

SOURCES, EFFECTS AND RISKS OF IONIZING RADIATION

UNSCEAR **2012 Report**

Report to the General Assembly

SCIENTIFIC ANNEXES A AND B

Annex A. Attributing health effects to ionizing radiation exposure and inferring risks

Annex B. Uncertainties in risk estimates for radiation-induced cancer



SOURCES, EFFECTS AND RISKS OF IONIZING RADIATION

United Nations Scientific Committee on the
Effects of Atomic Radiation

UNSCEAR 2012
Report to the General Assembly
with Scientific Annexes

Scientific Annexes



UNITED NATIONS
New York, 2015

NOTE

The report of the Committee without its annexes appears as *Official Records of the General Assembly*, Sixty-seventh Session, Supplement No. 46 (A/67/46).

The designations employed and the presentation of material in this publication do not imply the expression of any opinion whatsoever on the part of the Secretariat of the United Nations concerning the legal status of any country, territory, city or area, or of its authorities, or concerning the delimitation of its frontiers or boundaries.

The country names used in this document are, in most cases, those that were in use at the time the data were collected or the text prepared. In other cases, however, the names have been updated, where this was possible and appropriate, to reflect political changes.

UNITED NATIONS PUBLICATION
Sales No. E.16.IX.1
ISBN: 978-92-1-142307-5
eISBN: 978-92-1-057798-4

© United Nations, December 2015. All rights reserved, worldwide.

This publication has not been formally edited.

Information on uniform resource locators and links to Internet sites contained in the present publication are provided for the convenience of the reader and are correct at the time of issue. The United Nations takes no responsibility for the continued accuracy of that information or for the content of any external website.

CONTENTS

	<i>Page</i>
Report of the United Nations Scientific Committee on the Effects of Atomic Radiation to the General Assembly	1
 Scientific Annexes	
Annex A. Attributing health effects to ionizing radiation exposure and inferring risks	17
Annex B. Uncertainties in risk estimates for radiation-induced cancer	91
Glossary	309

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

Contents

<i>Chapter</i>	<i>Page</i>
I. Introduction	1
II. Deliberations of the United Nations Scientific Committee on the Effects of Atomic Radiation at its fifty-ninth session	3
A. Completed evaluations	3
B. Present programme of work	3
1. Nuclear accident following the great east-Japan earthquake and tsunami in 2011	3
2. Radiation exposure from electricity generation and an updated methodology for estimating human exposures due to radioactive discharges	5
3. Effects of radiation exposure on children	6
4. Biological effects from selected internal emitters	6
5. Epidemiology of low-dose-rate exposures of the public to natural and artificial environmental sources of radiation	6
6. Biological mechanisms of radiation actions at low doses	6
C. Future programme of work	7
D. Administrative issues	7
III. Scientific report	9
1. Attributing health effects to radiation exposure and inferring risks	9
2. Uncertainties in risk estimates for cancer due to exposure to ionizing radiation	10
Appendices	
I. Members of national delegations attending the fifty-seventh to fifty-ninth sessions of the United Nations Scientific Committee on the Effects of Atomic Radiation	13
II. Scientific staff and consultants cooperating with the United Nations Scientific Committee on the Effects of Atomic Radiation in the preparation of its scientific report for 2012	15

Chapter I

Introduction

1. Since the establishment of the United Nations Scientific Committee on the Effects of Atomic Radiation by the General Assembly in its resolution 913 (X) of 3 December 1955, the mandate of the Committee has been to undertake broad assessments of the sources of ionizing radiation and its effects on human health and the environment.¹ In pursuit of its mandate, the Committee thoroughly reviews and evaluates global and regional exposures to radiation, and also evaluates evidence of radiation-induced health effects in exposed groups, including survivors of the atomic bombings in Japan and people exposed after the reactor accident at Chernobyl. The Committee also reviews advances in the understanding of the biological mechanisms by which radiation-induced effects on human health or on non-human biota can occur. Those assessments provide the scientific foundation used, inter alia, by the relevant agencies of the United Nations system in formulating international standards for the protection of the general public and workers against ionizing radiation;² those standards, in turn, are linked to important legal and regulatory instruments.

2. Exposure to ionizing radiation arises from sources such as natural background radiation, including from radon; medical diagnostic and therapeutic procedures; nuclear weapons testing; electricity generation, including by means of nuclear power; events such as the nuclear power plant accidents at Chernobyl in 1986 and following the great east-Japan earthquake and tsunami of March 2011; and occupations that increase exposure to artificial or natural sources of radiation.

¹ 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). The Committee was originally composed of the following Member States: Argentina, Australia, Belgium, Brazil, Canada, Czechoslovakia (later succeeded by Slovakia), Egypt, France, India, Japan, Mexico, Sweden, Union of Soviet Socialist Republics (later succeeded by the Russian Federation), United Kingdom of Great Britain and Northern Ireland and United States of America. The membership of the Committee was subsequently enlarged by the Assembly in its resolution 3154 C (XXVIII) of 14 December 1973 to include the Federal Republic of Germany (later succeeded by Germany), Indonesia, Peru, Poland and the Sudan. By its resolution 41/62 B of 3 December 1986, the Assembly increased the membership of the Committee to a maximum of 21 members and invited China to become a member. In its resolution 66/70, the Assembly further enlarged the membership of the Committee to 27 and invited Belarus, Finland, Pakistan, the Republic of Korea, Spain and Ukraine to become members.

² For example, the international basic safety standards for protection against ionizing radiation and for the safety of radiation sources, currently co-sponsored by the International Labour Organization, the Food and Agriculture Organization of the United Nations, the World Health Organization (WHO), the International Atomic Energy Agency (IAEA), the Nuclear Energy Agency of the Organization for Economic Cooperation and Development and the Pan American Health Organization.

Chapter II

Deliberations of the United Nations Scientific Committee on the Effects of Atomic Radiation at its fifty-ninth session

3. The Committee held its fifty-ninth session in Vienna from 21 to 25 May 2012.³ Wolfgang Weiss (Germany), Carl-Magnus Larsson (Australia) and Leif Moberg (Sweden) served as Chair, Vice-Chair and Rapporteur, respectively. It welcomed representatives and delegations from the six new States members: Belarus, Finland, Pakistan, Republic of Korea, Spain and Ukraine.

A. Completed evaluations

4. The Committee discussed substantive documents on the attribution of health effects to different levels of exposure to ionizing radiation, and on uncertainties in risk estimates for cancer due to exposure to ionizing radiation. The principal findings on these subjects are summarized in a scientific report (see chap. III below) and, together with the two detailed scientific annexes that underpin them, will be published separately in the usual manner.

B. Present programme of work

1. Nuclear accident following the great east-Japan earthquake and tsunami in 2011

5. At its fifty-eighth session, the Scientific Committee had decided to carry out, once sufficient information was available, an assessment of the levels of exposure and radiation risks attributable to the nuclear power plant accident following the great east-Japan earthquake and tsunami of March 2011. It had envisaged a preliminary document for consideration at the fifty-ninth session of the Committee, and a more complete report for its sixtieth session, in 2013. The General Assembly had endorsed that decision in its resolution 66/70. The Committee discussed the preliminary document that summarized the planning, organization and technical progress of the work, as well as interim technical findings. The assessment is a major undertaking and requires extensive quality-assurance checks of the data to ensure that the final report will be authoritative.

6. States members and observers of the Committee and other selected countries had been invited to nominate experts to conduct the assessment at no cost to the United Nations. As of 18 March 2012, 72 experts from 18 countries had been offered, and they are now engaged in the work. In addition, three countries had made financial contributions to the general trust fund established by the Executive Director of the United Nations Environment Programme (UNEP) to receive and manage voluntary contributions to support the work of the Committee. Finally, in response to a request to consider offering an expert under a non-reimbursable loan

³ The fifty-ninth session of the Committee was also attended by observers for WHO, the World Meteorological Organization (WMO), IAEA, the European Commission and the International Commission on Radiological Protection.

arrangement, an expert from the Government of Japan had been offered and was now serving with the secretariat in Vienna.

7. Five international organizations are participating in the work: the Preparatory Commission for the Comprehensive Nuclear-Test-Ban Treaty Organization, the Food and Agriculture Organization of the United Nations, the International Atomic Energy Agency (IAEA), the World Health Organization (WHO) and the World Meteorological Organization (WMO). The Preparatory Commission for the Comprehensive Nuclear-Test-Ban Treaty Organization has shared from its global network relevant data on measurements of radionuclides in the air. FAO is making available a database on radioactivity levels in foodstuffs since March 2011 and is assisting in the interpretation of relevant data for the assessment of radiation exposures resulting from food consumption. IAEA made available results of measurements that its monitoring teams had conducted in Japan. WHO made available a preliminary dose assessment based on official information available up to mid-September 2011, and agreed to share its expertise particularly for the assessment of radiation exposures due to food consumption. WMO will gather relevant meteorological data and related information, and develop a set of suitable meteorological analyses that can be used to estimate the atmospheric concentration and surface deposition of radionuclides released.

8. Work so far has been focused on collecting and reviewing the material published in the scientific literature, defining the assessment methodologies and working arrangements, and defining processes for quality assurance of the data and assessment. There are many sources of data for the Committee's evaluation: (a) specific datasets in electronic formats, together with supplementary information, requested from the Government of Japan and authenticated Japanese sources; (b) information on measurements made by other United Nations Member States, especially all other States members of the Scientific Committee, as well as Malaysia, the Philippines, Singapore and Thailand, and solicited by the secretariat; (c) compiled and checked datasets that are being made available by other United Nations organizations, including the Comprehensive Nuclear-Test-Ban Treaty Organization, FAO, IAEA, WHO and WMO; (d) information and independent analyses that are being published in peer-reviewed scientific journals; and (e) crowdsourcing websites, where the public can upload their own measurements, which have also sprung up in Japan (while the use of such data calls for caution, they are nevertheless seen as having some value because they are independent from government sources).

9. The Committee is currently reviewing information that has been reported to it (in particular, the numerical data have not as yet been verified), which includes the following:

(a) To date, there have been no health effects attributed to radiation exposure observed among workers, the people with the highest radiation exposures. To date, no health effects attributable to radiation exposure have been observed among children or any other member of the population;

(b) As of 31 January 2012, a total of 20,115 occupationally exposed people, comprising company workers (17 per cent) and external contractors (83 per cent) of the Tokyo Electric Power Company (TEPCO), were involved in the on-site mitigation activities. About 66 per cent of the workforce are reported to have

received effective doses equal to or below 10 millisieverts (mSv). In addition, rescuers and volunteers were occupationally exposed. Six TEPCO workers received effective doses above 250 mSv (the maximum reported dose as of 31 January 2012 was 679 mSv); the largest part of those doses resulted from intakes of ^{131}I , ^{134}Cs and ^{137}Cs . About 170 occupationally exposed people received effective doses above 100 mSv. It should be emphasized that there are no data available in the open literature that allow estimates to be made of thyroid dose for occupationally exposed people. The Committee has requested further information from the Japanese authorities on worker doses and monitoring data;

(c) A system was established on 20 May 2011 for the management of radiation exposures and medical monitoring of occupationally exposed people involved in dealing with the emergency situation. As of 10 March 2012, none of the six deaths noted since 11 March 2011 had been attributed to exposure to ionizing radiation;

(d) Although there were several cases of occupationally exposed people with exposure to radiation from documented skin contamination, no clinically observable effects were reported;

(e) Thyroid monitoring of 1,080 children aged 15 years or younger in Iitate village, Kawamata town and Iwaki city (which are outside the 30-km zone) found no individual exceeding a screening level that was derived from a thyroid dose of 100 mSv (the maximum thyroid dose reported was 35 mSv). Some of the details of those measurements still need to be reviewed by the Committee. The Committee will assess the thyroid doses of the exposed populations, particularly of young children;

(f) In late June 2011, the government of Fukushima Prefecture (2 million residents) initiated a survey of residents of Iitate village, Namie town and the Yamakiya district of Kawamata town. The survey is being extended to people living in other parts of the Prefecture. Its aim is to evaluate radiation exposure levels for all the people who were living in the Prefecture on 11 March 2011;

(g) Since March 2011, a database has been compiled on radionuclide concentrations in foodstuffs, under the guidance of FAO and IAEA and in collaboration with the Japanese authorities, including the Ministry of Agriculture, Forestry and Fisheries. As of 23 May 2012, approximately 165,000 records on food monitoring were available, including data for over 500 types of foodstuffs, sampled in 47 prefectures in Japan. The Committee will analyse that database for use in assessing the radiation exposure of the general public from food consumption;

(h) Only a few studies have been published on exposure to non-human biota arising from the releases of radionuclides in which dose rates to biota have been estimated explicitly. Those studies show somewhat contrasting results. The highest exposures of wildlife appear to be associated with the marine environment.

2. Radiation exposure from electricity generation and an updated methodology for estimating human exposures due to radioactive discharges

10. The Committee reviewed documents on radiation exposure from electricity generation and an updated methodology for estimating human exposures due to radioactive discharges. While primarily for underpinning the Committee's

assessments, the methodology will be made available to the public. The Committee noted that the review of the existing methodology had been completed and several elements had been updated. In addition, electronic spreadsheets were being developed that would implement the methodology for use in conducting the assessment of exposures of populations from electricity generation. The work is expected to be finished by the sixty-first session.

3. Effects of radiation exposure on children

11. The Committee discussed a document that represented an extensive review of the effects of radiation exposure during childhood. Owing to the importance of this subject, given the public concerns following the 2011 nuclear accident in Japan, the Committee acknowledged that its goal was to finish the work by its sixtieth session.

4. Biological effects from selected internal emitters

12. The Committee discussed a document on the biological effects of exposure to selected internal emitters, with two parts addressing two specific radionuclides: tritium and uranium. It considered that further work was needed on that document, but that it would be finalized for approval by the Committee at its sixty-first session.

5. Epidemiology of low-dose-rate exposures of the public to natural and artificial environmental sources of radiation

13. The Committee discussed a document on the epidemiology of low-dose-rate exposures of the public to natural and artificial environmental sources of radiation. It recognized that the work was at an early stage and foresaw that the document would be further developed with a view to approval by the Committee at its sixty-first session.

6. Biological mechanisms of radiation actions at low doses

14. The Committee considered a short review document on the biological mechanisms of radiation actions at low doses. That document, unlike the Committee's standard full evaluations, was not intended to be comprehensive; it was rather intended to highlight major advances in the field that would provide guidance for developing the Committee's future programme of work. Because the document would be of wider interest, the Committee requested the secretariat to investigate means to issue it as a public document on its website.

15. The document concludes that understanding of the mechanisms of so-called non-targeted and delayed effects is improving and that there is some evidence for differential responses in gene and protein expression for high- and low-dose radiation exposures, but there is a lack of consistency and coherence among reports. There is as yet no indication of a causal association of those phenomena with radiation-related disease. With regard to immune response and inflammatory reactions, there is a clearer association with disease, but there is no consensus on the impact of radiation exposure, particularly at low doses, on those physiological processes. While the document focuses on mechanisms relevant to carcinogenesis, some of the processes considered may be relevant for tissue reactions, and improved

understanding may therefore be helpful for assessing the potential risk of non-cancer diseases at low and protracted exposures. The Committee agreed to:

- (a) Continue to encourage research into the mechanistic understanding of low-dose radiation action that may contribute to disease in humans;
- (b) Consider further developing biologically based risk models and a systems biology framework to integrate mechanistic data into risk assessment;
- (c) Make the document publicly available;
- (d) Review the subject again in three to four years, as appropriate.

C. Future programme of work

16. Regarding its future programme of work, the Committee acknowledged the significance of its evaluations of uncertainties in risk estimates for cancer due to exposure to ionizing radiation, which summarize the present methodologies to estimate health risks from exposure to ionizing radiation, including their uncertainties (see chap. III, sect. 2, below). The Committee considered that it might be worthwhile to extend the use of the methodologies to other sets of health-risk evaluations, but given the existing programme of work and its critical nature, decided to consider this matter at a later session.

17. The Committee took note of progress reports by the secretariat on public information and on improving the collection, analysis and dissemination of exposure data. Because (a) radiation exposures of patients undergoing medical procedures represented the most significant source of artificial exposures, (b) technology and practices in this area changed rapidly and (c) this was a thematic priority of the Committee's strategic plan (2009-2013), the Committee requested the secretariat to prepare for its sixtieth session a detailed plan for a report on this subject. It also requested the secretariat to initiate the Committee's next Global Survey of Medical Radiation Usage and Exposures and to cooperate closely with other relevant international organizations (such as IAEA and WHO), as appropriate. The Committee suggested that the General Assembly might (a) encourage Member States, the organizations of the United Nations system and other pertinent organizations to provide further relevant data about doses, effects and risks from various sources of radiation, which would help greatly in the preparation of future reports of the Committee to the Assembly; and (b) encourage IAEA, WHO and other relevant organizations to further collaborate with the Committee secretariat to establish and coordinate the arrangements for the periodic collection and exchange of data on radiation exposures of the general public, workers and, in particular, medical patients.

18. The Committee intends to formulate a strategic plan to guide its work for the period 2014-2020, for consideration at its sixtieth session.

D. Administrative issues

19. The Committee suggested that the General Assembly might request the United Nations Secretariat to continue to streamline the procedures for publishing the

Committee's reports as sales publications, recognizing that, while maintaining quality, the timeliness of their publication is paramount to fulfil expected accomplishments approved in the programme budget, and expecting that the report ought to be published within the same year as approval.

20. The Committee recognized that because of the need to maintain the intensity of work of the Committee, voluntary contributions to the general trust fund established by the Executive Director of UNEP to receive and manage voluntary contributions to support the work of the Committee would be beneficial. The Committee suggested that the General Assembly might encourage Member States to consider making voluntary contributions to the general trust fund for this purpose or to make contributions in kind.

21. The Committee agreed to hold its sixtieth session in Vienna from 27 to 31 May 2013.

Chapter III

Scientific report

1. Attributing health effects to radiation exposure and inferring risks

22. In its resolution 62/100 of 17 December 2007, the General Assembly, in recalling the intention of the Committee “to clarify further the assessment of potential harm owing to chronic low-level exposures among large populations and also the attributability of health effects”,⁴ encouraged the Committee “to submit a report on that issue at its earliest convenience”.

23. Furthermore, the General Assembly, in its resolution 63/89, endorsed the Committee’s strategic plan for its activities during the period 2009-2013. The strategic objective for the period was “to increase awareness and deepen understanding among authorities, the scientific community and civil society with regard to levels of ionizing radiation and the related health and environmental effects as a sound basis for informed decision-making on radiation-related issues”.⁵ That strategic objective highlighted the need for the Committee to provide information on the strengths and limitations of its evaluations, which are often not fully appreciated. This involves avoiding unjustified causal associations (false positives) as well as unjustified dismissal of real health effects (false negatives). Specifically, there was a need to clarify the degree to which health effects could be attributed to radiation exposure.

24. Moreover, the Assembly, in its resolution 66/70, called upon the Committee to submit to it at its sixty-seventh session the report requested by the Assembly on the attributability of health effects from radiation exposure.

25. The Committee has addressed the attribution of health effects to different levels of exposure to ionizing radiation, and has reached the following conclusions:

(a) An observed health effect in an individual could be unequivocally attributed to radiation exposure if the individual were to experience tissue reactions (often referred to as “deterministic” effects), and differential pathological diagnosis were achievable that eliminated possible alternative causes. Such deterministic effects are experienced as a result of high acute absorbed doses (i.e. about one gray or more), such as might arise following exposures in accidents or in radiotherapy;

(b) Other health effects in an individual that are known to be associated with radiation exposure — such as radiation-inducible malignancies (so-called “stochastic” effects) — cannot be unequivocally attributed to radiation exposure, because radiation exposure is not the only possible cause and there are at present no generally available biomarkers that are specific to radiation exposure. Thus, unequivocal differential pathological diagnosis is not possible in this case. Only if the spontaneous incidence of a particular type of stochastic effect were low and the radiosensitivity for an effect of that type were high (as is the case with some thyroid cancers in children) would the attribution of an effect in a particular individual to

⁴ *Official Records of the General Assembly, Sixty-first Session, Supplement No. 46 and corrigendum (A/61/46 and Corr.1)*, para. 5.

⁵ *Ibid.*, *Sixty-third Session, Supplement No. 46 (A/63/46)*, para. 8.

radiation exposure be plausible, particularly if that exposure were high. But even then, the effect in an individual cannot be attributed unequivocally to radiation exposure, owing to competing possible causes;

(c) An increased incidence of stochastic effects in a population could be attributed to radiation exposure through epidemiological analysis — provided that, *inter alia*, the increased incidence of cases of the stochastic effect were sufficient to overcome the inherent statistical uncertainties. In this case, an increase in the incidence of stochastic effects in the exposed population could be properly verified and attributed to exposure. If the spontaneous incidence of the effect in a population were low and the radiosensitivity for the relevant stochastic effect were high, an increase in the incidence of stochastic effects could at least be related to radiation, even when the number of cases was small;

(d) Although demonstrated in animal studies, an increase in the incidence of hereditary effects in human populations cannot at present be attributed to radiation exposure; one reason for this is the large fluctuation in the spontaneous incidence of these effects;

(e) Specialized bioassay specimens (such as some haematological and cytogenetic samples) can be used as biological indicators of radiation exposure even at very low levels of radiation exposure. However, the presence of such biological indicators in samples taken from an individual does not necessarily mean that the individual would experience health effects due to the exposure;

(f) In general, increases in the incidence of health effects in populations cannot be attributed reliably to chronic exposure to radiation at levels that are typical of the global average background levels of radiation. This is because of the uncertainties associated with the assessment of risks at low doses, the current absence of radiation-specific biomarkers for health effects and the insufficient statistical power of epidemiological studies. Therefore, the Scientific Committee does not recommend multiplying very low doses by large numbers of individuals to estimate numbers of radiation-induced health effects within a population exposed to incremental doses at levels equivalent to or lower than natural background levels;

(g) The Scientific Committee notes that public health bodies need to allocate resources appropriately, and that this may involve making projections of numbers of health effects for comparative purposes. This method, though based upon reasonable but untestable assumptions, could be useful for such purposes provided that it were applied consistently, the uncertainties in the assessments were taken fully into account, and it were not inferred that the projected health effects were other than notional.

2. Uncertainties in risk estimates for cancer due to exposure to ionizing radiation

26. Cancer risks from ionizing radiation are better understood than those from other carcinogens, largely because it is possible to quantify exposures and doses. Many studies of health effects from exposures to ionizing radiation exist, including the study of the Japanese survivors of the atomic bombings and studies of population groups that have been exposed at work or by medical procedures. However, differing estimates of radiation risks from low-dose exposures frequently give rise to controversy about the safe use of radionuclides and ionizing radiation in society. If uncertainties are not addressed properly by the scientific community,

apparent differences in risk estimates can cause anxiety and undermine confidence among the public, decision-makers and professionals. In order to provide a more rational basis for expressing radiation risk, the Committee has reviewed the state of science on analysing uncertainties in estimates of risks due to exposure to ionizing radiation.

27. Knowledge has reached a level where uncertainties in the risk estimates can be quantified. The concept “uncertainty” is used here to mean the distribution of possible true values of a quantity of interest and is often expressed as the range of likely values of that quantity. Uncertainty in radiation risk estimation arises from several sources, such as uncertainties in dose estimation, natural variation of disease occurrence in populations, limited information on exposed populations and incomplete understanding of the origins and development of cancer.

28. There are two general areas of interest. The first involves the characterization and quantification of uncertainties that arise in developing estimates of risk from a specific study or group of studies. Many epidemiological studies of health effects of radiation exposures report risk estimates with confidence levels that express the impact of statistical fluctuations of the data. However, there are various other types of uncertainties that are not usually expressed. These relate to information about health effects, estimates of radiation exposures and doses, and the models and methods used in evaluating epidemiological data. The second area of interest concerns risk projection, that is, when radiation risk estimates derived from specific studies are used to describe potential effects of radiation exposure in other populations of interest, such as workers exposed occupationally to radiation, people affected by an accidental release of radioactive material, or participants in a disease-screening programme involving radiation exposure.

29. In epidemiological studies, uncertainty and variability should be separated in dose quantification to account for their different effects on the estimate of risk. It is essential that common sources of mistakes associated with programming, data input and computation be identified and corrected prior to using dose estimates for epidemiological evaluation. In general, for external exposure to high-energy photons, the uncertainty in the estimation of an individual’s organ dose will be less than that for exposure to internal emitters. For external exposures to low-energy gamma radiation, however, the uncertainty in dose estimates can be considerable, depending on the energy and other variables. For internal exposures, doses are often evaluated using mathematical models that describe the distribution of radionuclides in the human body and the related delivery of dose to the various organs and tissues. In an optimal setting, internal doses are determined from individual whole body, partial body or excretion measurements. If such measurements are not available, then the intake has to be assessed on the basis of environmental measurements. The largest uncertainties exist when such concentrations have to be estimated by simulating the transport of radioactive material through the environment. Various computational methods have been used to quantify the uncertainties that are present at each stage of the exposure and dose calculation.

30. Neglecting uncertainties in estimating doses not only results in underestimating the uncertainty of the risk estimates, but may also lead to an underestimate of the risk itself. (If dose dependencies are non-linear, neglecting dose uncertainty can, under some conditions, lead to an overestimate of risk.) Various methods have been developed to account for these effects. For example,

dose estimates may be adjusted on the basis of assumptions about the distribution of doses in the study population. In a European study of lung cancer risk due to indoor radon exposure, making such an adjustment doubled the estimate of risk.

31. In an analysis of epidemiological data, various models may approximate the data set equally well but give different risk estimates. At low doses, the impact of the model assumptions is large. There are methodologies to combine risk estimates from various models. The first applications in the field of radiation risk analysis demonstrated that the estimates of uncertainties derived by multi-model inference are larger than those derived from well-fitting descriptive models by up to a factor of two, or even more.

32. Depending on the problem under consideration, there are a number of factors that can dominate the uncertainty in projecting risk:

- (a) Transfer of risk estimates from one population to another;
- (b) Extrapolation from acute to chronic and fractionated exposures;
- (c) Extrapolation from moderate- or high-dose to low-dose exposures; dose response may not be linear over the dose range of interest;
- (d) Extrapolation to different radiation types;
- (e) Absorbed dose values in the population of interest.

33. The Committee had informed the General Assembly at its sixty-first session that when its models were applied to the populations of any of five specific countries (China, Japan, Puerto Rico, United Kingdom of Great Britain and Northern Ireland, United States of America) of all ages, the lifetime risk of death from all solid cancers together following an acute dose of 1 sievert was estimated to be about 4.3 to 7.2 per cent, noting that those values varied among different populations and with different risk models.⁶ The additional insight provided by the current evaluation has now allowed the Committee to estimate that the uncertainty bounds of its calculations are approximately a factor of three larger or smaller than the best estimate.

⁶ Ibid., *Sixty-third Session, Supplement No. 46* and corrigendum (A/61/46 and Corr.1), para. 22.

Appendix I

Members of national delegations attending the fifty-seventh to fifty-ninth sessions of the United Nations Scientific Committee on the Effects of Atomic Radiation

Argentina	A. J. González (Representative), A. Canoba, M. di Giorgio
Australia	C. M. Larsson (Representative), P. Johnston, S. B. Solomon, R. Tinker
Belarus	J. Kenigsberg (Representative)
Belgium	H. Vanmarcke (Representative), H. Bijwaard, H. Bosmans, G. Eggermont, H. Engels, F. Jamar, L. Mullenders, P. Smeesters, A. Wambersie
Brazil	D. R. Melo (Representative), M. Nogueira Martins (Representative), M. C. Lourenço
Canada	B. Pieteron (Representative), D. Boreham, K. Bundy, D. B. Chambers, J. Chen, N. E. Gentner (Representative), R. Lane, C. Lavoie, E. Waller, D. Whillans
China	Pan Z. (Representative), Chen Y., Du Y., Liu J., Liu S., Liu Y., Pan S., Qin Q., Su X., Sun Q., Wang Y., Yang H., Yang X., Zhang W., Zhu M.
Egypt	T. S. Ahmed (Representative), M.A.M. Gomaa (Representative)
Finland	S. Salomaa (Representative), E. Salminen
France	A. Rannou (Representative), A. Flüry-Hérard, J. R. Jourdain, L. Lebaron-Jacobs (Representative), R. Maximilien, F. Ménétrier, E. Quémeneur, M. Tirmarche
Germany	W. Weiss (Representative), A. A. Friedl, P. Jacob, G. Kirchner, J. Kopp, R. Michel, W. U. Müller
India	K. B. Sainis (Representative), P. C. Kesavan, Y. S. Mayya
Indonesia	S. Widodo (Representative), Z. Alatas (Representative), G. Witono, B. Zulkarnaen
Japan	Y. Yonekura (Representative), S. Akiba, N. Ban, K. Kodama, M. Kowatari, M. Nakano, O. Niwa, S. Saigusa, K. Sakai, G. Suzuki, M. Takahashi, Y. Yamada
Mexico	J. Aguirre Gómez (Representative)
Pakistan	M. Ali (Representative), Z. A. Baig
Peru	A. Lachos Dávila (Representative), L. V. Pinillos Ashton (Representative), B. M. García Gutiérrez

Poland	M. Waligórski (Representative), L. Dobrzyński, M. Janiak, M. Kruszewski
Republic of Korea	S. H. Na (Representative), K.-W. Cho, J. K. Lee
Russian Federation	M. Kiselev (Representative), A. Akleyev, R. Alexakhin, T. Azizova, V. Ivanov, N. Koshurnikova, A. Koterov, I. Kryshev, B. Lobach, O. Pavlovsky, A. Rachkov, S. Romanov, A. Sazhin, S. Shinkarev
Slovakia	E. Bédi (Representative), M. Chorváth, Ž. Kantová, L. Tomášek, I. Zachariášová
Spain	M. J. Muñoz (Representative), B. Robles, E. Vaňo
Sudan	I. Salih Mohamed Musa (Representative), E.A.E. Ali (Representative), A. E. Elgaylani (Representative)
Sweden	L. Moberg (Representative), A. Almén, L. Gedda, L. Hubbard
Ukraine	D. Bazyka (Representative)
United Kingdom of Great Britain and Northern Ireland	J. Cooper (Representative), S. Bouffler, J. Harrison, J. Simmonds
United States of America	F. A. Mettler Jr. (Representative), L. R. Anspaugh, J. D. Boice Jr., N. H. Harley, E. V. Holahan Jr., R. J. Preston

Appendix II

Scientific staff and consultants cooperating with the United Nations Scientific Committee on the Effects of Atomic Radiation in the preparation of its scientific report for 2012

F. O. Hoffman

P. Jacob

C. Land

W. U. Müller

C. Muirhead

D. Preston

Secretariat of the United Nations Scientific Committee on the Effects of Atomic Radiation

M. J. Crick

F. Shannoun

ANNEX A

ATTRIBUTING HEALTH EFFECTS TO IONIZING RADIATION EXPOSURE AND INFERRING RISKS

CONTENTS

I. INTRODUCTION	21
II. BASIC ASPECTS	23
III. ATTRIBUTING HEALTH EFFECTS TO RADIATION EXPOSURE	24
IV. INFERRING RISKS AFTER RADIATION EXPOSURE	26
V. RESEARCH NEEDS	29
VI. SUMMARY AND CONCLUSIONS	29
APPENDIX A. SCIENTIFIC KNOWLEDGE ON HEALTH EFFECTS OF RADIATION EXPOSURE AND ITS USE	33
I. Introduction.....	33
II. Scientific method, science-based inference and application of scientific knowledge.....	34
III. Attributing observed health effects to radiation exposure.....	43
IV. Inferring risk of health effects from radiation exposure	53
V. Research needs.....	63
VI. Summary.....	65
APPENDIX B. CASE STUDIES	69
I. Skin burn after interventional cardiology procedure.....	70
II. Pregnancy with mentally retarded infant.....	71
III. Thyroid cancer after the Chernobyl accident.....	73
IV. Lung cancer from exposure to radon.....	75
V. Estimated risk from computed tomography scans	77
REFERENCES.....	81

I. INTRODUCTION

1. The Scientific Committee evaluates (a) levels of exposure to ionizing radiation, and (b) the effects of exposure on—and associated risks*¹ to—human health and the environment. It provides scientific evaluations for informed policy setting and decision-making (e.g. governments and organizations use these evaluations for establishing protective measures and other decisions). Thus, it is important that the Committee communicates not only the results of its evaluations, but also its confidence in, and limitations of, its evaluations in a balanced and considered manner, so that the findings not be misinterpreted or misused.

2. The Committee conducts its evaluations by reviewing scientific data and literature on clinical observations of health effects* in exposed individuals, laboratory studies at the molecular and cellular level, animal studies, and epidemiological studies of the frequency* of disease occurrence in exposed populations (see, for example, [U2, U3, U5, U6, U7, U8, U9, U10, U13]). Based on its evaluations of this information, the Committee has estimated risks associated with exposure to ionizing radiation. While the Committee has provided detailed reports on estimation of risk, it has not presented comprehensive information on the uses and limitations of its estimated risks for the general reader.

3. At the time of the twentieth anniversary of the Chernobyl accident in April 2006, there appeared to be widely diverging views, often based on misunderstanding, among the general public, media, authorities and scientists regarding the nature and scale of the health impact of the accident.² Subsequently, the General Assembly in its resolution 62/100 of 17 December 2007 requested the Committee “to clarify further the assessment of potential harm owing to chronic low-level exposures* among large populations and also the attributability* of health effects”. The Committee addressed this issue in annex D to its UNSCEAR 2008 Report [U14], and the current report expands on that. This scientific annex supports the Committee’s findings on the attribution* of manifest health effects to radiation exposure and the inference* of risk of health effects from exposure to ionizing radiation.

4. The Committee has not attempted in this annex to rigorously review the latest scientific developments, studies and data on the health effects of ionizing radiation exposure since the publication of the Committee’s last reviews [U10, U11, U13]. Instead, by synthesizing relevant elements of the philosophy of empirical science and science-based inference, it has drawn conclusions for the General Assembly on the attributability of health effects—and the inference of risk of health effects—to radiation exposure. Its principal aim is to help government officials, scientists of different disciplines, radiation protection professionals and other relevant experts understand the approaches taken by the Committee, and to promote informed use of the Committee’s findings among all readers of this annex.

5. The following chapters of the main text address two key issues:

(a) Whether a manifest health effect in an individual, or an observed increased frequency of occurrence of health effects in a population, can be attributed to radiation exposure;³

(b) Under what circumstances it is valid to infer risk or to predict absolute numbers of health effects following radiation exposure, particularly at levels and for time-courses of exposure for which an increased frequency of occurrence of radiation-related health effects has not been convincingly or consistently observed.

¹ Technical terms are explained in a detailed glossary, and are marked with an asterisk (*) the first time that they appear.

² *Official Records of the General Assembly, Sixty-first Session, Supplement No. 46 (A/61/46)*.

³ This annex does not rule out the possibility that at low and very low doses, radiation exposure may have some beneficial health effects that could lead to a decrease in the frequency of stochastic effects [U7].

6. There are two appendices for specialists. In appendix A, the Committee describes its approaches to the above issues:

- (a) Summarizing the fundamentals of scientific rationale, and the scientific knowledge base as it relates to the attributability of health effects to radiation exposure;
- (b) Clarifying the differences between attributing manifest health effects to radiation exposure and inferring risks of future health effects from radiation exposure for both individuals and populations;
- (c) Addressing whether observed health effects can be attributed to exposures, or risks of health effects can be inferred from exposures, when there are competing causes, limited data with large uncertainties, and biologically plausible* but unproven hypotheses for their development (which is particularly the case for low-level exposure).

Appendix B provides examples showing the possibilities and limitations of attribution and inference of risk for specific exposure situations.

7. For the purposes of facilitating the discussion of health effects of radiation exposure, the Committee has adopted a terminology to indicate bands of exposure, expressed as approximate ranges of the fundamental physical quantity, absorbed dose.* The terminology is intended to foster consistent interpretation of the terms: “high”, “moderate”, “low” and “very low” total doses of low-LET* radiation (e.g. gamma radiation), additional to those from normal background exposure to natural sources of radiation (see table 1). The Committee recognizes that scientifically it is the total dose from both natural and artificial sources that are of interest, there being no intrinsic difference between the types of radiation emitted. However, the focus in this annex is on the sum of the relevant incremental exposures above that from normal background exposure to natural sources, because that is usually the characteristic considered in epidemiological studies (and is also of interest to those who might use the Committee’s information as the basis for policy and decision-making). This focus, while helpful for discussing the issues of attribution and inference in this report, does not fully encompass the complication of attributing health effects to time-varying radiation exposures.

Table 1. Terminology for bands of radiation dose used in this report

The terminology used here indicates, in only approximate ranges, bands of total absorbed dose (to the whole body or to a specific organ or tissue of an individual) received in addition to the total from normal background exposure to natural sources of radiation. The bands of radiation dose do not account for the rate at which the dose is delivered

Terminology for dose bands	Range of absorbed dose for low-LET radiation ^{a, b}	Scenarios
High	Greater than about 1 Gy	Typical dose (whole or partial body) to individuals after severe radiation accidents or from radiotherapy
Moderate	About 100 mGy to about 1 Gy	Doses to about 100,000 of the recovery operation workers after the Chernobyl accident (annex D [U14])
Low	About 10 to about 100 mGy ^c	Dose to an individual from multiple whole-body computerized tomography (CT) scans
Very low	Less than about 10 mGy	Dose to an individual dose from conventional radiology (i.e. without CT or fluoroscopy)

^a There is clear evidence that the thresholds above which deterministic* effects (see para. 8) occur depend markedly on the rate at which the dose is delivered. For this reason, the Committee has defined low dose rate* to be less than 0.1 mGy/min when averaged over about an hour [U6]. The extent to which dose rate plays a role in determining the probability of stochastic effects* is still a matter of some debate in the scientific community.

^b For deterministic effects following high-LET radiation exposure in this high-dose range, an appropriate value of relative biological effectiveness (RBE)* needs to be applied (see paragraphs A74 to A75 of appendix A). For stochastic effects following high-LET radiation exposure at moderate or lower doses, nominal radiation weighting factors, reflecting generic values of RBE, are used by the radiation protection community to derive the equivalent dose expressed in sieverts (Sv) [I10]. Because of the generic nature of the radiation weighting factors, equivalent dose is strictly not appropriate for conducting risk assessment.

^c The terminology used to express ranges of doses of low-LET radiation below 100 mGy as “low” for the purpose of assessing cancer risks reflects annex A, “Epidemiological studies of radiation and cancer”, of the UNSCEAR 2006 Report [U10].

II. BASIC ASPECTS

8. *Radiation health effects.* More than 100 years of radiation research have provided extensive information on the relationship* between radiation exposure and specific health effects, both in the short and long term, and many mechanisms that may be relevant to explain the relationship. While the Committee’s remit is evaluation of scientific knowledge, for which other more appropriate classifications are used, the internationally accepted framework for radiation protection distinguishes between so-called “deterministic effects”, now often included under the term “tissue reactions”,* and “stochastic effects” [I10]. For the purposes of this annex, the Committee has also used this classification. Deterministic effects are those health effects that are caused by extensive cell death and/or cell malfunctioning. Examples are acute radiation syndrome, skin burns, epilation (loss of hair) and sterility. These health effects are characterized by a threshold, generally at a high dose, that must be exceeded before the health effect occurs and by an increase in the severity of the health effect with increasing dose. In contrast, stochastic effects are initiated by the modification of the genetic material of only one or perhaps a few cells in a way that is still compatible with cell survival. Examples are solid cancers, leukaemia, and heritable diseases. Such a health effect is characterized by a frequency of occurrence in a population that depends on radiation dose, whereas the severity of the health effect, if it

occurs, does not. There are some health effects for which it has not been possible to classify them as either deterministic or stochastic effects. Examples are circulatory diseases and cataracts. For the purposes of this annex, they are subsumed under the term tissue reactions.

9. *Scientific method.** For developing explanations for phenomena, scientific method is an important well-recognized approach. It is based on the assumption that nature follows certain laws, and that by using certain systematic approaches, these laws can often be revealed. Hypotheses about causation* are generated from observations and then tested by controlled experiments or careful observational (that is, other than experimental) studies, leading to better understanding. Modern approaches to the scientific method consider multiple plausible hypotheses, all of which are tested with new results of experiments and observations. Hypotheses that with time no longer explain the information are removed or adjusted, gradually reducing the number of plausible hypotheses. Those that do explain the results may eventually be deemed proven by the larger scientific community as established scientific fact.

10. *Science-based inference.* When causation has been sufficiently supported by empirical evidence and generally agreed by the broad scientific community, inferences can be made that are considered based on hypotheses deemed proven. Otherwise, if the evidence and level of agreement by the scientific community are insufficient, inferences cannot be considered as being based on hypotheses that have been deemed proven. Nevertheless, it is often possible to make science-based inferences using existing theory, mathematical models,* expert judgement and plausible assumptions. Such inferences can inform decision-making, provided that assumptions and uncertainties are also communicated. To distinguish between these situations for the purpose of this report, the Committee refers to inferences based on hypotheses deemed proven as “well-founded predictions”* and inferences based on hypotheses currently not deemed proven as “conditional predictions”* (i.e. conditional on the validity of the assumptions about the causal hypotheses made in making predictions).

11. *Uncertainties.* In testing hypotheses within the scientific method and in making science-based inferences, an important concept is that of uncertainty,* which describes and may quantify the limits of knowledge. It is an expression of having doubt, or being unsure, about study results, hypotheses, model-based estimations or results of measurements, and specifically the true value of a quantity of interest* (for a detailed discussion see annex B).

III. ATTRIBUTING HEALTH EFFECTS TO RADIATION EXPOSURE

12. Attribution is the action of ascribing an outcome to a cause, that is, in the context of this report, a health effect to radiation exposure.⁴ A crucial question is whether an outcome would have been observed, if the assumed cause had not been present, or in the context of this report: if radiation exposure had not occurred, would the health effect still have occurred? (This concept is dealt with in appendix A under the term “counterfactual analysis”*—paragraphs A10 to A12.)

13. In the context of deterministic effects, one can very often observe many characteristics (e.g. damage evolution and severity) in a differential pathological diagnosis, so that a health effect in an individual can be unequivocally attributed to a radiation exposure. In contrast, it is not, at present,

⁴ Attribution in this annex relates to establishing scientifically the set of conditions that are required to cause an event. It is not used as a relative concept. Note that the set of conditions may well be one in which radiation exposure is not a sole factor. The idea of conveying the degree of belief that an outcome was caused by something else is expressed using probability of causation or more correctly, assigned share (see paragraph 23(c)).

possible to unequivocally attribute a stochastic effect in an individual to radiation exposure; based on current scientific knowledge, such a health effect is not distinguishable from one that arises from other causes. Up to now, no marker has been found that beyond doubt identifies a cancer or a hereditary disease in an individual as being caused by ionizing radiation, irrespective of dose. Even if a biomarker could be found that identified a radiation-induced cancer, it would not be able to indicate whether it was induced by radiation from natural or artificial sources. At low and, now even, very low levels of dose, there are biological indicators of radiation exposure, such as haematological or cytogenetic modifications, but these modifications in themselves are not health effects and may not necessarily result in health effects.

