 10% relative to estimates that ignore the effect of these recording errors.

27. Another concern in the conduct of epidemiological studies involves the comparability of the exposed and control groups. This is particularly important when an exposed population rate is compared to general population rates, in which case the availability of valid appropriate population rates is critical. The so-called "healthy worker" effect [H44], in which workers tend to have lower mortality rates for cancer and for other diseases than the general population especially in the first few years after selection for employment, is one illustration of this problem. The healthy worker effect is only one aspect of the general problem of comparability of rates in any selected cohort to rates for a general population. Cause-specific death or incidence rates can also exhibit great variability within the general population for reasons other than employment status. Thus, when making comparisons to general population rates it is important, whenever possible, to emphasize relative risks and trend tests rather than to focus simply on standardized mortality ratios. Even if an unexposed internal comparison group is available, there must be concern for the appropriateness of the comparisons being made and any unusual features of the control population.

28. It is also essential to avoid bias due to differing probabilities of disease or to differing exposure detection between exposed and unexposed individuals. Detection bias can be a serious problem for some outcomes (if, for example, surveillance is increased as a result of concern about radiation exposures). As a result, many occult cases that would otherwise go undetected may be diagnosed, as happens, for example, in the detection of thyroid cancer with enhanced screening procedures.

29. Another concern involves biases resulting from exposures that may have taken place because of symptoms

of a subsequent disease or from differential recall of exposure for cases and controls. As an example of the former, the elevated risk of neoplasms other than leukaemia or colon cancer seen in the first five years after treatment in the British ankylosing spondylitis study is discounted by the authors because "some of the tumours presenting soon after treatment may have caused the symptoms that were incorrectly ascribed to spondylitis" [D6]. The possibility of recall bias was raised in criticisms of the initial studies of prenatal radiation: it was felt that parents of cases might have been more likely to report prenatal x-ray examinations than parents of controls.

30. The important issue of adequate statistical power was discussed in the preceding Section. Indeed, it is well known that epidemiological studies are problematic when the effects being studied are much less than half the normal baseline risk. Thus, increasing power by increasing the sample size is unlikely to provide reliable estimates of risk at low doses and low effect levels, because of the possible presence of competing or confounding risk factors that might safely be ignored at high doses and effect levels. There may well be unknown factors that increase or decrease risk by a few percentage points, i.e. near the level of effect in a low-dose study. Such factors will not have come to attention earlier because they seldom if ever are present at levels high enough to be apparent in an exploratory study of modest size, and they might be confounded with exposure to low doses of radiation. The problem can be addressed by increasing the amount of information on each study subject, but that solution can be very expensive for a large study, and it would be guided by very little prior information.

31. A related question concerns the influence of chance in statistical observations in studies in which multiple comparisons are made. If, for example, tests of significance are conducted at the 5% level for a series of comparisons between control and exposed groups, 5% (1 in 20) of the tests will result in an apparent difference due to chance alone. Thus, in a study involving many such comparisons (e.g. in a low-dose environmental study with many different cancer end-points evaluated) erroneous positive or negative results are likely to occur with a frequency that depends on the level of significance in the test.

32. The Committee notes that reliance on studies that have demonstrated statistically significant effects can be misleading. First, journals are more likely to publish (and authors more likely to report) studies that have some statistically significant result. Secondly, point estimates of risks for statistically significant effects are, especially for small studies, biased upward and can be misleading if not put in the context of other results. In addition, since epidemiological studies of radiation effects cannot usually be designed to ensure adequate power to detect effects, the ranges of risk estimates from positive and negative studies can provide useful information on risk.