14. If the baseline* frequency of occurrence of a particular type of stochastic effect in a population were low and the radiosensitivity for a health effect of that type were high (as is the case with some thyroid cancers following exposure in childhood), causation of a health effect in a particular individual by radiation exposure could be plausible, particularly if that exposure were high. But even then, the stochastic effect in an individual could not be unequivocally attributed to radiation exposure, owing to other possible causes.

15. It is possible, however, to attribute an increase in the frequency of occurrence of stochastic effects to exposure to ionizing radiation from studies of populations of people. This is done by comparing the frequency of their occurrence in a population exposed to radiation with that in one that was not exposed, using epidemiological methods. If the increased frequency of occurrence of the stochastic effect observed were sufficient to overcome the inherent statistical and other uncertainties (including those due to possible confounding factors*), the results of the study would provide some evidence for causation. For example, if the baseline frequency of occurrence of the health effect in a population were low and the radiosensitivity for the relevant health effect were high, and other factors were accounted for in the analysis, an increase in the frequency of stochastic effects could, at least, be associated with exposure to radiation, even when the number of cases were small. Consistent results from several independent studies of various exposed populations may be sufficient to confidently attribute the increased frequency of health effects to radiation exposure. However, attribution of a particular health effect in an individual within those populations to radiation exposure would still not be possible without a specific biomarker. Currently, an increased frequency of occurrence of certain health effects can be confidently attributed to radiation exposure at moderate and high doses, while the confidence decreases with lower doses. One possible exception might be that of exposure of the fetus: the UNSCEAR 2006 Report [U10] discussed several studies of children exposed in utero in the low-dose range, which indicated statistical association between increased frequency of childhood leukaemia and the mother's exposure to radiation during pregnancy; however whether these associations are causal is still debated by the scientific community.

16. Increased frequencies of occurrence of heritable disease have been demonstrated in animal studies involving moderate or high doses; however, they have currently not been demonstrated in human populations exposed to radiation in any range (e.g. even in the children of the survivors of the atomic bombings in Japan). One reason for this could be that any increased frequency of disease due to radiation exposure would have to be very large to overcome the large fluctuation in the baseline frequency of these diseases in humans.

IV. INFERRING RISKS AFTER RADIATION EXPOSURE

17. Inference is the process of drawing conclusions from scientific observations, evidence and reasoning in the presence of uncertainty. Two principal approaches for statistical inference are relevant: (a) frequentist inference,* which interprets probability as the limit of relative frequency observed in an increasingly large number of similar trials; and (b) Bayesian inference,* which interprets probability as a quantity assigned to represent a state of knowledge or state of belief, and involves a logical process to update estimates of quantities as new information becomes available.

18. For acute exposure* to high doses above the relevant thresholds, there is sufficient evidence, knowledge and scientific consensus regarding causal relationships to be able to predict relatively accurately whether or not there will be a deterministic effect in an exposed individual and, if so, the likely severity of that health effect. For exposures at moderate or high doses (or more strictly, at doses at which an increased frequency of occurrence of certain health effects in a population can be confidently attributed to radiation exposure), there is also sufficient evidence, knowledge and scientific consensus on causal relationships to be able to predict with some confidence an increased risk of stochastic effects in an exposed population similar to that for which evidence exists. These predictions would fall within the group of well-founded predictions, as defined in paragraph 10, and the results are essentially the same irrespective of the method of inference.

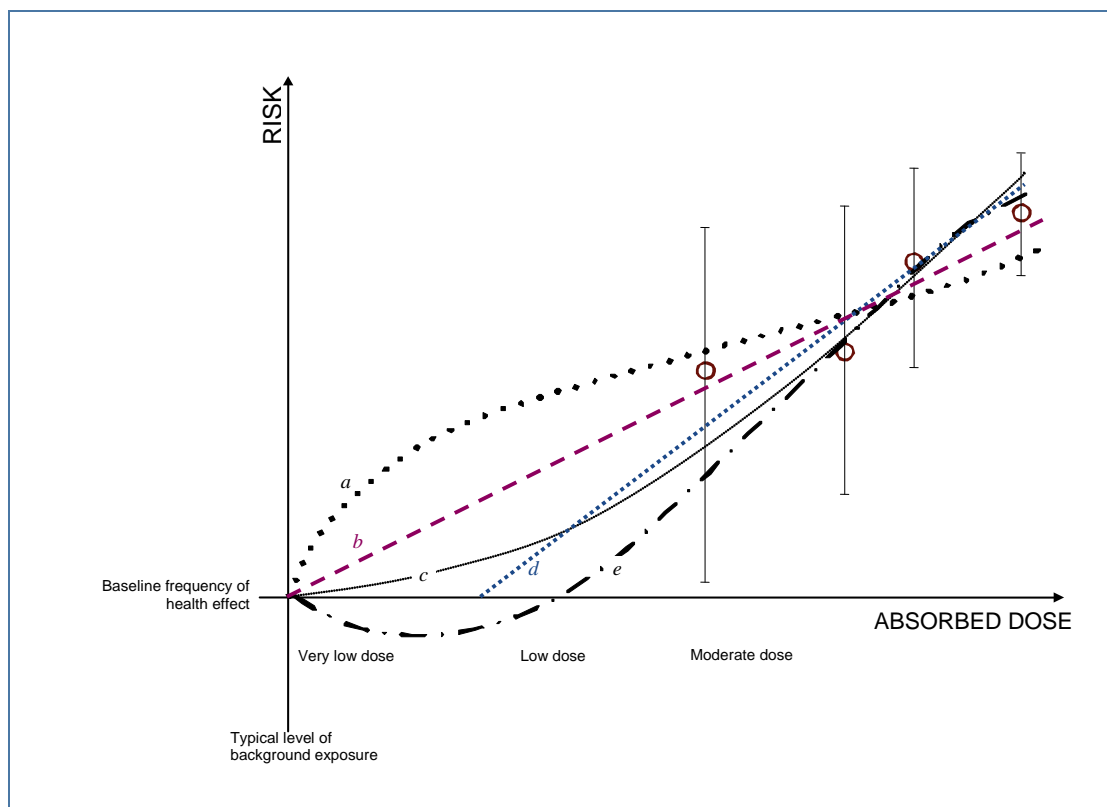
19. There are various obstacles to precisely quantifying risks of stochastic effects after exposure. These include extrapolating from studies of populations exposed at moderate and high doses, often delivered at high dose rates, to estimating risks for other populations with different age and sex compositions and with different baseline rates* of cancer, exposed to low or very low doses of radiation of different quality, at low dose rates (see annex B). For such situations, Bayesian inference may provide additional insights.

20. The problem is illustrated in figure I showing plausible dose–response relationships for the risk of cancer from exposures at very low, low and moderate doses. In the ranges of very low and low doses, there have been no studies that unequivocally indicate statistically significant increases (or indeed decreases) in the frequency of occurrence of cancer in epidemiological studies of the general population). However, the Committee considers that risks are unlikely to change dramatically just below the dose levels at which a statistically significant increased frequency of occurrence has been established. Moreover, a gross underestimation of the risk from low and very low doses using these various plausible dose–response relationships is most unlikely because this would have been detected by those epidemiological studies that have been conducted.

21. When one studies large groups of people (several tens of thousands of individuals), one may detect a statistically significant increase in the frequency of occurrence of various cancers following whole-body exposures to low-LET radiation in the range of moderate doses. However, as the dose decreases, the power of epidemiological studies becomes less and less, although there may be sensitive subgroups within the population for which increased frequency of occurrence of specific disease types might be discernible. Moreover, uncertainties become relatively larger, in part due to deficiencies in knowledge of dose–response relationships and mechanisms for cancer induction. In any case, projections of the absolute number of cancer cases in a population have less and less information value and can be increasingly misleading at lower and lower doses. As a matter of general practice, the Committee does not use the risks inferred from studies of populations following radiation exposure at moderate and high doses to project absolute numbers of radiation-induced cancers following exposure at low and very low doses.

Figure I. Schematic presentation of plausible dose–response relationships for the risk of cancer in the ranges of very low, low and moderate doses

The doses in the figure are in addition to the total background exposure to natural sources of radiation. The data points and confidence intervals* marked on the graph represent observations of increased frequency of occurrence of a specific cancer type in populations exposed to moderate doses. The various lines represent the following plausible dose–response relationships for inferred risk of cancer for exposures in the ranges of low and very low doses: (a) supralinear; (b) linear non-threshold (LNT); (c) linear–quadratic; (d) threshold; and (e) hormetic. These relationships are discussed in more detail in paragraph A82



22. The considerations addressed in the previous paragraph point to a very basic problem: what can be done, when the standard requirements for testing hypotheses cannot be fulfilled? Or to put it in the context of inference of cancer risk in populations after radiation exposure, the following hypotheses that would give rise to the following relationships cannot be convincingly verified or falsified at the moment:

- (a) The currently observed response in the moderate-dose range can be extrapolated linearly down to zero incremental dose above that from normal natural background radiation (this would be a linear non-threshold (LNT) relationship);
- (b) The risk at low and very low doses is substantially higher than expected from an LNT relationship (e.g. this would be a supralinear relationship);
- (c) The risk at low and very low doses is substantially lower than expected from an LNT relationship (e.g. this would be a threshold or hormetic relationship).

23. When hypotheses cannot be or have not been tested and verified or falsified, three main approaches are available:

(a) *Excluding untestable hypotheses from consideration*; this is the pure scientific approach, but it cannot be used when, for example, decisions regarding health protection are required.

(b) *Making conditional predictions (i.e. based on hypotheses currently not deemed proven) for risk estimation*. Based on interpretations of available scientific information, scientists can generate extrapolations and estimates, using science-based models and plausible assumptions, and characterize uncertainty (see annex B). Such science-based estimates can then be used to inform the decision-making process.

As an example of this approach, although there is no direct evidence from epidemiological studies of exposed human populations of an increased frequency of occurrence of heritable effects, the Committee has inferred risks of such heritable effects following human exposure by making plausible assumptions based on observations on animals. As another example, public health bodies may need to allocate resources appropriately, and this may involve making projections of numbers of health effects for comparative purposes. This method, although based upon reasonable but generally untestable assumptions, could be useful for such purposes provided that it were applied consistently, the uncertainties in the assessments were taken fully into account, and it were not inferred that the projected health effects were other than notional.

(c) *Incorporating non-scientific concerns*. This approach may or may not take account of science-based inferences. In this case, decision-makers may take account of norms* external to science such as social responsibility, ethics, utility, prudence, precaution and practicality of application. Such considerations, while important, are outside of the Committee's remit, and are mentioned here only for the sake of completeness.

As an example of these considerations, an LNT dose–response relationship is assumed for the purposes of radiation protection. However, predictions are conditional on this assumption—they are based on a hypothesis currently not deemed proven (option (b) above). For pragmatic reasons, the International Commission on Radiological Protection (ICRP) has calculated an average individual risk by dividing the inferred increased frequency of occurrence of cancer in a population by the number of exposed people in the population, and has used this concept to help establish protection criteria, such as dose limits. Moreover its adoption of an LNT dose–response relationship for the purposes of radiation protection also takes account of the importance of non-scientific concerns, such as practicality of application (option (c) above) [I10].

Another example is the concept of assigned share* (often referred to as “probability of causation”), used to analyse claims that radiation exposure in the past has caused a specific case of cancer. The idea is to use conditional predictions for risk estimation (option (b) above) to express a probability (reflecting the inferential weight) that the health effect in an individual occurred as a consequence of a known exposure. If the calculated value is high, decision-makers may choose to deem the health effect to have been caused by radiation exposure (option (c) above). Further discussions on these issues are given in appendix A.

V. RESEARCH NEEDS

24. In order to improve the ability to attribute health effects observed in individuals and populations exposed to radiation, and to infer risk from radiation exposure, the Committee emphasizes the need for research in the following areas (see also section V in appendix A):

(a) The search for a biomarker or a set of biomarkers to allow unequivocal attribution of a specific cancer (or health effect in general) in an individual to exposure to ionizing radiation;

(b) Epidemiological studies with complete follow-up of the exposed cohorts over the remainder of their lives (such as the Life Span Study of the survivors of the atomic bombings in Japan, studies of persons exposed to radiation for medical purposes as infants or in early childhood, and studies of workers who were occupationally exposed to radiation over a period of years), describing any increased frequency of occurrence of health effects by age and sex and how any increased frequency varies with different baseline frequencies of a particular health effect;

(c) Improvement in scientific knowledge of increased frequencies of occurrence of health effects in populations exposed to low and very low doses of ionizing radiation experienced chronically over time, i.e. at a low dose rate. One approach might be to undertake large-scale epidemiological studies of exposed populations that have a reasonable chance to provide consistent and reliable evidence for a causal relationship, such as case-control studies on childhood leukaemia. The Committee recognizes nevertheless that even large-scale epidemiological studies have inherent limitations, related to statistical variation in cancer rates* in populations and the inability to account for all the non-radiation causes of cancer, and thus may not be able to provide sufficient evidence that increased frequencies of occurrence of health effects in populations could be unequivocally attributed to radiation exposure when doses are very low;

(d) The integration of better physical and biological understanding of radiation actions at low doses with epidemiological findings of health effects in populations over a range of doses. The Committee expects four current scientific trends, namely developments in systems biology applied to radiation actions, molecular epidemiology,* modelling of pathogenesis, and radiation dosimetry to contribute synergistically to the inference of risks;

(e) Better characterization of non-cancer effects that occur in the longer term after protracted exposures* (such as fibrosis, cataracts and circulatory diseases);

(f) The rigorous quantification of uncertainty in such analyses (see annex B); and methods to integrate and synthesize the results of many studies to better make quantitative and qualitative statements on the confidence that can be placed in causal relationships, hypotheses and predictions.

VI. SUMMARY AND CONCLUSIONS

25. An observed health effect in an individual could be unequivocally attributed to radiation exposure if the individual were to experience tissue reactions that are deterministic effects, and differential pathological diagnosis were achievable that eliminated possible alternative causes. Such deterministic effects are experienced as a result of acute exposure to high absorbed doses (i.e. about one gray or more), such as might arise following exposures in accidents or from radiotherapy.

26. Other health effects that are known to be associated with radiation exposure, that is, stochastic effects, such as cancers cannot, if they occur in an individual, be unequivocally attributed to radiation exposure, because radiation exposure is not the only possible cause and there are at present no generally available biomarkers that are specific to radiation-induced health effects. Thus, unequivocal differential pathological diagnosis is not possible in this case. If, however, the baseline frequency of occurrence of a particular type of stochastic effect were low and the radiosensitivity for a health effect of that type were high (as is the case with some thyroid cancers after exposure in childhood) would the attribution of a health effect in a particular individual to radiation exposure be plausible, particularly if that exposure were high. But even then, the health effect in an individual cannot be unequivocally attributed to radiation exposure, owing to other possible causes.

27. An increased frequency of occurrence of stochastic effects in a population could be attributed to radiation exposure through epidemiological analysis—provided that, *inter alia*, the increased frequency of cases of the stochastic effect were sufficient to overcome the inherent statistical and other uncertainties. In this case, an increase in the frequency of occurrence of stochastic effects in the exposed population could be properly verified and attributed to exposure. If the baseline frequency of occurrence of the stochastic effect in a population were low and the radiosensitivity for the relevant stochastic effect were high, an increase in the frequency of occurrence of stochastic effects could at least be related to radiation exposure, even when the number of cases was small.

28. Although demonstrated in animal studies, an increase in the frequency of occurrence of heritable disease in human populations cannot at present be attributed to radiation exposure; one reason for this could be the large fluctuation in the baseline frequency of these diseases.

29. Specialized bioassay specimens (such as some haematological and cytogenetic samples) can be used as biological indicators of radiation exposure even at very low levels of radiation exposure. However, the presence of such biological indicators in samples taken from an individual does not necessarily mean that the individual would experience health effects due to the exposure.

30. In general, increases in the frequency of occurrence of health effects in populations cannot be reliably attributed to chronic exposure to low-LET radiation at levels that are typical of the global average background levels of radiation. This is because of the uncertainties associated with the assessment of risks at low doses, the current absence of radiation-specific biomarkers for health effects and the insufficient statistical power of epidemiological studies. Therefore, the Scientific Committee does not recommend multiplying very low doses by large numbers of individuals to estimate numbers of radiation-induced health effects within a population exposed to incremental doses at levels equivalent to or lower than normal natural background levels.

31. The Scientific Committee notes that public health bodies need to allocate resources appropriately, and that this may involve making projections of numbers of health effects (such as cancers) at very low doses for comparative purposes. This method, though based upon reasonable but untestable assumptions, could be useful for such purposes provided that it were applied consistently, the uncertainties in the assessments were taken fully into account, and it were not inferred that the projected health effects were other than notional.

ACKNOWLEDGEMENTS

The Committee would like to acknowledge: W.-U. Müller, who helped develop and integrate material according to the Committee's directions; J. Boice, A. González, N. Harley, B. Hofmann, F.O. Hoffman, C.-M. Larsson and F. Mettler for their contributions; and L. Dobrzyński, P. Jacob, P. Smeesters, R. Wakeford and A. Wrixon for their critical review and helpful suggestions. The interpretations expressed remain those of the Committee and do not necessarily represent the views of the experts, or of the United Nations or its Member States.

APPENDIX A. SCIENTIFIC KNOWLEDGE ON HEALTH EFFECTS OF RADIATION EXPOSURE AND ITS USE

I. INTRODUCTION.....	33
II. SCIENTIFIC METHOD, SCIENCE-BASED INFERENCE AND APPLICATION OF SCIENTIFIC KNOWLEDGE.....	34
A. Scientific method.....	34
B. Science-based inference.....	41
C. Summary of basics.....	43
III. ATTRIBUTING OBSERVED HEALTH EFFECTS TO RADIATION EXPOSURE.....	43
A. Deterministic effects.....	46
B. Stochastic effects.....	47
IV. INFERRING RISK OF HEALTH EFFECTS FROM RADIATION EXPOSURE.....	53
A. Predicting health effects and inferring risks where hypotheses regarding causal relationships have been deemed proven.....	53
B. Inferring risks where hypotheses regarding causal relationships have not been deemed proven.....	54
C. Application of science-based inference.....	61
V. RESEARCH NEEDS.....	63
VI. SUMMARY.....	65

I. INTRODUCTION

A1. This appendix is aimed at more specialist readers and provides material that underpins the conclusions of the annex. The terminology used is more specialized but the structure broadly follows that of the main text.

A2. Section II of this appendix elaborates further on the nature of scientific endeavour in general and the way in which scientific information, in combination with other inputs, is used by society. The relevant literature on the philosophy of science has not been reviewed exhaustively. Nevertheless, understanding the way in which science operates and the results of scientific investigation are at the crux of the subject matter and, thus, the section starts with some more detailed discussion on the

scientific method. The intention has been to provide background that clarifies the distinctions between information that results from empirical science and the inferences that can be drawn from those results, which may then, in turn, be used by those concerned with policy matters. A key issue is the retrospective concept of attributing observed health effects to an exposure, and the prospective concept of inferring risk of health effects from an exposure.

A3. Section III then summarizes the current scientific knowledge on the health effects of radiation exposure and the attributability of observed health effects to radiation exposure, distinguishing between deterministic and stochastic effects. Section IV discusses the basis for making inferences regarding health effects from an exposure, which can then be used as input for various purposes including establishing policy.

A4. While much scientific research on the health effects of radiation exposure has been carried out over the last 100 years, further refinement and new development in scientific knowledge is essential. Section V therefore elaborates on the research that the Committee considers necessary in order to improve the ability to attribute observed health effects to radiation exposure and consequently to refine inferences of the risk of health effects occurring in individuals and populations as a result of radiation exposure. Finally, section VI summarizes the information provided in this appendix.

II. SCIENTIFIC METHOD, SCIENCE-BASED INFERENCE AND APPLICATION OF SCIENTIFIC KNOWLEDGE

A5. Science has been defined as “the intellectual and practical activity encompassing the systematic study of the structure and behaviour of the physical and natural world through observation and experiment” [C3]. A key scientific endeavour is to investigate causal claims and eventually to explain them by understanding the mechanisms involved. A fundamental distinction is made here between this endeavour and the application of that scientific knowledge. Application involves the use of science-based inferences, which may be used as an input to broader decisions that may involve other considerations (e.g. ethics, human rights and practicality).

A. Scientific method

A6. The scientific method for developing explanations for phenomena (also known as “the hypothetico-deductive method” [B10]) is based on the principle that there is an underlying order to the nature of things, and that by following certain systematic approaches, this nature can often be revealed. Proposed explanations (hypotheses) for the phenomena are generated from observations and then tested by controlled experiments or careful observational (i.e. other than experimental) studies, leading to better understanding. Empirical science (i.e. science based on observation or experimentation rather than theory or pure logic) is thus concerned with seeking understanding about nature by systematically building knowledge in the form of testable explanations and predictions. A scientific hypothesis is therefore a proposed explanation for something that can actually be tested.

A7. The scientific method proceeds as follows: observations of a phenomenon are made, questions are asked, one or more hypotheses are formulated to explain the observations, falsifiable* predictions

are made based on the hypotheses,⁵ analytical studies are designed to test the hypotheses and discriminate between them, the resulting data are collected and analysed, outcomes are evaluated, and predictions are tested that either support or refute the hypotheses. A better understanding leads to more questions. Testable hypotheses that are repeatedly refuted must be either modified or rejected, or, if necessary, additional hypotheses generated, with a view to gradually reducing the number of plausible hypotheses to explain the phenomenon.

A8. The scientific method does not operate in isolation, but is conducted by the scientific community, which has specific internal norms to guide the activities of scientists in applying the scientific method. These norms include truthfulness, consistency, coherence, testability, reproducibility, validity, reliability, openness, impartiality and transparency [T6]. An important aspect of scientific work is open and transparent publication of details of the methods used and results. The process of scientific publication should involve critical review, conducted anonymously by impartial peers, of the methods and results. Publication of these details also provides the opportunity for other scientists to repeat, substantiate or challenge work.

A9. When hypotheses have been tested under a wide variety of conditions (“reproducibility”), and there is strong evidence and critical argument to generalize the results from the large, but still limited set of data, and the scientific community reaches a high degree of consensus on the validity of a causal hypothesis to best explain all the information, the hypothesis may be deemed proven as an established scientific fact.⁶ When enough experimental results have been gathered in a particular area of inquiry, scientists may propose an explanatory framework that accounts for as many of these results as possible. If this explanation makes falsifiable predictions with consistent accuracy (“testability”) and is well-supported by many independent strands of evidence, scientists may adopt this framework as part of a broad “scientific theory”.

1. Establishing causal relationships

A10. There are many philosophical approaches to discussing causality and causal relationships (e.g. see [R2]). For the purposes here, three closely interrelated concepts are relevant to the discussion, namely (see figure A-I):

(a) *Causation* is the action of producing an outcome. In figure A-I, A (an exposure, event or set of conditions) is said to be a sufficient cause of the outcome B if, whenever A occurs, B follows. This concept can be extended to include a probabilistic component that, whenever A occurs, there is a corresponding probability that B will occur;

(b) *Counterfactual analysis* of causation relates to considering a (counterfactual conditional) question in the form: “If A had not occurred, would B also not have occurred?” Thus it considers whether there are other possible causes of the outcome of interest;

(c) *Attribution* is the act of ascribing an outcome to a cause. If an outcome B occurs, attribution is the act of concluding that a previous exposure, event or set of conditions, A, was the cause. If A were a necessary condition for B to occur (i.e. A uniquely causes B), then B can be unequivocally

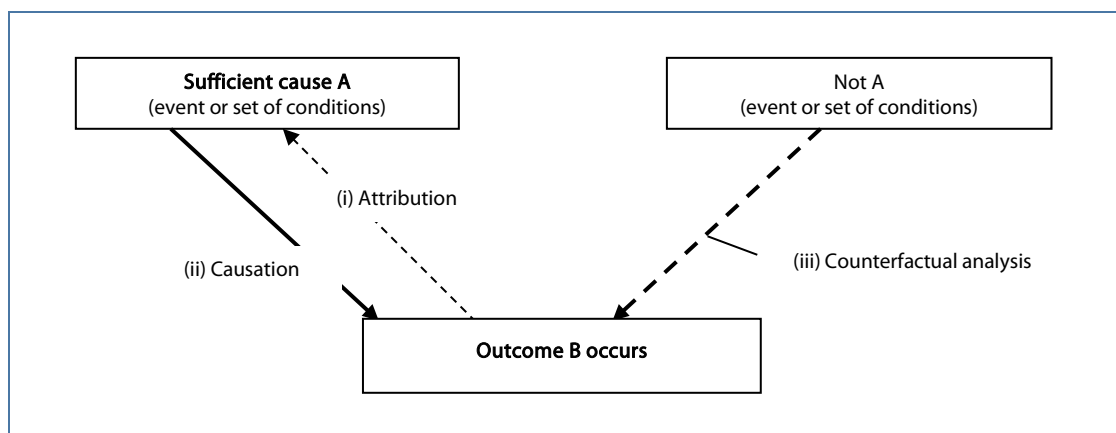
⁵ According to critical rationalism as advanced by Popper and dominating the empirical sciences, only hypotheses that can be falsified with a severe empirical test belong to the field of science proper [P4]. Note that falsifiable is used here with the meaning of “being able to be shown/proved to be false”; it does not mean “alter information so as to mislead”.

⁶ Note while the concept of absolute proof exists in the abstract and can apply in mathematical theorems, in the real world, hypotheses can only be “deemed” proven, i.e. there is a very high degree of confidence generally in their validity.

attributed to A. If, on the other hand, A were a sufficient cause of B (i.e. other possible events or conditions could cause B), then, by counterfactual analysis, B cannot be unequivocally attributed to A. The term “attributability” here is used to express the ability to attribute B to A.

Figure A-1. Schematic illustration of the relationships between the concepts of causation, counterfactual analysis and attribution as used in this annex

(i) Attribution is the act of ascribing an outcome B to a cause (event or set of conditions) A, as opposed to another possible cause. It is therefore retrospective (i.e. looking backwards from outcome to cause). (ii) If A is a sufficient cause of B, it does not follow necessarily that B can be attributed to A, because other possible sufficient causes could have resulted in B. (iii) The causation hypothesis can be tested by counterfactual analysis which involves asking, would B have occurred, if A had not occurred?



A11. For example, the poliovirus is the necessary cause of poliomyelitis, and there are no other known causes. Thus, a counterfactual analysis would ask, “If exposure to the poliovirus had not occurred, would a case of poliomyelitis also not have occurred?”. For this example, the answer to the counterfactual question is clearly that the case of poliomyelitis would not have occurred. Thus, a manifest case of poliomyelitis can be attributed to infection by the poliovirus.

A12. In contrast, smoking is known to be a cause of lung cancer, but it is not a necessary cause. Following a counterfactual analysis (“If the patient had not smoked, would a case of lung cancer also not have occurred?”), one can conclude that a case of lung cancer cannot be attributed to smoking. All that can be done is to express confidence in a judgement about whether smoking may have caused or contributed to the manifestation of the cancer.

A13. Causal relationships in science can best be established by experimentation, where specific hypotheses can be directly tested, with counterfactual conditional questions, under controlled conditions. Such experiments differ fundamentally from observational (i.e. non-experimental) studies. In experiments, parameters are deliberately manipulated for the purpose of studying outcomes and this permits testing and verification of hypotheses and eventually the establishment of causal relationships. In observational studies, no such manipulation is undertaken and therefore causal relationships are much more difficult to establish. For example, in medicine, randomized controlled trials of a new drug under laboratory conditions would be seen as experiments and may well lead to the establishment of causal relationships. On the other hand, studies of the health of populations exposed to a hazard (epidemiological studies) are essentially observational in nature and, without the ability to control relevant parameters and the application of the internal norms of empirical science (e.g. coherence and reproducibility), causal relationships are difficult to establish; a strong association in itself is not

sufficient to prove causation. A brief recollection of the key features of epidemiological studies of populations exposed to a noxious agent and their limitations follows (see also annex A of [U10] and annex B to this report for more detailed discussion with respect to radiation exposure).

2. Epidemiological studies

A14. For obvious ethical reasons, humans cannot usually be deliberately exposed to a noxious agent under experimental conditions. Thus, observational (epidemiological) studies are essential if one wishes to determine the actual health impact of a noxious agent on human populations. To conduct these studies, epidemiologists have to take advantage of situations in which populations have already been exposed or may be exposed in the future to the noxious agent under conditions over which the investigators have no control.

A15. Epidemiological studies can be “descriptive” or “analytical”. Descriptive studies (e.g. geographical correlation studies, often termed “ecological studies”, in which disease rates based on data aggregated over geographical areas are compared with aggregated data on levels of exposure to a noxious agent) are conducted to generate hypotheses. The possibilities for bias* and confounding* in such studies are well known and they cannot be used to evaluate convincingly causal relationships (see annex A of [U10]). In contrast, analytical studies are conducted to test hypotheses and establish quantitative relationships. They are commonly of two types: cohort and case–control. In a cohort study, subjects are selected on the basis of their exposure and then the frequency of occurrence of health effects is observed over a period of time. In a case–control study, they are selected on the basis of observed health effects and then their exposure is determined.

A16. Observational studies by themselves rarely establish causality, but rather indicate associations, correlations and trends, for which confidence can be expressed for the fit of various mathematical descriptions to the data. A major challenge in observational studies is to balance (*a*) the chance of missing an important result or missing a signal against the statistical noise (false negative) with (*b*) the chance of wrongly characterizing a spurious result or detecting and modelling the noise as if it were significant (false positive) [A3].

A17. When a statistically significant association is repeatedly found in different and independent analytical studies, the confidence that a causal relationship exists is increased. When a statistically significant association is repeatedly not found in different epidemiological studies, the confidence that a causal relationship exists is decreased, although, even then, the absence of an association does not necessarily imply the absence of a causal relationship. Causal inferences are strengthened when dose–response gradients are apparent and when the strength of the associations are high.

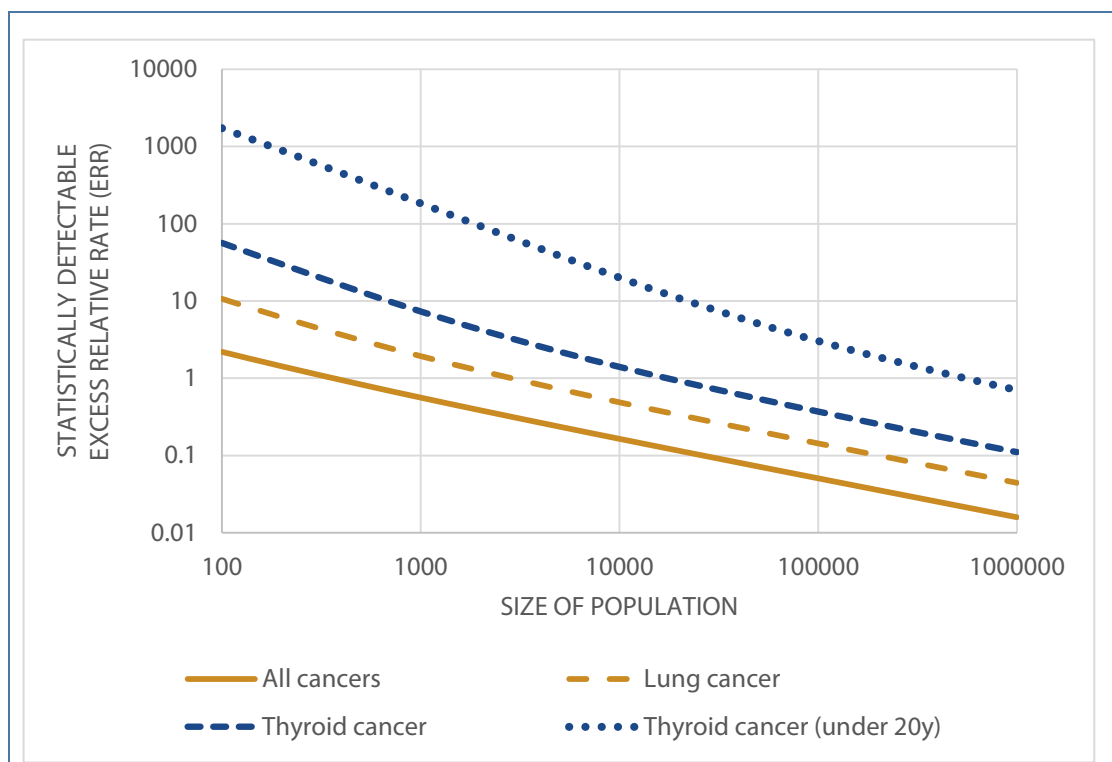
A18. *Uncertainties.* The results of observational studies can be spurious because of uncertainties of two types: (*a*) those resulting from chance, also known as “aleatory uncertainties”,* which are due to stochastic (random) variation in observations or measurements (e.g. the statistical power and sample size is too small to detect the outcome under investigation ([U10] annex A on cancer epidemiology), [I13, N5]); or (*b*) systematic errors,* also known as “epistemic uncertainties”,* which are due to a lack of knowledge (see also [N2]), and include possible bias (e.g. there is something inherently wrong in the study design [M1], or there is confounding, i.e. there are other causes—counterfactual conditional questions that need to be considered—that could not be adequately accounted for in the analysis [T3]).

A19. A major source of aleatory uncertainty in epidemiological studies relates to the random fluctuations in the numbers of health effects observed in any given time interval. This influences the ability to discern small changes relative to the baseline frequency of disease occurrence. This problem

is analogous to that of discerning a signal from among the background noise in the physical sciences. The ability to discern a genuine signal depends on the statistical power, the size of the epidemiological study and the baseline frequency of disease occurrence. Figure A-II illustrates the difficulty of discerning an excess relative rate (ERR)* of radiation-induced cancer for different sizes of ideal cohorts.

Figure A-II. Illustrative example of size of cohort study needed to detect an excess relative rate

The graphic illustrates the minimum detectable excess relative rate (ERR) for ideal cohort studies of two equal population sizes, assumed to be perfectly matched with no confounding factors or bias [W8]. The baseline incidence rates for the four disease classes were based on [N1]; the significance level used was 5% and the statistical power 80%; a one-sided test was used; and the notional studies were assumed to continue for 10 years. The four disease classes considered were (a) all cancers combined; (b) lung cancer; (c) thyroid cancer; and (d) thyroid cancer diagnosed below age 20 years. The graph shows that for two perfectly matched populations of 100,000 people, the minimum detectable ERR is around 0.05 for all cancers; for smaller populations and other cancers the minimum detectable rate is much higher. In practice, the minimum detectable ERR will be higher still because of the difficulty to perfectly match the two populations and to eliminate the effects of confounding factors



A20. In addition, epistemic uncertainties, such as the presence of “selection bias” and “information bias” and the ability to account for confounding factors, limit the confidence that can be placed in a signal, even if it is statistically significant (see annex B for further discussion of these sources of uncertainty). Key to avoiding some of these and other biases that can occur when analysing data is to ensure that a protocol be defined in advance of a study, which defines the health outcomes to be measured, criteria for measuring disease rates, the baseline frequency to be used, how to account for people lost to follow-up, and what statistical tests are to be used [M1].

A21. Effectively, there is a minimum detectable increase in the frequency of disease occurrence for epidemiological studies of any realistic size of the study population [D3], below which the chance of finding spurious results becomes ever larger [I13] (essentially any excess frequency of disease

occurrence is in the noise). Nevertheless, there remains a possibility that sensitive subgroups exist within the population (such as young children or cancer-prone subgroups) for which high excess relative rates of specific disease types might still be discernible.

A22. *Consequence of multiple comparisons in epidemiological studies.* In many epidemiological studies, tests are made for increased frequency of several types of disease simultaneously (the problem of “multiple comparisons” as discussed in section I.F, annex A of [U10]). Consequently, because statistically significant results can arise by chance alone, the more diseases that are considered in the same study, the more likely that a statistically significant result can appear by chance, and thus lead to spurious conclusions. Although there are statistical methods that attempt to account for multiple comparisons [R2], caution is still needed in interpreting any association as causal. Multiple comparisons are of particular concern in studies when the signal (apparent increased frequency of disease occurrence) is small compared with the noise (baseline frequency of disease occurrence in the population studied). For example, one statistical test in twenty will, on average, be statistically significant (at the 5% level) by chance. Furthermore, in a study that considers the frequency of occurrence of ten independent types of (for example) cancer, the probability of at least one of these cancer types having a statistically significant increased frequency of occurrence at the 5% level is about 40% purely by chance alone and thus any such observed increase should not be attributed to radiation exposure without corroboration [U10]. In order to increase confidence in a conclusion from one study, additional independent studies are needed that give consistent results.

A23. Other sources of uncertainty include publication bias, whereby studies that have a positive result are more likely to be published than ones which do not indicate anything significant. Some techniques exist to indicate the extent of publication bias [E2, M1]. The Committee itself has to be aware of such possibilities for bias when evaluating published studies and drawing general conclusions.

A24. There is no generally accepted theory of “provability” to combine the results of many independent and often disparate studies to establish causation. Nevertheless, the consistency of results of many independent studies—epidemiological as well as laboratory experiments, for example, with animals—coupled with sound biological reasoning can be evidence for a causal association. Confidence that a factor A (e.g. radiation exposure) might be the actual cause of an observed increase in the frequency of disease occurrence B (e.g. cancer) can be obtained by application of the “Bradford Hill guidelines” (table A1). This common-sense approach to judge causality was used in the Surgeon General’s Report [O1] that concluded that cigarette smoking was a cause of lung cancer, and in reports of the International Agency for Research on Cancer (IARC) [I2, I3, I5] that concluded that ionizing radiation was a cause of cancer. These bodies relied most heavily on the consistency of findings in multiple studies, the strength of the association, whether a dose–response relationship (biological gradient) was observed and biological plausibility. These guidelines have been extended in recent years, particularly in the development of evidence-based medicine [M1].

Table A1. Bradford Hill guidelines

A checklist for assessing evidence of causality [H6]

<i>Factor</i>	<i>Guideline</i>
Strength	Strong associations (i.e. large relative rates) are particularly compelling because, for weak associations, it is “easier” to imagine that another possible cause might be responsible for the association. However, a small association does not mean that there is no causal relationship
Consistency	Consistent findings observed in different studies, by different investigators, in different places, circumstances and times, increases confidence in causation
Specificity	Two variants of specificity are (a) that a cause leads to a single outcome, not multiple outcomes; and (b) that an outcome has one cause, not multiple causes ^a (e.g. polio is caused by the poliovirus)
Temporality	The cause has to occur first, followed by the outcome, and within a credible timescale, i.e. for cancer the increase does not occur immediately after exposure because there is a minimal latent period* (interval between exposure and disease manifestation) of a few years
Biological gradient	Greater exposure to the hazard should generally lead to larger outcomes. Sometimes the mere presence of the hazard can trigger the outcome. In other cases, an inverse relation is observed: greater exposure reduces the outcome at high exposure because of increased cell killing
Plausibility	A plausible biological mechanism between cause and outcome is helpful, although not always available, owing to limited knowledge
Coherence	Coherence between epidemiological data and generally known facts of the natural history and biology of the disease increases confidence in causation—e.g. radiation exposure does not cause polio (although it could conceivably increase susceptibility)
Experiment	Occasionally it is possible to appeal to experimental evidence (does the removal of a suspected factor change the frequency of occurrence of a specific health effect in a population?), although it is unusual to have genuine experimental evidence available from epidemiological studies of populations exposed to noxious agents
Analogy	Analogy relates to similar types of exposure as the one under study causing similar health effects (e.g. if one type of radiation (e.g. gamma rays) causes a particular cancer, then another type (e.g. neutrons) might also be expected to cause that cancer). Like specificity, it is a relatively weak guideline and is not often used

^a This aspect of specificity is related to conducting a counterfactual analysis, i.e. whether other causes of the disease under study can be excluded as alternate explanations for the observed association.

A25. If the evidence is sufficiently compelling, and consensus among the scientific community so high that all reasonable challenges are successfully addressed, then the causal relationship may be deemed proven⁷ as an established scientific fact (such as the link between smoking and increased frequency of occurrence of lung cancer). After successful counterfactual analysis, an increased frequency⁸ of disease occurrence may thus be attributed to the cause, even if an individual instance of the disease cannot be attributed to the cause.

⁷ As mentioned earlier, hypotheses and causal relationships can only be “deemed” proven, i.e. the scientific community at large has a very high degree of confidence in them. It cannot be ruled out that, over time, with new information, confidence may fall, and there may be a need to change the explaining hypothesis and causal relationship.

⁸ These studies often quote results in terms of risk (e.g. excess relative risk) but in this annex risk is used in a prospective sense (see glossary), and observations are expressed in terms of frequency or rates (e.g. excess relative rates).

B. Science-based inference

A26. Inference is the process of drawing conclusions from scientific observations in the presence of uncertainty. Two principal approaches for statistical inference are relevant: (a) frequentist inference, where an experiment is considered as one of an infinite sequence of possible repetitions of the same experiment, each capable of producing statistically independent results. It interprets probability as the limit of its relative frequency in a large number of trials; and (b) Bayesian inference, which interprets probability as a quantity assigned to represent a state of knowledge or state of belief, and involves a logical process to update estimates of quantities as new information becomes available.

A27. If causation has been deemed proven, well-founded predictions (i.e. statements that a particular thing will happen in the future) can be made (based on experimental evidence, together with estimates of uncertainty) that can be considered as being based on hypotheses that have been tested and deemed proven. The inferences drawn from frequentist and Bayesian approaches often yield similar results in terms of confidence in the predictions. Otherwise, if the evidence and consensus are as yet insufficient to confirm causation, only conditional predictions (i.e. statements that a particular thing will happen that are conditional on the assumptions and models used in making the predictions) can be made (again with estimates of uncertainty); these predictions are however based on hypotheses that are not deemed proven. Bayesian inference is usually preferred over frequentist inference to make such conditional predictions, because other data and assumptions can be more explicitly incorporated.

A28. Often, information that a particular agent may be hazardous to human health derives from experiments with animals exposed to relatively high levels. As mentioned above, it may not be feasible to test hypotheses generated from such information through observational (epidemiological) studies of humans exposed to that agent, because:

- (a) The health effects are very difficult to measure for technical reasons;
- (b) The health effects occur infrequently and thus the number of health effects in an exposed population is so small (and, correspondingly, the study group would have to be extremely large) in order to obtain a valid result; a serious problem for an extremely large study is that it is difficult, if not impossible, to control for bias and confounding factors) [L1, L2];
- (c) The study design would be unethical (e.g. deliberately exposing people to the noxious agent without any benefit to them);
- (d) The studies would take too long (i.e. many years or even several decades).

A29. Hence, in this case, the crucial internal norms of empirical science of testability (and reproducibility) cannot be fulfilled. Three main alternatives are available:

- (a) Excluding untestable hypotheses from consideration;
- (b) Making conditional predictions for risk estimation;
- (c) Incorporating non-scientific concerns.

A30. *Excluding all untestable hypotheses from consideration.* This is the pure scientific approach, but may simply not be an option, if science-based decisions, for example, regarding health protection are required.