33. In epidemiological studies of radiation effects, suitable measurements of individual doses made at the time of exposure are usually unavailable. In such cases estimates are developed by reconstructing the radiation fields based on theoretical constructs or computational models of the original exposures (e.g. the life span study) or by carrying out post hoc measurements for representative exposures believed to be comparable to those that occurred originally (e.g. the tinca capitis study in Israel). Dose estimates may be assigned to groups of subjects believed to have been exposed under comparable conditions or, as was done for the ankylosing spondylitis study in the United Kingdom, individual dose estimates computed for a sample of subjects may have been used to estimate population-average doses to selected organs. These estimates were more accurate for some organs than for others. More precise estimates of organ dose were possible in the cervical cancer study [B21] and in the study of benign gynaecological disease [I8]. Average organ doses must be used with caution when the nature of the exposure varies widely between subjects. Even when individual monitoring measurements are available, as for example in many studies of nuclear workers, there are often questions about adequacy and completeness, since the data were collected for purposes other than the study of radiation effects and may not exactly suit the needs of an epidemiological study. Furthermore, the derivation of organ doses from personal monitoring measurements is subject to some uncertainties owing to the nature of the exposure and the orientation of the individual in the radiation field.

34. In epidemiological studies whose sole aim is the simple identification of an effect, such as cancer, with a causative agent, such as radiation, it can be sufficient to distinguish between exposed and unexposed individuals, i.e. a precise knowledge of individual exposure levels is not critical. However, in more quantitative studies, in which the goal is to provide an estimate of the dose-response function, the quality of the dosimetric data is as important as the quantity and quality of the data on the outcome of interest.

35. The impact of errors in dosimetry has been examined most extensively for the data of the life span study of survivors of the atomic bombings. Jablon [J1], who first considered this problem, concluded that uncertainties in the data on location and shielding for individual survivors would lead to errors of 35%-40% in individual dose estimates (T65D dosimetry system). Using data on discrete symptoms such as epilation and bleeding, Gilbert and Ohara [G10] found evidence of either systematic differences or differing amounts of random error in the methods used to construct the T65D dose estimates. Gilbert's results supported average errors in individual dose estimates comparable to those noted by Jablon. Following revision of the dosimetry (to DS86) for the survivors of the atomic bombings in Japan [R22], several

studies have examined the nature of random errors in individual dose estimates. Pierce et al. [P9, P31] developed methods to adjust risk estimates for the biases resulting from random errors in individual dose estimates. They concluded that random errors of 30%-40% can lead to risk estimates for solid cancers that are 7%-11% lower and risk estimates for leukaemia that are 4%-7% lower than they would be if "true" doses could be used in risk estimation. Thus, to correct for this effect, risk estimates would need to be increased by those amounts. Stram et al. [S22] found that for the same estimated doses epilation rates differed very significantly by shielding category. Sposto et al. [S55] compared chromosome aberration dose-response curves for epilators and non-epilators and concluded that 40%-50% random errors in individual DS86 dose estimates would be needed to explain the observed steeper slope seen for survivors who reported severe epilation.

36. The studies just noted have focused on random errors in individual dose estimates and the impact of such errors on risk estimates. They do not deal with possible systematic errors in the DS86 dosimetry, such as those described by Straume et al. [S56], which are discussed later (paragraphs 156-158). The attention is given to the impact of dose errors in the data on survivors of the atomic bombings does not imply that the dose estimates are worse than those in other studies of radiation effects; rather, it reflects the availability of a large amount of data on individual survivors and the concern of those involved in the Japanese studies to provide a thorough summary of the strengths and limitations of the data.

37. The quality of the dosimetry has also been examined for some other studies of radiation-exposed populations. For example, in a study of the estimated radiation doses to 12 bone marrow sites and various other organs of ankylosing spondylitis patients treated in the United Kingdom with x rays, Lewis et al. [L6] compared the mean marrow doses obtained from the Monte Carlo calculations with those obtained from experiments on a physical phantom. Although the results obtained using the two methods were very highly correlated, the Monte Carlo estimates were, on average, 19% higher. The most likely explanations for the difference are the different distributions of energies in the primary photon beam and the different compositions of bone marrow used in the two studies. The results of Lewis et al. suggest that the coefficient of variation, i.e. the standard deviation divided by the mean, for individual dose estimates ranges from 10% for organs close to the beam to about 50% for less directly exposed organs. More recently, Stovall et al. [S18] described efforts to reconstruct doses for medical exposures. Dose estimates developed by Stovall et al. are used in a number of epidemiological studies.