A31. *Making conditional predictions for risk estimation.* Based on the available scientific information and understanding, it may be possible to generate science-based extrapolations, models and estimates, and to characterize uncertainty. Such science-based estimates can then be used to inform the decision-making process. The strategy is to apply the scientific method, insofar as this is feasible, in order to ensure that the knowledge is as well characterized as possible. Even though the underlying hypotheses have not been (or cannot be) tested and thus some of the traditional internal norms of empirical science are not respected, the hypotheses still have to be well founded and subscribe to other internal norms of empirical science, such as consistency, coherence, openness and plausibility [T6].

A32. This approach uses science-based models and improves them by incorporating empirical knowledge (possibly using Bayesian approaches, discussed in detail in annex B). Multiple model inference has also been used to represent more than one biologically plausible hypothesis (see annex B, section III.C, paras. 60-61). However, knowledge stemming from these hypotheses, which are currently not deemed proven, is considered not scientific in the strict sense, because certain internal scientific norms—testability and reproducibility—cannot be followed. Nevertheless, it has important contributions to make in the application of science.

A33. It is important that scientists communicate not only the inferred risk, but also its associated uncertainties and assumptions, and make statements as to the general credibility of the analysis in terms of health outcomes. The work is often performed by the same scientists that otherwise do rigorous hypothesis testing, and the results are presented in the same (quantitative) way as well-corroborated evidence on which there is scientific consensus. To avoid confusion, it is crucial to recognize the special status of these conditional predictions.⁹ Unfortunately, the distinction is not always made clear.

A34. *Incorporation of non-scientific concerns.* The third alternative—incorporation of non-scientific concerns—may or may not use conditional predictions. In this case, account is taken of norms external to science such as social responsibility, ethics, utility, prudence, precaution and practicality of application. The use of such approaches is outside of the Committee’s remit, but, for the sake of giving context to the discussion, some of the approaches are mentioned here. They include:

- (a) *Prioritizing hypotheses:* Although it may not be feasible to test a hypothesis, knowledge of mechanisms, models, and inferences may make one hypothesis more plausible than another;
- (b) *Assuming a consequence:* A health effect can be assumed to be a consequence of exposure to a noxious agent when a defined set of criteria are satisfied;
- (c) *Precautionary approach:* The precautionary approach can be described in the following way: “When human activities may lead to morally unacceptable harm that is scientifically plausible but uncertain, actions shall be taken to avoid or diminish that harm” [C4, E1, G2, H4, H7, H8, J4, J5, T1, W9]. In some situations, however, where it is not possible to know whether there is a positive or negative impact from exposure to a hazard, it may be important to consider the consequence of false positive as well as false negative assumptions when making decisions.

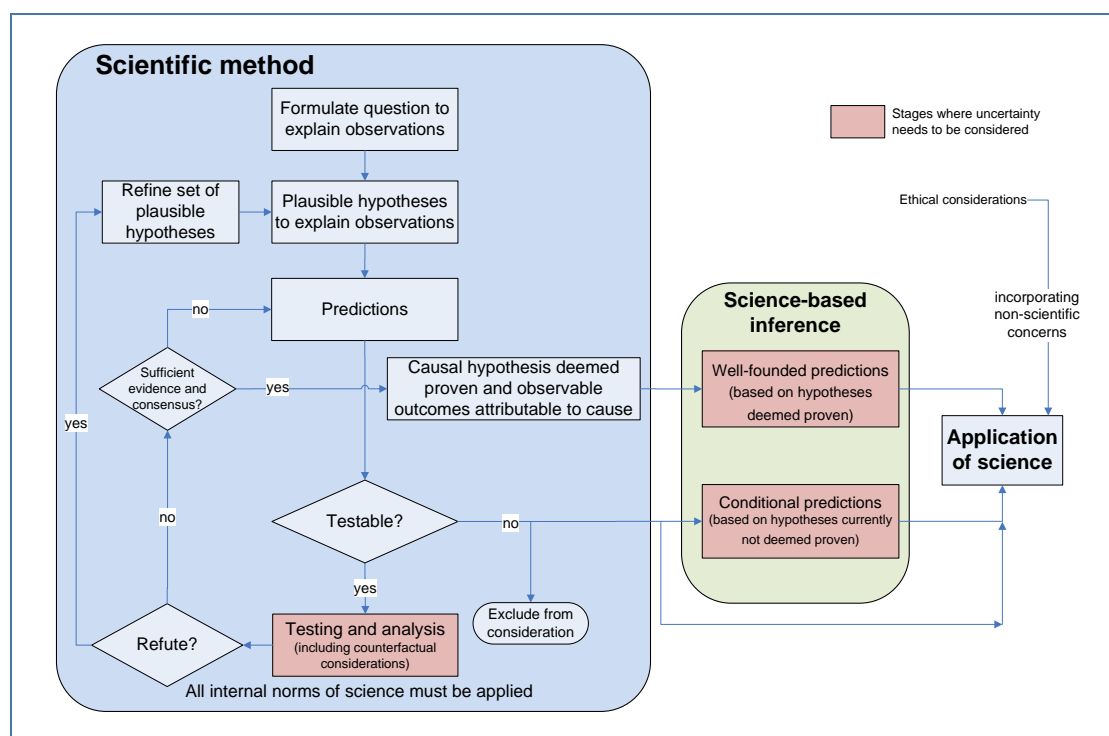
⁹ Popper defined hypotheses that were not testable or falsifiable as “non-science” [P4]. Weinberg coined the term “trans-science” to be “questions that can be asked of science, but cannot as yet be answered by science” [W4].

C. Summary of basics

A35. The relationship between scientific method, science-based inference and the application of science is illustrated schematically in figure A-III. A clear distinction is made between (a) what results from hypotheses in empirical science that can be deemed proven—and thus what can be attributed to a particular cause; (b) what can then be a well-founded prediction (i.e. stated with confidence that, under defined conditions, a particular thing will happen in the future); and (c) what conditional predictions can reasonably be made based on scientific evidence but for which the underpinning hypotheses are currently not deemed proven.

Figure A-III. Relationship between scientific method, science-based inference and application of science

The specific internal norms that guide the activities of scientists in applying the scientific method include truthfulness, consistency, coherence, testability, reproducibility, validity, reliability, openness, impartiality and transparency [T6]



III. ATTRIBUTING OBSERVED HEALTH EFFECTS TO RADIATION EXPOSURE

A36. More than 100 years of experimental radiation research have provided extensive information on the mechanisms by which radiation exposure can lead to health effects. Radiation exposure can have actions at the level of molecules, chromosomes, cells, tissues, organs and complete organisms. The main subcellular targets for radiation damage are the DNA molecules residing in the chromosomes. The damage might be directly within the DNA molecule (such as strand breaks or modification of

nucleotides) and/or epigenetic effects (like alterations of gene expression). While the damage is usually repaired, the integrity of the DNA may not always be restored perfectly, which can cause the cell to die. Alternatively, viable cells may survive with DNA mutations that affect cellular behaviour.

A37. Some cellular changes following radiation exposure may ultimately result in observed health effects, but some may not. For example, radiation can induce chromosomal aberrations in circulating white blood cells that may not result in observable health effects in the individual (see paragraph A50). Moreover, the killing of a small number of cells is unlikely to result in health consequences. On the other hand, extensive death of stem and progenitor cells in various tissues after high doses of ionizing radiation causes observed health effects, such as severe haematopoietic or gastrointestinal damage, skin burns and ulcers. These so-called “deterministic effects” usually occur within a short time (hours or days) after the exposure, although they can occur later in life. Deterministic effects typically occur after acute exposure to high doses, in excess of a “threshold” dose, with the severity of the health effect increasing with the dose above this threshold dose. They result from the depletion or the malfunctioning of a sufficient number of cells to cause observable damage to the organ or tissue, and, if the damage interferes with critical functions of the body, they can lead to the death of the individual—for example, about half of a healthy adult human population would die within 60 days, if exposed to an acute whole-body dose of 4 Gy of gamma rays and no medical care were given. There are well-documented observations of deterministic effects in the scientific literature, primarily on people accidentally exposed to high doses of radiation [U5, U14].

A38. If a damaged cell is not killed or otherwise rendered inactive, DNA mutations may be transmitted to the cell’s progeny and, ultimately, it is believed, result in observed health effects in the individual. If mutations in genes in somatic cells lead to initiation, promotion and/or progression of malignant cells, cancer may develop in the tissue or organ of the individual. Such cancers may occur a long time (many years) after exposure. An increased frequency of occurrence of some cancer types has been observed in epidemiological studies of populations exposed to moderate doses of radiation [U10]. If the mutations are in germ cells (namely, those that transmit genetic information to an offspring of the individual), this may result in heritable health effects in an offspring. The possibility of heritable health effects has been demonstrated in animal studies [U9]. However, extensive studies of the children (resulting originally from the germ cells) of survivors of the atomic bombings in Japan and of the children of patients treated with radiotherapy have not been able to discern a statistically significant increased frequency of occurrence of heritable effects [U9].

A39. Because the frequency of occurrence, rather than the severity, of the health effect is related to the exposure characteristics, these health effects—cancer and heritable effects—are termed “stochastic effects”. At moderate doses, the frequency of occurrence of certain cancers in an exposed population appears to increase with increasing radiation dose, while at higher doses, the rate of change of frequency per unit dose decreases because of the competing influence of cell killing or sterilization (annex F [U5], annex A [U10]). A critical point is that, at present, there is currently no way of distinguishing pathologically whether or not a specific observed cancer in an individual is caused by that person’s exposure to radiation.

A40. The classification of harmful health effects from radiation exposure into deterministic and stochastic is summarized in table A2. This classification, while not entirely appropriate from a purely scientific perspective, is made because the Committee has used the terms previously and they are widely used for the purposes of health protection. The scientific evidence for these health effects is discussed in the following paragraphs.

Table A2. Features of deterministic and stochastic effects [U2, U3, U6, U8, U9, U10, U11, U14, U15]

Feature	Deterministic effect ^a	Stochastic effect ^a
Initiating radiation action ^b and presumed biological mechanisms	Radiation-induced killing or loss of function of many cells simultaneously at the tissue level	Radiation action on a single cell The cell with a radiation-induced transformation must survive and may need to undergo further transformations to lead to a cancer or heritable disease
Manifestation	Health effect occurs following acute exposure above threshold values of dose. The severity of the health effect increases with dose above the threshold values	The probability, but not the severity, of the health effect is related to the dose, the exposure conditions and characteristics of the individual exposed, in particular, the sex of the individual exposed and the age at exposure; in addition, there are people who may be genetically predisposed to such health effects
Examples	Non-cancerous skin lesions (such as erythema, burns, dry or moist desquamation), the radiation syndromes (cutaneous, haematopoietic, gastrointestinal, and central nervous system), epilation; impact on fertility; congenital malformations and mental retardation after in utero exposure	Cancers which individually are indistinguishable from those arising from other causes
Evidence	Direct robust evidence from the responses of patients undergoing radiotherapy and of individuals who have received high exposures as a consequence of radiological accidents Results of experiments on animals	Direct evidence mainly from statistically significant increases in frequency of occurrence of various cancers in populations exposed to moderate or high doses. There are statistical limitations & confounding influences that hinder demonstrating health effects at low levels of exposure Heritable health effects demonstrated in animal studies at high doses, but not in human populations
Scientific consensus	High degree of consensus on how radiation induces tissue damage; some understanding of repair mechanisms with time More scientific debate about late health effects	A degree of consensus on role of DNA mutation. Cancer development is believed to proceed in a multistep fashion. Other factors, such as adaptive response,* impact on the immune system, genomic instability,* and bystander effects,* may also modify development. These factors may not be relevant at moderate/high doses (because they are integrated into the exposure–response relationship evaluated in epidemiological studies), but their roles at low and very low doses are the subject of scientific debate [U7, U15] Consensus that heritable health effects in humans are plausible, but at a much lower frequency than the induction of cancer in the population exposed

^a *Deterministic effects appear relatively soon after exposure, and not as a result of doses accumulated from chronic low-dose-rate exposure. Because they involve major loss of cell function within a tissue, they are also referred to as “tissue reactions” [I10]. However, tissue reactions also include some health effects (such as cataracts and fibrosis) that are not determined solely at the time of irradiation but can be modified after radiation exposure. Historically, radiation-induced cataracts were considered to be deterministic effects with relatively high threshold doses. Recent studies have suggested a much lower threshold dose (0.5 Gy) than previously thought [I11] and even the possibility of a non-threshold response has been raised [A1]. Similar uncertainties for diseases of the blood circulatory system after radiation exposure have also been raised [I11, N2]. For scientific purposes, Hulse and Mole had proposed alternative terminology: “polycytic effects” (for deterministic effects) and “haplocytic effects” (for stochastic effects) [H9], although such terminology is rarely used.*

^b *The Committee distinguishes here between “radiation actions”, meaning all modifications induced in an organism, and “health effects”, meaning observed health disorders with recognizable symptoms.*

A. Deterministic effects

A41. There is a significant and robust body of scientific evidence about the occurrence of deterministic effects at high doses (table A3). Such health effects often have a progression of characteristic signs and symptoms, which facilitate discrimination between radiation exposure and other causes as the principal causing agent. There is a high degree of consensus among specialists on this body of knowledge and its interpretation [I11, U5]. Professionals, nevertheless, need to have a solid knowledge of the specific signs and symptoms that occur after radiation exposure in order to be able to attribute a deterministic effect in an individual to radiation exposure [G4].

Table A3. Approximate threshold doses for deterministic effects from acute exposure of adults to low-LET radiation

These examples have been selected to illustrate the approximate levels of dose that cause deterministic effects in adults and the associated time for the health effects to develop. The threshold doses were derived by the International Commission on Radiological Protection (ICRP) for radiation protection purposes [I11]

Health effect	Organ/tissue	Time to develop	Acute exposure (Gy)
MORBIDITY^a			
Temporary sterility	Testes	3–9 weeks	~0.1
Permanent sterility	Testes	3 weeks	~6
Permanent sterility	Ovaries	<1 week	~3
Depression of haematopoiesis	Bone marrow	3–7 days	~0.5
Main phase of skin reddening	Skin (large areas)	1–4 weeks	<3–6
Skin burns	Skin (large areas)	2–3 weeks	5–10
Temporary hair loss	Skin	2–3 weeks	~4
Acute pneumonitis	Lung	1–3 months	6–7
MORTALITY^b			
Bone marrow syndrome	Bone marrow	30–60 days	~1 ^c
Gastro-intestinal syndrome	Small intestine	6–9 days	~6 ^c
Pneumonitis	Lung	1–7 months	7–8

^a Derived by ICRP on the basis of approximately 1% incidence of morbidity or dysfunction in tissues and organs in adults.

^b Derived by ICRP on the basis of approximately 1% incidence of mortality in adults.

^c Assuming no medical care.

A42. For severe deterministic effects, many cells have to be either functionally inactivated [B4] or killed [F4]. Such a major impact on a tissue or the whole organism can be achieved only by absorbed doses typically in the high-dose range and delivered acutely. Many deterministic effects occur shortly after radiation exposure, frequently within a few days or months, so that a link between exposure and health effect is evident. Further, in general, these health effects rarely occur without radiation exposure. The sequence of events is informative: for example, in the case of skin damage, this can start with reddening of the exposed area of skin, followed by itching and skin breakdown within a few weeks, and non-healing ulceration at about 6–12 months. Thus, severe deterministic effects appearing soon after high-dose exposure can, in principle, be diagnosed in an exposed individual by a radiation expert and the health effect can be attributed to the high exposure with a high degree of confidence.

A43. However, at moderate doses and at longer times after exposure, individual cases of diseases such as fibrosis, cataracts and circulatory diseases that may be deterministic effects of radiation exposure cannot be attributed to radiation exposure. This is because (a) clinical diagnosis and pathological findings for such health effects cannot discriminate between radiation and other causes at the present time; (b) the baseline frequency of these diseases is high; (c) there are many other possible causes of these diseases; and (d) there are no characteristics that are specific for radiation (i.e. biomarkers).

A44. In the case of cataracts and circulatory diseases, it is currently unclear whether or not a dose threshold exists and whether the amount of damage is dependent on dose. According to the most recent findings, cataracts, which have a high baseline frequency, are not typical deterministic effects as was originally thought [A1].

A45. Because of the well-known and readily observable consequences of high doses, radiation experts may in many cases confidently attribute a particular deterministic health effect to acute radiation exposure (and attest as such). In attributing, radiation experts must nevertheless still be able to eliminate possible alternative causes (i.e. by conducting a counterfactual analysis). Case studies I and II in appendix B illustrate some of the challenges facing radiation experts in attribution, even for deterministic effects.

B. Stochastic effects

1. Prospects for attribution of an observed stochastic health effect in an individual to radiation exposure

A46. In contrast to deterministic effects, the occurrence of a stochastic health effect depends on transformation, that is, on the modification of a cell that changes its original characteristics without preventing its proliferation. There are known to be several agents that can initiate such a transformation, and the relatively high baseline rates of cancer and heritable effects in an unexposed population provide evidence that there are many possible causes. What is critical for discussing attributability is whether a stochastic effect caused by radiation exposure can be distinguished from one that is not caused by radiation exposure (i.e. applying counterfactual analysis). A number of avenues need to be explored.

A47. Firstly, there is no doubt that genetic predisposition to contracting cancer exists. Various diseases with congenital chromosomal aberrations and genetic diseases are associated with increased frequencies of either very specific types of cancer or with a general increase of all types of cancers (for a comprehensive review see [I6]). Some very prominent examples are: (a) Down's syndrome (increased frequency of childhood leukaemia [D5]); (b) ataxia telangiectasia (increased frequency of acute lymphoblastic leukaemia [T4] and other cancers [M3, S2]); and (c) xeroderma pigmentosum (increased frequency of melanoma due to exposure to ultraviolet radiation [K4]). Some of these diseases, such as ataxia telangiectasia, are characterized by an increase in cancer frequency, but also by an enhanced radiosensitivity resulting in severe side effects after radiotherapy [P3]). However, even if someone with ataxia telangiectasia, for example, contracted acute lymphoblastic leukaemia following radiation exposure, the leukaemia could not be unequivocally attributed to the radiation exposure.

A48. Individual radiosensitivity is not confined to those with congenital chromosomal aberrations and genetic diseases, but is a general phenomenon. As individual radiosensitivity is very important in radiotherapy, many studies have looked for ways to assess the radiosensitivity of individual patients before radiotherapy [B5, C5, T5]. However, many factors are involved, and it is unlikely that the determination of a single factor would be sufficient. In addition, it is still a matter of discussion which cell type and end point is suitable for a test of individual radiosensitivity. Even then, if suitable factors could be identified that could be applied to exposures substantially below those received in radiotherapy, it would still not be possible to use them to attribute a manifest cancer in an individual to radiation exposure.

A49. Epidemiological studies combined with information from radiobiological studies and some understanding of the mechanisms involved in the induction of cancer following radiation exposure have been successful in determining the radiosensitivity of certain groups to developing a particular cancer. Only if the baseline frequency of a particular type of stochastic effect were low and the radiosensitivity for a health effect of that type were high would the attribution of a health effect in a particular individual to radiation exposure be plausible, particularly if that exposure were high. For example, for a child who contracted papillary thyroid cancer about three or more years [H5] after receiving a high dose to the thyroid from exposure to radioiodine in the months after the Chernobyl accident, then attribution of the thyroid cancer to the high dose to the thyroid may be plausible [W7]. But even then, the health effect in an individual cannot be unequivocally attributed to radiation exposure, owing to other possible causes (recognizing that radiation may not act as a sole cause, but as a contributory factor in the manifestation of disease). In order to attribute a cancer in an individual to radiation exposure, it would be necessary to establish some marker that specifically serves this purpose.

A50. Another avenue to consider is that of biological indicators of radiation exposure, such as those summarized in table A4. However, these indicators only provide a means of determining radiation dose; again, they do not guarantee that a health effect will subsequently manifest in the exposed individual or descendants. Furthermore, none is uniquely associated with radiation exposure. Consequently, they cannot be used to attribute a manifest cancer in an individual to exposure received previously.

A51. Up to now, no biological indicator has been found that is able to uniquely identify radiation-related cancers or heritable effects and thus could be used as a biomarker. If such a biomarker could be found, it would greatly improve the ability to attribute a stochastic health effect in individuals to radiation exposure. There are, however, techniques available that can be used to attribute cancers to chemical inducers (e.g. by an analysis of DNA adducts [F1]) or to ultraviolet radiation [B12]. These techniques are valuable in the sense that if a specific cancer can be unequivocally attributed to another agent, then ionizing radiation can be ruled out as the cause of this health effect.

A52. Thus, in conclusion, a manifest stochastic effect in an individual cannot be unequivocally attributed to radiation exposure, because radiation exposure is not the only possible cause and there are at present no generally available biomarkers that are specific to radiation exposure. Unequivocal differential pathological diagnosis is not possible in this case.

Table A4. Biological indicators of radiation exposure

<i>Biological indicator</i>	<i>Lowest dose range detectable in individuals after acute exposure^a (Gy)</i>	<i>Comment</i>	<i>Reference</i>
Blood cells	0.5–1	Reduction in numbers of lymphocytes. Early response to radiation exposure	[F3]
Hair	depends on the end point; ^b 0.05 to 2	Allows quantification of partial-body exposure	[H2]
Dicentric chromosomes	0.05–0.1	Some chemicals also cause dicentric chromosomal aberrations	[I1]
Reciprocal translocations	0.3–0.5	Useful to assess radiation exposures that occurred a long time previously	[T9]
Micronuclei	0.1–0.3	Sometimes important for monitoring many people within a short time interval	[M5]
Chromosomal breaks that are identified in prematurely condensed chromosomes	0.1–0.5	This indicator does not require a metaphase for expression, so that selection against heavily damaged cells does not occur	[H3]
Comets ^c		Valuable in the context of determination of repair capacity of individuals	[M6]
γ -H2AX foci	0.003	The most sensitive biological indicator found up to now	[S3]

^a The doses quoted give only a crude idea of the lowest dose range where radiation actions can be detected, because many factors play a role (e.g. how many events are scored, how experienced are the scorers, and whether scoring is conducted manually or with assistance from a computer).

^b End points are: chromosomal aberrations in the epithelium of plucked hair, apoptotic cells in the follicle (very sensitive), dysplastic hair, and width of the hair. Unfortunately, the most easily accessible indicators (dysplastic hair and hair width) are the least sensitive to dose (1 to 2 Gy).

^c Comets are not very suitable for the determination of radiation dose, because the DNA damage is repaired comparatively quickly. Comets are useful, however, as indicators of repair capacity after *in vitro* exposure of cells with about 2 Gy and tracking of the speed of repair for about 3 hours.

2. Prospects for attribution of an observed increased frequency of occurrence of a stochastic health effect in an exposed population to radiation exposure

A53. Specifically in the context of radiation exposure, observational (epidemiological) studies have involved a wide range of populations previously exposed to radiation for various reasons (e.g. exposure to natural sources of radiation, and to artificial sources, such as in military operations, in medicine, occupationally or accidentally). Descriptive studies can identify a possible association for further study. However, analytical epidemiological studies are the primary scientific tool used to critically examine whether exposures to radiation increase the rate of occurrence of specific diseases. Examples of analytical studies that have provided information on the causal association between radiation exposure and frequency of occurrence of health effects include the Life Span Study of the survivors of the atomic

bombings in Japan, children exposed to radiation in the course of treatment for medical conditions, underground miners exposed to radon and its progeny, and patients who underwent radiotherapy.

A54. In quantifying the increased frequency of occurrence of cancer in an exposed population, the Committee has relied heavily on the results of epidemiological investigations (see, for example, figure A-IV). The Committee's latest evaluations of the relevant epidemiological studies of exposed populations were published in its UNSCEAR 2006 Report [U10]. These demonstrate statistically meaningful increases in the frequency of occurrence of certain cancers in populations exposed to moderate or high doses. They also provide quantitative estimates for the magnitude of those increases.

A55. Although radiation exposure is an established cause of cancer, there are a number of cancer types that have not been convincingly shown to be caused by radiation exposure. These include cancers of the rectum, prostate, pancreas and uterine cervix, and Hodgkin's lymphoma and chronic lymphocytic leukaemia. This does not necessarily mean that radiation-induced transformations do not occur in those tissues. For example, latency periods* might be so long that the cancers do not become manifest during lifetime (in a sense, a practical threshold) or the frequency of radiation-induced cancers in those tissues might be too low, relative to the baseline frequencies for those cancers, to be observable.

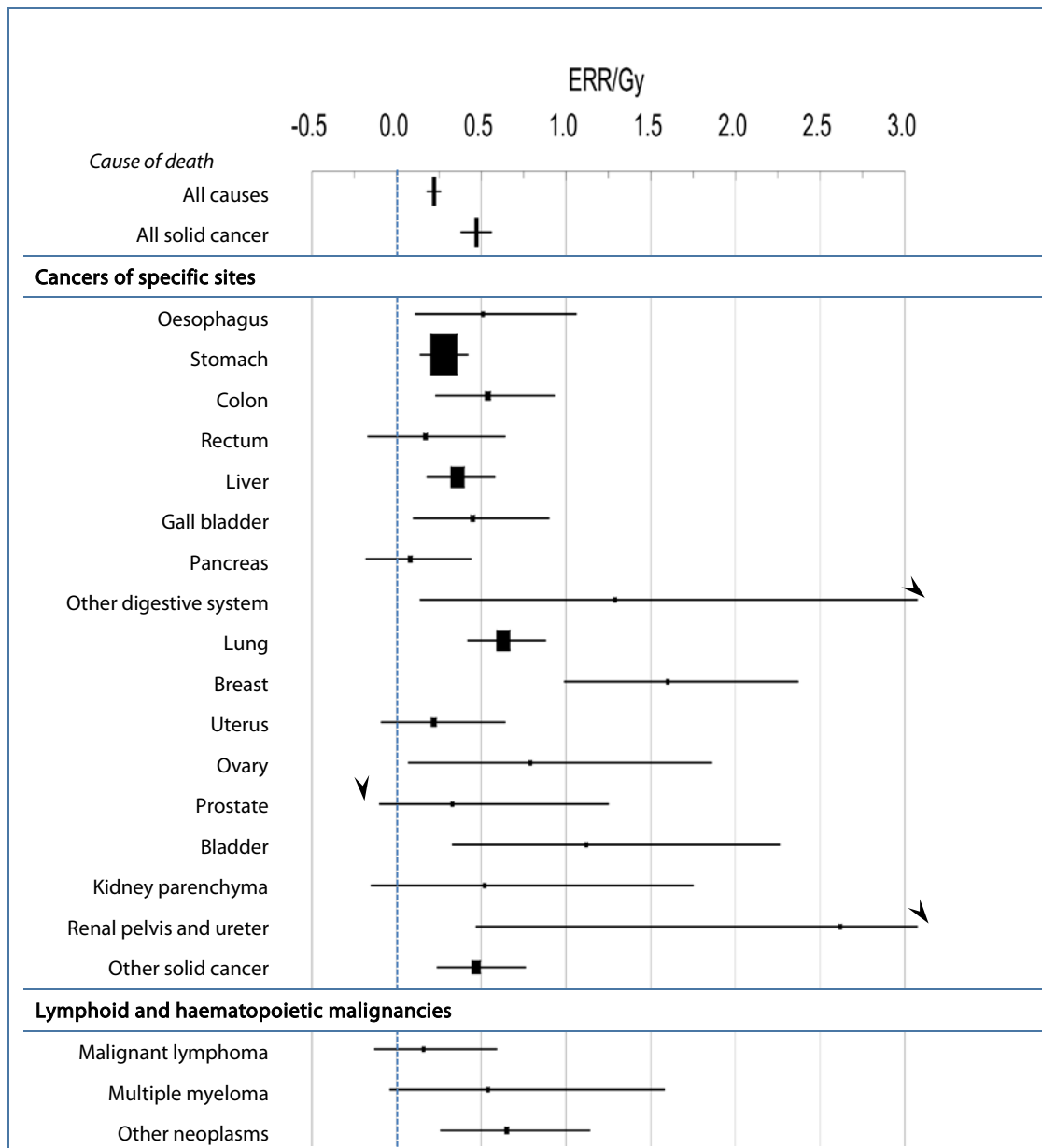
A56. Applying counterfactual analysis to the attribution problem for a population implies consideration of the question: if a population had not been exposed to radiation, would an observed increased frequency of occurrence of disease have been observed at the same time and of the same magnitude. As mentioned earlier, there is no generally accepted theory of provability to establish causation. Nevertheless, increased frequencies of occurrence of certain stochastic health effects in a population can be attributed to exposures in the moderate- and high-dose range when the evidence is compelling and consensus among the scientific community is high, in part by use of the Bradford Hill guidelines (table A1) and more recent developments [M1]. This can nevertheless be challenging because: (a) latent periods for cancer development are long; and, as mentioned earlier, (b) the baseline frequency of cancer occurrence and the variability* of that frequency with time are relatively high, and other uncertainties in both exposure and disease frequency estimation obscure any increased frequency of occurrence of disease in a population that might be due to radiation exposure, in particular, following exposure at low and very low doses (see annex B for detailed considerations of uncertainties).

A57. Knowledge of minimum latent periods, that is, the time interval between radiation exposure and the first possible diagnosis of a health effect, is important. In adulthood, the shortest latent period for leukaemia is around two years, and for solid cancers, a period of eight to ten years is frequently quoted (annex G [U8]). Nevertheless, a cancer that is diagnosed, for example, one month after radiation exposure definitely cannot be caused by such an exposure. The shortest latent periods have been seen for some types of cancer in children, typically a few years (annex I [U8], annex B [U16]). However, latent periods strongly depend on diagnostic capacities. With more sophisticated techniques that identify a solid cancer at a smaller size, latent periods will apparently shorten.

A58. Radiobiological experiments have established various causal relationships between radiation exposure and resulting actions in biological material. Epidemiological investigations have identified an association between an increased frequency of occurrence of many types of cancer and radiation exposure [U10]. However, there is not a complete understanding of how to combine the radiobiological and epidemiological information. Further, the various mathematical models that attempt to describe the radiobiological mechanisms are unable to quantify or describe a priori the increased frequency of cancer seen in human studies, especially following relatively low-dose exposures [D3, M2].

Figure A-IV. Observed increases in the frequency of mortality from site-specific solid cancers among the survivors of the atomic bombings of Japan

This graphic adapted from Ozasa et al. [04] is used here to illustrate observed excess relative rates per unit dose and the associated aleatory uncertainties at 90% confidence intervals. The uncertainty associated with extending the excess frequency observed among a living cohort over the rest of their lives is an example of epistemic uncertainty. The values for rectum, pancreas, uterus, prostate, kidney parenchyma and malignant lymphoma, while positive, are not statistically significant. An increased frequency of mortality from cancers in these organs cannot be ruled out, but there is no compelling evidence from this study to support causation. The arrows indicate confidence intervals that are beyond the limits of the graph or not specified



A59. *Uncertainties in dose estimation.* There are both aleatory and epistemic uncertainties in the measurements used in estimating doses. The aleatory uncertainties are particularly important when the levels of exposure are close to those that are typical from natural sources of radiation. For example, the stochastic nature of radioactive decay is inevitably reflected in any measurements of count rate or dose rate. Studies that investigate possible health effects from exposure at these very low levels are rarely, if ever, able to account for all the uncertainties in the dose estimation, and usually interpretation of the results depends on making reasonable but untested assumptions. Annex B discusses the questions of uncertainties (both aleatory and epistemic) in dose estimation in more detail.

A60. *Uncertainties in frequency estimation.* It is extremely difficult to detect excess frequency of occurrence of cancer and heritable effects by studying population exposures limited to low dose and very low doses [I9]. This is because, at low doses and, in particular, at very low doses, the plausible increased frequency of occurrence of stochastic effects is normally dwarfed by statistical and other variations in the baseline frequency of their occurrence. As a result, extremely large sample sizes (typically millions of people) would theoretically be required in these dose ranges for a statistically significant increase in frequency to be observed. The zone of noise depends primarily on the number of subjects in the population studied and the baseline frequency of incidence of the specific disease (see figure A-II earlier). However, because factors such as age and sex are apparently very important in determining the frequency of occurrence, it is important that the populations must be relatively homogeneous with regard to age and sex, or else these factors taken into account in analysis. Even then, the estimate would often be untrustworthy because of the lack of knowledge of, and thus inability to adjust for, other possible risk factors such as diet, genetic susceptibility, other environmental exposures and other demographic and lifestyle factors [L1].

A61. For rare diseases and highly radiosensitive subgroups of the population, for example, thyroid cancer following exposures in early childhood, a smaller sample size might be sufficient for a statistically meaningful increase to be detected than that required for a more common disease at older ages. Childhood leukaemia is also thought to be particularly susceptible to induction by radiation. Some studies of in utero radiation exposure have reported associations with leukaemia and other childhood cancers at doses from the use of X-rays estimated from historical literature to be of the order of 10 mGy [D4, W2] and the excess relative rate per unit dose for childhood leukaemia reported in the largest of these studies was comparable to that derived from the survivors of the atomic bombings in Japan exposed to higher doses as young children [W1, W3]. However, the conclusions of these studies are not accepted by many in the scientific community, and the causal nature of the association with low-dose prenatal X-ray examinations is still much debated [B11, I5, I8]. The case of in utero exposure illustrates the difficulty in interpreting—and obtaining scientific consensus on the interpretation of—reported increases in frequency when exposures are in the low-dose range, even when the populations exposed are large and assumed to be particularly radiosensitive.

A62. In summary, an increased frequency of occurrence of stochastic effects in a population could be confidently attributed to radiation exposure—provided that, among other things, the increased frequency of occurrence of the stochastic effect were sufficient to overcome the inherent statistical and other uncertainties. In this case, an increase in the frequency of occurrence of stochastic effects in the exposed population could be properly verified and attributed to exposure. If the baseline frequency of occurrence of the health effect in a population were low and the radiosensitivity for the relevant stochastic effect were high, an increase in the frequency of occurrence of stochastic effects could at least be related to radiation, even when the number of cases was small.

A63. Although demonstrated in animal studies, an observed increase in the frequency of occurrence of heritable disease in human populations cannot at present be attributed to radiation exposure; one reason for this is the large fluctuation in the baseline frequency of occurrence of these diseases.

IV. INFERRING RISK OF HEALTH EFFECTS FROM RADIATION EXPOSURE

A64. This section considers drawing inference from the existing scientific knowledge base (see figure A-III), specifically to make inferences about the risk of future health effects either for a population or an individual exposed to radiation. As discussed earlier (section II.B of this appendix), two main situations are considered: (a) where hypotheses regarding causal relationships have been deemed proven (i.e. well-founded predictions); and (b) where hypotheses regarding causal relationships have currently not been deemed proven (conditional predictions).

A. Predicting health effects and inferring risks where hypotheses regarding causal relationships have been deemed proven

A65. For exposure to high acute doses above the relevant thresholds, there is sufficient evidence, knowledge and scientific consensus regarding causal relationships to be able to predict relatively accurately whether or not there will be a deterministic effect in an exposed individual and, if so, the likely severity of that health effect. Such predictions have been sufficiently well tested in observations of the consequences of past high-dose accidental exposure such that they can be based on hypotheses regarding causal relationships that have been deemed proven and therefore can be regarded as valid. Thus, for example, physicians, on the basis of knowledge of the distribution in local tissue of the dose received in an accident, can determine with reasonable confidence the evolution of necrosis and, as a consequence, any surgical or other mitigating interventions needed. (This is not the case with those tissue reactions for which the deterministic nature is unclear, such as cataracts and circulatory diseases.)

A66. For exposures at moderate or high doses (or more strictly, at doses at which an increased frequency of occurrence of stochastic health effects has been observed in a population), there is also sufficient evidence, knowledge and scientific consensus on hypotheses regarding causal relationships to be able to predict with some confidence an increased risk of such stochastic effects in an exposed population similar to that for which evidence exists, based on so-called “frequentist inferences”. Again, such predictions can be regarded as well-founded.

B. Inferring risks where hypotheses regarding causal relationships have not been deemed proven

A67. As discussed earlier in section II.B of this appendix, for the cases where the crucial internal norms of empirical science (reproducibility and testability) cannot be fulfilled, three main alternatives are available: (a) excluding all untestable hypotheses from consideration; (b) making conditional predictions for risk estimation; and (c) incorporation of non-scientific concerns. While approach (a) could be argued to be the pure scientific approach, this is not an option, if science-based decisions, for example, regarding health protection are required,¹⁰ and it is not considered further here. This subsection now discusses matters related to approach (b), making conditional predictions for risk estimation. Approach (c), incorporation of non-scientific concerns, is discussed in the next subsection, application of science-based inference.

A68. With regard to approach (b) on making conditional predictions for risk estimation, there are a number of issues in extending the data from epidemiological studies to situations other than those under which the data were obtained. These include: (i) extrapolation of risks over lifetime, (ii) transference to another population; (iii) transference from one type of radiation to another; (iv) inferring risks from low-dose-rate exposure and (v) inferring risks from low and very low doses.

A69. These inferred risks of cancer are for a population. There are problems in applying them to an individual within a population. Firstly the concept of relative frequency has no meaning for the individual (the outcome for the individual is either that the health effect occurs or it does not). Average individual risks can be derived from populations of individuals with similar characteristics (e.g. age, sex, smoking, diet, lifestyle and other possible confounding factors) and this can inform the likelihood* of a disease occurring in the individual. However the reality is that any population will be made up of individuals with an “inter-individual” variability in their risks, and what is usually considered as the dose–response relationship is actually the relationship between the calculated population-averaged or average individual risk and the radiation exposure.

1. Extrapolation of risks over lifetime

A70. Because few cohorts have been followed until all individuals have died, epidemiological studies only provide data on increased frequency of cancer in irradiated populations that have been followed up to a certain date. Thus any observed increased frequency of occurrence of disease has to be projected over the lives of the remaining individuals to infer lifetime risks* for the population. Bayesian inferences (based on degrees of belief) or subjective assumptions have been used to take account of epistemic uncertainties (i.e. lack of knowledge) and to project increases in frequency of occurrence observed up to now into the future.

A71. Epidemiological studies provide information on the radiation-related increased frequency of many different cancer types as a function of age. This is compared with baseline rates of each cancer

¹⁰ The Scientific Committee’s mandate is to assess and report levels, effects and risks of exposure to ionizing radiation. Moreover the General Assembly in the preambular paragraphs to its annual resolutions on the effects of atomic radiation (e.g. resolution 66/70) specifically states its concern about the *potentially harmful* effects on *present and future generations* resulting from the levels of radiation to which mankind and the environment are exposed. While some have argued that the Committee should confine itself to information resulting from empirical science and hypotheses that have been tested and deemed proven, excluding all untestable hypotheses from consideration is not an approach that the Committee itself can adopt to meet the expectations of the General Assembly. As a consequence, the Committee has provided science-based inferences for risk estimation that are based on hypotheses currently not deemed proven, but considered to be scientifically plausible (see, for example, [U10]).

type as a function of age (ideally across many different exposed populations) with a view to modelling the difference between them, and projecting that to where observations do not exist. The two main modelling approaches are a multiplicative risk extrapolation (which assumes an increased risk from irradiation that is proportional to the underlying frequency of cancer) or an additive risk extrapolation (which assumes an increased risk from irradiation that is independent of the underlying frequency of cancer) [U10]. For some cancer types, it is not at all clear whether either of these approaches is correct, and expert judgement is required to select a plausible model or combination of models (see annex B).

A72. Other temporal factors often complicate the general application of evidence obtained from cohort follow-up studies of increased frequency of health effects in a population to estimating risks from radiation exposure. Difficulties arise with the multiplicative risk extrapolation model because its projections depend on underlying disease rates, which change over time owing to important non-radiation factors. For example, in western countries cigarette smoking has declined since 1945 and thus the underlying rates of disease have also declined. Health care has also changed over time and survival has increased for cancer patients. Thus, the application of multiplicative risk extrapolation models is problematic for projecting cancer risks due to irradiation. This and other issues related to extrapolating risks over lifetime are discussed further in annex B.

2. Transference to another population

A73. Despite the relatively large amount of data on the frequency of occurrence of radiogenic health effects,* the question of how to transfer risk estimates derived from one population, such as the Japanese survivors of the atomic bombings, to a different population remains unanswered. The available data suggest that there is no simple solution to the problem. It is also not clear in terms of mechanisms or biology how data on excess frequencies observed for one population should be transferred to another population with different baseline rates of the pertinent health effects. Approaches using Bayesian inference and assumptions have been applied to the problem, and the multiplicative and additive risk transfer models introduced above have also been used for the purposes of extrapolating results to other populations, taking account of factors such as age and sex [U12]. The inferred increases in cancer risk vary with age, with younger people generally, but not always, being more sensitive, and with the type of cancer [U16]. The uncertainties associated with such inference are discussed in further detail in annex B.

3. Transference from one type of radiation to another

A74. It is well known that to obtain the same biological result, different absorbed doses are needed depending on the type of radiation, expressed by the relative biological effectiveness (RBE). This is due to differences in ionization density, resulting in closely adjacent sites of damage in the case of neutrons, alpha particles and heavy ions, whereas X-rays and gamma and beta radiation ionize only sparsely along most parts of their tracks. Clustered sites of damage are more difficult for the cell to repair, which explain in part the higher RBE for densely ionizing types of radiation. RBE is a quantity that is determined experimentally by comparing the doses required to achieve a specific level of biological result.

A75. One issue with RBE is the choice of the reference radiation: X-rays or gamma rays are used frequently, but X-rays appear somewhat more effective in producing some end points than energetic gamma rays. The RBE also strongly depends on the end point studied. If, for example, chromosomal aberrations are used as an end point, X-rays may be more than a factor of two more effective than high-

energy gamma rays, whereas there is little evidence for differences in cancer induction in animal or human studies. Transference from one type of radiation to another and the associated uncertainties are discussed in much more detail in appendix C to annex B.

4. Inferring risks from low-dose-rate exposure

A76. In all the extrapolations and assumptions considered here, confident estimation of low risks is difficult with epidemiological studies, because of the underlying statistical limitations (aleatory uncertainties) and epistemic uncertainties (e.g. confounding). This is particularly a problem for low dose rates, and for low and very low doses (next subsection). An understanding of the mechanisms of cancer development after radiation exposure can assist in applying the information obtained from epidemiological studies to infer risks from exposure at low dose rates. In particular, the application of a dose and dose-rate effectiveness factor (DDREF) and the possibility of non-linear and threshold relationships need to be considered ([U6] annex F). The DDREF reflects the observation that, at least with respect to studies of cell killing and of cancer induction in animals, low dose rates have tended to result in fewer biological outcomes than expected on the basis of simple extrapolation from the results at high dose rates. However, doubts have been raised whether this also applies to cancer in humans [J3]. UNSCEAR in its 2006 Report estimated radiation risks without applying a DDREF [U10].

A77. A specific dose within a short time (a few days at most, usually less) will induce all the damage within that short duration of time, whereas the same dose given over longer time intervals either fractionated (in small portions followed by radiation-free intervals) or protracted (continuously, thus resulting in low dose rates) induces damage separated in time. The latter situation is more favourable with respect to mitigating the consequences for the entire organism. First, there are fewer possibilities for interaction among damaged sites. Second, there are not too many sites that need repair at the same time, thus, reducing the problem of damage not being repaired or being misrepaired. Third, the organism can tolerate that cells go into apoptosis, because not too many of them are affected at the same time; controlled repopulation eliminates problems associated with radiation-induced cell death in such a situation.