38. Better descriptions of the uncertainties in individual dose estimates are needed in most studies of radiation effects. The fact that such issues are not addressed in the

presentation of results of a specific study should not be taken as an indication that the dose estimates are particularly accurate or that uncertainties in individual dose estimates would have a negligible impact on the reported risk estimates.

C. METHODS OF DATA ANALYSIS

39. The analysis of epidemiological studies should involve life-table methods to fit regression models that take into account sex- and age-specific death or incidence rates and any other factors influencing disease incidence that may be correlated with exposure and for which data are available. Statistical methods were summarized by Breslow and Day [B28, B29], and modelling issues in the context of epidemiological studies of radiation effects were discussed by Preston [P32] and Vaeth [V12].

40. For the most part, the questions of interest in the analysis of studies of the effects of radiation in persons known to have been exposed to appreciable doses have gone beyond answering the basic question of whether there is an association between exposure and disease. Interest now centres on issues of a more complex nature, such as the magnitude and duration of any effects, and the variation in risk among those exposed at different ages. For many studies data are now available to address these questions, at least in part. However, correct inferences can be made only if they are based on models that accurately reflect the variation in disease rates indicated by the data. If inappropriate or oversimplified models are used, highly misleading inferences can be made. For example, when the annual change in the excess relative risk of non-leukaemia cancer mortality among survivors of the atomic bombings in Japan after 1960 was calculated ignoring the effect of age at exposure, the excess relative risk was found to be increasing at 3.5% per year. However, when it was calculated adjusting for the effect of age at exposure, the excess relative risk was found to be decreasing slightly [S7].

41. In presenting the results of specific studies, investigators usually focus on relatively simple descriptive statistics or models of the experience of the study population. The results may average over or adjust for differences in the study population, such as age and sex, and may include extrapolation and projection to extend risk estimates to lifetime experience. To make results understandable and to allow comparisons to be made with other studies, it is necessary to give some attention to the definition and use of the risk estimates.

42. Radiation effects are usually described in terms of various simple measures of the excess risk. The most commonly used summary statistics are relative and absolute risk estimates. In simple terms, if O is the number of events observed in a population and E is the

number of events expected in the population in the absence of exposure, the relative risk (RR) is defined as

$$RR = \frac{O}{E} \quad (1)$$

and the excess risk (ER) is defined as

$$ER = O - E \quad (2)$$

When comparing relative risks or presenting risks per unit dose, as described below, it is preferable to summarize results in terms of the excess relative risk (ERR), defined as

$$ERR = \frac{O}{E} - 1 = \frac{O - E}{E} \quad (3)$$

instead of the relative risk. In order to compare estimates derived from populations with different levels of exposure, it is useful to work with risks per unit dose, called risk coefficients. Thus, if D is the average dose received by an exposed population, the linear excess relative risk coefficient is defined as

$$ERR = \frac{O - E}{ED} \quad (4)$$

The term dose and the symbol D are used in a general sense to represent absorbed dose (in gray) or weighted dose (in sievert) with neutron RBE = 10, for the atomic bomb survivors (see paragraph 64). Both quantities determined in equations (3) and (4) are commonly referred to as excess relative risk, the context making clear the distinction. To compute roughly comparable values for the excess risk in different studies it is necessary to consider both the dose and the amount of follow-up time. This is often done through the use of the excess absolute risk (EAR) per unit dose and per unit time at risk:

$$EAR = \frac{O - E}{PY D} \quad (5)$$

where PY is the number of person-years of follow-up.