A78. Indeed, while acute doses exceeding the relevant threshold dose result in deterministic effects, the same dose delivered in a fractionated or protracted fashion may not ([H1, U3] annex J). The situation is much less clear in the case of stochastic effects, for cancer induction in particular. (For a more detailed discussion of dose and dose rate effectiveness, see annex B.)

5. Inferring risks from low and very low doses

A79. The fact that epidemiological studies of populations exposed at low and very low doses have so far generally not been able to unequivocally demonstrate an increase in the frequency of stochastic effects in a population, does not mean that there was no increase, but rather that any increase (had there been one) was too small to be detected or the power of the epidemiological analysis was too low to detect it. Those positive associations that have been reported (e.g. between fetal exposure to X-rays and an increased frequency of childhood cancer) could reflect an underlying action of low doses of radiation, but not necessarily, because of the difficulty in taking account of all confounding factors. Causation has therefore not yet been deemed proven in this case [U10, U13, W2].

A80. At low and very low doses, risk can be inferred using Bayesian inferences that consider: knowledge from disciplines other than epidemiology. Current understanding of the mechanisms that are

intermediate between radiation exposure and subsequent health effects is substantial enough to deem that the existence of risk at low and very low doses is plausible [U13, U15]. In principle, models that specifically represent biological mechanisms involved in carcinogenesis could help to improve confidence in quantifying estimates of cancer risk associated with low and very low doses. However, because understanding of the mechanisms is still limited, application of mechanistic models has, up to now, not appreciably improved the quantification of cancer risks at these levels of dose. Nevertheless, a strength of these models is their potential to explore the influence of the various postulated radiobiological mechanisms on cancer induction and thus to help provide insight into the inference of risk at these levels of dose [N3, P8].

A81. Extrapolations from data on the increased frequency of cancer among the survivors of the atomic bombings in Japan, who received acute exposures at either moderate or high doses, to the estimation of cancer risk for populations exposed at low or very low doses have been supported by, at least, two arguments:

(a) Among the survivors of the atomic bombings in Japan, the observed increased frequency of all cancers combined is largely consistent with a linear or linear-quadratic dose-response relationship over a wide range of dose levels (see UNSCEAR 2006 Report annex A [U10]). There is not, however, complete agreement on this [D6];

(b) The scientific consensus is that radiation-related DNA damage plays a fundamental role in the induction of carcinogenesis, even at doses as low as those from exposure to normal natural background radiation [I9, N7]. The DNA damage and repair per unit dose at low and very low doses has been assumed to be similar in nature to that at moderate doses, except that fewer cells are affected than at moderate doses.

A82. A number of plausible dose-response relationships for the risk of cancer following exposure at moderate, low and very low doses were shown in figure I of the main text. Some reasons for the specific shapes of the dose-response relationships are addressed in the following. This survey is not exhaustive, but is only meant to indicate that the curves are based on known mechanisms for cancer induction and are not just imaginary. This does not mean that all five are equally plausible; however, scientific debate continues as to which is the correct causal relationship. It might well be that under various conditions, different curves apply under different circumstances. Various plausible hypotheses are currently being considered:

(a) *Supralinear*. Some mechanisms would appear to indicate that the rate of change of risk per unit exposure would increase in the low- and very-low-dose ranges. A frequently cited example is the bystander effect, meaning that not only the cell that actually was hit by radiation shows damage, but also the neighbouring cells. Because the bystander effect diminishes with increasing dose, this mechanism taken on its own would suggest that the risk per unit exposure be higher in the low and very low dose-range than expected from observations in the range of moderate to high doses. Another hypothesis is that repair mechanisms need a certain amount of DNA damage in order to be activated. After low and, particularly, very low doses, the amount of damage might be too low to trigger repair. However, those unrepaired lesions might cause problems later in life;

(b) *Linear*. The essential hypothesis to support linear extrapolation (i.e. the LNT hypothesis) are: one modified cell is sufficient to generate a cancer, one hit by radiation can induce the necessary modification, and the defence systems (e.g. repair mechanisms and immune systems) are less than 100% effective. Under this hypothesis, even one energy quantum could induce a clinically manifest cancer, although the probability would be extremely low. With increasing dose, more cells would be modified and, thus, the chances that the defence systems fail, would increase, with an increasing

probability that a cancer will develop. Scientific results obtained during the past one or two decades challenge the LNT hypothesis. Recent studies of non-targeted effects and of gene expression suggest that cellular responses to radiation exposure at low doses may differ in nature from processes induced by exposures at moderate or high doses ([U10] annex B and [U11] annex C). The Committee has reviewed the evidence for non-targeted and delayed effects of radiation exposure ([U11] annex C). Biological responses have been shown to have non-linear dose dependences or even differ in nature at low doses from the response at high doses [M4, N4]. The dose-dependence of bystander effects clearly differs from linearity. It is characterized by a response at low doses that does not increase at higher doses. Portess et al. [P5] found that the induction of programmed death (apoptosis) of precancerous cells by normal cells is increased by exposures to gamma radiation with doses as low as 2 mGy. The response increased with doses up to around 100 mGy, but no further increase was observed at higher doses. Thus, bystander effects could in principle influence carcinogenesis at low doses, but may be obscured at moderate or higher doses by direct radiation actions. Linear extrapolation of estimates of cancer risk from exposures at moderate or high doses to lower doses does not take such bystander effects into account;

(c) *Linear–quadratic*. The hypothesis underpinning a linear–quadratic relationship is the idea that repair might be more effective following exposure at very low and low doses than at higher doses, simply because not so much work has to be done by the repair enzymes. In addition, fewer sites of damage in the DNA would result in fewer opportunities of interactions among the various sites of damage (e.g. among two double-strand breaks leading to a chromosomal aberration). It is also conceivable that some types of damage need several hits in order to be induced and the probability of several hits will decrease with decreasing dose;

(d) *Threshold*. One very basic hypothesis that would imply a threshold dose has to do with the question whether one modified cell is sufficient to generate a cancer. If more than one cell would be necessary, then a threshold, in the very-low-dose range, is probable. One possibility to avoid this conclusion might come from the reasoning that the bystander mechanism can modify the additional cells required to generate a cancer. The situation is even more complicated when one considers that other agents may contribute to the development of a cancer, so that radiation could not be deemed the only cause of a specific cancer.

Another mechanism that might introduce a threshold has to do with immunology. One of the functions of the immune system is the permanent control of the cells in the body. This is done by checking the outer cell membrane for specific markers that signal that this cell belongs to the body. Cancer cells frequently change their outer membrane giving the immune system the chance to detect and destroy them. If low radiation doses were to increase the effectiveness of the immune defence, it is conceivable that some additional spontaneously occurring cancer cells would be eliminated. If as many cancer cells were destroyed by the radiation-stimulated immune system as are produced by radiation, then a threshold dose would be expected, and an increase in the number of cases would be observed only when more cancer cells were produced by radiation than prevented by the more effective immune system.

There might also be a “practical threshold” if latency periods of specific cancer types were longer than the life time of the person;

(e) *Hormetic*. Extending what has been addressed in the last paragraph, if more cancers are prevented by radiation than induced, one gets some amount of protection against cancer, meaning that in a population exposed to rather low or very low doses, fewer cancers would be found, when compared to a population without exposure to radiation above that due to natural sources.

A83. The radiation protection community has assumed the so-called “linear non-threshold” dose–response relationship modified by a fixed DDREF for its purposes (see next section). This and the other dose–response relationships are plausible but currently none of them are definitively verifiable and therefore cannot be deemed proven or disproven. Further, some scientists [D6] and organizations such as the French Académie des Sciences have argued in support of a practical threshold for management of the risk of radiation-induced cancer [T7, T8], although this interpretation of the available evidence is controversial [B14, L5]. However, epidemiology alone will not be able to resolve the issue of whether there are dose thresholds for radiation risks. A better understanding of biological mechanisms is necessary, and many deserve attention in the ranges of low and very low doses: e.g. adaptive response, apoptosis, genetic predisposition, and genomic instability. Hopefully, experimentation to test the hypotheses surrounding the relevant mechanisms will help improve understanding of cancer risks in the ranges of low and very low doses.

6. Other issues related to inference

A84. *Inference from animal studies.* There is a considerable body of literature [K1] on the numerous factors that can influence radiation-related carcinogenesis in animals. These factors include the specific characteristics of the radiation (such as radiation type and dose, dose rate, dose fractionation, and dose distribution) as well as many other contributing elements that are not specific to the radiation exposure (such as the genetic characteristics, age and environment of the animal, dietary factors and whether specific modifying agents for radiation-related carcinogenesis have been utilized in the studies). Modifying factors for radiation-related carcinogenesis have been observed in both in vivo and in vitro systems. Agents have been identified that enhance (e.g. promoting agents) or suppress (e.g. preventive agents) radiation-related carcinogenesis. These agents in experimental model systems have been shown to lead to health effects equally as significant as other known modifying factors for radiation-related carcinogenesis (e.g. dose rate, dose fractionation, and linear energy transfer). Dietary factors play an important role in determining the yields of radiation-related cancers in animal model systems. It is likely that all these factors also influence estimation of radiation-related cancer risks in human populations.

A85. In some animal experiments, either threshold-type dose–response relationships have been observed (e.g. cancers of the ovary or thymic lymphoma in mice) or practical thresholds, meaning that the latency period is so long that it exceeds life expectancy (e.g. bone sarcoma in dogs and mice after alpha-particle exposure from long-lived bone-seeking radionuclides) [U4, U10].

A86. *Inferring risks of heritable disease.* In the case of a heritable disease, the modification of one cell (either sperm or oocyte) can be sufficient to induce the disease. There are indications that this also applies to the induction of the majority of cancers, meaning that they are of monoclonal origin [T2]. Both situations (heritable disease and monoclonal origin of cancers) are compatible with a linear non-threshold model. In contrast, there are other indications that quite a number of cancers are of polyclonal origin [P1]. If this were true, then one could imagine an effective threshold in the low-dose range unless the bystander effect produces the multicellular response required to initiate a cancer.

A87. While information on cancer risk has been obtained from epidemiological studies of populations exposed to moderate or high doses, the existence of a risk of heritable effects in humans has not been demonstrated even in populations exposed to doses of such magnitude. Models have, however, been developed to infer the risk of heritable effects in humans from the data on animals

exposed to high doses¹¹ [U9]. Clearly, such inferences of risk cannot be unequivocally verified or refuted at the present time.

A88. *Expressing confidence in the inference.* Uncertainty analyses attempt to quantify what is unknown, unreliable or indefinite. The quantitative expression of uncertainty is discussed in more detail in annex B, using the mathematical language of probability as an expression of the doubt about the true value of a quantity of interest. The Committee considers that it is reasonable to quantify the uncertainty about these projections when sufficient data exist to underpin the subjective uncertainty distributions. This can be done by generalizing estimates of risk from radiation exposure derived from epidemiological studies to populations that are substantially different, or exposed under very different conditions (see annex B). The projected increased risk of stochastic effects in an exposed population represents the population-averaged lifetime risk presumed to be due to the radiation exposure.

A89. The Committee has addressed the epistemic uncertainties associated with extending the observations of increased frequency of various stochastic effects in living cohorts over their predicted lifetimes. It had estimated excess lifetime mortality (averaged over both sexes and all ages in the population) for five specific populations: (a) for all solid cancers combined, 0.36–0.77% for an acute dose of 0.1 Gy and 4.3–7.2% for an acute dose of 1 Gy; and (b) for leukaemia, 0.03–0.05% for an acute dose of 0.1 Gy and 0.6–1.0% for an acute dose of 1 Gy [U13]. The statistical uncertainty of the estimates was assumed to be in the order of a factor of 2, and lower bounds of the confidence interval included zero. The Committee discusses a more detailed consideration of the epistemic uncertainties in annex B as part of a selected risk evaluation.

A90. The Committee notes that risks are unlikely to change dramatically just below the situation in which a statistically significant increased frequency in cancer has been detected [B13]. However, at lower and lower doses, quantification of epistemic uncertainty due to indeterminacy and ignorance (lack of knowledge) would have less and less information value and can be increasingly misleading. This combined with the aleatory (random) uncertainties makes accurate and valid quantification of risks at very low doses at the present time an impossible challenge. However, a gross underestimation of the risk from low and very low doses using these various plausible dose–response relationships is most unlikely since this would have been detected by those epidemiological studies that have been conducted.

A91. Annex B discusses representing uncertainty in risk estimation associated with incomplete understanding of biological processes by applying subjective weights to different models and assumptions. The resulting weighted quantity represents the ensemble degree of belief in the risk estimate, and has been termed “plausibility” by Beninson and Lindell [B3]. An expert elicitation process to quantify degrees of belief given the evidence can be applied [G3], but such assessments always have to be treated with utmost care, because expert opinion may well differ in the absence of clear evidence. Probably the best that can be done is to quantify uncertainty, insofar as this is feasible and honest, to be transparent about the premises for the models, to be subject to critical peer review processes, and to increase knowledge through research on specific issues. There have been considerable developments in approaches in recent years that employ expert judgement within frameworks that can convey the level of evidence and level of consensus to express a level of confidence in the results of an evaluation [I14, M1].

¹¹ The radiation-risk factor was expressed as 0.41–0.64% of the baseline rate per gray of parental irradiation in the next generation.

C. Application of science-based inference

A92. Inference of cancer risk at low and very low doses (including cumulative doses received at chronic low dose rates) can be applied to real-life problems. The objectives of these problems affect the choice of how to represent risk at these doses. For some purposes, norms external to science, such as social responsibility, utility, prudence, precaution and practicality of application, are used. Some examples of inferences used for various purposes are discussed below and include:

- (a) Early indication of potential health impact and directing future scientific research (e.g. assumptions about credible risks can be used to plan epidemiological and laboratory studies to possibly confirm and quantify them);
- (b) Public health resource planning (e.g. comparisons of burdens of disease from various competing causes can be used to allocate resources efficiently, or to optimize health-screening studies);
- (c) Radiation protection and risk management (which influence for example, the derivation of protection criteria);
- (d) Legal liability purposes (e.g. compensation payments to individuals exposed to radiation from weapons tests or in the workplace).

A93. *Early indication of potential health impact and directing future scientific research.* Estimates of the risk at low and very low doses and doses received at chronic exposure at low dose rates may need to be made in order to identify gaps in knowledge and the direction of future research, to provide an early indication of potential health impact, or to design future epidemiological studies. In this respect, considerations such as the need to avoid false negatives can be important (i.e. there is a need to recognize that studies of high statistical power are necessary in order to be sure that health effects at these doses have not been missed). This application does not need to adopt norms external to science.

A94. There are numerous examples of the estimation of risk for such purposes, for example, even in its 1958 Report, the Committee made assumptions to estimate the genetically significant dose and corresponding risk of heritable effects that might result from exposure due to the atmospheric testing of nuclear weapons [U1]. Nonetheless, the Committee cautioned that “any present attempt to evaluate the effects of sources of radiation to which the world population is exposed can produce only tentative estimates with wide margins of uncertainty” and “although much is known, quantitative estimates of the mutational consequences of genetically significant irradiation of human populations remain subject to grave limitations”. Subsequent research has permitted a better understanding of radiation-induced risks, including heritable risks, but the consequences of exposure to low and very low doses are still not fully understood.

A95. *Public health resource planning.* While the Committee considers the risks of cancer or heritable effects are plausible at low and even very low doses, it has concluded that it should continue to refrain from estimating the numbers of radiation-induced health effects at these levels of dose because they have not been demonstrated scientifically. The Committee notes, however, such estimations may be made for science-based decision making. If they are carried out for this purpose, the numbers should be regarded as no more than hypothetical because:

- (a) Below the minimum detectable excess frequency of cancer, such inferences are not amenable to being verified by testing, and are not falsifiable); in the case of heritable effects, no statistically significant excess frequency in humans has yet been detected and therefore any inference cannot again be tested and verified;

(b) Cancers and heritable effects cannot be attributed individually or collectively owing to the current absence of a known biomarker to discriminate between radiation-induced and baseline health effects and the inability to control for all the other factors, known and unknown, that cause cancer (i.e. counterfactual conditional reasoning);

(c) The complex network of processes contributing to pathogenesis after exposure at low and very low doses is not understood, and thus the uncertainties at very low doses render such inferences highly uncertain and potentially misleading (and, in many cases, quantitative uncertainty analysis would not exclude zero excess as a possible outcome).

A96. The Committee recognizes though that public health bodies need to allocate resources appropriately, and this may involve making estimates of numbers of health effects from low and very low doses for comparative purposes. Such conditional predictions, although based upon reasonable but unverified hypotheses, could be useful for such purposes provided that it were applied consistently, the uncertainties in the assessments were taken fully into account, and it were not inferred that the projected numbers of health effects were other than notional. For example, this has been done for the purposes of gaining insight into the appropriate age at which to commence screening for breast cancer among asymptomatic women [B9]. It has also been done to gain insight into the possible health impact on a population of the Chernobyl accident (e.g. [B1, C1]) and of the diagnostic use of radiation in medicine (e.g. [B6]). The Chernobyl Forum approached the problem of possible health impact of the Chernobyl accident by differentiating between populations with moderate doses for which the possibility of cancer induction can be predicted and those with low and very low doses for which risk can only be inferred through the use of dose–response models [W6]. For its part, the Committee has estimated the collective effective doses¹² to people outside the former Soviet Union where doses were low or very low and has made scientific statements that emphasize that any risks would be too low to be detectable. At the same time, the Committee highlights that the inability to detect any increase in the cancer frequency does not exclude the possibility of a small increase in the percentage of disease at these doses.¹³

A97. *Radiation protection and risk management.* The ICRP [I10] has taken the Committee’s findings and used the linear, non-threshold model, which has practical advantages for radiation protection purposes in order to derive nominal radiation risk coefficients for “a representative population”. These nominal risk coefficients are coherent with radiobiological knowledge, adhere to epidemiological information, and incorporate ethical judgements on the relative harm associated with different health effects. The ICRP refers to the overall measure of harm as “detriment” and its weighted risk coefficients as “detriment-adjusted nominal risk coefficients”, which have been developed for specific groups of people (workers and members of the public) [I10]. These, in turn, have been used in the derivation of the protection quantity, effective dose. Effective dose is not a physical quantity, but rather, has the nature of a utility; that is, it can be used to represent preferences for comparative purposes (such as preferring one radiological procedure to another one). Effective dose is not, however, an appropriate quantity to determine cancer risk.

A98. *Legal liability purposes.* In spite of the fact that the risk of a stochastic health effect cannot be determined for a specific individual, decisions may be required on the possibility that an observed

¹² For its evaluations of levels and trends of exposures, the Committee has used two radiation protection quantities, namely effective dose and collective effective dose. These have the advantage of simplifying comparison of doses from different types of radiation and different distributions of dose within the body, and of averaging over age and sex; moreover, many regulatory authorities keep records in terms of these quantities.

¹³ The Committee has subsequently used the specific word “discernible” to convey the idea that, e.g. at certain level of exposure, risks cannot be excluded but can be inferred to be so small that any associated effects in the health statistics will not be “discernible” [U17]. Conversely, at high levels of exposure, such effects may become “discernible”.

health effect in an individual might have been caused by a specific exposure to radiation. For this purpose, analysts use the concept of assigned share (also known as the probability of causation) to respond to legal liability questions following radiation exposure [L3, N3]. The assigned share is defined as the probability that an observed health effect in an individual was caused by a specific radiation exposure [I12]. As indicated above, the concept of relative frequency for an individual strictly has no meaning; the outcome for the individual is either that the health effect occurs or it does not. Thus the probability of a health effect in an individual can only be estimated by assuming that the risk to the individual was the same as the relative frequency observed in a population of similar exposed individuals. However, this relative frequency often cannot be determined, and there are particular challenges when multiple causative agents are present, and thus analysts will need to draw inferences from studies of populations that share some of the relevant characteristics and make allowance for factors considered to influence the risk (e.g. family history, race, smoking habits). Moreover, the underlying biological model assumed for the disease process and a precise definition of causation is critical [B8]. The assigned share (AS) is calculated as follows:

$$AS = ERR/(ERR + 1) = (RR - 1)/(RR) = ERR/RR$$

where ERR is the excess relative risk* and RR the relative risk.*

V. RESEARCH NEEDS

A99. Given the fact that currently there is insufficient scientific evidence to be able to unequivocally attribute health effects to low and very low doses of ionizing radiation, the Committee suggests that the following research needs be addressed:

- (a) On epidemiological studies with complete follow-up of the exposed cohorts over the remainder of their lives (such as the Life Span Study of the survivors of the atomic bombings in Japan, studies of persons exposed to medical radiation as infants or in early childhood, and studies of workers who were occupationally exposed to radiation over a period of years), describing any increased frequency of health effects by age and sex;
- (b) On improving the quality of epidemiological studies (e.g. reducing bias by publishing protocols in advance of studies, addressing incomplete follow-up and determination of outcomes, and the quality of dosimetry);
- (c) How increased frequency of specific types of cancer in an exposed population vary with radiation dose; dose rate; the particular type/energy of radiation; the age at exposure and age at manifestation of health effect; the time after exposure;
- (d) The latency period between exposure and manifestation of a health effect;
- (e) The impact of variations in human genetic susceptibility;
- (f) Interactions* with other carcinogens/factors (e.g. smoking, viruses, and diet/lifestyle factors);
- (g) Rigorously quantifying uncertainty in such analyses (see annex B).

Large-scale epidemiological studies of exposed populations can be attempted if they have a reasonable chance to answer questions about increased frequency of health effects with dose. For example,

conventional risk models suggest that a case–control study involving around 10,000 matched pairs of cases and controls could theoretically (i.e. if other sources of bias and confounding factors can be reasonably addressed) have sufficient statistical power to detect an increased frequency of childhood leukaemia for variations in exposure to natural sources of gamma radiation. The Committee recognizes, however, that even large-scale epidemiological studies have inherent limitations, related to statistical variation in cancer rates in populations and the inability to account for all the non-radiation causes of cancer, and that such studies may never be able to unequivocally demonstrate that health effects result from low doses of radiation. Attempts to integrate biological understanding of radiation actions at low doses with epidemiological findings of health effects over a range of doses should be encouraged. The Committee expects four current scientific trends, namely developments in radiation dosimetry, radiation systems biology, molecular epidemiology and modelling of pathogenesis, to continue to contribute synergistically to this task.

A100. *Radiation dosimetry.* In the low- and, in particular, the very-low-dose range, not all cells are hit. The concept of absorbed dose is not useful in such a situation, because this quantity is based on the assumption that all cells receive more or less the same energy when exposed to radiation. The energy deposition in just a fraction of cells may markedly change the reaction of a tissue to radiation exposure. In addition, it is very important to identify the pattern of energy deposition within the cell, for example, after exposure to organically bound tritium.

A101. *Systems biology.* A main aim of radiation systems biology is an improvement in the understanding of the complex cellular and tissue responses, and their interdependencies, to exposures to ionizing radiation [B2, W5]. A vast amount of information is, at present, created by modern molecular methods including genomics, proteomics and metabolomics (the systematic study of the unique chemical fingerprints that specific cellular processes leave behind). Mathematical systems aimed at a description of the cellular and tissue-specific processes are becoming increasingly complex [Q1]. Future research is expected to help improve understanding of the relevant reaction pathways and distil key knowledge that will be of use for the estimation of risks from low doses.

A102. *Molecular epidemiology.* Molecular epidemiology¹⁴ has revealed molecular factors related to cancer occurring after exposure to ionizing radiation [S1]. Such studies may contribute to improving understanding of individual predisposition to radiogenic cancer and should be encouraged. One aspiration of molecular epidemiology for improving the quantification of risks from low-dose exposure is the identification of one or more early molecular markers for radiation-induced cancer. Such markers might be detectable with epidemiological studies at lower doses than a fully developed disease such as cancer.

A103. *Modelling pathogenesis.* The integration of molecular data on cancer and samples of normal tissue into models of pathogenesis and the evaluation of risk due to radiation exposure with such models is becoming increasingly feasible. Such approaches need large scale studies and have the potential to improve significantly understanding of risks from low doses of radiation.

A104. In addition, the Committee considers that research should continue: (a) into better characterizing tissue reactions that occur in the longer term after protracted exposures (such as cataracts and circulatory diseases); (b) into developing and applying methods to integrate and synthesize the results of many studies (e.g. using Bayesian inference) to better make quantitative and qualitative statements on the confidence that can be placed in causal relationships, hypotheses and predictions.

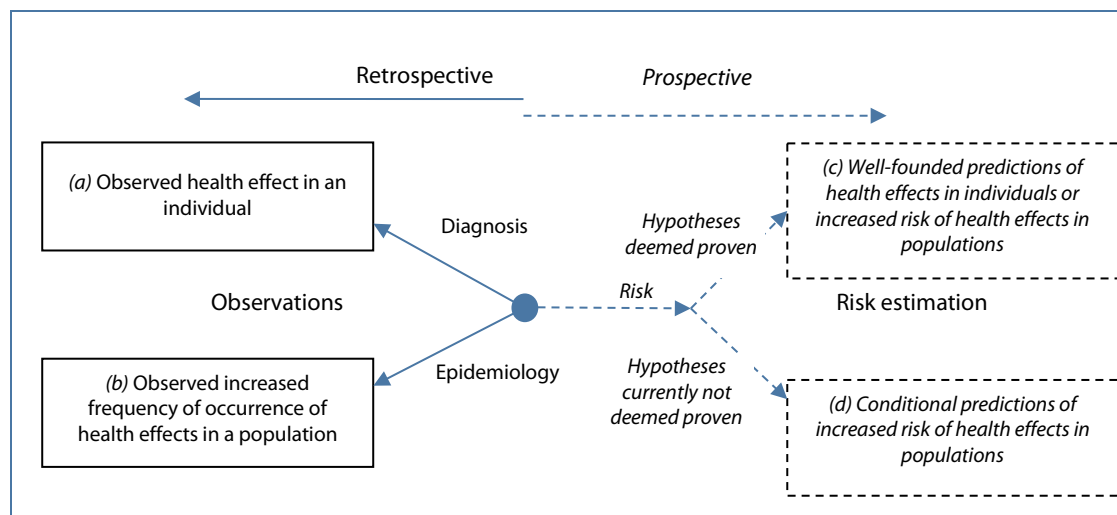
¹⁴ Molecular epidemiology is a branch of medical science that focuses on the contribution of potential genetic and environmental risk factors, identified at the molecular level, to the aetiology, distribution and prevention of disease within families and across populations [I4].

VI. SUMMARY

A105. Figure A-V highlights in diagrammatic form—the distinction to be made between observed health effects and inferred risk of health effects.

Figure A-V. Diagram to illustrate the distinction between observed health effects and inferred risk of health effects

This diagram distinguishes between observed health effects and risk of health effects occurring in the future: (a) observed health effects in an individual; (b) observed increased frequency of health effects in a population; (c) well-founded predictions (i.e. based on hypotheses deemed proven) of health effects in individuals or increased risk of health effects in populations; and (d) conditional predictions (i.e. based on hypotheses currently not deemed proven, but biologically plausible) of increased risk of health effects in populations. While risk of a health effect (i.e. the probability that the health effect will occur) can be estimated, a health effect cannot be confirmed until it is observed



A106. *Observations from scientific method.* It has been established by applying the scientific method that acute exposure to ionizing radiation above certain high-dose levels (thresholds) will cause deterministic effects in individuals. Such health effects can often be confidently attributed to radiation exposure by pathological diagnosis.

A107. Furthermore, statistically significant increases in the frequency of cancers (stochastic effects) have been observed in populations that have previously been exposed to moderate or high doses. After account has been taken of such matters as bias and confounding, these increases have also been attributed to radiation exposure. However, it is currently not possible to attribute a cancer in a particular individual in these populations to radiation exposure.

A108. Table A5 summarizes the conclusions regarding the attributability of observed health effects to radiation exposure.

Table A5. Attribution of observed health effects to radiation exposure

Dose band	Scientific knowledge	Attribution to radiation exposure	
		Individual	Population
SEVERE DETERMINISTIC EFFECTS			
High, acute	Robust direct evidence with individuals. (However, severe deterministic effects have also been observed after moderate doses to embryo/fetus) High degree of consensus on how damage is induced; some understanding of repair with time	Following high acute dose, exceptionally unlikely that sequence and pattern of signs and symptoms in short term caused by other factors. An observed deterministic health effect can thus be attributed if diagnosis eliminates possible alternative causes ^a	Attribution of cases at the population level is the total number of cases that have been individually attributed
High and moderate, chronic	Unclear at present whether some health effects in long term such as cataracts and fibrosis are deterministic	Other possible causes cannot be excluded. Unequivocal attribution unlikely	
CANCER			
High and moderate	Direct robust evidence from coherent and statistically significant increases in frequency for various exposed populations of increased frequency of various types of cancer Medium consensus on role played by DNA mutation and mechanism for cancer development	Radiation is not the only possible cause. At present, no specific biomarkers distinguish between cancer caused by irradiation and one due to another cause An observed cancer in an individual cannot be unequivocally attributed to radiation If the baseline frequency is low for a particular cancer and radiosensitivity high, attribution is plausible, particularly if exposure was high	Observed increase in cancer frequency can be attributed to radiation exposure through epidemiological analysis provided that increased frequency is large enough to overcome inherent statistical and other uncertainties ^b and a counterfactual analysis has been adequately conducted For a particular cancer, if baseline frequency low and radiosensitivity high, an increase in frequency could at least be associated with exposure, even if number of cases were small
Low and very low	No unequivocal direct evidence of statistically significant increases in frequency in populations Moderate consensus on role played by the mutation of DNA, and mechanism for cancer development	An observed cancer in an individual cannot be unequivocally attributed to exposure to radiation	An observed increase in the frequency of a cancer cannot at present be unequivocally attributed to radiation exposure. The increase may not be reproducible and confounding cannot be ruled out
HERITABLE EFFECTS			
High, moderate, low and very low	Demonstrated in animal studies at high doses. No direct evidence in human populations. Medium consensus they could be caused in humans	Radiation not the only possible cause. An observed heritable effect cannot at present be attributed to radiation exposure of the parent	An observed increase in the frequency of heritable effects cannot at present be attributed to radiation exposure. The increase may not be reproducible and confounding cannot be ruled out

^a The health effect could be attributed to the exposure through a qualified radiopathological procedure (and attested as such).

^b An increase in cancer frequency could be properly verified and attributed to exposure by means of a qualified radioepidemiological process.

A109. *Well-founded predictions.* On the basis of these observed radiogenic health effects, well-founded predictions can be made on the consequences of radiation exposure. Thus, above the thresholds for deterministic effects, it can be stated with confidence that these consequences will occur in individuals, although there may be some variation in the actual threshold for a particular health effect between individuals. Below the thresholds, no such health effects are predicted. In addition, it can be stated with confidence that there is an increased risk of certain cancers in a population exposed to moderate or high doses. For populations exposed under similar conditions to those from which data on the increased frequency was obtained, the risks of those cancers can be quantified, and thus valid predictions of future numbers of cases can be made with some confidence.

A110. *Conditional predictions.* In contrast, only conditional predictions can be generally made about the possible stochastic effects of exposure to low and very low doses or even of the possible heritable effects of exposure to high doses. This is because these health effects have not been demonstrated for these situations. Such conditional predictions can be made using plausible assumptions about the possible occurrence of such health effects, and the available scientific information, for example, on the interaction of radiation with cells. Such assumptions are necessary for the purposes of policy and decision-making. A number of science-based models have been proposed and the radiation protection community has adopted the linear non-threshold model—but none are based on hypotheses that have presently all been deemed proven.

A111. Table A6 summarizes the conclusions regarding well-founded and conditional predictions based on inference of risk.

Table A6. Inference of risk of health effects from radiation exposure

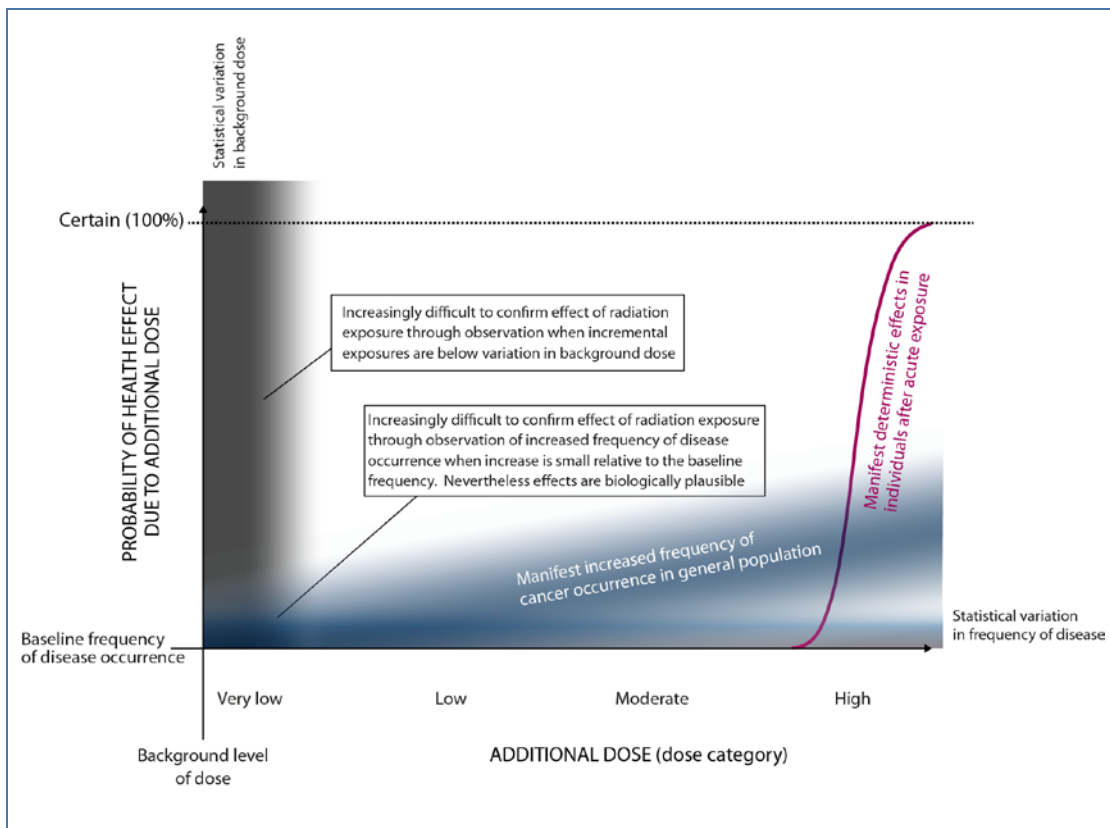
<i>Class of effect</i>	<i>Dose band</i>	<i>Confidence in inference</i>
Severe deterministic effect	High, acute	Sufficiently well-understood science and sufficient data to predict the occurrence and the severity of health effects with a high degree of confidence (when doses are significantly above relevant threshold)
	High and moderate, chronic	Well-founded prediction is difficult owing to uncertainties
Cancer	High and moderate	In most cases, sufficient direct information to make well-founded predictions with a high degree of confidence of increased risk of certain cancers in specific populations after acute exposures similar to those that have been exposed in the past, and chronic exposure to radon, and quantify uncertainties Assumptions are necessary to infer risk of cancer in populations that are different from those for which observations were made and the exposure conditions are different. These assumptions are based on an understanding of the mechanisms of radiation-induced carcinogenesis. Uncertainties are however somewhat larger and different analysts may make different assumptions. Predictions should be regarded as conditional, and have only a medium degree of confidence associated with them
	Low and very low	Increased risk of cancer is plausible but not based on observed increased frequencies in populations that are deemed proven. Risk estimates are generally not verifiable through testing with credible-sized radioepidemiological studies; although there is an upper bound to the value of the absolute risk (i.e. to the increased frequency that could be observed with such studies) Conditional predictions can be made to estimate the risk of cancer in exposed populations. Uncertainties are much larger and more debatable and any predicted increase in the risk of cancer should be regarded as having low relative confidence and be no more than notional

<i>Class of effect</i>	<i>Dose band</i>	<i>Confidence in inference</i>
Heritable effect	High, moderate, low and very low	Increased risk of heritable effects is plausible but not based on observed increased frequency in populations. Conditional predictions can be made based on data from animal studies to estimate the risk of heritable effect in exposed populations. Uncertainties are very large and debatable and any predicted increase in the risk of heritable effects should be regarded as having low relative confidence and be no more than notional

A112. Figure A-VI illustrates schematically the current limitations to knowledge, in a general sense, regarding the health effects from radiation exposure. It highlights the distinctions between attributability of deterministic effects in individuals following acute exposures to high doses, the attributability of increased frequency of occurrence in populations following exposures to moderate doses and higher, and the inferred risks for exposures to low and very low doses.

Figure A-VI. Schematic of the relationship between dose, additional to that from typical exposure to natural background radiation, and probability of occurrence of health effects

At acute doses above 1 Gy, deterministic effects that are clinically observable in individuals can be attributed to radiation with increasing confidence as the dose increases. Stochastic effects (e.g. cancer) in an individual cannot be unequivocally attributed to radiation exposure, however collectively an observed increase in the incidence of such health effects in a population can in some situations be attributable to radiation exposure when the dose is moderate or high. For low doses, risks are biologically plausible, though they are not currently verifiable through testing



APPENDIX B. CASE STUDIES

I. SKIN BURN AFTER INTERVENTIONAL CARDIOLOGY PROCEDURE.....	70
A. Scenario.....	70
B. Analysis.....	71
C. Conclusion	71
II. PREGNANCY WITH MENTALLY RETARDED INFANT.....	71
A. Scenario.....	71
B. Analysis.....	72
C. Conclusion	72
III. THYROID CANCER AFTER THE CHERNOBYL ACCIDENT	73
A. Scenario.....	73
B. Analysis.....	73
C. Conclusion	75
IV. LUNG CANCER FROM EXPOSURE TO RADON.....	75
A. Scenario.....	75
B. Analysis.....	76
C. Conclusion	77
V. ESTIMATED RISK FROM COMPUTED TOMOGRAPHY SCANS	77
A. Scenario.....	77
B. Analysis.....	78
C. Conclusion	79

B1. The Committee has applied the concepts discussed in the main text of the annex to five case studies to illustrate the considerations involved in attributing health effects from empirical science and in applying science-based inference. The case studies are only intended as examples of some of the considerations and should be interpreted neither as complete analyses nor as formal Committee statements on these subjects.

B2. It was stated in the main text of the annex (see paragraph 13) that (a) the sequence of signs and symptoms after high-dose radiation exposure that result in a deterministic effect is well characterized and (b) these observable consequences allow radiation experts to make confident diagnoses that a particular deterministic effect can be unequivocally attributed to radiation exposure (i.e. deemed

proven). In making such diagnoses, the radiation expert must exclude other possible causes (i.e. through conducting a counterfactual analysis).

B3. Case I is an example of a situation in which it is straightforward to attribute the observed health effect to radiation exposure. Case II is an example of a situation in which it is possible to deny the causative role of radiation in an observed health effect for a number of reasons including the results of a counterfactual analysis. Case III is an example of where health effects have been observed in an exposed population; consideration is given to whether these health effects in the population and in individuals can be attributed to radiation exposure.

B4. Case IV is concerned with whether an increased risk of cancer in a particular population can or should be predicted. The case concerns the exposure of a given population to radon in their homes.

B5. The general thesis of the annex is that it is acceptable to predict an increased risk of cancer in a population due to radiation exposure, if and only if, an increased frequency of that cancer in a population with similar characteristics has been attributed to radiation exposure at the levels of exposure involved. Where this is not the case, however, predictions are conditional on various assumptions, but the hypothesis regarding the predicted increased risk would not be testable with credible-sized radioepidemiological studies. Bodies that have responsibilities for assessing possible health implications of a particular technology and for decision-making may need to predict such risks. However, the results of such predictions are conditional and should only be considered as being based on hypotheses currently not deemed proven. Case V is an example of how such predictions can be made; it also clarifies the limitations of assessments of this sort.

I. SKIN BURN AFTER INTERVENTIONAL CARDIOLOGY PROCEDURE

A. Scenario

B6. The subject was a 69-year-old, 140 kg diabetic male with long-standing heart disease. He had had three prior coronary angiograms in the two preceding years. Because he was having recurrent chest pain, he underwent a diagnostic nuclear medicine study using myocardial imaging that showed severe ischaemia in the distribution of the left anterior descending (LAD) coronary artery. As a result, he underwent a fourth cardiac catheterization that included several attempts at coronary angioplasty (dilatation) and stenting. The fluoroscopy time was recorded as 34 minutes. There were 50 cine runs with a total of about 6,200 frames.

B7. About three weeks after the procedure, the subject noted intense itching, pain and blistering lesions in a square pattern on his back (later reported as an area of 6 cm × 10 cm). Various non-prescription remedies were tried without success. He went to see several physicians without a clear diagnosis. About seven months after the procedure, there was a chronic eschar with marked induration and inflammation that was extending out several centimetres from a central necrotic area (10 cm × 8 cm) [G1, I7, K2, K3, V2].

B8. The question was whether the symptoms could be attributed to radiation exposure during the interventional cardiology procedure.

B. Analysis

B9. Firstly, there are two temporal aspects: (a) the lesion was not present before the “very difficult and quite lengthy” cardiac catheterization and attempted stent placement in the coronary artery—it appeared shortly afterwards; and (b) the temporal sequence of the appearance of reddening, itching followed by skin breakdown within a few weeks and non-healing ulceration at about 6–12 months was characteristic of many radiation burns following high doses.

B10. The second point is the site of the lesion on the patient’s back. The radiation from a fluoroscope used during a cardiac procedure enters from the patient’s back and exits from the front. The highest dose is to the skin on the back. The site of the lesion in this case was consistent with a right anterior oblique projection that would be utilized for visualization of the LAD coronary artery. In addition, a review of the actual images from the procedure showed an exact correlation with anatomical structures underlying this lesion.

B11. The third point is that the size of the lesion was consistent with the diameter of the radiation beam used for this procedure.

B12. The fourth point is that the absorbed dose to the chest wall or skin almost certainly exceeded 15–20 Gy, a level of dose that is known to result in the observed temporal course and appearance of the lesion. The patient’s records indicated that the dose–area product (DAP) was 1,631 Gy cm² compared to an average of 83 Gy cm² for similar procedures [V1] (in order to compensate for attenuation by the patient’s body mass and still get an acceptable image, the radiation dose may have needed to be 4–6 times higher than that for a normal patient). The literature also indicates that patients usually get skin changes when the DAP exceeds 1,000 Gy cm² and that the average number of cine images for a coronary angioplasty is about 1,000; in this case there were more than 6,000.

C. Conclusion

B13. Based upon the analysis by the radiation experts, a lesion of this type would be very likely following such high doses of radiation under these conditions. Moreover, it would be exceptionally unlikely that any other possible cause could have created such a lesion, i.e. it would not have occurred if the subject had not incurred the radiation exposure (thus, this counterfactual conditional question was satisfied). Thus, the subject’s lesion on his back was confidently attributed to the radiation exposure.

II. PREGNANCY WITH MENTALLY RETARDED INFANT

A. Scenario

B14. A 26-year-old mother of two children took her 2-year-old son to the hospital after a head injury. A skull film was ordered, and the mother was asked to hold the child during the procedure. There is some doubt as to whether she wore a lead apron. Subsequently, she discovered that she was approximately nine weeks pregnant at the time. She carried the pregnancy to term without incident.

Following a normal delivery of a female infant, the child was subsequently diagnosed to be mentally retarded. No physical stigmata were associated with the retardation.

B15. The question was whether the mental retardation could be attributed to the radiation exposure incurred by the pregnant mother while holding her son for the skull film.

B. Analysis

B16. During the period from 8 to 25 weeks, and, in particular, 8 to 15 weeks, post conception, the central nervous system (CNS) of the fetus is very sensitive to radiation exposure. Doses to the fetus in excess of 100 mGy may result in a lower than expected intelligence quotient (IQ). The IQ has been found to reduce with increasing dose. Doses of around 1 Gy result in a high probability of severe mental retardation [O3]. The CNS is rather resistant from 26 weeks post conception until birth. In addition, 95% of those who were exposed in utero as a consequence of the atomic bombings in Japan and subsequently found to be mentally retarded, also demonstrated microcephaly [O2, O3].

B17. On the sole basis that the radiation exposure was incurred nine weeks post conception, mental retardation caused by radiation exposure cannot be immediately excluded. Had the exposure occurred at two to three weeks post conception or, for example, late in the third trimester, mental retardation could definitely not be attributed to radiation exposure.

B18. The mother claims that she was not given a lead apron to wear during the procedure. As an extremely conservative estimate, one might suppose that the mother's pelvis was in the direct X-ray beam. Most skull films are taken using a peak voltage of 80 kV; on the basis that the uterus was 8 cm deep in the tissue, a maximal dose to the fetus would have been 2 mGy. If the mother's pelvis had not been in the direct beam, which is a much more reasonable assumption, the assessed dose would have been 10–20 μ Gy. Thus, on the basis of dosimetric considerations alone, the mental retardation of the infant could not be attributed to radiation exposure. Furthermore, in this particular case, there was no evidence of microcephaly, which often accompanies radiogenic mental retardation.

B19. At the present time, most relevant bodies define mental retardation as having an IQ of below 70. The normal frequency of people with an IQ below 70 is approximately 3%. The baseline rate of severe mental retardation (in which an individual is unable to care for themselves) is about 1 in 200 (0.5%) births. At the present time, over 250 causes of mental retardation have been identified, including malnutrition, lead poisoning, rubella infections during pregnancy, and maternal alcoholism [M7]. Thus, many other causes than radiation exposure could have been responsible for mental retardation in this particular case.

C. Conclusion

B20. Although the exposure occurred during the period of pregnancy when the fetus has been shown to be sensitive to radiation exposure, the dose to the fetus was far below any level at which mental retardation has been documented; moreover there were no signs of physical findings that may be associated with radiation-induced mental retardation. Given that the normal frequency of mental retardation is about 3%, and that there are numerous other possible causes, radiation experts—after conducting a counterfactual analysis—would conclude that the mental retardation could not be attributed to the radiation exposure.

III. THYROID CANCER AFTER THE CHERNOBYL ACCIDENT

A. Scenario

B21. Since the 1986 Chernobyl accident, a substantial increase in frequency of thyroid cancer has been observed in the whole of Belarus and Ukraine, and the four most affected regions of the Russian Federation, among those exposed at the time as children or adolescents. Among those under age 18 years in 1986, 6,848 cases of thyroid cancer were reported between 1991 and 2005 (annex D of [U14]). The question is whether this increased frequency in the population and individual cases can be attributed to radiation exposure from the accident.

B. Analysis

B22. Figure B–I shows that in Belarus, the frequency of thyroid cancer among children under 10 years of age increased dramatically after the accident. For those born after 1986 (see the data for those under 10 years in 1996–2005), there was no evidence for an increase in the frequency of thyroid cancer. The increase in the frequency of thyroid cancer among children and adolescents started about 3 years after the accident [H5] and persisted, at least until 2005. This temporal pattern already suggests that the dramatic increase in frequency in 1991–1995 was associated with the accident, though not necessarily with radiation exposure [J2].

B23. Various epidemiological studies have shown that the thyroid gland is highly susceptible to the carcinogenic consequences of external radiation exposure during childhood ([U10] annex A). These include studies of the survivors of the atomic bombings in Japan and those exposed in childhood for various medical reasons (e.g. treatment of tinea capitis). A combined analysis of these studies [R1] showed a marked influence of the age at exposure with little apparent increase in frequency of disease after age 20 years; it also showed that the increased frequency began to decline about 30 years after the first exposure. A pooled analysis* of five epidemiological studies of children exposed to external radiation showed an average excess relative rate of 7.7 (95% CI: 2.1, 28.7) at 1 Gy. (Further discussion on the uncertainty of the risk estimates is provided in annex B.)

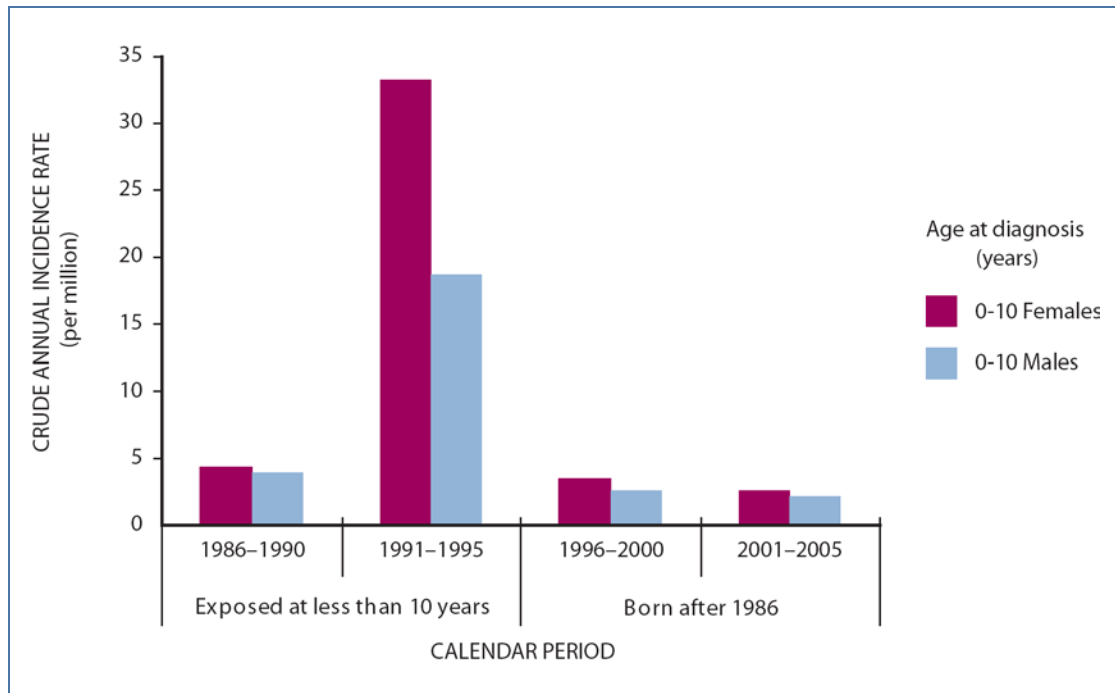
B24. The average dose to the thyroid of those who were evacuated was estimated to have been about 500 mGy (with individual values ranging from less than 50 mGy to more than 5,000 mGy). For the more than six million residents of the contaminated areas of the former Soviet Union who were not evacuated, the average dose to the thyroid was about 100 mGy, while for about 0.7% of them, the doses to the thyroid were more than 1,000 mGy ([U14] annex D).

B25. The increase in frequency of thyroid cancer following the Chernobyl accident was first identified in a number of geographical (ecological) studies (see para. 462 of annex A [U10]). Although these studies indicated an association between the increased frequency and the accident, they had inherent methodological problems. Subsequent case–control and cohort studies gave values of excess relative rate that are consistent with those obtained from epidemiological studies of other groups of children (see appendix D to annex B of this report) and show trends of increased frequency of thyroid cancer with absorbed dose to the thyroid primarily from internal exposure.

B26. Nevertheless, other possible causes would need to be considered before attributing the observed increased frequency to radiation exposure. The increased use of screening of the thyroid may have played a role in the observed increased frequency of cancer. Ideally, it would be important to review analytical studies that use estimates of dose to individuals, and to compare the results with studies of children who were not exposed but were subject to similar screening techniques. Strong indication that increased use of screening was not the main reason for the higher observed frequency of thyroid cancer is obtained from studies of those born after 1986 (as indicated above), which showed no evidence for an increase in the frequency of thyroid cancer, even though they could have been subjected to increased medical surveillance. It has been estimated that 60% of the Belarusian thyroid cancer cases and 30% of the Ukrainian cases may be related to the radiation exposure [J1]. The remaining increase in frequency is likely to be related to enhanced surveillance, improved diagnostic technology and other non-radiation factors.

Figure B–I. Frequency in Belarus of thyroid cancer for children under 10 years old at diagnosis (annex D of [U14])

The baseline rate of thyroid cancer among children under age 10 years is very low (a few cases per million children per year)



C. Conclusion

B27. Before the accident, an increased frequency of thyroid cancer had already been shown to be attributable to external radiation exposure in childhood. As a consequence, an entirely reasonable hypothesis would have been that internal exposure due to iodine-131 from the Chernobyl accident was responsible for the observed increased frequency of thyroid cancer in Belarus, Ukraine and the four most affected regions of the Russian Federation. Use of the Bradford Hill guidelines (in particular, strength, plausibility, consistency, specificity, temporality, and biological gradient, see [H6]) would provide strong support for attributing, at least in part, the observed increased frequency to radiation exposure in this particular case.

B28. Counterfactual analysis would indicate that increased screening of the population could account for some of the observed increased frequency of thyroid cancer, but certainly not all. Such screening that was undertaken following the accident would have led to the detection of many thyroid nodules that would never lead to any clinically observed health effects and, therefore, would never be detected outside of such screening programmes.

B29. The analysis was facilitated by the fact that the thyroid of children is particularly radiosensitive and the baseline rate of childhood thyroid cancer is very low (a few cases per million children per year). This case study demonstrates that attribution of the increased frequency of cancer within a radiosensitive population can be relatively straightforward.

B30. In the absence of a biomarker to distinguish a radiation-related thyroid cancer from one that occurs due to other causes, an observed thyroid cancer in an individual among the population of those exposed as children or adolescents at the time of the accident cannot be unequivocally attributed to radiation exposure from the accident.

IV. LUNG CANCER FROM EXPOSURE TO RADON

A. Scenario

B31. The arithmetic and geometric mean radon concentrations in 117 randomly selected homes in Winnipeg, Canada, were found in a survey to be 148 and 112 Bq/m³, respectively [C2]. The geometric standard deviation was 2.07 with 20% of homes exceeding a radon concentration of 200 Bq/m³. The measured radon concentrations ranged from 20 to 483 Bq/m³. The question is whether it would be reasonable to predict an increased risk of lung cancer among the population and whether in any future epidemiological study an increased frequency of lung cancer would be discernible.

B. Analysis

B32. Radon decay products are well established as a cause of lung cancer, and a number of epidemiological studies had clearly shown an increased frequency of lung cancer associated with the radon exposure of miners ([U11] annex E). Based on this information and the general scientific knowledge regarding the interaction of radiation with living cells, a reasonable hypothesis was that exposure to radon in homes could also cause lung cancer (even recognizing that the exposure levels and conditions in mines are significantly different from those in homes). Risks from radon exposure in homes had originally been estimated by extrapolations from the miner studies.

B33. Now, however, there are more than 20 case–control studies of lung cancer and radon exposure in homes. While individual studies have limited power, pooled analyses of European [D1, D2], North American [K5, K6] and Chinese [L6] studies provide a clear demonstration that an increased frequency of lung cancer is significantly associated with radon exposure. Taken together with application of the Bradford Hill guidelines (in particular, strength, plausibility, consistency, specificity, temporality, and biological gradient, see [H6], there is good evidence that an increased frequency of lung cancer can be attributed to radon exposure in dwellings when concentrations are significantly higher than average. In one study [D1], the dose–response relationship appeared to be linear without threshold and the excess relative rate at a concentration of 100 Bq/m³ was statistically significant at the 95% confidence level (annex E of UNSCEAR 2006 Report [U11]). Thus, it could be concluded that an increased risk of lung cancer in a population exposed to a concentration of radon of 100 Bq/m³ could be predicted under certain conditions.

B34. On the basis of the results from these studies, the Committee inferred an excess relative risk of 0.16 (95% CI: 0.05, 0.31) per 100 Bq/m³ as an appropriate, if possibly conservative, estimate of the lifetime risk from exposure to radon in homes.

B35. Inferences of the lifetime risk of lung cancer for given exposures to radon based on this analysis of the epidemiological information and the assumption that the exposure conditions are maintained over 30 years are given in Table B1. Thus, for a population exposed to an average radon concentration of about 150 Bq/m³, as in the Winnipeg study, an increased risk of 24% above the baseline for each sex and smoking category can reasonably be predicted (i.e. can be regarded as well-founded). The actual number of additional cases of lung cancer due to exposure to radon would be dominated by those who smoke, but is unlikely to be observable in the population in the homes that were surveyed here (number of homes, 117, which implies a population of around 500 on the basis of an average of four individuals in each home). In fact, one case-control study of radon and lung cancer in 1,438 persons in Winnipeg showed no increase in lung cancer for any histologic type [L4]. However, if the results of the survey were truly representative of the levels of exposure of the population of Winnipeg as a whole (say 700,000 people), then an increased frequency of lung cancer ought to be observable in that population.

B36. An observed lung cancer in a particular individual cannot be unequivocally attributed to exposure to radon because, at the present time, there is no way of distinguishing a radon-induced lung cancer from one that occurs through other causes, particularly smoking (based on a counterfactual analysis).

Table B1. Baseline lung cancer risk and inferred lifetime risk of lung cancer to the average individual in a population from exposure to radon: values are given separately for men and women, according to whether they smoke or not

²²² Rn concentration (Bq/m ³)	Increased risk	Inferred lifetime risk of lung cancer ^a (%)			
		Men who smoke	Men who don't smoke	Women who smoke	Women who don't smoke
Baseline ^b	0%	12	0.9	6.8	0.6
100	16%	14	1.0	7.9	0.7
150	24%	15	1.1	8.4	0.7
300	48%	18	1.3	10	0.9
400	64%	20	1.5	11	1.0

^a The value used in calculation 0.16 (95% CI: 0.05, 0.31) for exposure to 100 Bq/m³ [D1].

^b Baseline rate from [N6].

C. Conclusion

B37. An increased frequency of lung cancer among miners had been attributed to exposure to radon in mines. On the basis of the pooling of results from large epidemiological studies, an increased frequency of lung cancer in the general population can now be attributed to exposure to radon in homes at elevated levels, specifically at concentrations greater than about 100 Bq/m³. Consequently, the lifetime risk of lung cancer in a population exposed to such elevated levels of radon (which is the case in the Winnipeg study), can be predicted provided that the exposure conditions remain constant for extended periods. The predicted increased frequency of lung cancer is unlikely to be observable among the people living in the Winnipeg homes sampled because of the small numbers involved; however, if the size of the population exposed at the same levels were large enough, then the predicted increased frequency is potentially observable (i.e. the prediction is, in principle, testable).

B38. An observed lung cancer in an individual cannot be unequivocally attributed to radon exposure (other possible causes cannot be excluded on the basis of a counterfactual analysis).

V. ESTIMATED RISK FROM COMPUTED TOMOGRAPHY SCANS

A. Scenario

B39. Scientific knowledge is to be applied to compare the potential benefits and risks of various types of imaging procedures used in medicine. The specific task is to express the confidence in inferred risks for future cancer from radiation exposure due to computed tomography (CT) scanning in a specific year. It is based on a published case study for the United States of America in 2007 (see [B7]). Some 72 million CT scans were performed there that year. The frequencies of the different types of examination were estimated from various data sources.

B. Analysis

B40. A key factor in the estimation of lifetime risk of cancer due to radiation exposure is the life expectancy of people receiving CT scans. Typically, there is at least a 5-year lag period between radiation exposure and diagnosis of a solid cancer; therefore, it is very unlikely that patients who do not survive that long could have developed an observable cancer as a consequence of the exposure. When scans taken in the last 5 years of life as well as those scans related to the diagnosis of a cancer were excluded, the number of CT scans considered in the study reduced to 57 million. Because radiation-related cancer risks are known to depend on sex and age at exposure, data were obtained on the age and sex distribution for each type of CT scan.

B41. Technical parameters (e.g. peak voltage and tube current–time product) for each scan type were available from surveys [F2]. From this, doses to specific organs by age and sex were estimated for each type of scan and model of scanner. Absorbed doses to organs in the field of the CT scan are of the order of a few tens of milligrays, which are within the low-dose range defined in table 1 of the main text of this annex.

B42. The published case study made conditional predictions of the risk to the population taking account of the doses to individual organs and tissues, age at exposure and the inferred risks for each cancer type for people exposed at various ages, based on extrapolation of data from epidemiological studies of populations exposed at moderate or high doses. Models for the inference of risk (except for breast and thyroid cancer) were developed using data from the latest follow-up of the survivors of the atomic bombings in Japan, because that study had the most detailed information available for most cancer sites [P7]. The models for breast and thyroid cancer were based on the data obtained from pooled analyses of cohorts of the survivors of the atomic bombings and medically exposed people [P6, R1]. For solid cancers, a 5-year lag period and a linear dose–response model was assumed; moreover it was assumed that the risk per unit dose was 1.5 times lower for doses equal to or less than 100 mGy than that at higher doses [N7]. For leukaemia, a 2-year lag period and a linear–quadratic dose–response model were assumed.

B43. Monte Carlo* simulation methods with sampling were used to estimate risks with uncertainty intervals, accounting for statistical uncertainties in the risk parameters and subjective uncertainties in the value of the dose and dose-rate effectiveness factor, as well as the transference of the observed excess frequency in the population of the survivors of the atomic bombings in Japan, to estimate the risk for the United States population. Account was also taken of the uncertainty in the estimates of the baseline cancer rate. The mean estimates with 95% uncertainty intervals were calculated from the simulations [B7]. Whether these uncertainty intervals fully account for the uncertainties in the transference from the 1945 Japanese population to United States children today remains an issue.

B44. Large-scale epidemiological studies of cancer frequency in individuals who underwent CT scans as children or adolescents are now being undertaken and some findings have been reported [P2].¹⁵ These reports indicate an increased frequency of cancer among those exposed to radiation during CT scans, but one confounding factor is the potential influence of reverse causation: i.e. that the cancer, or factors predisposing to cancer, were present at the time of the scan, so that the cancer caused the CT scan rather than the CT scan caused the cancer [U16]. While current studies may not demonstrate unambiguously a link between radiation exposure due to a CT scan and the development of cancer, future studies may overcome current difficulties in interpretation and provide (or not) increased confidence in the interpretation (see appendix A).

¹⁵ The Committee is aware that studies of CT and cancer have been published after the 2012 findings were submitted to the United Nations General Assembly. These studies focus on those considered to be at greater risk (i.e. exposed at young age) and their interpretation needs to take into account such factors as pre-existing conditions and pre-disposition to disease. It was not possible to fully evaluate them for the purpose of this annex.

C. Conclusion

B45. The study results are conditional predictions. It was concluded that approximately 29,000 (95% CI: 15,000, 45,000) future cancers could arise as a consequence of the use of CT scans in the United States in 2007. It also showed that, because of the high frequency of use, the potential public health impact would be highest for adults aged 35 to 54 years, particularly among women. These cancers would arise over several decades following exposure. For the purpose of decision-making by policy-making bodies and clinicians, this estimate could be used to compare the potential impact on health of alternative diagnostic procedures. Even so, there are several points to note:

(a) It may seem contradictory that the Committee has decided not to calculate absolute numbers of cancers after radiation exposure at low and very low doses and, nevertheless, presents this case study. There are several reasons for this. Firstly, these analyses have been published on a current medical practice of great public interest. Secondly, as already stated above, such studies may help to compare the potential benefits and risks of various types of imaging procedures used in medicine. And thirdly, some limitations that are outlined in the following have to be observed;

(b) The estimated impact was inferred using science-based models. The evidence from observational studies is currently insufficient to confirm that the estimated numbers of cancers will occur as a consequence of CT scans;

(c) The estimated risk relates to CT scans conducted in one year. If the number of CT scans continues at the same rate under the same conditions, then eventually the number of cancers due to CT scans would be expected to reach 29,000 (95% CI: 15,000, 45,000) each year. This would be on top of a baseline cancer frequency, which, in the United States is of the order of 1.4 million cases each year [A2]. Thus, the inferred increase in the number of cancers would be of the order of 2% above the normal frequency in the general population, although more than 2% in the population subjected to CT. An epidemiological study to demonstrate such an increase would involve following hundreds of thousands of people over many years and a similar-sized, matched-control group. It would also require adequate account to be taken of other factors that might influence the observed frequency, which may be very difficult.

REFERENCES

- A1 Ainsbury, E.A., S.D. Bouffler, W. Dorr et al. Radiation cataractogenesis: a review of recent studies. *Radiat Res* 172(1): 1-9 (2009).
- A2 American Cancer Society. *Cancer Facts & Figures 2008*. American Cancer Society, Atlanta, GA, 2008.
- A3 Anderson, D.R. *Model Based Inference in the Life Sciences: A Primer on Evidence*. Springer, New York, 2008.
- B1 Balonov, M. and D. Louvat. The Chernobyl Forum completed. *J Radiol Prot* 25(4): 499-501 (2005).
- B2 Barcellos-Hoff, M.H. and S.V. Costes. A systems biology approach to multicellular and multi-generational radiation responses. *Mutat Res* 597(1-2): 32-38 (2006).
- B3 Beninson, D. and B. Lindell. The evasive plausibility. *J Radiol Prot* 21(1): 39-44 (2001).
- B4 Bentzen, S.M. Preventing or reducing late side effects of radiation therapy: radiobiology meets molecular pathology. *Nat Rev Cancer* 6(9): 702-713 (2006).
- B5 Bentzen, S.M. From cellular to high-throughput predictive assays in radiation oncology: challenges and opportunities. *Semin Radiat Oncol* 18(2): 75-88 (2008).
- B6 Berrington de González, A. and S. Darby. Risk of cancer from diagnostic X-rays: estimates for the UK and 14 other countries. *Lancet* 363(9406): 345-351 (2004).
- B7 Berrington de González, A., M. Mahesh, K.P. Kim et al. Projected cancer risks from computed tomographic scans performed in the United States in 2007. *Arch Intern Med* 169(22): 2071-2077 (2009).
- B8 Beyea, J. and S. Greenland. The importance of specifying the underlying biologic model in estimating the probability of causation. *Health Phys* 76(3): 269-274 (1999).
- B9 Bijwaard, H., A. Brenner, F. Dekkers et al. Breast cancer risk from different mammography screening practices. *Radiat Res* 174(3): 367-376 (2010).
- B10 Blackburn, S. *The Oxford dictionary of philosophy, Second edition revised*. Oxford University Press, New York, 2008.
- B11 Boice, J.D., Jr. and R.W. Miller. Childhood and adult cancer after intrauterine exposure to ionizing radiation. *Teratology* 59(4): 227-233 (1999).
- B12 Brash, D.E., J.A. Rudolph, J.A. Simon et al. A role for sunlight in skin cancer: UV-induced p53 mutations in squamous cell carcinoma. *Proc Natl Acad Sci U S A* 88(22): 10124-10128 (1991).
- B13 Brenner, D.J., R. Doll, D.T. Goodhead et al. Cancer risks attributable to low doses of ionizing radiation: assessing what we really know. *Proc Natl Acad Sci U S A* 100(24): 13761-13766 (2003).

- B14 Brenner, D.J. and R.K. Sachs. Estimating radiation-induced cancer risks at very low doses: rationale for using a linear no-threshold approach. *Radiat Environ Biophys* 44(4): 253-256 (2006).
- C1 Cardis, E., G. Howe, E. Ron et al. Cancer consequences of the Chernobyl accident: 20 years on. *J Radiol Prot* 26(2): 127-140 (2006).
- C2 Chen, J., E. Schroth, E. MacKinlay et al. Simultaneous ^{222}Rn and ^{220}Rn measurements in Winnipeg, Canada. *Radiat Prot Dosim* 134(2): 75-78 (2009).
- C3 COED. Concise Oxford English Dictionary. Oxford University Press, New York, 2008.
- C4 COMEST. The precautionary principle. World Commission on the Ethics of Scientific Knowledge and Technology. United Nations Educational, Scientific and Cultural Organization, Paris, 2005.
- C5 Crompton, N.E., M. Ozsahin, P. Schweizer et al. Theory and practice of predictive assays in radiation therapy. *Strahlenther Onkol* 173(2): 58-67 (1997).
- D1 Darby, S., D. Hill, A. Auvinen et al. Radon in homes and risk of lung cancer: collaborative analysis of individual data from 13 European case-control studies. *Br Med J* 330(7485): 223 (2005).
- D2 Darby, S., D. Hill, H. Deo et al. Residential radon and lung cancer--detailed results of a collaborative analysis of individual data on 7148 persons with lung cancer and 14,208 persons without lung cancer from 13 epidemiologic studies in Europe. *Scand J Work Environ Health* 32(Suppl 1): 1-83 (2006).
- D3 Dauer, L.T., A.L. Brooks, D.G. Hoel et al. Review and evaluation of updated research on the health effects associated with low-dose ionising radiation. *Radiat Prot Dosim* 140(2): 103-136 (2010).
- D4 Doll, R. and R. Wakeford. Risk of childhood cancer from fetal irradiation. *Br J Radiol* 70: 130-139 (1997).
- D5 Dordelmann, M., M. Schrappe, A. Reiter et al. Down's syndrome in childhood acute lymphoblastic leukemia: clinical characteristics and treatment outcome in four consecutive BFM trials. Berlin-Frankfurt-Munster Group. *Leukemia* 12(5): 645-651 (1998).
- D6 Doss, M. Evidence supporting radiation hormesis in atomic bomb survivor cancer mortality data. *Dose Response* 10(4): 584-592 (2012).
- E1 EEA. Late lessons from early warnings: the precautionary principle 1896–2000. Environmental issue report no. 22. European Environment Agency, Copenhagen, 2001.
- E2 Egger, M., G. Davey Smith, M. Schneider et al. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 315(7109): 629-634 (1997).
- F1 Farmer, P.B. and R. Singh. Use of DNA adducts to identify human health risk from exposure to hazardous environmental pollutants: the increasing role of mass spectrometry in assessing biologically effective doses of genotoxic carcinogens. *Mutat Res* 659(1-2): 68-76 (2008).
- F2 FDA. Nationwide Evaluation of X-Ray Trends (NEXT): Tabulation and graphical summary of 2000 survey of computed tomography. CRCPD Publication E-07-2. US Food and Drug Administration, Conference of Radiation Control Program Directors Inc., Washington, DC, 2007.

- F3 Fliedner, T.M., D. Graessle, V. Meineke et al. Pathophysiological principles underlying the blood cell concentration responses used to assess the severity of effect after accidental whole-body radiation exposure: an essential basis for an evidence-based clinical triage. *Exp Hematol* 35(4 Suppl 1): 8-16 (2007).
- F4 Fry, R.J. Deterministic effects. *Health Phys* 80(4): 338-343 (2001).
- G1 Gerber, T.C., J.J. Carr, A.E. Arai et al. Ionizing radiation in cardiac imaging: a science advisory from the American Heart Association Committee on Cardiac Imaging of the Council on Clinical Cardiology and Committee on Cardiovascular Imaging and Intervention of the Council on Cardiovascular Radiology and Intervention. *Circulation* 119(7): 1056-1065 (2009).
- G2 Gray, J.S. Statistics and the precautionary principle. *Mar Pollut Bull* 21(4): 174-176 (1990).
- G3 Greenland, S. Introduction to Bayesian statistics. pp.328-344 in: *Modern Epidemiology*, Third edition (K.J. Rothman et al., eds.). Lippincott Williams & Wilkins, Philadelphia, 2008.
- G4 Gusev, I.A., A.K. Guskova and F.A. Mettler Jr. *Medical Management of Radiation Accidents*. Second edition. CRC Press, New York, 2001.
- H1 Hall, E.J. and A.J. Giaccia. *Radiobiology for the Radiobiologist*. Sixth edition. Lippincott Williams & Wilkins, Philadelphia, 2006.
- H2 Hamilton, C.S., C.S. Potten, J.W. Denham et al. Response of human hair cortical cells to fractionated radiotherapy. *Radiother Oncol* 43(3): 289-292 (1997).
- H3 Hatzi, V.I., G.I. Terzoudi, C. Paraskevopoulou et al. The use of premature chromosome condensation to study in interphase cells the influence of environmental factors on human genetic material. *Sci World J* 6: 1174-1190 (2006).
- H4 Health Council of the Netherlands. Prudent precaution. Publication no. 2008/18E. Health Council of the Netherlands, The Hague, 2008.
- H5 Heidenreich, W.F., J. Kenigsberg, P. Jacob et al. Time trends of thyroid cancer incidence in Belarus after the Chernobyl accident. *Radiat Res* 151(5): 617-625 (1999).
- H6 Hill, A.B. The environment and disease: association or causation? *Proc R Soc Med* 58: 295-300 (1965).
- H7 Hofmann, B., S. Holm, J. Iversen et al. Chapter 1: Philosophy of Science. pp.1-32 in: *Research Methodology in the Medical and Biological Sciences* (P. Laake et al., eds.). Elsevier, London, 2007.
- H8 Holm, S. and T. Takala. High hopes and automatic escalators: a critique of some new arguments in bioethics. *J Med Ethics* 33(1): 1-4 (2007).
- H9 Hulse, E.V. and R.H. Mole. Reflections on the terms stochastic and non-stochastic as currently used in radiological protection. *Br J Radiol* 55(653): 321-324 (1982).
- I1 IAEA. *Biological dosimetry: chromosomal aberration analysis for dose assessment*. Technical Reports Series No. 260. International Atomic Energy Agency, Vienna, 1986.
- I2 IARC. *IARC Monographs on the evaluation of carcinogenic risks to humans. Ionizing radiation, Part 1: X- and gamma (γ)-radiation, and neutrons. Volume 75*. International Agency for Research on Cancer, Lyon, 2000.

- I3 IARC. IARC Monographs on the evaluation of carcinogenic risks to humans. Ionizing radiation, Part 2: Some internally deposited radionuclides. Volume 78. International Agency for Research on Cancer, Lyon, 2001.
- I4 IARC. Molecular epidemiology: principles and practices. IARC Scientific Publications No. 163 (N. Rothman et al., eds.). International Agency for Research on Cancer, WHO Press, Geneva, 2011.
- I5 IARC. IARC Monographs on the evaluation of carcinogenic risks to humans. A review of human carcinogens. Radiation. Volume 100D. International Agency for Research on Cancer, Lyon, 2012.
- I6 ICRP. Genetic susceptibility to cancer. ICRP Publication 79. Annals of the ICRP 28(1-2). International Commission on Radiological Protection, Pergamon Press, Oxford, 1998.
- I7 ICRP. Avoidance of radiation injuries from medical interventional procedures. ICRP Publication 85. Annals of the ICRP 30(2). International Commission on Radiological Protection, Elsevier, Oxford, 2001.
- I8 ICRP. Biological effects after prenatal irradiation (embryo and fetus). ICRP Publication 90. Annals of the ICRP 33(1-2). International Commission on Radiological Protection, Pergamon Press, 2003.
- I9 ICRP. Low-dose extrapolation of radiation-related cancer risk. ICRP Publication 99. Annals of the ICRP 35(4). International Commission on Radiological Protection, Elsevier Ltd., 2005.
- I10 ICRP. The 2007 Recommendations of the International Commission on Radiological Protection. ICRP Publication 103. Annals of the ICRP 37(2-4). International Commission on Radiological Protection, Elsevier Ltd., 2007.
- I11 ICRP. ICRP statement on tissue reactions / Early and late effects of radiation in normal tissues and organs – Threshold doses for tissue reactions in a radiation protection context. ICRP Publication 118. Annals of the ICRP 41(1-2). International Commission on Radiological Protection, Elsevier Ltd., 2012.
- I12 ILO, IAEA and WHO. Approaches to attribution of detrimental health effects to occupational ionizing radiation exposure and their application in compensation programmes for cancer. Occupational Safety and Health Series No. 73 (S. Nui et al., eds.). International Labour Organization, Geneva, 2010.
- I13 Ioannidis, J.P. Why most published research findings are false. *PLoS Med* 2(8): e124 (2005).
- I14 IPCC. Guidance note for lead authors of the IPCC fifth assessment report on consistent treatment of uncertainties. IPCC Cross-Working Group Meeting on Consistent Treatment of Uncertainties, Jasper Ridge, CA, USA, 6-7 July 2010. Intergovernmental Panel on Climate Change, 2010.
- J1 Jacob, P., T.I. Bogdanova, E. Buglova et al. Thyroid cancer among Ukrainians and Belarusians who were children or adolescents at the time of the Chernobyl accident. *J Radiol Prot* 26(1): 51-67 (2006).
- J2 Jacob, P., T.I. Bogdanova, E. Buglova et al. Thyroid cancer risk in areas of Ukraine and Belarus affected by the Chernobyl accident. *Radiat Res* 165(1): 1-8 (2006).
- J3 Jacob, P., W. Ruhm, L. Walsh et al. Is cancer risk of radiation workers larger than expected? *Occup Environ Med* 66(12): 789-796 (2009).

- J4 Johnston, P. and M. Simmonds. Precautionary principle. *Mar Pollut Bull* 21(8): 402 (1990).
- J5 Johnston, P. and M. Simmonds. Green light for precautionary science. *New Sci* 1780: 4 (1991).
- K1 Kennedy, A.R. Factors that modify radiation-induced carcinogenesis. *Health Phys* 97(5): 433-445 (2009).
- K2 Koenig, T.R., F.A. Mettler and L.K. Wagner. Skin injuries from fluoroscopically guided procedures: part 2, review of 73 cases and recommendations for minimizing dose delivered to patient. *AJR Am J Roentgenol* 177(1): 13-20 (2001).
- K3 Koenig, T.R., D. Wolff, F.A. Mettler et al. Skin injuries from fluoroscopically guided procedures: part 1, characteristics of radiation injury. *AJR Am J Roentgenol* 177(1): 3-11 (2001).
- K4 Kraemer, K.H., N.J. Patronas, R. Schiffmann et al. Xeroderma pigmentosum, trichothiodystrophy and Cockayne syndrome: a complex genotype-phenotype relationship. *Neuroscience* 145(4): 1388-1396 (2007).
- K5 Krewski, D., J.H. Lubin, J.M. Zielinski et al. Residential radon and risk of lung cancer: a combined analysis of 7 North American case-control studies. *Epidemiology* 16(2): 137-145 (2005).
- K6 Krewski, D., J.H. Lubin, J.M. Zielinski et al. A combined analysis of North American case-control studies of residential radon and lung cancer. *J Toxicol Environ Health A* 69(7): 533-597 (2006).
- L1 Land, C.E. Estimating cancer risks from low doses of ionizing radiation. *Science* 209(4462): 1197-1203 (1980).
- L2 Land, C.E. Uncertainty, low-dose extrapolation and the threshold hypothesis. *J Radiol Prot* 22(3A): A129-135 (2002).
- L3 Land, C.E., E. Gilbert, J.M. Smith et al. Report of the NCI-CDC Working Group to Revise the 1985 NIH Radioepidemiological Tables. NIH Publication 03-5387. National Cancer Institute, Bethesda, MD, 2003.
- L4 Letourneau, E.G., D. Krewski, N.W. Choi et al. Case-control study of residential radon and lung cancer in Winnipeg, Manitoba, Canada. *Am J Epidemiol* 140(4): 310-322 (1994).
- L5 Little, M.P., R. Wakeford, E.J. Tawn et al. Risks associated with low doses and low dose rates of ionizing radiation: why linearity may be (almost) the best we can do. *Radiology* 251(1): 6-12 (2009).
- L6 Lubin, J.H., Z.Y. Wang, J.D. Boice, Jr. et al. Risk of lung cancer and residential radon in China: pooled results of two studies. *Int J Cancer* 109(1): 132-137 (2004).
- M1 Mark Elwood, J. *Critical Appraisal of Epidemiological Studies and Clinical Trials*. UOP, Oxford, 2007.
- M2 Morgan, W.F. and W.J. Bair. Issues in low dose radiation biology: the controversy continues. A perspective. *Radiat Res* 179(5): 501-510 (2013).
- M3 Morrell, D., E. Cromartie and M. Swift. Mortality and cancer incidence in 263 patients with ataxia-telangiectasia. *J Natl Cancer Inst* 77(1): 89-92 (1986).
- M4 Mullenders, L., M. Atkinson, H. Paretzke et al. Assessing cancer risks of low-dose radiation. *Nat Rev Cancer* 9(8): 596-604 (2009).

- M5 Müller, W.-U. and C. Streffer. Micronucleus assays. pp.185-194 in: *Advances in Mutagenesis Research* (G. Obe, ed.). Springer-Verlag, New York, 1994.
- M6 Müller, W.-U. Comet assay. pp.161-176 in: *Chromosomal Alterations: Methods, Results and Importance in Human Health* (G. Obe and Vijayalaxmi, eds.). Springer-Verlag, Berlin, 2007.
- M7 Murphy, C.C., C. Boyle, D. Schendel et al. Epidemiology of mental retardation in children. *Mental Retardation and Developmental Disabilities Research Reviews* 4: 6-13 (1998).
- N1 NCI/SEER. Cancer Stat Fact Sheets. National Cancer Institute, Surveillance, Epidemiology, and End Results Program. [Internet] Available from (<http://seer.cancer.gov/statfacts/>)
- N2 NCRP. Second primary cancers and cardiovascular disease after radiation therapy. NCRP Report No. 170. National Council on Radiation Protection and Measurements, Bethesda, 2011.
- N3 NCRP. Uncertainties in the estimation of radiation risks and probability of disease causation. NCRP Report No. 171. National Council on Radiation Protection and Measurements, Bethesda, 2012.
- N4 Neumaier, T., J. Swenson, C. Pham et al. Evidence for formation of DNA repair centers and dose-response nonlinearity in human cells. *Proc Natl Acad Sci U S A* 109(2): 443-448 (2012).
- N5 Nicolich, M.J. and J.F. Gamble. What is the minimum risk that can be estimated from an epidemiology study? Chapter 1 in: *Advanced Topics in Environmental Health and Air Pollution Case Studies* (A. Moldoveanu, ed.). InTech, 2011.
- N6 NRC. Risk assessment of radon in drinking water (Committee on Risk Assessment of Exposure to Radon in Drinking Water). National Research Council, National Academy Press, Washington, D.C., 1999.
- N7 NRC. Health risks from exposure to low levels of ionizing radiation. Committee to Assess Health Risks from Exposure to Low Levels of Ionizing Radiation, BEIR VII - Phase 2. National Research Council, The National Academies Press, Washington D.C., 2006.
- O1 Office of the Surgeon General and Office on Smoking and Health. The health consequences of smoking: A report of the Surgeon General. Centers for Disease Control and Prevention, Atlanta, GA, 2004.
- O2 Otake, M. and W.J. Schull. In utero exposure to A-bomb radiation and mental retardation; a reassessment. *Br J Radiol* 57(677): 409-414 (1984).
- O3 Otake, M. and W.J. Schull. Radiation-related brain damage and growth retardation among the prenatally exposed atomic bomb survivors. *Int J Radiat Biol* 74(2): 159-171 (1998).
- O4 Ozasa, K., Y. Shimizu, A. Suyama et al. Studies of the mortality of atomic bomb survivors, Report 14, 1950-2003: An overview of cancer and noncancer diseases. *Radiat Res* 177(3): 229-243 (2012).
- P1 Parsons, B.L. Many different tumor types have polyclonal tumor origin: evidence and implications. *Mutat Res* 659(3): 232-247 (2008).
- P2 Pearce, M.S., J.A. Salotti, M.P. Little et al. Radiation exposure from CT scans in childhood and subsequent risk of leukaemia and brain tumours: a retrospective cohort study. *Lancet* 380(9840): 499-505 (2012).
- P3 Pollard, J.M. and R.A. Gatti. Clinical radiation sensitivity with DNA repair disorders: an overview. *Int J Radiat Oncol Biol Phys* 74(5): 1323-1331 (2009).

- P4 Popper, K.R. *The Logic of Scientific Discovery*. Basic Books, New York, 1959.
- P5 Portess, D.I., G. Bauer, M.A. Hill et al. Low-dose irradiation of nontransformed cells stimulates the selective removal of precancerous cells via intercellular induction of apoptosis. *Cancer Res* 67(3): 1246-1253 (2007).
- P6 Preston, D.L., A. Mattsson, E. Holmberg et al. Radiation effects on breast cancer risk: a pooled analysis of eight cohorts. *Radiat Res* 158(2): 220-235 (2002).
- P7 Preston, D.L., E. Ron, S. Tokuoka et al. Solid cancer incidence in atomic bomb survivors: 1958-1998. *Radiat Res* 168(1): 1-64 (2007).
- P8 Preston, R.J., J.D. Boice Jr., A. Bertrand Brill et al. Uncertainties in estimating health risks associated with exposure to ionising radiation. *J Radiol Prot* 33(3): 573-588 (2013).
- Q1 Qi, J.P., S.H. Shao, J. Xie et al. A mathematical model of P53 gene regulatory networks under radiotherapy. *Biosystems* 90(3): 698-706 (2007).
- R1 Ron, E., J.H. Lubin, R.E. Shore et al. Thyroid cancer after exposure to external radiation: a pooled analysis of seven studies. *Radiat Res* 141(3): 259-277 (1995).
- R2 Rothman, K.J., S. Greenland and T.L. Lash. *Modern Epidemiology*. Third edition. Lippincott Williams & Wilkins, Philadelphia, 2008.
- S1 Sigurdson, A.J. and D.O. Stram. Genetic predisposition to radiation-related cancer and potential implications for risk assessment. *Ann ICRP* 41(3-4): 108-116 (2012).
- S2 Swift, M., D. Morrell, R.B. Massey et al. Incidence of cancer in 161 families affected by ataxia-telangiectasia. *N Engl J Med* 325(26): 1831-1836 (1991).
- S3 Szumiel, I. Analysis of DNA double-strand breaks by means of γ -H2AX foci. pp.145-160 in: *Chromosomal Alterations: Methods, Results and Importance in Human Health* (G. Obe and Vijayalaxmi, eds.). Springer-Verlag, Berlin, 2007.
- T1 Tallacchini, M. Before and beyond the precautionary principle: epistemology of uncertainty in science and law. *Toxicol Appl Pharmacol* 207(2 Suppl): 645-651 (2005).
- T2 Tanooka, H. X chromosome inactivation-mediated cellular mosaicism for the study of the monoclonal origin and recurrence of mouse tumors: a review. *Cytogenet Genome Res* 104(1-4): 320-324 (2004).
- T3 Taubes, G. Epidemiology faces its limits. *Science* 269(5221): 164-169 (1995).
- T4 Toledano, S.R. and B.J. Lange. Ataxia-telangiectasia and acute lymphoblastic leukemia. *Cancer* 45(7): 1675-1678 (1980).
- T5 Torres-Roca, J.F. and C.W. Stevens. Predicting response to clinical radiotherapy: past, present, and future directions. *Cancer Control* 15(2): 151-156 (2008).
- T6 Tranøy, K.E. Science and ethics. Some of the main principles and problems. pp.111-136 in: *The Moral Import of Science: Essays on Normative Theory, Scientific Activity and Wittgenstein* (A.J.I. Jones, ed.). Sigma Forlag, Bergen, 1988.
- T7 Tubiana, M., A. Aurengo, D. Averbeck et al. Dose-effect relationships and estimation of the carcinogenic effects of low doses of ionizing radiation. Joint Report No. 2. Académie des Sciences, Académie nationale de Médecine, Paris, 2005.