43. A variety of methods are used for computing the expected numbers of cases used in the above definitions. It is common practice in epidemiology to allow for the effects of age, sex and other characteristics of the study population when computing the expected numbers of cases. Estimates that are computed allowing for such effects are called adjusted risks. However, when (as current data on radiation effects suggest) excess risks vary with age at exposure, sex or follow-up time, the summary statistics defined above are weighted averages involving an implicit weighting that depends on the composition of the population, with the largest weight being given to groups that have the largest number of cases. This means, for example, that the risk estimates generally cited for the life span study, which were used as the basis for many calculations in the UNSCEAR 1988 Report [U2], are heavily influenced by the experience of the older survivors and that, owing to the nature of the study, risks for

persons exposed as young adults contribute relatively little. When excess relative risks of cancers other than leukaemia from the life span study are computed by averaging risk estimates for a small number of groupings of age at exposure and sex using equal weights, the resulting excess relative risks are about 50% greater than the usual age-averaged estimate that gives the greatest weight to the older members of the cohort [P3]. Since the age-averaged summary risk estimates depend heavily on the demographics of the population on which they were based, similarities or differences in such simple average risk estimates should be interpreted with caution.

44. The most common approach to exploring variation in the risks of radiation-induced disease is to carry out separate analyses of subsets of the full data set. Examples include analyses of subsets defined by sex, age at exposure or time since exposure. In a subset analysis, a simple summary measure is computed, and separate tests of the null hypothesis of no excess risk are carried out for each subset. Such analyses tend to promote overreliance on significance tests and overinterpretation of sampling errors. Modern analytical methods and software make it easy to carry out generalized regression analyses that emphasize tests for heterogeneity in response functions, e.g. that determine whether or not risks differ significantly by age at exposure or sex and that estimate the size of the differences [P35]. These methods can be usefully employed even in studies without individual dose estimates.

45. In many studies, excess cancer believed to be associated with radiation is reported without regard to dose, usually because of the poor quality of individual dose estimates. Summarizing risks in this way complicates the comparison of results from different studies, since such comparisons are of little use in understanding the magnitude and nature of radiation risks. When dosimetric data are available and linear risk estimates are deemed to be appropriate, the risk per unit dose should be presented. When non-linear dose functions are used, they should be described clearly and accompanied by evidence for a lack of fit of the linear model. Any presentation of risks should be accompanied by a clear indication of the nature and quality of the dose estimates used.

46. In considering the risk of radiation-induced cancer projected in time, it is common to make use of what are often referred to as lifetime risk estimates. Several studies [P11, T14] have examined the definition, interpretation and presentation of lifetime risk estimates. Three principles can be identified that underlie the computation of lifetime risks:

- (a) independence of the follow-up period in the studies contributing information;
- (b) recognition of the impact of cultural and environmental differences such as smoking on normally occurring cancer rates;

- (c) allowance, as necessary, for the modifying effects on radiation risks of sex and age at exposure.

47. The first principle, stated in (a), concerns what is called risk projection. Few epidemiological studies of radiation carcinogenesis have more than 40-50 years of follow-up information, so it is inevitable that the calculation of lifetime risks involves extrapolation beyond the time period covered by most studies, especially for persons exposed early in life. When presenting lifetime risks it is important to indicate explicitly the approach taken and the effects of projection beyond the period covered by the data on which the underlying risk models are based. In several reports, including the UNSCEAR 1988 Report [U2], the projection effects were assessed by comparing lifetime risks calculated for constant absolute risk models with those calculated for constant relative risk models. Since constant absolute risk models no longer appear to adequately describe the variation in risk of radiation-induced cancer with time, this comparison does not provide useful information on the effects of risk projection.

48. The principle stated in (b) involves using descriptions of risk estimated for one population to predict what might be seen in a population with different site-specific cancer rates. Extensive data on the variation in cancer rates around the world have been presented by the International Agency for Research on Cancer [M17, P10]. Some examples of high and low cancer rates in various populations are given in Table 1, from which it can be seen that site-specific cancer rates can differ by as much as two orders of magnitude, as do, for example, rates for nasopharyngeal cancer, and that such great differences are not uncommon. While some of the differences are due in part to reporting methods, they also undoubtedly reflect real differences in incidence rates. Of particular interest is the contrast between rates for cancers of the stomach, lung and breast in the population of the whole of Japan and in the populations of some countries, particularly western ones. Although Japanese stomach cancer annual rates have been falling in recent years, they are still much greater than those in western Europe or the United States (50-60 per 100,000 per year compared to 6-10 per 100,000 per year). Stomach cancer rates in the Russian Federation and other parts of the former Soviet Union average 40 per 100,000 per year but are quite variable across the country. On the other hand, despite the fact that breast cancer rates in Japanese women (about 25 per 100,000 per year) are increasing, they are still less than half those in Europe and the United States (55-90 per 100,000 per year). Lung cancer rates also tend to be lower in Japan (25 per 100,000 per year) than in many other countries (40-60 per 100,000 per year). The differences reflect variation in the levels of exposures to carcinogens other than radiation and, in some cases, variation in the susceptibility of different ethnic groups.

49. Such differences in background rates of cancer raise questions about the applicability of risk estimates to a

population other than the one for which they were derived. Modern analytical methods allow the development of time-dependent models for excess absolute or relative risks that provide comparable descriptions of the current data for a specific population, but they can lead to different lifetime risk estimates when applied to populations with different cancer incidence. Despite the large number of studies of radiation and cancer in humans, it is still unclear how best to transfer risk estimates to different populations. This issue is discussed further in Chapter II.

50. The calculation of lifetime risks requires a set of normally occurring death rates from all causes and from the specific causes of interest for models of radiation effects. These are usually cross-sectional rates, i.e. rates for a specific year or averages over a limited number of consecutive years, for a specific national or international population. Since radiation-induced cancer risks vary with age at exposure and sex, the basic calculations are carried out for each age at exposure and sex. The resulting estimates are then averaged with respect to the population of interest, e.g. the current population of Japan. While lifetime risk estimates provide a convenient summary of radiation effects, it should be noted that cancer rates change with time. The lifetime risks are not therefore estimates of what would be expected in either the population(s) from which the risk models were developed or in the populations used to obtain the background rates for the lifetime risk computations.

51. In the UNSCEAR 1988 Report [U2] the primary measure of lifetime detriment was the risk that an individual would die from a cancer that arose owing to the exposure in question. In this Annex the term "risk of exposure-induced death" (REID) is used for this quantity. For an instantaneous dose D to the whole body or to an organ at age e , the lifetime risk of exposure-induced death from cause c (all cancers or a single cancer) is given by

$$\text{REID}_c(D,c) = \int_e^{\infty} [m_c(a|D,e) - m_c(a)] S(a|D,e) da \quad (6)$$

where $m_c(a|D,e)$ and $m_c(a)$ are the death rates from cause c at attained age a , with and without, respectively, instantaneous exposure to total dose D at age e , and where $S(a|D,e)$ is the probability that the individual survives to age a given that he or she was alive and received total dose D at age e .

52. The risk of exposure-induced death is not the only measure of lifetime detriment that can be used. Indeed, a different measure, the excess lifetime risk (ELR), has been used by the BEIR IV and BEIR V Committees [C6, C12]. The excess lifetime risk is the increase in the lifetime risk of the cancer in question experienced by an individual as a result of the specific exposure. For instantaneous

exposure to a dose D at age e , the excess lifetime risk for cause c is given by

$$\text{ELR}_c(D,e) = \int_e^{\infty} m_c(a|D,e) S(a|D,e) da - \int_e^{\infty} m_c(a) S(a|e) da \quad (7)$$

where $S(a|e)$ is the probability that an individual survives to age a given that he or she was alive at age e and the other quantities are the same as in the definition of REID.