- T8 Tubiana, M., A. Aurengo, D. Averbeck et al. Recent reports on the effect of low doses of ionizing radiation and its dose-effect relationship. *Radiat Environ Biophys* 44(4): 245-251 (2006).
- T9 Tucker, J.D. Low-dose ionizing radiation and chromosome translocations: a review of the major considerations for human biological dosimetry. *Mutat Res* 659(3): 211-220 (2008).
- U1 UNSCEAR. Official Records of the General Assembly, Thirteenth Session, Supplement No. 17 (A/3838). UNSCEAR 1958 Report. United Nations Scientific Committee on the Effects of Atomic Radiation. United Nations, New York, 1958.
- U2 UNSCEAR. Sources and Effects of Ionizing Radiation. UNSCEAR 1977 Report. United Nations Scientific Committee on the Effects of Atomic Radiation, 1977 Report to the General Assembly, with annexes. United Nations sales publication E.77.IX.1. United Nations, New York, 1977.
- U3 UNSCEAR. Ionizing Radiation: Sources and Biological Effects. UNSCEAR 1982 Report. United Nations Scientific Committee on the Effects of Atomic Radiation, 1982 Report to the General Assembly, with annexes. United Nations sales publication E.82.IX.8. United Nations, New York, 1982.
- U4 UNSCEAR. Genetic and Somatic Effects of Ionizing Radiation. UNSCEAR 1986 Report. United Nations Scientific Committee on the Effects of Atomic Radiation, 1986 Report to the General Assembly, with annexes. United Nations sales publication E.86.IX.9. United Nations, New York, 1986.
- U5 UNSCEAR. Sources, Effects and Risks of Ionizing Radiation. UNSCEAR 1988 Report. United Nations Scientific Committee on the Effects of Atomic Radiation, 1988 Report to the General Assembly, with annexes. United Nations sales publication E.88.IX.7. United Nations, New York, 1988.
- U6 UNSCEAR. Sources and Effects of Ionizing Radiation. UNSCEAR 1993 Report. United Nations Scientific Committee on the Effects of Atomic Radiation, 1993 Report to the General Assembly, with scientific annexes. United Nations sales publication E.94.IX.2. United Nations, New York, 1993.
- U7 UNSCEAR. Sources and Effects of Ionizing Radiation. UNSCEAR 1994 Report. United Nations Scientific Committee on the Effects of Atomic Radiation, 1994 Report to the General Assembly, with scientific annexes. United Nations sales publication E.94.IX.11. United Nations, New York, 1994.
- U8 UNSCEAR. Sources and Effects of Ionizing Radiation. Volume II: Effects. UNSCEAR 2000 Report. United Nations Scientific Committee on the Effects of Atomic Radiation, 2000 Report to the General Assembly, with scientific annexes. United Nations sales publication E.00.IX.4. United Nations, New York, 2000.
- U9 UNSCEAR. Hereditary Effects of Radiation. UNSCEAR 2001 Report. United Nations Scientific Committee on the Effects of Atomic Radiation, 2001 Report to the General Assembly, with scientific annex. United Nations sales publication E.01.IX.2. United Nations, New York, 2001.
- U10 UNSCEAR. Effects of Ionizing Radiation. Volume I: Report to the General Assembly, Scientific Annexes A and B. UNSCEAR 2006 Report. United Nations Scientific Committee on the Effects of Atomic Radiation. United Nations sales publication E.08.IX.6. United Nations, New York, 2008.

- U11 UNSCEAR. Effects of Ionizing Radiation. Volume II: Scientific Annexes C, D and E. UNSCEAR 2006 Report. United Nations Scientific Committee on the Effects of Atomic Radiation. United Nations sales publication E.09.IX.5. United Nations, New York, 2009.
- U12 UNSCEAR. Sources and Effects of Ionizing Radiation. Volume I: Sources: Report to the General Assembly, Scientific Annexes A and B. UNSCEAR 2008 Report. United Nations Scientific Committee on the Effects of Atomic Radiation. United Nations sales publication E.10.XI.3. United Nations, New York, 2010.
- U13 UNSCEAR. Report of the United Nations Scientific Committee on the Effects of Atomic Radiation 2010. Fifty-seventh session, includes Scientific Report: Summary of low-dose radiation effects on health. UNSCEAR 2010 Report. United Nations Scientific Committee on the Effects of Atomic Radiation. United Nations sales publication M.II.IX.4. United Nations, New York, 2011.
- U14 UNSCEAR. Sources and Effects of Ionizing Radiation. Volume II: Effects. Scientific Annexes C, D and E. UNSCEAR 2008 Report. United Nations Scientific Committee on the Effects of Atomic Radiation. United Nations sales publication E.11.IX.3. United Nations, New York, 2011.
- U15 UNSCEAR. Biological Mechanisms of Radiation Actions at Low Doses (White Paper). United Nations Scientific Committee on the Effects of Atomic Radiation. United Nations, New York, 2012.
- U16 UNSCEAR. Sources, Effects and Risks of Ionizing Radiation. Volume II: Scientific Annex B. UNSCEAR 2013 Report. United Nations Scientific Committee on the Effects of Atomic Radiation. United Nations sales publication E.14.IX.2. United Nations, New York, 2013.
- U17 UNSCEAR. Sources, Effects and Risks of Ionizing Radiation. Volume I: Report to the General Assembly and Scientific Annex A. UNSCEAR 2013 Report. United Nations Scientific Committee on the Effects of Atomic Radiation. United Nations sales publication E.14.IX.1. United Nations, New York, 2014.
- V1 Vaño, E., J. Goicolea, C. Galvan et al. Skin radiation injuries in patients following repeated coronary angioplasty procedures. *Br J Radiol* 74(887): 1023-1031 (2001).
- V2 Vlietstra, R.E., L.K. Wagner, T. Koenig et al. Radiation burns as a severe complication of fluoroscopically guided cardiological interventions. *J Interv Cardiol* 17(3): 131-142 (2004).
- W1 Wakeford, R. and M.P. Little. Risk coefficients for childhood cancer after intrauterine irradiation: a review. *Int J Radiat Biol* 79(5): 293-309 (2003).
- W2 Wakeford, R. Childhood leukaemia following medical diagnostic exposure to ionizing radiation in utero or after birth. *Radiat Prot Dosim* 132(2): 166-174 (2008).
- W3 Wakeford, R. The risk of childhood leukaemia following exposure to ionising radiation--a review. *J Radiol Prot* 33(1): 1-25 (2013).
- W4 Weinberg, A.M. Science and trans-science. *Minerva* 10(2): 209-222 (1974).
- W5 Whitehead, K., A. Kish, M. Pan et al. An integrated systems approach for understanding cellular responses to gamma radiation. *Mol Syst Biol* 2: 47 (2006).
- W6 WHO. Health effects of the Chernobyl accident and special health care programmes. Report of the UN Chernobyl Forum Expert Group "Health" (B. Bennett et al., eds.). World Health Organization, Geneva, 2006.

- W7 Williams, E.D., A. Abrosimov, T. Bogdanova et al. Thyroid carcinoma after Chernobyl latent period, morphology and aggressiveness. *Br J Cancer* 90(11): 2219-2224 (2004).
- W8 Woodward, M. *Epidemiology: Study Design and Data Analysis*. Second edition. Chapman & Hall/CRC, Boca Raton, Florida, 2005.
- W9 Wynne, B.E. and S. Mayer. How science fails the environment: If politicians don't like uncertainties and scientists often conceal them, how can we make policies that deal with the vagaries of the world around us? *New Sci* 139(1876): 33-35 (1993).

ANNEX B

UNCERTAINTIES IN RISK ESTIMATES FOR RADIATION-INDUCED CANCER

CONTENTS

I. INTRODUCTION	95
II. FUNDAMENTAL CONCEPTS	96
A. Statistical concepts of uncertainty	96
B. Epidemiological concepts	98
III. SOURCES OF UNCERTAINTIES IN RADIOEPIDEMIOLOGICAL STUDIES	99
A. Uncertainties in health effect information	99
B. Uncertainties in exposure and dose assessment	99
C. Uncertainties in risk assessment	101
1. Impact of uncertainty in health effect information on risk estimates and statistical power of epidemiological studies.....	101
2. Impact of exposure uncertainty.....	102
3. Impact of model uncertainty*	105
IV. UNCERTAINTIES IN TRANSFERRING RISK QUANTITIES FROM GIVEN STUDIES TO OTHER EXPOSURE CONDITIONS OR POPULATIONS OF INTEREST	106
A. Transfer to another population or time period	106
B. Transfer to risks from LSS to other exposure conditions.....	107
V. UNCERTAINTIES OF SELECTED RISK EVALUATIONS	108
A. Solid cancer risks after external exposure to cumulative doses of the order of 100 mGy above typical background exposure	109
B. Thyroid cancer after radiation exposure during childhood	110
C. Lung cancer after residential exposure to radon	111
VI. KEY RESEARCH NEEDS	112
VII. CONCLUSIONS.....	113
ACKNOWLEDGEMENTS.....	114
APPENDIX A. FUNDAMENTAL CONCEPTS.....	115
APPENDIX B. SOURCES OF UNCERTAINTY IN RADIOEPIDEMIOLOGICAL STUDIES.....	139
APPENDIX C. UNCERTAINTY IN TRANSFERRING RISK QUANTITIES FROM GIVEN STUDIES TO OTHER EXPOSURE SITUATIONS OR POPULATIONS OF INTEREST	211
APPENDIX D. UNCERTAINTIES IN SELECTED RISK EVALUATIONS.....	241
REFERENCES.....	285

I. INTRODUCTION

1. Cancer risks* of exposure to ionizing radiation are much better known than those of most other carcinogens. The Committee has previously summarized the results of numerous epidemiological studies of populations exposed to moderate to high doses of radiation exposure [U11, U12]. However, as discussed in annex A, at lower doses (generally below an absorbed dose* of about 100 mGy from low-LET* radiation), the uncertainties* associated with epidemiological studies become increasingly large and tend to mask any possible effect. The estimation of risk from such exposures requires judgements against a backdrop of different sources of uncertainty and ongoing scientific debate. The uncertainties involved in these judgements and hence the estimation of risk need to be properly addressed and communicated in order to improve understanding by decision-makers and others.

2. In order to support its findings and provide a more rational basis for discussions of the risk from radiation exposure, the Committee has prepared this scientific annex on the uncertainties in estimates of risk following exposure to ionizing radiation. Many epidemiological studies of the health effects* of radiation exposure derive risk estimates with confidence intervals* that express only the impact of statistical fluctuations of the data in the frame of the risk model* chosen. Other specific sources of uncertainty, such as those due to incomplete knowledge of exposures, or factors and mechanisms influencing the development of the disease, must also be addressed in order to more realistically describe the current state of knowledge. A main purpose of this annex then is to describe the current state of knowledge on (a) the various factors influencing estimates of risk from radiation exposure; and (b) the methodologies to integrate information on different sources of uncertainties so as to describe uncertainties on estimates of risk from radiation exposure more comprehensively than have previous reports of the Committee.

3. This scientific annex includes: (a) an evaluation of current knowledge on the impact of various sources of uncertainty on estimates of risk from radiation exposure and how they may be treated; (b) a comparison of frequentistic and Bayesian interpretations of uncertainty and probability for deriving information from new data; (c) a discussion of uncertainties in transferring risk estimates derived from a study to another population or a situation of interest; and (d) three examples of evaluations of cancer risk to demonstrate the structure and analysis of uncertainty. The main text of the annex is supported by four detailed technical appendices that provide more extensive discussion. A glossary supports the interpretation of terms for both this annex and annex A.

4. Uncertainty analyses in the field of risk estimation for radiation exposure have up to now focussed mainly on the risk of cancer. Consequently, much of the material summarized in this annex relates to radiation-induced cancer. The methods outlined, however, are equally well applicable to the analysis of other radiation-induced health effects.

5. The estimation of risks to human health from exposure to ionizing radiation is mainly based on epidemiological studies either of large exposed populations (cohort studies) or of the exposure distribution of persons with and without the disease of interest (case-control studies). There are also many radiobiological studies, including animal experiments, related to the effects of exposure to ionizing radiation [U11, U12]. These studies provide some insight into the mechanisms and processes that are involved in carcinogenesis after exposure to ionizing radiation. However, the studies cannot yet be used to improve quantitative estimation of the risks for humans of radiation exposure.

6. Risk estimates are derived generally for a group of people, defined by sex, birth year, ethnicity, occupation, smoking behaviour or other characteristics, and to specified exposure conditions. However, whether or not an individual will be affected depends on further, unknown factors, such as genetic or familial predisposition, pre-existing illnesses or pre-cancerous lesions, repair capacity, or immunological characteristics. At present, the possibilities for determining individual sensitivity are still limited and there is insufficient understanding of its interaction* with radiation exposure. Therefore this report does not treat the assessment of individual sensitivity to radiation exposure.

II. FUNDAMENTAL CONCEPTS

7. This chapter recapitulates some fundamental statistical concepts, including types of error* and uncertainty, and statistical inference,* as well as key concepts and terminology of epidemiology. Appendix A provides more detailed explanatory material on these concepts and on methods for quantifying and analysing uncertainties.

A. Statistical concepts of uncertainty

8. The difference between an estimate of a quantity of interest* (e.g. a dose or the excess relative risk* per unit dose in some exposed population) and the true but unknown value of that quantity is called the “error”, which itself cannot be observed or quantified. “Uncertainty” refers to the probability distribution of the possible errors and “uncertainty analysis” to the characterization of the error distribution taking account of all known sources of uncertainty.

9. Uncertainty in estimation of cancer risk from radiation exposure comes from several sources, including the inherently random nature of processes that lead to cancer, limitations in data, and the use of idealized models to describe the nature of the risks in both an exposed and a non-exposed population.

10. Uncertainties are composed of mixtures of systematic and random errors.* The nature of the different types of error contributing to the uncertainty is important. Errors that are statistically independent between individuals are called “unshared errors”,* while correlated ones are called “shared errors”.*

11. There are two types of unshared errors:

(a) “Measurement error”* is independent of the true value, and typically arises when using an imprecise (but unbiased) measuring device. The main determinants of the measurement error are characteristics of the measurement device, the study protocol and skill of the measuring personnel. In the case of measurement error, the variance of the observed values* exceeds that of the true values by the variance of the measurement error. It is known that the regression coefficients in a dose–response analysis will be biased towards zero depending on the importance of measurement errors in the dose estimates. Measurement errors are also called “classical errors”.

(b) “Assignment error”* arises when individuals are assigned representative values, often as a result of grouping, and is independent of the assigned value. Assignment errors describe random inter-individual variability* of true values about a single value assigned to every individual

belonging to a distinct group. The variance of the assigned values will be less than that of the true variance by the variance of the individual peculiarity in the values about a given assigned value. When dose values are assigned in a dose–response analysis, the regression coefficients tend to be unbiased. Assignment errors are also called “Berkson errors”.*

12. Shared errors include shared measurement errors (such as the use of an improperly calibrated measuring device) and shared assignment errors (such as mis-specification of values for parameters used in computation of observed values). Shared errors almost inevitably lead to biased estimates of the quantity of interest, and failure to account for them can lead to overconfidence in deriving risk estimates.

13. Statistical inference is critical in characterizing and quantifying uncertainty in both estimation of risk from radiation exposure for specific studies and in projection of risk to other populations and exposure scenarios. Statistical inference is based on data (observations) and models used to analyse the data. The probability density function* for the data given a model, \mathcal{M} , its parameters, β , and the values of any explanatory variables, Z , is denoted by $f(\text{data} | \mathcal{M}, \beta, Z)$. When viewed as a function of the parameters given the data, the model and the values of the explanatory variables, the probability density function is called the likelihood* function (L), which plays a central role in statistical inference. A hypothetical and unrealistic example would be the likelihood of a set of breast cancer incidence data being observed in a cohort of women given a model of the incidence rate* that, say, were:

$$I = \beta_1 a (1 + \beta_2 d)$$

Here, the age, a , and the dose, d , would be explanatory variables, and best estimates of the parameters β_1 and β_2 would be determined, e.g. by identifying the maximum of the likelihood function of the observed data.

14. There are two main approaches of statistical inference:

(a) “Frequentist” inference* uses observed data and aims at establishing the probability of the truth of statements about quantities of interest given the data and the model used to analyse the data. Frequentist probability can be interpreted as the relative frequency* in a hypothetical set of realizations given the true parameter values of the assumed model;

(b) “Bayesian” inference interprets probability as a measure of the degree of belief or state of knowledge concerning the true values of the quantities of interest. With this interpretation, one’s “prior” state of knowledge about the quantity of interest can be explicitly updated with new information to make Bayesian probability statements about one’s “posterior” state of knowledge. From this probability density function of possibly true values, a central value (usually the arithmetic mean, median or mode) and a 90% or 95% credible interval* can be obtained. A review of the application of Bayesian methods in epidemiology can be found in [G17].

15. Although the two concepts are fundamentally different, they often lead to similar conclusions, especially when their implementation is well-informed by the scientific context or when the data are strong enough to make the choice of the prior distribution less relevant.

16. Frequentist methods for quantification and assessment of uncertainties have generally served well in the estimation of risk in specific exposed populations, such as the survivors of the atomic bombings in Japan. However, Bayesian methods become more appropriate with increasing complexity, such as when estimating uncertainties in deriving cancer-specific risks from limited data or in doses calculated using complex Monte Carlo dosimetric modelling systems. They also become more important in

making informed but qualified judgements about risk estimates so that they may be applied appropriately to address important societal questions.

17. Depending on the objective of an assessment, it may be necessary to distinguish variability from uncertainty. Variability describes the variation of values between individuals, while uncertainty refers to the variation in values due to unexplained stochastic processes or the state of knowledge about imperfectly known fixed quantities.

18. The Committee recommends that uncertainty in the measurements, variables, and models used to estimate exposures, doses and risks—both for specific individuals and for groups—be defined as probability density functions, representing the analyst’s state of knowledge, with account being taken of the dependencies or correlations between the distributions.

19. “Uncertainty propagation”^{*} is the process of combining all contributing components into an overall statement of uncertainty about the estimate of the quantity of interest. Monte Carlo uncertainty propagation^{*} is preferred to closed-form algebraic solutions for all but the very simplest models. If it is necessary to distinguish between the variability of dose or risk among individuals and the uncertainty about values of fixed quantities, a two-dimensional Monte Carlo approach to uncertainty propagation is the preferred approach. This produces (a) sets of possibly true values of fixed quantities that are shared among groups of individuals; and (b) alternative realizations of possibly true sets of individual values representing the variability in the quantity of interest.

20. A “sensitivity analysis” of the effect of changes in values of the model input on its output determines which parameters or processes have the largest influence on a model result or on the uncertainty in that result.

B. Epidemiological concepts

21. Cohort studies, which involve the long-term follow-up of an exposed population having individually characterized exposures, can provide unbiased risk estimates for various outcomes. Analyses typically focus on how rates for the outcome of interest depend on radiation exposure allowing for “modifying” factors such as sex or age at exposure. The strength of cohort studies arises from the fact that rates of the disease of interest can be computed directly from the follow-up data. However, such studies are challenging to establish and costly to maintain over the long follow-up period needed, and lack statistical power for studying rare outcomes. Also, competing risk factors can often not be explicitly taken into account.

22. Case–control studies identify cases for an outcome of interest in a population together with a control sample of disease-free individuals from the same population. Cases and controls are matched on factors such as sex, or vital status at the age and time of diagnosis of the cases to reduce the chance that observed differences in the exposure distributions between cases and controls are due to factors other than radiation exposure. Such studies can be retrospective and can be undertaken with smaller population groups than those required for cohort studies. Thus they cost much less than cohort studies, but without careful design, risk estimates are likely to have more bias^{*} than those from cohort studies.

23. Epidemiological studies of radiation-induced health effects are observational and may suggest associations between some exposure and an outcome of interest. However, a single epidemiological investigation is unlikely to establish unequivocally a cause–effect relationship,^{*} in part because of the possible impact of risk factors that are correlated with both the outcome of interest and the exposure

(“confounding factors”).* Nevertheless, the consistency of results of many independent studies coupled with plausible* biological reasoning can be convincing. Guidelines suggested by Bradford–Hill [H14] are often used to judge the confidence that a risk factor (e.g. radiation exposure) might cause increased incidence in a population of health outcomes (e.g. cancer).

III. SOURCES OF UNCERTAINTIES IN RADIOEPIDEMIOLOGICAL STUDIES

24. This chapter discusses the sources of uncertainty in analysing the results of epidemiological studies of populations exposed to ionizing radiation, specifically the uncertainties in information on health effects, in information on exposure and dose assessment. It considers the impact of these uncertainties and uncertainties in the dose–response model on risk assessment. Appendix B provides more detailed explanation, technical information and review.

A. Uncertainties in health effect information

25. Sources of uncertainty in information on health effects can be broadly classified into two groups: (a) “Selection bias” occurs when the study population is not representative of the population of interest. Examples are discussed in appendix B. Readily available information on disease status and exposure history, and truly random cohort or case–control sampling can help avoid this; and (b) “Information bias” involves erroneous or incomplete information about disease and exposure. Examples include cases recalling their exposure history differently than non-cases (recall bias), and subjects who may have left the geographical study area (ascertainment or follow-up bias). Previous UNSCEAR reports [U11, U12] have given examples of the ways in which errors can arise when assessing disease frequencies. Appendix B discusses various examples of information bias and how they have been accounted for in major radioepidemiological studies.

26. Failure to adjust for confounding factors can distort risk estimates. For example, increases in cancer rates and decreases of exposure levels over time might suggest that normalized risks (expressed in terms of risk per unit dose) are increasing when actually improvements in medical diagnostics are helping to detect cancers earlier and before these cancers would otherwise manifest. Confounding is usually dealt with at the analysis stage, either by incorporating such factors into the regression model or by stratifying the data according to levels of the confounding factor. Cigarette smoking is one of the most serious potential confounding factors that have to be dealt with in epidemiological studies of the health effects of radiation exposure (radioepidemiological studies); clearly this is especially important when analysing diseases that are known to be related to smoking [U12].

B. Uncertainties in exposure and dose assessment

27. Uncertainties in the assessment of exposure and dose may affect the evaluation of the statistical significance of the dose response, the shape and steepness of slope, and the width of the confidence

interval. Common errors and mistakes in dose estimation can arise, for example, with measurements, laboratory procedures, record keeping, programming, data input, and computation. Sources of such errors must be addressed before estimating doses for epidemiological evaluation. Rigorous quality assurance/quality control procedures should include checks of model inputs, equations, intermediate results and individual dose estimates with calculations performed by different persons using independent computational platforms. If common errors and mistakes are not detected and corrected, expressions of uncertainty in dose estimation may be invalid. In general, some form of mathematical modelling is required to estimate the radiation dose to specific organs and tissues of the human body, because these cannot be measured directly. Assumptions made and uncertainties introduced by the modelling need to be taken into account in the analysis.

28. For external exposure to photons with an energy of more than 0.03 MeV, uncertainty in the estimation of organ dose is generally less than that for internal exposure. However, the more that models must be employed to estimate individual exposure and dose, the greater the anticipated uncertainty. The uncertainty varies from low for workers who wore individual dosimeters, to very large, e.g. when only the source term of an atmospheric release might be relatively well-known and modelling of atmospheric dispersion and radionuclide deposition is needed to estimate doses. Depending on the radiation type and the number of unknown variables, uncertainty in estimates of organ dose from external exposure to photons of less than about 0.03 MeV can be considerable.

29. Doses due to internal exposure must be determined indirectly using mathematical models that describe the distribution of the radionuclides in the body (biokinetic models) and delivery of dose over time (dosimetric models). The models used are similar to the widely used models developed by the International Commission on Radiological Protection for calculating dose coefficients for radiation protection purposes [I9, I13, I16]. Various methods are used to quantify the uncertainties in each stage of the dose calculation for internal exposure.

30. For radionuclides emitting photons or electrons of sufficiently high energy, measurements of the radiation leaving the human body allow a direct determination of the absorbed dose rate* in the body or in a specific organ such as the thyroid. Models for the time course of uptake and the biokinetics following the uptake are needed to assess the cumulative dose.

31. The types of measurement used to estimate dose from internal exposure depend on whether the exposure setting is environmental, occupational or medical. For environmental exposure settings, dose assessments for internal exposure are often based on measurements of radionuclide concentrations in environmental media. If such measurements are not available for a specific location, models must use measurements made at other locations and times. Furthermore, the diet of specific individuals is seldom monitored directly, and thus the uncertainty in estimates of intakes by ingestion may be larger than in the doses per unit intake estimated by biokinetic and dosimetric models.

32. In occupational settings, doses can be derived from bioassay analysis using biokinetic models and assumptions about when intakes occurred, as well as from measurements of radionuclides in the environment and models of intake rates. An important source of uncertainty in estimating doses due to inhalation is the physico-chemical form of the inhaled material. The magnitude and uncertainty of intakes derived from bioassay data depend mainly on the solubility of the inhaled material in the lung. Mistaken assumptions regarding the rate of dissolution and uptake to blood can lead to significant systematic errors* in estimated intakes and doses, especially those derived from measurements of radionuclides in urine.

33. In medical settings, often the quantity of radionuclides administered is known. In these cases the uncertainty in the dose estimation is dominated by uncertainties in the biokinetic and dosimetric models.

34. Because biokinetic models are generally designed to assess doses for representative members of exposed populations, uncertainty in the structure of biokinetic models represents a shared error in an epidemiology study. However, uncertainties of the parameter values for these models can be both shared and unshared. For retrospective assessments, bioassay data generally provide additional information about parameter values that will reduce uncertainties on dose estimates. However, there are parameters that do not strongly influence bioassay quantities, but may nevertheless significantly affect dose estimates. An illustrative example of this is long-term binding of inhaled plutonium to bronchial airways of the lung; here, a small bound fraction (in the order of a few per cent) can increase absorbed doses to bronchial cells from inhaled plutonium by over two orders of magnitude [B12]. Over the past decade, Bayesian methods have proved useful in refining estimates of intakes and quantifying the uncertainties on intakes and doses estimated from bioassay data [D4].

35. Uncertainties in the absorbed fractions calculated using dosimetry models arise because of uncertainty in the positions of source and target tissues, and in the geometry and masses of these tissues. It is necessary to perform Monte Carlo radiation transport calculations for a set of phantoms that represent particular combinations of source and target geometries in the determination of the uncertainty distribution of interest. Estimation of uncertainty in absorbed fractions may need to account for a systematic difference between the idealized (reference) phantom and the average individual in the population of interest.

36. Uncertainties of dose estimates in various major epidemiological studies are discussed in appendix B. A limited number of studies have used parameter uncertainty analysis to quantify uncertainties on doses per unit intake. None of them distinguish variability from uncertainty in the distributions derived for model parameters since many of these studies were not intended for epidemiological purposes.

C. Uncertainties in risk assessment

1. Impact of uncertainty in health effect information on risk estimates and statistical power of epidemiological studies

37. Uncertainty in health effect information, namely, selection bias, information bias, the effect of confounding factors and changes in information over time may lead to systematic errors in the estimates of risks from radiation exposure and/or affect the precision of these risk estimates. Statistical methods have been developed to deal with multiple sources of bias. However, concerns have been raised about the methodological basis for such approaches (see discussion in [G16]). To date, these methods have been used infrequently in epidemiological analyses.

38. Studies with low statistical power, typically owing to small sample size and/or low radiation doses, usually yield indeterminate results whether or not there is a true underlying association between radiation dose and the disease of interest. However, confidence intervals at, say, the 95% level, each obtained from one of a very large number of independent studies, will over the long term give a significant result at least 5% of the time regardless of whether or not there is a true association between

radiation dose and disease. For these reasons, the evidence regarding risk from radiation exposure relies heavily on studies of high statistical power with, when possible, replications of study findings in different exposed populations.

39. Combining data from several existing studies is a useful way to improve risk estimates or gain insights into the patterns of risk in different populations. There are two primary approaches: meta-analyses* of published findings and combined analyses using original data.

40. Meta-analyses use data from existing studies without re-analysing the data. The published results are averaged with weights determined by the precision of the findings and in some cases judgements as to the overall quality or comparability of the specific studies. A concern is whether the variations between studies, either in the control for confounding factors or in modifying factors that influence the risk from radiation exposure, could lead to incompatibility in the results across the studies. A statistical approach that is often used in meta-analyses is the “random-effects” model that takes account not only of uncertainties within the studies, but also between the studies [L27]. Typically, the confidence interval for the overall risk estimate is wider under a random-effects model than in a straightforward meta-analysis (“fixed-effect” model), particularly if there is strong evidence of heterogeneity in the findings between the studies.

41. Combined analyses involve joint analyses of the original data pooled from various studies. With access to the data from the individual studies, it is possible to use the same approach to analyse all of the data; for example, by using common exposure categories and by applying the same form of adjustment for confounding factors. This should enhance the compatibility of the findings across the studies. Since a combined analysis is easier to perform if the individual studies are of a similar design, a prospective approach whereby studies are constructed around a common protocol may be more advantageous than a retrospective pooling exercise. Questions not in the original studies may also be addressed. For example, based on studies with comparable protocols, Darby et al. [D3] were able to look at how radon-related risks varied between continuing smokers, ex-smokers and never-smokers. Nevertheless, if there is statistically significant heterogeneity in estimates of risk between studies, careful examination is required of the possible reasons for this heterogeneity before deciding whether it is sensible to pool all or even part of the data.

2. Impact of exposure uncertainty

42. Uncertainty in dose estimates is a recognized and important source of potential bias and increased uncertainty in the estimation of risk from radiation exposure. While the nature of the impact of uncertainty in dose estimates on risk estimates is understood reasonably well, it is important to understand how the different types of dose uncertainty can affect risk estimates and the limits of existing approaches. More effort is needed to improve practical methods to ensure that risk estimates properly account for the impact of uncertainty in dose estimates.

43. In practice, the magnitude of systematic errors—expressed either as a proportion or as an absolute value—may vary according to the level of dose, possibly in a complex fashion. Consequently, the impact of these errors would need to be evaluated on a case-by-case basis. Generally this involves sensitivity analyses, in which different assumptions are made about the form and magnitude of the systematic errors. For example, in analysing the United Kingdom National Registry for Radiation Workers, Muirhead et al. [M21, M22] explored the impact of dose recording practices by conducting sensitivity analyses that excluded some or all of the correction factors applied to recorded doses.

44. Shared errors in the estimation of dose increase uncertainty in estimates of risk from radiation exposure and can result in biased estimates of the risk. The shared errors in the estimation of dose are rarely considered for two reasons: (a) dose estimates rarely, if ever, include information on the nature or likely magnitude of shared errors; and (b) even if useful information on shared errors is provided there are no well-established methods for incorporating this information into risk estimation. In some analyses of nuclear industry workers, including of workers at Oak Ridge National Laboratory (ORNL) [S25] and at Hanford [G8] in the United States, account was taken not only of correction factors to allow for differences between recorded doses and organ doses, but also for the uncertainty in these correction factors [T2]. In essence, these analyses took account of shared errors that arose from applying the same correction factors to doses for groups of people. Methods to effectively use two-dimensional Monte Carlo dosimetry systems providing information on shared errors in estimating doses for risk estimation are in the early stages of development. Thus, the main aim in dealing with shared errors in dose estimation is to develop methods to ensure that their effect is reflected in the uncertainty on estimates of risk from radiation exposure.

45. Differential measurement errors, such as when greater efforts are made to determine the dose for persons with the disease of interest than for persons without it, can introduce serious and unpredictable bias. While it may be possible to assess whether risk estimates have been underestimated—or overestimated—as a consequence of differential errors, quantifying the impact on dose–response analyses is almost impossible without a detailed understanding of the structure and magnitude of these errors. Avoiding such errors is a major concern in study design.

46. How non-differential unshared errors in the estimation of dose affect risk estimates is well understood and methods for dealing with them are well-developed, at least for relatively simple situations. For example, risk estimates based on observed doses that include unshared measurement errors are biased toward zero, while if dose errors result from assignment error then there is little or no bias in the risk estimates [C7, H18, S6].

47. An example of measurement error occurs when individual dosimeter readings are used to estimate individual doses to occupationally-exposed workers over a certain period; the error reflects a (random) lack of precision in each of the individual measuring devices. Here, assuming a multiplicative error model for dose and a linear dose–response model, the effect of error in the estimated dose is to flatten the fitted dose response gradually with increasing dose, creating an apparent negative curvature and a bias toward reduced slope [C7]. Similarly, if the true dose–response relationship were linear–quadratic with positive curvature, the fitted curve might show a reduced, zero, or even negative curvature.

48. A statistical method, regression calibration,* can be used to adjust the doses and, at least approximately, adjust the risk estimate uncertainty for the effects of unshared errors in the dose estimates. The basic idea underlying regression calibration is rather intuitive: each measured (or assigned) individual dose is replaced by the expected value of the true individual dose given the measured (or assigned) dose and the distribution of true individual doses in the population [C7]. However, the distribution of true individual doses in the population is strictly not known and has to be replaced by an assumed distribution, which can be based, e.g. on a validation study for the dose estimates. If an additive and unshared non-differential measurement error and the true dose* independently have normal distributions, with variances σ_c^2 and σ^2 respectively, then in linear regression the correction for measurement errors would increase the slope of the dose–response curve by a factor of $1 + \sigma_c^2 / \sigma^2$. Schafer and Gilbert discussed other error structures that can be approached analytically [S6]. In a recent analysis by Pierce et al. [P6] of the Life Span Study (LSS) of the survivors of the atomic bombings in Japan, the correction for measurement errors with geometric standard deviations in the range 35% to 40% increased estimates of the risk per unit dose by 12% to 14%.

49. Except in the simplest situations, computations for regression calibration can be challenging. Considerable research, often in the context of studies of radiation-induced health effects, is facilitating its use in solving real problems. One line of research is the development of methods to perform regression calibration with fewer assumptions about the distribution of true doses in the population.

50. Regression calibration was originally developed to handle situations in which all of the dose error came from unshared either measurement or assignment error. However, in reality the unshared errors in radiation dose estimates come from a combination of the two types. Methods for handling this more realistic situation have been studied using a generalized model for unshared errors that can include both measurement and assignment errors.

51. While regression calibration and related methods to address unshared dose errors rely on frequentist methods, Bayesian methods provide an attractive, conceptually simple approach to characterize the influence of dose error on risk estimates (see, e.g. [L14]). The Bayesian approach involves specifying a dose–response model together with a prior distribution on the relative likelihood of specific parameter values. The data are then used to update the state of knowledge about possible values of the parameters. Recent advances in Monte Carlo-based Bayesian computational methods have made it possible to obtain samples from the posterior distribution of model parameters for many of the models of interest in studies of radiation-induced health effects. The information in these samples can then be used to provide estimates with credible uncertainty intervals for parameters of interest. In principle, the basic Bayesian approach can be extended to allow for unshared and shared dose errors by incorporating information on the nature of the dose errors and prior probabilities for parameters associated with these errors. However, further development of practical Bayesian methods applicable to large radiation studies is needed before they can be routinely used in estimation of risk from radiation exposure.

52. With increased awareness of the importance of dose uncertainties, the need for better ways to characterize uncertainties in individual dose estimates has become more obvious. A general statement about the average relative uncertainty in the dose estimates (e.g. 30% uncertainty) or statement of the uncertainty for individual doses, is not sufficient to properly assess the impact of dose uncertainty on risk estimation. Some indication of the relative contributions of measurement and assignment error to the dose estimates would be helpful. Information on shared errors is rarely provided, partly because of difficulties in determining their likely magnitude, but also because methods for using such information are still under development.

53. Over the past decade, dosimetrists have begun to develop complex Monte Carlo dosimetry systems that provide multiple realizations of individual dose estimates based upon a characterization of uncertainties about the individual's exposure situation and in the dosimetric models. These systems aim to capture the effect of both shared and unshared errors. One of the biggest challenges is the removal of the effects of unshared measurement error, otherwise risk estimates will likely be biased and the uncertainty of those estimates understated.

54. Proper use of the dose realizations from such systems requires weighting that combines information about realization-specific risk estimates using likelihood-based weights. A relatively simple approach to obtain risk estimates would be to compute a likelihood-weighted average of the realization-specific risk estimates. Somewhat better estimates can be obtained using Monte Carlo maximum likelihood (MCML) calculations, in which one computes the profile likelihood for the parameter of interest for each realization and uses the average of these functions for inference about the parameter. Stayner et al. [S25] used data on cancer mortality in the cohort of ORNL nuclear workers to illustrate the use of the MCML method to adjust for shared errors.

55. Bayesian analyses that combine information from both the outcome data and the dose realizations from such systems with prior information on the risk model parameters, while fraught with computational challenges, have the potential to provide more information on risk uncertainty than MCML or related frequentist approaches. However, little work has been done to develop such methods or to address the computational and data management issues to apply them to relatively large and complex data sets from many radioepidemiological studies.

3. Impact of model uncertainty*

56. Models are designed to give a simplified description of the main processes or an assessment of key parameters of complex processes. The results of various models may approximate a given data set equally well but yet give different estimates for some quantities of interest. Evaluating the results from several models provides insight into the information contained in the data and possible artefacts introduced by specific models. Evaluating several models increases confidence in results that are common among them and that exhibit good quality of fit. Taking into account several models generally results in uncertainty intervals that are wider than those given by the single models.

57. Generally, the impact of model assumptions is small for upper dose categories (if they have sufficient statistical power) and for the central regions of the co-variables considered in a study, such as birth year, age at exposure, age at diagnosis or death, or smoking rate. At low doses and at the borders of the range of the co-variables considered, however, the impact might be quite large. For example, in an analysis of Preston et al., for survivors aged 60 at the time of the atomic bombings in Japan and who received a colon dose of 1 Gy, considering the incidence of solid cancer at age 70, the estimates of excess relative risk using two preferred models differed by a factor of 2.5 [P14]. In another example, for the risk of fatality from lung cancer among male Mayak workers at age 50 following an exposure to plutonium between the age of 20 and 40 years with a cumulative dose of 0.1 Gy, the estimates of ERR using preferred empirical and mechanistic models differed by a factor of four [J3].

58. Quantification of model uncertainty is complicated by the fact that it represents a conceptual uncertainty; however, one approach is to represent model uncertainty in an uncertainty analysis by assigning discrete probabilities to plausible alternative model structures.

59. Model that are too simplistic obviously describe the data poorly, while models with too many parameters may result in uncertainties of estimated quantities of interest too large to be real or may produce spurious effects. So-called “information criteria” have been derived to optimize the number of model parameters and select between different models. Criteria frequently used are the Akaike information criterion* (AIC) [A3, A4, B25, C10], derived from information theory, and the Bayesian information criterion* (BIC) derived from Bayesian statistics [S10, Y2]. Walsh suggested the application of the information criteria in analyses of radioepidemiological data [W2].

60. Multi-model inference* is a methodology that combines results for a quantity of interest that were derived from the same data with different models. Weights based on an information criterion are assigned to probability density functions derived from different models. There is a large body of publications on model uncertainties (for summaries, see [B25, C10, H15]). However, applications in the field of radiation research are rare.

61. In some cases, publications of multi-model inference in the field of risk from radiation exposure demonstrated that uncertainty intervals derived by multi-model inference are wider than those derived from well-fitting descriptive models by up to a factor of two or even more; in other cases, results that were significant in a well-fitting descriptive model were no longer significant when more models were

considered [K2, W4]. The Committee notes that neglecting model uncertainties may lead to considerable over-confidence in risk estimates, and considers that multi-model inference techniques should be used in future risk evaluations, and that model uncertainties should be explored using both empirical and mechanistic models.

IV. UNCERTAINTIES IN TRANSFERRING RISK QUANTITIES FROM GIVEN STUDIES TO OTHER EXPOSURE CONDITIONS OR POPULATIONS OF INTEREST

62. This chapter discusses the transfer of risk estimates derived from observational studies to draw inferences for other populations of interest who may be exposed under different conditions from the observational studies. Appendix C provides more detailed explanation, technical information and review, including consideration of the uncertainty in the dose and dose-rate effectiveness factor (DDREF), and in modifying factors to estimate risks from exposure to high-LET radiation, lower-energy photons and low-energy electrons.

A. Transfer to another population or time period

63. The UNSCEAR 2006 Report [U12] considered that the best way to transfer estimates of risk from radiation exposure between populations was unknown, and that currently the most useful and relevant information came from multinational comparisons of cancer-specific, radiation-related risk. If two populations have distinctly different age-specific baseline rates* for a given cancer site, additive and multiplicative projections of risk from one irradiated population (e.g. the LSS cohort of the atomic bombings survivors) to a second population yield discordant risk estimates. Though not necessarily correct, results of the projections differ little if the two populations have similar baseline rates.

64. Both additive and multiplicative projections are plausible in terms of possible biological mechanisms. If exposure to ionizing radiation—and other possible risk factors—act mainly as cancer initiators, then one might expect the effect of the exposure to be approximately additive. If this were the case, the dose-specific excess absolute risk* (EAR) would be expected to be relatively independent of the baseline rate* and the same for the two countries. In contrast, to the extent that differences in baseline rates reflect differential population exposure to cancer promoters, the dose-specific EAR might be expected to be proportional to the baseline rate. Thus, if this were the case, the dose-specific excess relative risk (ERR) would be expected to be about the same for the two countries [N7]. However, mechanisms of carcinogenesis are not sufficiently well understood to allow a decision on the appropriate risk transfer model. Instead, comparisons of estimates of risk from radiation exposure derived from different epidemiological studies are used (see, e.g. [N19, P11]). Uncertainty about the choice of projection model needs to be incorporated into estimates of radiation-related risk for the population of interest, particularly for public policy purposes such as radiation protection or adjudication of compensation claims for possible radiation-related cancer.

65. Useful site-specific data on baseline cancer rates as functions of attained age are readily available for many populations [I5]. Information on radiation-related cancer risk as functions of age is available from studies of exposed populations, including the LSS cohort and numerous studies of medically and

occupationally-exposed populations [N19]. The relationship between the two sets of data varies by organ site and population, and is not straightforward. For example, age-specific baseline rates of female breast cancer are markedly lower in Japan compared to those in the United States, but radiation-related excess absolute risks are comparable between the LSS study cohort and medically irradiated populations in the United States. Assuming the dose-specific ERR to be the same for the LSS and for the United States population results in a risk estimate for the United States population that is four times higher than that obtained using an additive transfer model (table 1). Baseline rates for gastric cancer, on the other hand, are much higher in Japan than in the United States, yet radiation-related excess relative risks are similar in the two countries [N19]. Appendix C of this annex discusses these and further examples in more detail.