53. Although both the REID and the ELR are useful summaries of lifetime detriment, they measure slightly different quantities. The risk of exposure-induced death can be interpreted as the risk that an individual will die from a cancer that has been caused by the exposure in question, while the excess lifetime risk is the difference between the proportion of people dying of cause c in an exposed population and the proportion dying of this cause in an otherwise identical, but unexposed, population. The difference between the REID and the ELR concerns the counting of cases who would have died of cause c in the absence of exposure but who die of this cause at an earlier date following exposure. Such cases contribute to the risk of exposure-induced death but are ignored in the excess lifetime risk [T14]. The ratio of the ELR to the REID is approximately equal to $(1 - B_r)$, where B_r is the lifetime risk for all exposure-induced causes among unexposed persons [V4]. This implies that if one considers lifetime risk for all cancers combined, the excess lifetime risk will be 15%-20% less than the risk of exposure-induced death, since the lifetime risk of dying of cancer is about 15%-20% in most populations.

54. The excess lifetime risk has some possibly undesirable properties, all of which are related to the fact that an exposure that increases an individual's chance of dying from one cause necessarily decreases his or her chance of dying from other causes. Thus the excess lifetime risk can be negative, even if the exposure increases the risk of cause c , if it increases the risk of other causes even more. If an exposure increases the risk of all causes of death to the same extent, then the excess lifetime risk for any cause would be zero. Individuals would then die sooner, but the distribution of causes of death would be unchanged. On the other hand, an advantage of the excess lifetime risk over the risk of exposure-induced death is that it has a more direct interpretation; it is, strictly speaking, the increase, attributable to the exposure, in the probability that a person's eventual death is due to the cause c . The undesirable properties of both the excess lifetime risk and the risk of exposure-induced death are largely a consequence of efforts to reduce a time-dependent quantity to a single value.

55. Since neither the risk of exposure-induced death nor the excess lifetime risk provide direct information on the times at which the exposure-induced events occur, it is useful to supplement estimates of these quantities with a statistic that describes these times. In the UNSCEAR 1988 Report [U2] this was done using a measure called "loss of life expectancy" (LLE). The loss of life expectancy is the difference between the expectation of life for an individual exposed at age e and the expectation for an unexposed individual. For an instantaneous dose D given at age e , it is given as

$$\text{LLE}(D,e) = \int_e^{\infty} S(a|e) da - \int_e^{\infty} S(a|D,e) da \quad (8)$$

The loss of life expectancy depends on the times at which exposure-induced events occur in the affected persons (the risk of exposure-induced death). However, if the loss of life expectancy is divided by the risk of exposure-induced death, the result is the years of life lost per radiation-induced case (YLC). This quantity is more independent of the risk of exposure-induced death and can thus be thought of as giving additional information about the risks. Since both the risk of exposure-induced death and the years lost per radiation-induced case combine information over all ages at exposure and also all ages at expression, they do not fully describe the impact of exposure on a population. Measures that display the impact separately for the different age groups may also be useful. One approach to this would be to present the excess lifetime risk as a function of attained age (A) and age at exposure (e) by, for example, plotting $\text{ELR}(A|D,e)$ against A , where $\text{ELR}(A|D,e)$ is given by equation (7) with the integrals evaluated between e and A .

56. Finally, it should be noted that even when the rate $m_c(a|D,e)$ is linear in D , as for solid tumours in the life span study, neither the REID nor the ELR is linear, since $S(a|D,e)$ is not linear in dose, especially at high dose. As will be illustrated in the presentation of lifetime risk estimates later in this Annex, the non-linearity is such that linear extrapolation from 1 Sv to 0.2 Sv, for example, understates the low-dose estimates of risk of exposure-induced death and excess lifetime risk for solid tumours by 10%-20%.

57. Another issue in risk estimation is how to determine expected mortality rates following exposures to low-LET radiation at dose rates substantially lower than those that prevail in the majority of epidemiological studies on which estimates of risk following exposure can be based. Given the paucity of epidemiological data, the best approach at present is probably to carry out the risk projection for an exposure of interest, ignoring the possible need for a dose-rate effectiveness factor, and then to multiply the resulting estimate of lifetime risk by a factor based on radiobiological as well as epidemiological considerations (see UNSCEAR 1993 Report [U1], Annex F, "Influence of dose and dose rate on stochastic effects of radiation").