66. Estimates of risk from radiation exposure obtained from epidemiological studies apply to the period of observation in those studies. For most members of a cohort study, the observation period does not, in general, extend up to the end of their lives. In order to derive lifetime risk* estimates, extrapolations have to be performed that are based on the time dependencies seen during the observation period. Attained age is the independent variable most closely associated with extrapolating risks over a lifetime. Radiation-related risks tend to decrease exponentially with age attained. Annex A of the UNSCEAR 2006 Report of the Committee [U12] summarizes a number of quantities that are used to describe lifetime risks.

Table 1. Best estimates and 90% confidence intervals of excess cancer rates per unit dose in the United States based on different transfer models of LSS risk factors

The risk projection applies to age 70 after exposure at age 30

<i>Cancer</i>	<i>Risk quantity on which transfer is based</i>	<i>Extrapolated excess rate per unit dose (cases per 10⁴ PY Gy)</i>
Breast cancer	ERR per unit dose	36 (23, 54)
	EAR per unit dose	9.2 (6.8, 12)
Gastric cancer	ERR per unit dose	1.2 (0.8, 1.7)
	EAR per unit dose	9.5 (6.1, 14)
Colon cancer	ERR per unit dose	8.2 (4.6, 12)
	EAR per unit dose	8.0 (4.4, 12)

B. Transfer to risks from LSS to other exposure conditions

67. In this annex, the Committee uses a value of 0.1 Gy as an upper value of the low-dose range for low-LET radiation, and doses up to 1 Gy are called moderate, while doses above 1 Gy are called high. Low dose rate* is used to express doses-rates for low-LET radiation below 0.1 mGy/min averaged over one hour. Although the Committee had previously reviewed the evidence related to transferring risk estimates derived from studies of acute exposures* at moderate or high doses to exposure situations at low doses or low dose rates, it did not quantify uncertainty. The United States BEIR VII analysis derived a distribution of the dose and dose-rate effectiveness factor (DDREF) with a mode of 1.5 and a 95% credible interval of 1.5 to 2.3 [N19]. However, the resulting uncertainty distribution was considered to be misleadingly narrow and a wider distribution was used subsequently. The Committee considers that the present knowledge of the DDREF may be expressed by a ratio of the 95th percentile of the uncertainty interval to the 5th percentile of at least a factor of four.

68. In the past decade, a number of reports have shown evidence that the biological response to exposures at low dose is different from that at moderate and high dose (in terms of DNA double-strand repair, gene expression and abundance of proteins). Because carcinogenesis following low doses is not completely understood, estimates of cancer risks from radiation exposure are necessarily more uncertain when extrapolating from moderate- or high-dose studies to low dose.

69. Despite the increasing statistical power of epidemiological studies, the statistical power of single studies of cancer risk after protracted exposures* with cumulative doses of at most a few hundred millisieverts is still low. Nevertheless, a meta-analysis of cohorts with prolonged occupational exposure has indicated that risks per unit dose are not inconsistent with those derived from the LSS cohort of the atomic bombing survivors [J5].

70. Estimates of cancer risks from exposure to ionizing radiation are based primarily on analyses of data on dose response in the Japanese atomic bombing survivors, who mainly received an acute exposure to high-energy photons. In estimating cancer risks from exposure to other types of radiation (e.g. neutrons, alpha particles, and lower-energy photons and electrons), estimated risks for the atomic bombing survivors must be modified to address the dependence on radiation type. An exception involves the risk of lung cancer from inhalation of radon and its decay products, where the risk from radon exposure can be estimated directly from epidemiological data, without the need to estimate absorbed dose and the biological effectiveness of alpha particles.¹

71. Modifying factors to represent the effectiveness of different radiation types compared with high-energy photons can be applied to estimates of absorbed dose at the site of an organ or tissue to obtain a biologically significant dose on which the risk of cancer at that site is assumed to depend [K6]. The Committee has discussed values for these modifying factors and their uncertainties that were developed for use in estimating cancer risks from actual exposures on the basis of data on relative biological effectiveness* (RBE) obtained from radiobiological studies. Modifying factors for some radiation types can also be estimated from epidemiological data. The Committee has reviewed published analyses of modifying factors and their uncertainties for radiation types of most general concern (neutrons, alpha particles, lower-energy photons, and low-energy electrons) and for inducing cancer in humans (appendix C to this annex).

V. UNCERTAINTIES OF SELECTED RISK EVALUATIONS

72. The Committee has considered three examples of risk evaluation that summarize the present state of knowledge, estimate the value of various quantities that express risk and indicate the impact of different sources of uncertainty:

- (a) Solid cancer after external exposure to radiation with cumulative doses of the order of 100 mGy above that from exposure to typical levels of background radiation;
- (b) Thyroid cancer after radiation exposure during childhood;
- (c) Lung cancer after residential exposure to radon decay products.

¹ In radiation protection, the dependence of cancer risks on radiation type is represented by the quality factor (Q) and radiation weighting factor (w_R). Point values of Q and w_R are defined by the ICRP for use in calculating the radiation protection quantities: dose equivalent, equivalent dose, and effective dose. However, Q and w_R are not intended for use in estimating cancer risks from actual exposures of identified individuals or groups.

For each of the first two cases, two calculations were performed. One was based on a recent major study. The second was based on extrapolating risk using data from other studies. This aims to show how the more recent studies have improved knowledge on the specific risk under consideration. More details on the risk evaluations are given in appendix D.

A. Solid cancer risks after external exposure to cumulative doses of the order of 100 mGy above typical background exposure

73. Risk estimates for the combined group of solid cancers are usually based on comparatively large numbers of cases thereby increasing statistical power and reducing statistical uncertainty. However, the group comprises a large number of different cancer sites and types. Carcinogenic processes and causal associations with radiation exposure vary substantially between individual sites.

74. Overall, there is a strong body of evidence on solid cancer risks after external irradiation with cumulative doses exceeding 100 mGy based upon sophisticated analyses of data from the atomic bombing survivors and a growing number of other studies of people with occupational or environmental exposures.

75. Most work on sources of uncertainty beyond that on statistical sampling error has focussed on dosimetric errors, notably in the LSS and the international workers study [S25]. Uncertainty from other sources, such as procedural aspects of conducting the study or insufficient information on potential confounding factors, are often noted qualitatively, but usually not formally incorporated into risk estimation.

76. The Committee considered a risk evaluation for a population of workers who began work at age 30 and were occupationally exposed to low-LET radiation from the ages of 30 to 44 with a total dose of 100 mGy. Two approaches were taken to estimate radiation-related solid cancer risks and associated uncertainties:

(a) The first relies on a study of the United Kingdom National Registry of Radiation Workers (NRRW) for the risks of all cancers combined and considers possible age-related changes in the magnitude of the so-called “healthy worker effect” [M21]. The results indicate that the expected baseline lifetime risk of developing a solid cancer (other than non-melanoma skin cancer) is 40.3 (95% CI: 38.5, 41.4) per 100 exposed workers, with an expected risk of an exposure-associated cancer of 1 (95% CI: 0.07, 1.97) per 100 exposed workers. This indicates that roughly 2 (95% CI: 0.2, 4.8) per cent of all the cancers are expected to be associated with the exposure. This proportion was found to be essentially constant for all ages at diagnosis.

(b) The second characterized the effect of radiation exposure on solid cancer rates using site-specific and age-dependent risk models derived primarily from LSS cancer incidence data but excluding any consideration of the NRRW results [K7]. The estimate of radiation-related lifetime risk at age 45 was 0.81 (95% CI: 0.32, 1.6) per 100 exposed workers, and a total number of expected cases (baseline plus radiation-related) of 41.8 (95% CI: 38, 44) cases per 100, leading to an attributable fraction* of 1.9 (95% CI: 0.8, 3.7) per cent (table 2). The uncertainty in the DDREF dominates the uncertainty in these estimates.

Table 2. Estimates of exposure-related risk of cancer incidence, based on the BEIR VII/NCI risk assessment methodology, for United Kingdom nuclear workers who received an absorbed dose of 100 mGy between the ages of 30 and 44 with no additional occupational exposure

Statistic	Mean	95% credible interval	
		Lower	Upper
Total cancer cases ^a	41.8	38.6	43.5
Excess cancer cases ^a	0.81	0.32	1.6
Attributable fraction (%)	1.9	0.8	3.7

^a Total cancer cases and excess cases are expected values for an assumed population of 100 workers with follow-up from age 45 through to the end of life. The number of cases includes all solid tumours, except non-melanoma skin cancer.

77. The two approaches agree very well on a lifetime excess cancer rate of 1 case among 100 United Kingdom exposed workers after a total dose of 100 mGy between ages 30 and 44. Thus the new study of the United Kingdom NRRW data increased confidence in the transfer of risk estimates for all cancers from the LSS cohort to other populations. Although this approach took into account uncertainties due to the risk transfer from Japanese to United Kingdom populations, and from exposures ranging from acute to protracted, the calculated uncertainty interval (0.3 to 1.6 cases) is considerably smaller than the interval derived from the NRRW study alone (0.07 to 1.97 cases). (The large uncertainty for the NRRW study is due to its limited statistical power, in spite of its large size—177,000 workers). Whether or not the uncertainty interval based on the risk transfer is too narrow cannot be answered presently.

B. Thyroid cancer after radiation exposure during childhood

78. Previous UNSCEAR reports concluded that the thyroid is highly susceptible to the carcinogenic effects of external exposure to radiation during childhood, and thyroid cancer risks remain elevated for many decades [U12]. The excess risk* decreases strongly for older ages at exposure. Evidence of the carcinogenic effects of exposure to ¹³¹I came from studies of individuals exposed to radiation from the Chernobyl accident during childhood or adolescence. A number of epidemiological studies resulted in consistent estimates of the ERR for thyroid cancer after an exposure during childhood or adolescence with a thyroid dose of 1 Gy. It was emphasized that medical surveillance of thyroid diseases escalated in the affected countries after the accident, increasing the number of thyroid cancer cases reported in registries.

79. Two new analytical studies on children who received external exposures during medical treatment resulted in risk estimates either similar [B11] to the previous study of the same cohort, or in a lower estimate of the ERR per unit dose [A1] (probably because of a decrease of risk with the longer follow-up times). The new study after the Chernobyl accident investigated data for a longer time since exposure than before and also tended to have a lower estimate of the ERR per unit dose.

80. Methods to correct estimates of thyroid cancer risk for the large random dose errors in two studies have been implemented [K10, L14]. For these cases, corrected estimates of the ERR per unit dose are larger by a factor of about three than those using a regression calibration with mean values for individual dose. Shared errors can influence the dose response further, but the impact remains to be evaluated explicitly. The Committee emphasizes that reliable risk estimates are normally derived from studies that have reliable dose estimates, and thus are less affected by dose uncertainties.

81. The impact of the choice of model on risk estimates has been analysed in two studies with more reliable dose estimates [W3]. At 12 years after exposure, ERR estimates for young ages at exposure appear to be strongly influenced by the baseline modelling, while EAR estimates were more stable.

82. The Committee evaluated thyroid cancer risk for a hypothetical group of Ukrainians who were 10 years of age at the time of the Chernobyl accident. Their cumulative thyroid dose was assumed to be 200 mGy almost exclusively due to incorporation of ¹³¹I. Surveillance of thyroid diseases in the group was assumed to correspond to the situation one to two decades after the accident in parts of Ukraine with higher levels of deposition. Two approaches to analyse risk and uncertainties were again used:

(a) A first approach used only studies conducted before the accident. According to the best estimates, the baseline rate of 14 cases of thyroid cancer during the lifetime of 10,000 males would be increased by the radiation exposure to about 20, while the baseline rate of about 60 cases during the lifetime of 10,000 females would approximately double (table 3). Baseline rates are larger for females than for males, and the rate ratios (relative risks)* from radiation exposure were also assumed to be larger for females than for males. The 95% credible interval for the radiation-associated rate ranges for males from 1.2 to 21 per 10,000, and for females from 11 to 210 per 10,000. The large uncertainty is dominated by the statistical uncertainty in the estimate of the ERR per unit dose for acute exposure followed by the uncertainty in the DDREF. In these calculations, the ERR was assumed to be independent of time after exposure.

(b) Studies conducted after the accident have, however, demonstrated high ERR values at a few years after exposure that decrease over the following one or two decades. Furthermore, in the first approach, above, the ERR was used to transfer risk from the LSS to the hypothetical Ukrainian population. However, studies conducted after the accident indicate that the EAR for thyroid cancer may also be appropriate to transfer thyroid cancer risk. Risk projections based on the EAR model transfer were higher than those based on an ERR model transfer, generally by a factor of two. It may be noted that the difference here is because of an uncertainty in the risk model, and not because of an uncertainty in the transfer model. If the EAR model estimate for the EAR is replaced by the product of the ERR and the baseline in the LSS, then the difference in the lifetime risks of the two transfer models is relatively small.

Table 3. Estimates of hypothetical numbers of rates of thyroid cancer (best estimates and 95% credible intervals) among 10,000 Ukrainians, who were of age 10 years at the time of the Chernobyl accident and received a thyroid dose of 200 mGy from incorporation of ¹³¹I, using the BEIR VII models [N19]

Sex	Baseline (per 10,000)	Excess (per 10,000)	Total (per 10,000)
Males	14 (-)	6.6 (1.2, 21)	20 (15, 35)
Females	62 (-)	59 (11, 210)	121 (73, 272)

C. Lung cancer after residential exposure to radon

83. The main health effect from inhalation of radon decay products is an increased risk of lung cancer. More than 20 analytical studies (mostly case-control studies) of lung cancer and residential exposure to radon, and three pooled analyses of the individual data of the European [D3], North American [K15] and Chinese studies [L30] have been published. These pooled studies consistently showed an approximately linear increase in the risk of lung cancer with increasing long-term radon exposure.

84. The greatest challenge in such studies is to assess radon concentrations accurately for the relevant period of interest (from 5 years to about 35 years before lung cancer was diagnosed or, for the controls, before the date of their interview). Usually radon is measured for one year in one or two rooms of the current home and of all other dwellings inhabited by the cases and controls during the period of interest. Uncertainty in the exposure assessment arises from detector measurement error, the use of current measurements of radon concentrations in air to reflect past levels for up to 30 or more years ago, spatial variations within a home, missing radon concentration measurements, and failure to link radon concentration measurements with subjects' occupancy patterns.

85. So far, the largest and most informative study on lung cancer and indoor radon is the pooled analysis* of 13 European case-control studies [D3]. It includes 7,148 cases and 14,208 controls, all with detailed information on smoking histories and radon measurements in homes that the individual had occupied during the previous 15 years or more. The risk estimates were formally adjusted for measurement (year-to-year variability of measurements) and assignment (imputation of missing values) errors using regression calibration. Without these adjustments, the estimate for the ERR per unit average radon concentration was 0.08 (95% CI: 0.03, 0.16) per 100 Bq/m³. After adjustment the ERR estimate per unit average radon concentration increased to 0.16 (95% CI: 0.05, 0.31) per 100 Bq/m³.

86. Several other methods have been applied to account for the uncertainties in exposure assessment such as those associated with deriving doses from track-etch measurements or from direct measurements of radon in air, or with using a study design that limits participants to long-term residents. Other methods include conducting sensitivity analyses that limit subjects to those with more accurate information, or improving the exposure assessment by linking it with spatial and temporal occupancy patterns. Applying these methods consistently increased the estimate of excess relative risk of lung cancer by around 50% to 100% (see appendix B). In addition, uncertainty in the assessment of potential confounding factors, such as smoking, may distort estimates of the true risk. The true ERR per unit radon concentration could thus be somewhat higher, even after correction for year-on-year variation in measured radon concentrations [W8].

VI. KEY RESEARCH NEEDS

87. Research is needed to identify sources of measurement error, which leads to over-estimation of random variability of true dose in a cohort, and develop procedures to either remove them or account for them using regression calibration on each realization of a set of possibly true doses.

88. Because of the complex nature of risk analyses making full use of Monte Carlo uncertainty propagation to produce multiple realizations of cohort dose sets, there is a need to develop and distribute tools to make efficient implementations of these computationally intensive methods readily available to researchers. Guidelines would be useful to help researchers evaluate when shared errors in dose reconstruction models are likely to have a marked effect on dose response or its uncertainty.

89. Many exposures to ionizing radiation involve low-LET radiation at low doses or low dose rates or radiation types other than high-energy photons. To improve estimates of cancer risk and their uncertainties for such situations, further research is needed to quantify risks at low-dose and low-dose-rate exposures to low-LET radiation and modifying factors to represent the effectiveness of radiation types other than high-energy photons in inducing cancer in humans, and their uncertainties. A particularly important need is further research on the biological effectiveness of lower-energy photons, especially X-rays of various energies, given their common use in medicine.

90. While most studies of radiation-induced health effects focus on a single model to analyse the radiation dose response and quantify the uncertainty of the risk estimate, alternative models can also often describe the data. In general, not allowing for uncertainty about the form of the risk model underestimates uncertainty in estimates of the quantities of interest. There is a need to develop methods that incorporate uncertainty about the form of the model for radiation dose response.

91. New approaches are essential to improving understanding of radiation-related health risks and to reduce uncertainty of risk estimates at doses of general concern. One of these approaches is to incorporate radiobiological knowledge by analysing epidemiological data with models of carcinogenesis. The identification of a possible marker of radiation-induced cancer and performing measurements of the marker in a large epidemiological study is another approach that may also improve knowledge of low-dose radiation-induced health effects.

VII. CONCLUSIONS

92. Estimates of cancer risk from exposure to ionizing radiation derived from radioepidemiological studies are uncertain because of the power of the study, the intrinsic stochastic variability of cancer cases, imprecise characterization of risk factors, and the effects of risk factors other than radiation exposure that can distort results unless properly addressed. Reports of estimates of risk from radiation exposure should include a clear and thorough discussion of limitations of the data and a realistic assessment of how these limitations might affect the results.

93. In recent years, increased attention has been paid to the uncertainty in risk estimates associated with uncertain estimates or measurements of dose. Failure to account for dose uncertainty can lead to biased risk estimates (often underestimates) and to overly optimistic statements about the confidence in these estimates. The different effects of errors in individual doses result from measurement or the assignment of representative values. There is increasing awareness that shared dose errors may bias risk estimates or underestimate the uncertainty of these estimates. In many situations, regression calibration (in which observed dose estimates are replaced by their expected values given what is known about the individual and the population dose distribution) is a relatively straightforward and often quite effective method for dealing with random individual dose errors. The development of multiple-realization dosimetry systems and computationally intensive Bayesian methods that make full use of the dose realizations to allow for the effects of dose uncertainty on risk estimates are topics of great interest. There is a need to develop practical methods for such analyses.

94. Risk analyses are based on models that describe the health effects of interest. These analyses typically involve only a single model, even though various models can describe the data with comparable quality but imply different values of risk. Neglecting model uncertainties may considerably underestimate the total uncertainty of risk estimates. Multi-model inference is a method that considers multiple models in risk analyses. The Committee suggests that future risk evaluations use multi-model inference techniques.

95. The contribution of the different sources of uncertainty in transferring risk estimates from an epidemiological study to another population or exposure situation of interest depends on the objective of the specific risk assessment. Usually, only a few factors dominate. For example, for protracted uniform whole-body irradiation and risk for all cancer sites combined, the uncertainty in transferring LSS risk estimates to low-dose and low-dose-rate exposure is usually an important contributor. For internal exposure of single organs, the uncertainty in the absorbed organ dose and in the organ-specific

risk coefficients may dominate. Uncertainty in transferring risk coefficients from one population to another are of importance when these populations exhibit large differences in the baseline rates of disease. Additional uncertainties must be considered when using estimates of the excess relative risk to calculate the likelihood that the manifestation of a diagnosed cancer in a specific individual can be attributed to radiation exposure.

96. Selected examples of risk evaluations have shown that lifetime risks are well studied for all solid cancers combined after acute and after protracted exposure with cumulative whole-body absorbed doses of greater than about 100 mGy and for lung cancer after living for decades in homes with radon concentrations of greater than about 100 Bq/m³ above average. Addressing known sources of uncertainty, the 95% credible intervals span about an order of magnitude. However estimates of site-specific cancer risks have larger uncertainties still, as shown by an example evaluating thyroid cancer risk after an absorbed dose to the thyroid of 200 mGy in childhood.

ACKNOWLEDGEMENTS

The Committee would like to acknowledge: P. Jacob, F.O. Hoffman, C. Land, and D. Preston, who prepared the substantive material for the Committee's scrutiny; I. Apostoaei, N. Harley, D. Kocher, M. Kreuzer, R. Michel, C. Muirhead, and H. Zeeb for their contributions; and L. Dobrzyński (Poland), who critically reviewed drafts for the Committee.

APPENDIX A. FUNDAMENTAL CONCEPTS

I. STATISTICAL CONCEPTS OF UNCERTAINTY	115
A. Basic concepts and terminology.....	115
B. Approaches to statistical inference.....	119
C. Quantifying uncertainty.....	125
D. The distinction between variability and uncertainty.....	126
E. Accounting for dependences among uncertain model inputs and assumptions	128
F. Uncertainty propagation and sensitivity analysis.....	128
II. EPIDEMIOLOGICAL CONCEPTS	134
A. Cohort studies.....	135
B. Case-control studies	137
C. Geographical correlation studies.....	138

I. STATISTICAL CONCEPTS OF UNCERTAINTY

A. Basic concepts and terminology

A1. Uncertainties on estimates of risk from radiation exposure include both those that arise in developing models and in estimating parameters based on a specific data set and those that arise when the resulting risk estimates are used to assess risks for some other population.

A2. Uncertainty in the characterization of cancer rates and risk estimation arises from a number of sources. The inherently stochastic nature of the processes leading to the response is a primary and omnipresent source of uncertainty in any attempt to describe radiation-induced health effects. Additional uncertainty arises because the amount of data available to characterize the risk is limited or even, in some cases, non-existent. Furthermore since risk estimates are virtually always based on idealized (and incomplete) models, the choice of model is another source of uncertainty in risk estimation. When risk estimates are based on data, imprecise specification of risk factors, particularly measures of dose or exposure, can be an important source of uncertainty in the resulting risk estimates.

A3. Additional uncertainties arise when risk estimates developed on the basis of a population exposed in a particular way (for example, survivors of the atomic bombings in Japan who received acute, relatively high-dose exposures) are used to assess the risk in a different population (for example, workers in the German nuclear industry who received low-dose-rate chronic exposures,* or children who undergo CT scans). Sources of such uncertainties are described later in this report.

A4. Because of the importance of the relationship between the characterization of the dose–response function and the inherent, but often ignored, uncertainties in measuring or estimating radiation doses, the report gives considerable attention to methods of adjusting for dose uncertainties and to quantifying uncertainties in risk estimates that arise from using uncertain dose estimates.

A5. In this document the term “uncertainty” refers to the distribution of the possible true values of a quantity of interest. The actual difference between the true value of a quantity of interest and an estimate or measurement of that value, which is here called an “error”, is generally unobservable. Uncertainty analysis concerns the characterization of the distribution of the possible true values taking into account all known sources of uncertainty.

A6. In all but the simplest cases uncertainty arises from multiple sources and in ascertaining the effects of uncertainty it is useful and important to consider the different types of error that contribute to the uncertainty for a given quantity of interest. One useful classification concerns the mechanism by which errors occur and involves whether or not errors are independent (on some scale) of the true or observed value of the quantity of interest. This leads to a distinction between (a) “classical measurement” errors (for which the error is independent of true value) and (b) “assignment” or “Berkson” errors (for which the error is independent of the observed or assigned value). Another classification concerns whether or not the errors are independent between individuals. Errors that are dependent between individuals are called “shared” errors while those that are independent are called “unshared” errors. Both shared and unshared errors can arise as a result of either measurement or assignment error.

A7. *Measurement (classical) error:* If a quantity is measured with an imprecise measuring device then we have:

$$\text{observed value} = \text{true value} + \text{measurement error} \quad (\text{A.1})$$

where “measurement error” is a random variable that is uncorrelated² with the “true value”. An important feature of the classical error* model is that the (population) variance of the observed values, $\sigma_{\text{obs}}^2 = \sigma_{\text{true}}^2 + \sigma_{\text{merr}}^2$, where σ_{true}^2 is the variance of the true (unobserved) values and σ_{merr}^2 is the measurement error variance. Thus, in the case of measurement error the variance of the observed values exceeds that of the true values. In linear regression models in which the dependent variable has classical error, slope estimates based on observed values are biased towards zero because inter-individual variability of true values is overestimated.

A8. *Assignment (Berkson) error* is typically the result of some form of assignment in which individuals in a group are assigned a nominal representative surrogate value. Ideally the assigned value is equal to the true mean value for that group (in which case the assignment is said to be *unbiased*). Thus, using the terminology from [S6]:

² Errors that are uncorrelated on one scale may be correlated on another scale. The text for this discussion focuses on additive measurement error (such as those described in this paragraph), but for many situations errors are multiplicative, i.e. observed value = (true value) × (multiplicative measurement error). In this case the errors are additive (and uncorrelated) on the log scale, that is $\log(\text{observed value}) = \log(\text{true value}) + \log(\text{multiplicative measurement error})$, even though the additive errors (i.e. observed value – true value) are correlated with the true values.

$$\text{true value} = \text{assigned value} + \text{individual peculiarity} \quad (\text{A.2})$$

where “individual peculiarity”, which refers to the assignment error, is a random variable that is statistically independent of the assigned value and depends on (generally unknown) characteristics of an individual that affect their true value. In other words, assignment errors describe random inter-individual variability of true values about a single value assigned to every individual belonging to a distinct group. The value assigned to each individual in the group is assumed to be the true mean value for that group. (For the case of additive assignment errors the “true mean” refers to the arithmetic mean, while for multiplicative assignment errors the “true mean” refers to the geometric mean.) Incorrect specification of the group mean will introduce shared error (discussed below) and can lead to bias in quantities estimated using the incorrectly assigned values. In contrast to the situation with measurement error, with assignment errors the variance of the assigned values (σ_{av}^2) will be less than that of the true variance of values since $\sigma_{true}^2 = \sigma_{av}^2 + \sigma_{ip}^2$ or $\sigma_{av}^2 = \sigma_{true}^2 - \sigma_{ip}^2$, where σ_{ip}^2 is the variance of the individual peculiarity in the values about a given assigned value.

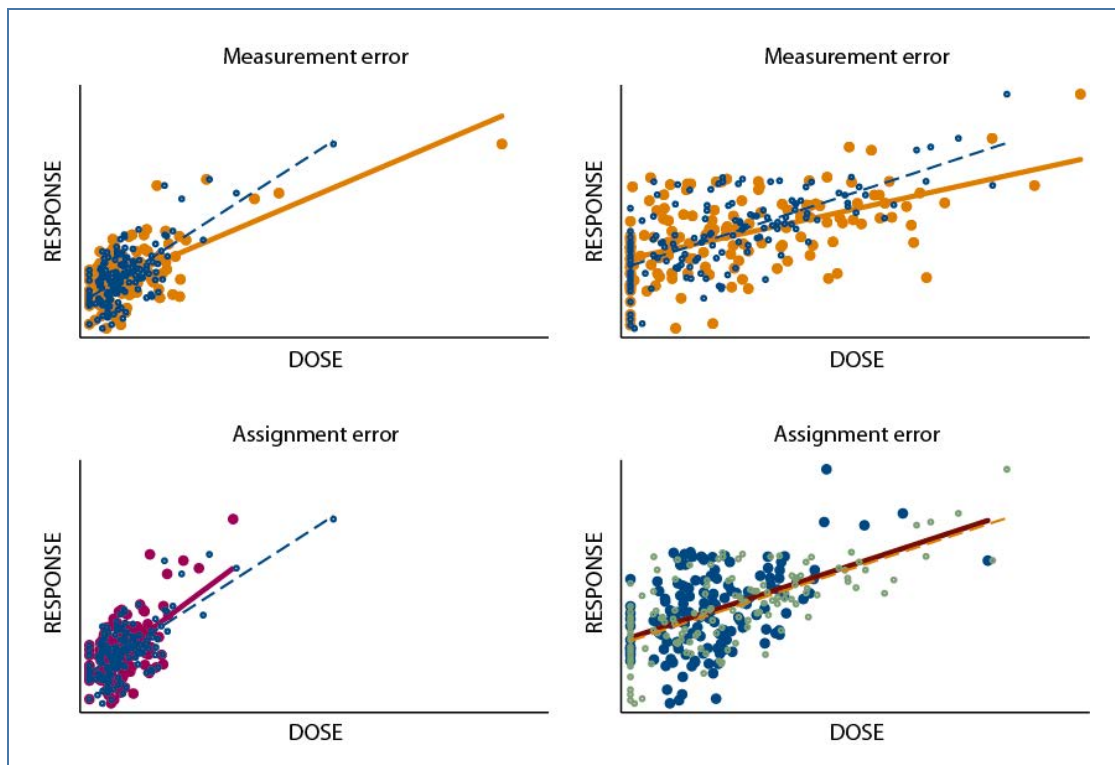
A9. In the presence of unbiased additive assignment error (i.e. when the expected value of the individual peculiarity is zero), risk estimates derived from a model that is linear in the true values (e.g. dose) that is fit using the assigned values will provide unbiased estimates of the slope of the regression on the true values. On the other hand, in the presence of unbiased multiplicative assignment error there will be a small systematic upward bias in the slope estimate. The magnitude of this bias is a function of the variance of the individual peculiarity factors.

A10. Assignment errors are quite common in radiation dose estimation. Examples include: (a) situations in which there is a single dose monitoring device at some workplace and all people who work in this location are assigned a dose based on the value recorded by this device, or (b), as is the case for the DS02 dosimetry used to compute doses for survivors who were in typical houses at the time of the atomic bombings, limited information on the nature of the house and the survivor’s location within the house is used to pick one of a small number of representative house models for which distance-dependent dose adjustment factors have been computed; the assigned value of these factors is used to convert estimated free-in-air kerma to an estimated shielded kerma for the survivor’s location.

A11. Figure A-I contains plots that illustrate the impacts of random measurement (top row) and random assignment (bottom row) errors on linear dose–response parameter estimates in the presence of multiplicative (left column) or additive (right column) dose uncertainties. The parameters for the fitted dose–response functions (solid lines) were estimated using the responses at the observed doses (large solid points). The plots also include the responses at the true doses (smaller open points) and the corresponding regression for the true doses (dashed lines). As can be seen, there is some downward bias in the regression estimate in the presence of either multiplicative or additive errors in the measured doses. However for additive random errors in individual assigned doses the fitted regressions are quite similar to those one would obtain if the true doses were available. There is a suggestion of small upward bias in the slope in the case of multiplicative assignment errors, which is as one would expect.

Figure A-I. Plots illustrating the effect of different types of random “dose” uncertainty on estimates of the parameters of a linear dose–response function

The plots in the top row involve dose measurement errors while the plots in the bottom row involve errors resulting from the assignment of representative doses to individuals (assignment errors). Each plot includes both the measured or assigned doses (large closed points) and the true doses (small open circles). The solid lines indicate the fitted value of the linear regression of the response on the measured or assigned dose, while the dashed lines are the fitted value of the linear regression on the true dose. The measured and assigned doses for the plots in the left hand column were generated with the assumption of multiplicative dose errors in which the magnitude of the error is on average about 40% of the true value. The observed doses for the plots in the right column were generated using normal additive uncertainties (mean 0 and variance 1)



A12. *Shared errors* are errors that are correlated between “individuals”. In the presence of shared error, the expected value of the difference between the observed or estimated value of the quantity of interest and its true value need not, and indeed generally is not, equal to 0. Thus shared error can lead to *bias* or *systematic* uncertainty. Shared errors can arise for many reasons. For example, improper calibration of a measuring device can result in measurements (for example, of doses) that differ in a systematic manner from the true value of the quantity of interest. Shared errors also arise when the quantity of interest is described as a function of some parameters and observed data and either the parameters or the functional form are mis-specified.

A13. Examples of shared errors include assignment of an incorrect mean dose to a group of people and use of incorrect parameters in a dose estimation model (for example, mis-specification of the yield or hypocentre location for the atomic bombings).

A14. *Unshared errors* are uncorrelated between individuals on an appropriate scale and for the purposes of this discussion, can be taken to have a mean of zero. Unshared errors might be the result of imprecise measurement of some quantity of interest (for example, dose) or because of the assignment of

representative values to groups of similar individuals. In the latter case, all uncertainty is due to random inter-individual variability of true values about the assigned value (that is, this situation is identical to what is referred to in paragraph A.8 as assignment error).

A15. Unshared errors can arise when quantities of interest are based on individual measurements or observations (for example, a reading from a personal dosimeter or statements about whether or not an individual was actually exposed or whether or not they consumed contaminated food products at the time of exposure and if so, how much).

A16. Hofer [H16, H18] has noted that it can also be useful to classify uncertainties as either “aleatory” (Type A)*, or “epistemic” (Type B)*. Aleatory uncertainties* are those that reflect statistical variability in repeated observations or between different individuals in a population, whereas epistemic uncertainties* are related to the state of knowledge or degree of belief about the unknown value of some specific quantity of interest. Random variability of repeated measurements or random variability of unknown true doses among unspecified persons are aleatory (Type A) uncertainties, while uncertainty about the true dose to specific individuals or in the value of the excess cancer incidence associated with a given radiation exposure in a population of interest is an epistemic (Type B) uncertainty.

A17. The terms “Type A evaluation of uncertainty” and “Type B evaluation of uncertainty” are used to describe key concepts in the Guide to Uncertainty in Measurements (GUM) [J8, J10, J11], which is a formal Bayesian approach to the characterization of measurement uncertainty widely used in the field of metrology. The GUM defines Type A evaluation of uncertainty as an assessment of uncertainty in measurements that is based on the statistical analysis of a series of observations. In contrast, Type B evaluation of uncertainty refers to non-statistical evaluation of measurement uncertainties (e.g. based on earlier measurements and evaluations or other information). These definitions differ from those of Hofer. Unless noted otherwise, throughout this document “Type A” and “Type B” are used to refer to classification of uncertainties in the sense of Hofer.

A18. Uncertainties on estimates of risk from radiation exposure are a consequence of “complex uncertainties” resulting from a mixture of shared and unshared errors of various types. Some of these uncertainties are a consequence of individual variability (aleatory uncertainty) while others reflect limited knowledge of mechanisms by which specific radiation-induced health effects occur (epistemic uncertainty).

B. Approaches to statistical inference

A19. As noted above, characterization of uncertainty involves describing the distribution of uncertainty in a quantity of interest. Examples of quantities of interest that are relevant to this annex include:

- (a) Estimates of dose from external exposures for members of a cohort of occupationally-exposed workers based on measurements from personal dosimeters;
- (b) Organ dose estimates arising from internal exposures to inhaled or ingested radionuclides for members of a worker population derived from a limited number of in vivo measurements (for example, from a single urine bioassay), data on occupational history, and computer models of nuclide transport and metabolism;

(c) The magnitude and shape of the radiation dose–response and how this relationship varies with time, gender, age and other factors, based on the follow-up of cancer mortality or incidence in a specific cohort from a well-defined exposed population;

(d) An estimate of the assigned share* (probability of causation)* for a cancer that has occurred in a person with a prior radiation exposure based on a (possibly uncertain) exposure history and estimates of risk from radiation exposure derived from observations on some other exposed population;

(e) Estimates of the cancer risk that might be expected to arise as a consequence of routine ongoing childhood CT exposures in a large population.

A20. Statistical inference plays a key role in estimating, describing and quantifying the uncertainties in quantities such as those listed above. Statistical inference is used to combine data (observations), models, and, in some cases, informed but uncertain judgements, to help reach conclusions about quantities of interest.

A21. There are two principal approaches to making statistical inference: the frequentist approach and the Bayesian approach. These two approaches will be briefly outlined here with an emphasis on the key contrasting features of these two approaches.

A22. The text in this section is intended solely to introduce key aspects of statistical inference that underlie material described later. Fuller descriptions of these concepts are given in numerous statistical textbooks. Cox and Hinkley [C17] provide a good discussion of frequentist methods. Gelman et al. [G3] provide a clear presentation of modern applied Bayesian methods, Bernardo and Smith [B6] and Jaynes [J7] provide a general discussion of the ideas underlying Bayesian statistics, and Greenland [G17] discusses the application of Bayesian methods in epidemiology.

A23. The key aspect of statistical inference is the use of data in order to arrive at conclusions concerning values of quantities of interest. In general, data do not permit exact calculation of these quantities. Rather, the observations can be considered as realizations of random variables from a probability density function (pdf) that describes the distribution of these random variables given the true but unknown values of various parameters and, in many cases, the possibly uncertain values of various explanatory variables (for example, radiation dose, age, time, and exposure to other risk factors). In general the parameters of the pdf are defined in terms of a model (\mathcal{M}), and the quantities of interest are functions of model parameters (β) and explanatory variables (Z). The pdf can be represented as $f(\text{data} | \mathcal{M}, \beta, Z)$, which one reads as the probability density for the data given a model and its parameters³ and the values of any explanatory variables. This probability density, which when viewed as a function of the parameters given the data, is called the likelihood function (L) and plays a central role in both frequentist and Bayesian inference.*

³ While it may seem that introducing models here unnecessarily complicates the presentation, it is important to stress that the nature of the parameters are almost always determined by a model. For example in a study of the effect of radiation exposure on cancer incidence one might usefully consider models that describe the data in very different ways (for example, excess relative risk (ERR) models, excess absolute rates (EAR), or two-stage clonal expansion (TSCE) models). On the other hand, in many cases, such as investigation of the shape of the radiation dose response for the ERR, one model (for example, linear in dose) might involve only a subset of the parameters in another model (linear–quadratic in dose). Models of this latter type are said to be nested, whereas the former type of models (ERR, EAR, and TSCE models) are non-nested.

1. Frequentist approach

A24. In the frequentist approach to inference the observed data are viewed as one of many hypothetical realizations of the data given the unique true values of imperfectly known parameters which are not considered to be random variables [I1, J8, J10, N6, N9, N11]. The pdf is interpreted as a measure of the relative frequency of the observed data in this set of hypothetical realizations. Since the parameters are viewed as unique values, it does not make sense to make probability statements about their values.

A25. Frequentist inference is typically based solely on the pdf (likelihood) of the data. The probabilities in frequentist inference (P values for hypothesis tests, confidence intervals) are concerned with the truth of statements about some parameter(s) (or functions of the parameters) given the actual values of the parameters.

A26. *Parameter estimation.* Although other approaches are possible, parameter estimates are often determined by choosing values that maximize the likelihood function for the observed data and explanatory variables. Parameter estimates determined in this way are called maximum likelihood estimates (MLEs).

A27. MLEs have a number of desirable properties. In some simple situations, the expected value of the MLE (that is, the arithmetic mean from many hypothetical realizations of the data) is close or equal to the true value of the quantity of interest. More generally, under certain conditions, the expected value of the MLE will approach the true value of the quantity of interest as the amount of data collected increases; however, the properties of the MLE may be affected adversely if many parameters are estimated simultaneously. Further details can be found elsewhere (for example, [B1]).

A28. The likelihood can be used to provide estimates of the variance (one measure of the uncertainty) of the parameter MLEs, which, in frequentist inference, is the variance of the parameter estimates from many hypothetical realizations of the data given the true model parameters. The most common way to do this involves an assumption that, given the true parameters, the distribution of the parameter estimates can be described by a normal distribution. Variance estimates obtained in this way are called Wald estimates. Wald estimates can be used to approximate the variance of functions of the parameters. Alternatively one can view the logarithm of the likelihood as a function of the parameter(s) of interest and examine the shape of this function as the parameter(s) of interest are varied and the value of the function is maximized with respect to all other parameters. When the (log-)likelihood is viewed as a function of the parameters of interest maximized with respect to any other parameters it is called the (log-)profile likelihood.

A29. *Hypothesis tests.* Frequentist hypothesis testing involves the specification of null and alternative hypotheses concerning the model parameters and defining a function of the data and the relevant parameters (a test statistic) for which it is possible to evaluate (at least to a good approximation) the distribution over multiple hypothetical realizations of the data given the null hypothesis. This distribution is then used to determine the probability that one would obtain a value of the test statistic that is at least as extreme as that seen for the observed data if the null hypothesis were true. The null hypothesis is said to be rejected if this probability is small (typically less than 0.05). This probability is called a P value. A typical null hypothesis in estimation of the risk from radiation exposure would be that cancer rates do not vary with dose while the alternative hypothesis would be that the rates do depend on radiation dose.

A30. Tests of the hypothesis that the true value of a parameter is zero are often based on the ratio of a parameter estimate and the Wald estimate of its standard deviation, which is assumed to follow a

normal distribution. Wald tests are widely used, but may be misleading when the data are limited or when the distribution of the parameter estimates is not symmetric. Generally somewhat more reliable tests can be obtained by looking at the difference between the maximized value of the log-profile likelihood function and the value of this function when the parameters of interest take on their values determined by a null hypothesis. Minus twice this difference, is called the likelihood ratio test (LRT). Under certain conditions when working with models in which the parameters in the model corresponding to the null hypothesis are a subset of or impose some constraints on the parameters under the alternative hypothesis, the LRT has a chi-squared distribution with degrees of freedom equal to the difference in the number of parameters for the null and alternative models.

A31. When comparing non-nested models (i.e. models in which the parameters in the null model are not simply a subset of the parameters of the alternative model) there are no simple methods for hypothesis testing. In recent years a number of measures, called information criteria, have been developed to help quantify and compare the information content in alternative models. These criteria generally involve functions of the log-likelihood and the number of free parameters in the model. One of the simplest and most widely used is the Akaike information criteria (AIC) [A4] which is defined as $AIC = -2 \ln(L) + 2p$, where $\ln(L)$ is the natural logarithm of the maximized likelihood for the model of interest and p is the number of free parameters in the model. The AIC and other information criteria play a central role in multi-model inference [B25] which is useful for addressing uncertainty in model specification. Multi-model inference is discussed in appendix B of this report.

A32. *Confidence intervals and confidence regions.* Parameter estimates and hypothesis test results do not provide information on uncertainty. In frequentist inference the uncertainties in specific parameter estimates are usually described using confidence intervals with some defined level of coverage, typically 95%. When parameter estimates are highly correlated (as might be the case, for example, for the coefficients of dose and dose-squared in a linear-quadratic dose-response model fit to cohort survival data) it can be informative to consider the joint confidence region for all of the parameters of interest. (In general it is challenging to compute confidence regions for two parameters, and almost always impractical to compute or summarize confidence regions for three or more parameters).

A33. Given the nature of frequentist inference, a confidence interval does not provide information on the probability that the true value of the parameter of interest is contained within the interval. Rather, the proper interpretation of a 95% confidence interval is that in repeated hypothetical realizations of the data, 95% of these confidence intervals would encompass the true value of the parameter of interest.

A34. Confidence intervals are most commonly determined using the point estimate of the parameter of interest together with the (estimated) variance (covariance matrix) of the parameter estimates. However, it is often better to define confidence intervals directly in terms of LRT. This is done by determining those values of the parameter(s) such that the LRT has the desired level of significance (e.g. $P = 0.025$ for a two-sided 95% confidence interval for a single parameter).

2. Bayesian approach

A35. The Bayesian approach makes use of a broader conceptualization of probability than is used in the frequentist approach. In the Bayesian approach probabilities are interpreted as a measure of one's state of knowledge or degree of belief concerning the true values of imperfectly known quantities of interest (which often correspond to parameters in frequentist inference). Given this interpretation it

makes sense to make probability statements about possible true values of some unknown quantities given the available information and to define a probability density function that describes one's current state of knowledge or degree of belief. Furthermore, as outlined below, one can use Bayes' theorem, to combine information based on the current state of knowledge with new information (for example, with new data from an experiment or study) to update the pdf describing the current state of knowledge and this updated pdf can be used to make probability statements about the true values of unknown quantities of interest.

A36. The Bayesian approach starts from a particular probability density function (pdf), called a "prior distribution", which summarizes the state of knowledge or degree of belief about values of the parameters of interest in the absence of the data under analysis. The prior distribution depends on the model and, possibly, the values of some explanatory variables or other information (Z). The model can be viewed in a general sense as a summary of existing knowledge, including knowledge obtained from other studies, about the quantity (quantities) of interest. This prior distribution can be used to define a pdf (prior density) that can be written as $f_{\text{prior}}(\beta | \mathcal{M}, Z)$. This prior density is then combined with a pdf for the data, $f(\text{data} | \mathcal{M}, \beta, Z)$. In the Bayesian framework, this pdf is interpreted not in terms of frequencies from multiple realizations, but rather as a summary of the betting odds that would be placed on the data realization for given true values of the parameters, quantities of interest and explanatory variables. Bayes' Theorem can then be used to combine these two pdfs to provide a posterior density for the parameters given the model and data, $f_{\text{post}}(\beta | \text{data}, \mathcal{M}, Z)$. The relationship between the posterior density, the prior density and the likelihood can be written as:

$$f_{\text{post}}(\beta | \text{data}, \mathcal{M}, Z) = \frac{f(\text{data} | \mathcal{M}, \beta, Z) f_{\text{prior}}(\beta | \mathcal{M}, Z)}{f(\text{data} | Z)} \quad (\text{A.3})$$

The denominator in this equation is the marginal density of the parameters given the explanatory variables and is obtained as a weighted sum (integral) of the likelihood over all values of the parameters with weights defined by the prior density. The posterior density reflects a combination of both one's prior knowledge and information gained from the current data. One could generalize the above formulation to allow, for example, for uncertainties about the nature of the model, in which case the data may change one's view of the nature of the model.

A37. The posterior distribution forms the basis of inference under the Bayesian approach. Until recently the application of Bayesian methods has been hampered by the difficulties in evaluating the posterior density for all except the simplest problems. However, in recent years, the applicability of Bayesian methods has been revolutionized by the development of Markov Chain Monte Carlo (MCMC) methods and associated computational software, which avoid the need to calculate the posterior distributions using analytical methods [G12]. MCMC methods use a Monte Carlo (simulation) approach to evaluate the often difficult integrals and hence the posterior distribution, as well as the quantities described below. One particularly popular MCMC method is Gibbs sampling [G4] under which—rather than sampling from the joint distribution of all of the relevant variables—sampling is conducted from the distribution of each variable in turn, conditional on the values specified for the other variables. It is generally easier to simulate from each of these conditional distributions rather than from the joint distribution, particularly if the conditional distributions have a simple form (for example, log-normal).

A38. In spite of the advances made in recent years in developing MCMC methods, some caution may be required in interpreting the results obtained in this way, owing to problems with convergence that might occasionally arise [G17]. Various tests of convergence have been proposed and these are particularly important in situations where there are multiple peaks in the distribution(s) from which

sampling is taking place. The number of computer simulation runs until the Markov Chain converges can typically be in the range from thousands to tens of thousands or more [G12].

A39. An especially attractive feature of MCMC methods is that they summarize the generally non-standard posterior distributions that arise for almost all interesting problems by samples from these distributions. These samples can easily be used to obtain information on the marginal posterior distribution for specific parameters or for functions of the model parameters that are of particular interest.

A40. Detailed discussion of MCMC methods is beyond the scope of this report. For more details, see for example Gilks et al. [G12] and Gelman et al. [G3] and the references therein. There are freely available, flexible and powerful software packages (e.g. [L33]) that implement MCMC methods.

A41. *Parameter estimation.* It is common to use the expected value (arithmetic mean) of the marginal posterior distribution to provide a “best estimate” of the value of a parameter or for a quantity of interest defined as a function of the model parameters. An alternative that is sometimes used is the mode of the posterior distribution, that is, the most likely value of the parameter according to the posterior distribution.

A42. *Hypothesis tests.* Rather than testing a null hypothesis (based on a simple model) against an alternative hypothesis (based on a more complex model that includes the null model as a special case), the Bayesian approach focuses on the calculation of betting odds in favour of each of possibly many hypotheses. This allows one to directly compare betting odds for multiple hypotheses (including comparisons involving non-nested models). This contrasts markedly with frequentist methods which focus on the probability of seeing the observed data if some null hypothesis is true, but provide no information on the odds in favour of any specific hypothesis. Thus, unlike in the frequentist approach, the Bayesian approach does not give special status to any specific hypothesis (that is, there is no need for the concept of a null hypothesis).

A43. *Credible intervals and regions.* Bayesian credible⁴ intervals (in the case of a single quantity of interest) or regions (for several quantities of interest) are defined so that, given the data and the prior information, the true values of the quantities of interest fall within a particular interval or range with a specified probability. The subjective probability that a single parameter value falls outside a (say) 95% Bayesian credible interval is 5%. Unlike frequentist confidence intervals, Bayesian credible intervals are based on probability statements about the true value of a quantity (or quantities) of interest. Credible intervals and regions can be determined directly from the marginal posterior distribution of the quantity (or quantities) of interest.

3. Comparison of frequentist and Bayesian approaches

A44. In spite of the fundamentally different conceptual basis for these two approaches, Bayesian and frequentist methods often lead to similar conclusions. This is especially likely to be the case when the implementation of these methods is well-informed by the scientific context [G17] or when the data are sufficiently strong to outweigh the choice of the prior distribution.

A45. When good prior information is available, the Bayesian approach provides a natural method for combining one’s current state of knowledge or degree of belief with information obtained from the data. Of course when the data are sparse prior information becomes increasingly important. However,

⁴ In the metrology and some other areas [J8, J10, J11], credible intervals are called “coverage intervals”.

when the data are limited and prior information is lacking, then the way in which the prior distribution is specified might have a notable impact on the posterior distribution. Indeed, if a “flat” prior distribution (that is, one with a constant pdf) were assigned to a variable that can only take values greater than zero, then the pdf for the logarithm of this variable would not be flat. Hence it is not possible in general to have a totally uninformative prior distribution; the posterior distribution could change according to which prior distribution is selected, particularly if the data are not strong enough to outweigh the influence of the prior distribution. Nevertheless, in this situation, inferences would be limited irrespective of whether a Bayesian or a frequentist approach is adopted.

A46. Statistical inference is central to the estimation of risks from radiation exposure and to the assessment of both the uncertainty in these risk estimates and the additional uncertainties that arise as the existing, but necessarily limited, knowledge of radiation-induced health effects is used to address societal needs and concerns. Both frequentist and Bayesian approaches to inference are useful for these efforts. Frequentist methods have generally served well in estimating radiation-induced health effects in specific exposed populations, such as the atomic bombing survivors. However, with increasingly complex issues, such as those related to the interpretation of site-specific cancer statistics estimated from limited data [P15] or efforts to make use of information on uncertainty in doses estimated by complex Monte Carlo systems for simulating doses, Bayesian methods are likely to become increasingly useful and important. Similarly, as current, uncertain risk estimates are used to address important societal questions, the need to allow for uncertainties in existing knowledge and make informed but qualified judgements about how to apply these risk estimates is likely to increase the importance of Bayesian methods in the quantification of uncertainty.

C. Quantifying uncertainty

A47. The Committee recommends that uncertainty in the measurements, variables, and models that are used to estimate exposures, doses and risks—both for specific individuals and for groups—be expressed in terms of probability density functions that represent the degree of belief about true values of imperfectly known quantities. In this document, the term “probability density function” will be used to represent the uncertainty about a true value of a fixed quantity (that is, a single value) within the context of the assessment of dose and risk for a specific situation. The term “frequency distribution” will be used to describe the inter-individual variability of true values or the variability of measurements or observations.

A48. In the case where there is uncertainty about the form of a frequency distribution that describes the variability, other probability density functions may be specified that represent alternative (possibly true) values for the mean, spread, shape or other aspects of the true but unknown frequency distribution. This gives rise to alternative realizations of the uncertain frequency distributions, each having a unique mean, variance, and shape [I1, N6, N9, N10, N11]. If the form of these frequency distributions is itself uncertain, then this may be addressed—to some extent at least—by placing probability density functions on the mean, variance and shape parameters of those frequency distributions. In a Bayesian context, this is known as a hierarchical Bayes approach [G17].

A49. Probability density functions representing uncertainty in models used to estimate dose and risk may be obtained from statistical analysis of repeated measurements (the frequentist approach) or from subjective representation of the full state of knowledge derived from evaluation of all evidence available about each fixed but uncertain quantity and the model used to evaluate dose and risk (the Bayesian approach) [I1, J8, J9, J10, J11, N6, N9, N11].

1. When sufficient data are available

A50. When an estimate of uncertainty about the true value of a quantity is obtained from a large number of repeated observations (or measurements) taken from a randomized design, the shape of the frequency distribution of values likely conforms to the laws of nature. Normal and log-normal distributions are commonly used in statistical analysis of the variability of data obtained from a randomized design. These and other probability density functions resulting from statistical analysis of the variability in data are discussed in numerous statistical textbooks and references on quantitative uncertainty analysis [I1, J8, J9, J10, J11, N6, N9, N11].

2. When data are sparse

A51. When uncertainty is defined as a probability density function of possibly true values for a unique quantity that is imperfectly known and for which directly relevant data are limited, the distribution can be of any form that subjectively describes the present state of knowledge or degree of belief for that quantity [N6, N9, N11]. Commonly used probability density functions representing possibly true values for unique quantities that are imperfectly known include the normal and log-normal, but also the uniform, triangular, log-uniform and log-triangular, beta, Weibull, gamma, and many other continuous or discrete distributions, including mixtures or hybrids of different distributions [J8, J10, J11, N9].

A52. When judgement and past experience are the primary basis for proposing a probability density function representing uncertainty, it is not unusual for the analyst to propose a piece-wise uniform or piece-wise log-uniform distribution. In a piece-wise uniform distribution, equal probability density is assigned to all values falling within specified intervals, but different subjective weights are assigned to each interval to reflect differences in degrees of plausibility associated with each interval [J8, J10, J11, K6, N6, N9]. The subjective weights will sum to unity for each distribution.

A53. Sometimes it becomes necessary to describe probability density functions that are a mixture (hybrid) of a continuous and a discrete distribution. Such is the case when there is evidence supporting the chance that the true value of a model parameter could be zero, and a chance that the parameter would take on positive (non-zero) values. For example, hybrid probability density functions have often been used to describe the state of knowledge or degree of belief associated with the modifying factor representing differences in risk for exposure to different energies and types of radiation, as compared with exposure to high-energy gamma radiation [K6].

D. The distinction between variability and uncertainty

A54. The terms variability and uncertainty are widely used throughout the literature on quantitative uncertainty analysis. Sometimes these two terms are used interchangeably, and sometimes they are used as separate components of an uncertainty analysis of a quantity of interest. This section will attempt to clarify the distinction in meaning of these two terms.

A55. *Variability* is the term used to describe the variation or dispersion of values resulting from (a) repeated measurements for a quantity of interest, (b) a group of single measurements or observations taken of a set of multiple quantities of interest (such as single “best estimate” doses made for each of a larger number of people who make up a cohort in an epidemiological study), or (c) the

variation or dispersion of true values (such as the variation or dispersion of true individual doses in a cohort). To a certain extent variability can be explained through the use of explanatory variables that indicate why values differ. However, to the extent that variability cannot be explained, variability is assumed to occur from natural stochastic processes. Distributions used to represent stochastic variability among a set of true but unknown values are referred to in this report as “frequency distributions.” The distributions are contrasted with “probability density functions” that represent the state of knowledge or degree of belief about a quantity of interest that is a single (true) value.

A56. *Uncertainty* refers to both (a) the variation in values of quantities due to unexplained stochastic processes (as described in the previous paragraph) and (b) the state of knowledge or degree of belief about imperfectly known fixed quantities. As noted earlier in this document, using the terminology of Hofer [H16, H18], uncertainty that reflects unexplained stochastic variability of true values among a group or population of unspecified individuals is referred to as “aleatory” or “Type A” uncertainty while the state of knowledge or degree of belief about possibly true values for a quantity for which there is only a fixed (single) true value is referred to as “epistemic”, or “Type B” uncertainty.

A57. If the variability of true values can be specified by the use of a mathematical model with a system of explanatory variables, and if all other remaining sources of uncertainty are due to unexplained random variability of true values about the estimated value, the system will involve only aleatory uncertainty. This uncertainty arises from the assignment of fitted values to represent the true values, under the condition that the assigned value is unbiased, i.e. equal to the expected value for each subgroup sharing the same attributes identified by the explanatory variables. If the observed, measured, or estimated variability of values is composed of (a) variability explained by a model and its system of explanatory variables, (b) unexplained variability of true values of quantities, and (c) random measurement error, then both assignment and classical measurement errors are present. Uncertainty in the assigned value applied to a group of individuals or to the standard deviation describing inter-individual variability of true values within that group is a form of systematic error that is shared by all members of the group.

A58. *Complex uncertainties* are composed of mixtures of systematic and random errors, including uncertainties that are shared and unshared among individuals in a cohort. Complex random uncertainties are composed of mixtures of assignment and measurement errors. When assigned values are based on an imprecise measurement or an uncertain fixed quantity that is shared by one or more subgroups, there will be the potential for systematic bias in the estimate of central or expected values.

A59. *The role of the assessment objective in determining the need to distinguish variability and uncertainty.* The objective of the assessment determines whether or not it is necessary to distinguish between inter-individual variability of true values versus uncertainty about quantities that are fixed. When the assessment objective itself is a fixed true quantity, information about variability of true values and uncertainty about fixed true quantities may be combined into a single subjective probability density function representing the state of knowledge or degree of belief about possibly true values for the quantity of interest [I1, J8, J9, J10, J11, N6, N9, N11]. However, when the assessment objective is the estimation of variability of true values, such as the inter-individual variability of true exposures or dose, estimates of the inter-individual variability of true values must be processed separately from the uncertainty about quantities that are imperfectly known but shared among members of a subgroup or groups of individuals. Separate processing of information about variability of true values and uncertainty about shared quantities is necessary to avoid substantial overestimation of the amount of variability of true values and to address uncertainty about quantities such as the mean dose and dose variance for the cohort [I1, N6, N9, N11].

E. Accounting for dependences among uncertain model inputs and assumptions

A60. In the case where the assessment quantity is a single unique value, all uncertain terms are described as either discrete or continuous probability density functions of possibly true values. In so doing, it is important to account for dependences or correlations between the probability density functions specified for each uncertain parameter with models used to estimate exposure, dose, or risk. If such dependences are ignored, the probability density function of the final result may be too broad (uncertainty is over-expressed) or too narrow (producing a statement of overconfidence).

A61. Dependences will usually have a noticeable effect on the probability density function of the final result when they occur among components of the model that contribute most to the overall uncertainty in the final result; and on the other hand, accounting for dependences among uncertain model components or parameters that are associated with low sensitivity and/or small uncertainty will usually not contribute substantially to the overall uncertainty of the final result [I1, N6]. An exception to this general rule is when extreme values in the tails of the probability density function of the final result are used for decision-making. These extremes would lie beyond the limits of a 90% or 95% credible interval. In these situations, the upper extremes are likely to be affected by even relatively weak dependences among uncertain inputs and model assumptions [I1, N6].

F. Uncertainty propagation and sensitivity analysis

A62. Uncertainty propagation is the process by which all components contributing to uncertainty in the estimate of the quantity of interest are combined into an overall statement of uncertainty about that quantity. Uncertainty propagation can account for most known sources of uncertainty, including uncertainty in measurements, and uncertainty in model coefficients and explanatory variables. Current approaches of uncertainty propagation are limited in taking into account uncertainties due to assumptions made in the analysis of the data (model uncertainty). Other approaches to deal with model uncertainty are described in appendix B.

A63. In the case where the uncertainty in model inputs is described by probability density functions of possibly true values, the model result (the estimate of the quantity of interest) will itself be described as a probability density function of possibly true values. From this distribution of possibly true values, a central value (usually the arithmetic mean, median or mode) and a 90% or 95% credible interval (also called credibility interval, subjective confidence interval, coverage interval, or uncertainty interval) can be obtained [I1, N6, N10, N11].

A64. In the rare case where the quantity of interest can be estimated using very simple equations, uncertainty propagation can be carried out using closed-form algebraic solutions. This is the case for simple models composed predominantly of a multiplicative series of uncertain terms, in which the product of the series of terms is represented by a log-normal distribution, or when normal distributions are assumed for the uncertain input to models composed of a summation of terms [I1, N6, N9, N10, N11]. A variety of closed-form algebraic solutions to the uncertainty propagation of simple combinations of uncertain terms are discussed in other references [J8, J10, N9]. When the quantity of interest is estimated using more complex equations, or when the probability density functions assigned to uncertain model inputs are neither normal nor log-normal, Monte Carlo uncertainty propagation is preferred to closed-form algebraic solutions.

1. Monte Carlo uncertainty propagation

A65. The method most commonly used for uncertainty propagation in equations and models used for dose and risk assessment is a computer-based numerical algorithm known as Monte Carlo simulation [I1, J11, N6]. This method is constrained neither by the complexity or structural form of the equations used for dose and risk assessment, nor by the shape and dependencies among probability density functions representing uncertainty in model inputs or outputs. Uncertain model results are expressed as numerous alternative realizations of possibly true values (as in the case of an assessment of dose or risk to an individual) or possibly true sets of cohort doses (as in the case where a two-dimensional Monte Carlo dose reconstruction is used to support an epidemiological study and where true random inter-individual variability is separated from uncertain degrees of systematic bias).

A66. Monte Carlo uncertainty propagation may be based on computer algorithms representing simple random sampling of values from probability density functions describing uncertain model inputs to produce random results of dose or risk. Monte Carlo uncertainty propagation may also be based on stratified sampling strategies, the most common being various forms of Latin hypercube sampling [I1, N9, N11]. Latin hypercube sampling is often preferred because stable results are produced with lower sample sizes than with simple random sampling. Monte Carlo uncertainty propagation can address dependences between uncertain model inputs and equations as statistical or functional relationships [I1, J10, J11, N9].

A67. *One-dimensional Monte Carlo uncertainty propagation.* When the assessment end point is a quantity with a single true but imperfectly known value, such as the dose or risk to a specific person, all uncertainties are of Type B. A one-dimensional Monte Carlo uncertainty propagation combines all known sources of input uncertainty (expressed as probability density functions that are either continuous or discrete) to produce a probability density function of model results (i.e. values for the assessment end point). This probability density function of model results is made up of numerous alternative realizations of possibly true values for the single true but uncertain value for the assessment end point (figure A-II). One-dimensional Monte Carlo uncertainty propagation combines all known sources of uncertainty, such as variability in repeated measurements and lack of knowledge about the values of fixed quantities for which directly relevant data are sparse or missing. Uncertainties resulting from the use of competing plausible models can also be addressed within one-dimensional Monte Carlo uncertainty propagation [I1, N6, N9, N10, N11].

A68. *Two-dimensional Monte Carlo uncertainty propagation.* The separation of inter-individual variability of true values from uncertainty about fixed true values of a quantity is often necessary when the assessment end point or quantity of interest is the exposure of or dose to a group or population of individuals. In this case, a two-dimensional Monte Carlo (2D MC) uncertainty propagation is often a preferred option. A 2D MC uncertainty propagation may be necessary when dose reconstruction for individuals in an epidemiological cohort is carried out using mathematical models instead of direct measurements.

A69. When models are used as surrogates for direct measurements of the quantity of interest, the results for each individual may be composed of varying amounts of systematic error shared by some or most of the individuals in the cohort. A 2D MC approach allows for sets of possibly true fixed values that are shared or alternatively unique to each individual to be simulated in one dimension and alternative realizations of possibly true sets representing individual variability of the quantity of interest in the second dimension. Each realization of a set representing inter-individual variability of true dose is conditioned on a unique set of possibly true fixed values (see example in figure A-III), which is explained in detail below.

A70. In 2D MC uncertainty propagation, each set of inter-individual variability of possibly true values for the quantity of interest is partially determined by fixed values of explanatory variables, such as residence history, diet, age, sex, lifestyle, occupation, and shielding. These fixed values are unique to each person or subgroup of persons. These values change only from one realization to the next. Another portion of inter-individual variability is due to stochastic variability of true dose (aleatory uncertainty).

A71. When producing alternative sets representing inter-individual variability of true values, it is essential to remove the effect of random classical measurement errors and avoid overestimating the amount of variability of true values [H18].

Figure A-II. One-dimensional Monte Carlo uncertainty propagation

Uncertain model inputs P_1, \dots, P_n are specified as probability density functions representing the analyst's state of knowledge or degree of belief for each uncertain input parameter P . Single values are sampled at random from each probability density function for P_1 to P_n to produce a single realization of the model result. This process is repeated many times, producing numerous alternative realizations of possibly true values for the model result (a quantity for which there is only one true but unknown value)

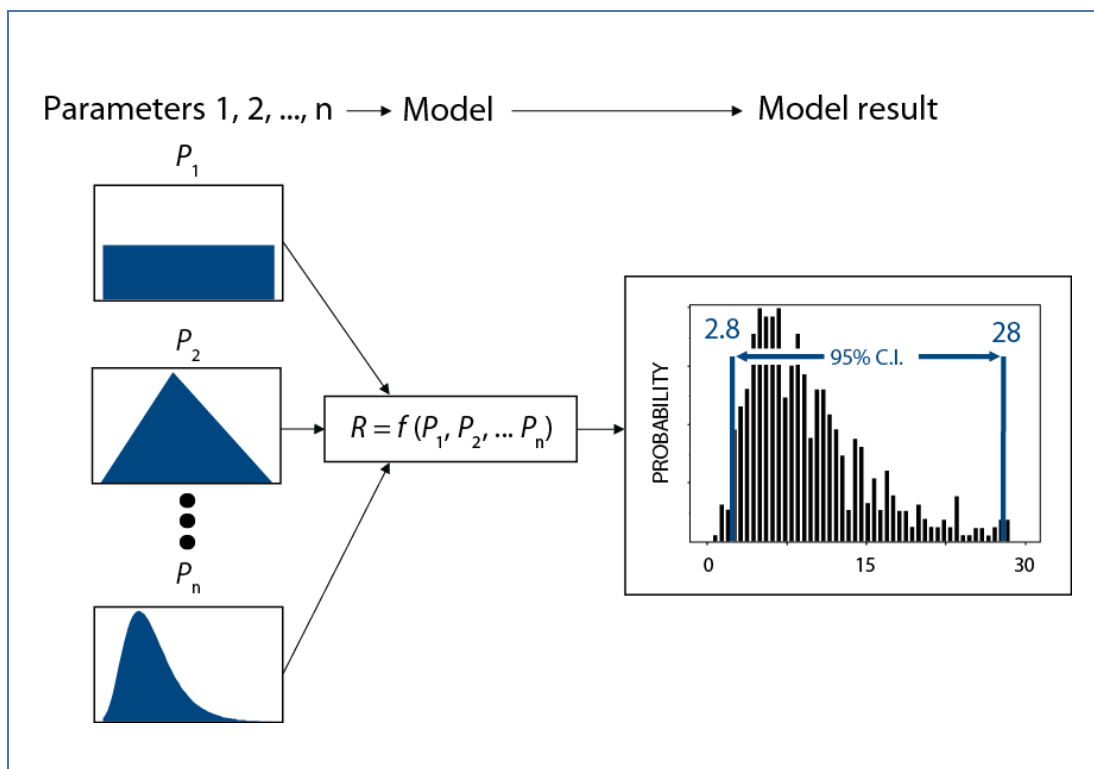
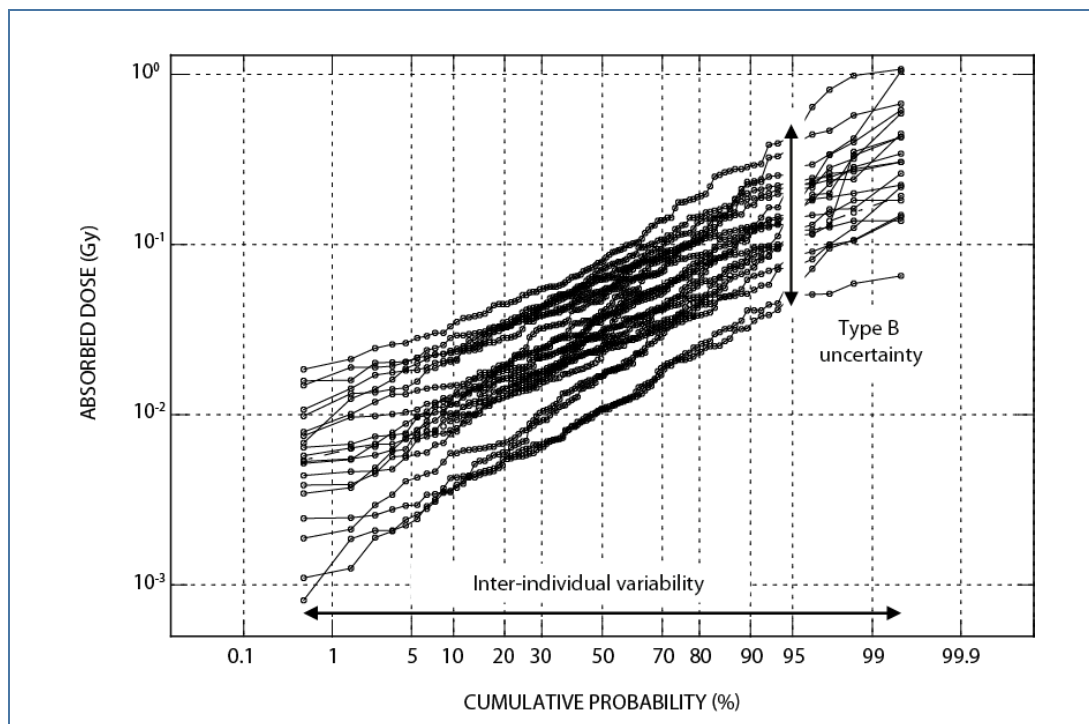


Figure A-III. Multiple realizations of the distribution of possible true doses in the selected cohort obtained using two-dimensional Monte Carlo uncertainty propagation

Each realization is a representation of one possibly true set of inter-individual variability of doses in the cohort, while the differences between realizations are interpreted as Type B uncertainty [N6]. Estimates of inter-individual variability of true values include the effect of stochastic inter-individual variability (Type A uncertainty)



2. Example of two-dimensional Monte Carlo uncertainty propagation to separate inter-individual variability of true values from uncertainty in fixed quantities

A72. This section illustrates the basic elements of a two-dimensional Monte Carlo (2D MC) uncertainty propagation for an idealized case in which inter-individual variability of the quantity of interest, R , is a function of three parameters X , Y , and Z

$$R = f(X, Y, Z)$$

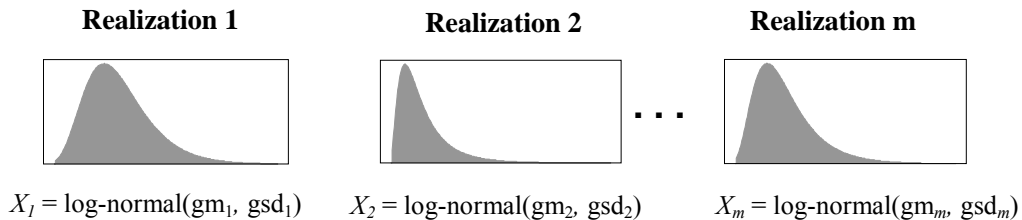
To be specific, $R = XYZ$ may be the dose to the heart, X the conversion factor from the dose measured in front of the breast at the place of the dosimeter, Y the calibration factor of the same dosimeter used by all study participants, and Z the dose in front of the breast, which is based on a measurement for each of the participants.

A73. In this example, X is a frequency distribution representing stochastic variability of true values of the calibration factor among each individual (Type A uncertainty). Parameter Y is an uncertain fixed quantity that is shared among all individuals, and it is assigned a probability density function of possibly true fixed values (Type B uncertainty that is shared). Parameter Z is unique to each individual, thus probability density functions that represent uncertainty in the true unknown value of Z are assigned separately to each individual (unshared type B uncertainty).

A74. The shape of X is assumed to be log-normal, but because the centre and spread of this frequency distribution are uncertain, probability density functions of possibly true fixed values (Type B uncertainty) are assigned to the uncertain geometric mean (GM) and geometric standard deviation (GSD). The probability density functions assigned to GM_x and GSD_x represent the analyst's state of knowledge or degree of belief about the true fixed but uncertain GM and GSD of X (Type B uncertainty).

$$X = \text{log-normal} \left(GM_x = \text{[rectangle]}, GSD_x = \text{[bell curve]} \right)$$

One alternative realization of GM_x and GSD_x produces an alternative realization of the true frequency distribution of X from which values of x are sampled at random and assigned to each individual. For each realization, a unique value (gm_x) is drawn at random from the probability density function assigned to GM_x and a unique value (gsd_x) is drawn at random from the distribution assigned to GSD_x . The values of gm_x and gsd_x sampled for each realization define a unique frequency distribution of X .



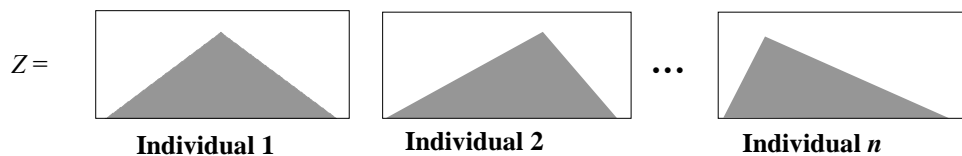
From each unique frequency distribution of X obtained for a given realization j , a single value is drawn at random for each of n individuals ($x_{1j}, x_{2j}, \dots, x_{nj}$).

A75. Y is a fixed but uncertain parameter whose true value is the same for all individuals in the population or subgroup (the subjective probability density function that is assigned to Y represents alternative realizations of a true value that is shared among all individuals).

$$Y = \text{[rectangle]}$$

For each realization j , a unique value of y_j is drawn from its subjective probability density function and is shared among all individuals.

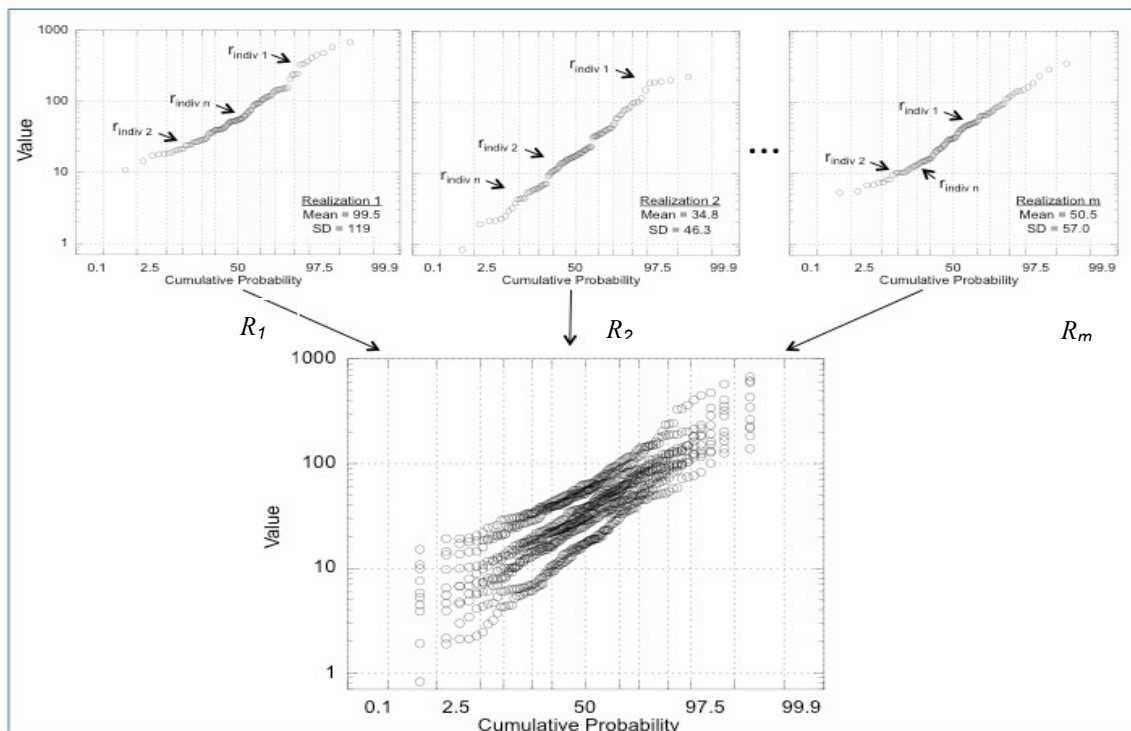
A76. Z is a fixed but uncertain parameter defined separately for each individual ($i = 1$ to n) in the population or subgroup.



For each realization, a unique value of z_i is drawn from the subjective probability density function assigned for each individual; thus, each person is assigned a unique value of z_i , which changes from realization to realization.

A77. The combination of values of x , y and z assigned to each individual produces a unique value of r per individual. This unique value of r represents one possibly true value. The set of all individual values of r for this realization represents one possibly true set R for the group of individuals. For each realization j , each individual value of r_i is partially explained by a unique value of y applied to all individuals, individual-specific values of z , and by randomly sampled values of x_i that vary from individual to individual. Each realization produces a unique set of results (R) representing a possibly true outcome of inter-individual variability. Each unique set of results (R) will have its own unique value of mean, variance, shape, and minimum and maximum.

Result for each individual (i) and realization (j)				
$r_{i,j} = f(x_{i,j}, y_j, z_{i,j})$				
	Realization 1	Realization 2	...	Realization m
Individual 1	$r_{1,1} = f(x_{1,1}, y_1, z_{1,1})$	$r_{1,2} = f(x_{1,2}, y_2, z_{1,2})$...	$r_{1,m} = f(x_{1,m}, y_m, z_{1,m})$
Individual 2	$r_{2,1} = f(x_{2,1}, y_1, z_{2,1})$	$r_{2,2} = f(x_{2,2}, y_2, z_{2,2})$...	$r_{2,m} = f(x_{2,m}, y_m, z_{2,m})$
⋮	⋮	⋮	⋮	⋮
Individual n	$r_{n,1} = f(x_{n,1}, y_1, z_{n,1})$	$r_{n,2} = f(x_{n,2}, y_2, z_{n,2})$...	$r_{n,m} = f(x_{n,m}, y_m, z_{n,m})$



3. Sensitivity analysis

A78. An analysis of the effect on a model output of changes made to values of model input (including model coefficients and explanatory variables), is often referred to as a “sensitivity analysis”. Sensitivity analysis can help determine which parameters or processes have the greatest impact on a model result or on the uncertainty in that result [I1, N6, N9, N11].

A79. Sensitivity analyses may be conducted at two levels, (a) local and (b) global. Local sensitivity expresses the impact of a parameter on a model result when the parameter is varied only in the region very near a specific value. Global sensitivity expresses the impact of a parameter when it is varied across the full range of possible values. An output variable may have a high local sensitivity to a parameter, but because of low parameter uncertainty, global sensitivity would be small. Likewise, an output variable may have a low local sensitivity to a parameter, but because of very large parameter uncertainty, global sensitivity would be large.

A80. Global sensitivity can be estimated using many different calculational and computational strategies. Some methods require computationally intensive sampling designs [I1, N9]. Global sensitivity analysis is used to evaluate the contribution of uncertain model input to the uncertainty in the model result produced by Monte Carlo uncertainty propagation [I1]. Such methods include statistical regression analysis of the rank order of uncertain model inputs versus model outputs and/or visual inspection of scatter plots of values obtained from probability density functions of model inputs and model results. Other sampling strategies for conducting a sensitivity analysis of the results of Monte Carlo uncertainty propagation are discussed in references [N6, N9].

II. EPIDEMIOLOGICAL CONCEPTS

A81. Epidemiology is the study of the distribution and determinants of disease in human populations. In this context “disease” could refer to a specific condition, e.g. breast cancer or myocardial infarction or to a grouping of conditions such as death from any cause. Epidemiological studies are primarily concerned with describing incidence rates (new cases arising per unit time in the population of interest), however there is also interest in other descriptions of disease occurrence including cumulative incidence (the proportion of the population that contracts the disease in some well-defined time period), and prevalence (the proportion of the population with the disease at a specified point in time). Some epidemiological studies, such as clinical and field trials, are experimental studies in which the exposed population is chosen and the assignment of exposures (“treatments”) is controlled by the investigator. However, most epidemiological studies, especially those concerned with the health effects of radiation exposure, are generally, observational (i.e. non-experimental) studies in which the occurrence and magnitude of the exposures of interest and the choice of the exposed populations are not controlled by the investigators. While the ultimate goal of epidemiological research often concerns the identification of causal factors, observational epidemiological studies can demonstrate associations between disease occurrence and factors of interest, but cannot prove causation. However, Hill [H14] proposed a set of criteria that are often used to guide conclusions about causality based on epidemiological data (see annex A of this report, and for example the discussion in the preamble to the IARC monograph on carcinogenic risks of ionizing radiation to humans [I3]). Causal inference is an important subject that is beyond the scope of this appendix. See reference [R4] for a discussion of causation and causal inference. If some variable is associated with a change in disease risks then that variable is called a risk factor. When an association has been observed, it may be

possible, given suitable data, to use epidemiological data to describe the nature and magnitude of the association (e.g. to describe the magnitude and shape of a dose–response relationship) and to describe how the magnitude of the association is affected by other factors (effect modification).^{*} It can also be possible to consider the nature of the joint effect^{*} (interaction) of two or more risk factors on the occurrence of a disease of interest. Since most epidemiological studies are observational in nature, the magnitude of effects of interest might be distorted if one fails to adjust for a risk factor that is also correlated with the exposure of interest. This effect is called *confounding* and the risk factor can be called a *confounding factor or confounder*. Unfortunately, the term *confounding factor* is often used to describe what is really a potential confounding factor.

A82. Studies of the effects of radiation exposure on the risk of health effects in humans are virtually all observational studies in which the subjects and nature of the exposures are determined by factors that are not under the control of the investigators. Findings of statistical significance on the basis of a hypothesis test in a specific observational study must be interpreted with some caution [S17, Y3].

A83. This section briefly describes several of the most important types of observational epidemiological study designs, comment on the strengths and limitations of these designs, and note some of the methods used to analyse data from the different types of studies. The focus here concerns the two major types of epidemiological approaches, namely cohort and case–control studies. However, geographical correlation studies (often called “ecological studies”) are also briefly discussed here. Annex A of the UNSCEAR 2006 Report [U12] contains a discussion of these concepts. For a more thorough description of epidemiology and epidemiological study designs and statistical methods see, for example [C11, J13, R7].

A. Cohort studies

A84. Cohort or follow-up studies involve the identification of a disease-free population whose members have different degrees of exposure to the factor of interest (e.g. radiation) and whose health is observed over time to determine when cohort members develop the disease(s) of interest. An essential characteristic of a cohort study is that the probability of inclusion in the cohort is independent of disease status. However, it is almost always the case that the selection probability will depend on the level of exposure. For example, the Life Span Study cohort of atomic bombing survivors was defined using records from Japan’s 1950 national census and some related local censuses. As originally defined, the cohort was limited to Japanese citizens who were living in or near Hiroshima or Nagasaki at the time of the census (*a*) who were not military personnel and (*b*) for whom the family registry was in one of the two cities. The cohort was defined on the basis of a core group who were determined to have been within 2 km of the hypocentres at the times of the bombings and who suffered acute radiation-induced health effects. This core group was augmented with three groups of the same size that were matched to the core group on age, sex, and city at the times of the bombings. These three groups were: (*a*) people who were exposed within 2 km of the hypocentre but did not report suffering from acute radiation-induced health effects; (*b*) people who were between 2.5 km and 10 km from the hypocentres at the times of the bombings; and (*c*) people who were not in the cities (that is, who were more than 10 km from the hypocentres at the times of the bombings). Over time, as methods to estimate individual doses became available, the cohort was expanded to include almost all civilian Japanese citizen respondents to the 1950 census and who were within 2.5 km of the hypocentres regardless of the family registry location (see references [B4, P9] for additional details).

A85. The strength of cohort studies arises from the fact that disease rates of interest can be computed directly from the follow-up data. Rates for cohort members with different levels of exposure can be compared to detect and characterize the nature of the association between the potential risk factor(s) of interest and the occurrence of the disease. Provided that it is possible to obtain complete data on the occurrence of specific outcomes, a cohort study can be used to look at the relationship between exposure and the occurrence of several different outcomes. The primary disadvantages of cohort studies relate to the cost and length of follow-up required to obtain the disease data and the difficulties (including cost) in obtaining detailed information on covariates of interest (including dose estimates, the factor(s) of primary interest) for all cohort members.

A86. The basic data for each individual in a cohort study include entry and exit (event occurrence or end of follow-up) times, some measures of exposure (e.g. radiation dose, which may be time dependent, and work history), basic characteristics such as sex, date of birth, ethnicity, and other risk factors/potential confounding factors (e.g. smoking history or family history of cancer).

A87. Analysis of data from cohort studies typically focuses on disease rates (hazard rates* or functions) though it is possible to look at other outcomes, such as life expectancy and cumulative incidence (e.g. lifetime risk). Cohort data are often analysed using log-linear proportional hazards models fitted directly to the individual survival data using semi-parametric partial-likelihood methods such as Cox regression modelling [C16]. In Cox regression modelling, the focus is on rate ratios (relative risks) with no direct methods to characterize rate differences (excess absolute rates). An important alternative to Cox regression, which is widely used in studies of radiation dose response, is Poisson regression in which one directly models the full hazard rate function [C11, F9, P10]. In order to use Poisson regression models one must restructure the cohort data as a stratified person-year (rate) table. The stratification typically includes time (with the potential for multiple time scales, e.g. attained age and calendar time), basic data (such as sex, race, and region), exposure (dose, age at first exposure, time since exposure), and other risk factors (e.g. smoking history, alcohol consumption, and family history of cancer). Some stratification factors can be time-dependent (e.g. lagged cumulative dose, time since exposure, duration of smoking, or time since smoking cessation). Poisson regression is attractive for the analyses of cohort studies, because it allows (but does not require) one to model the full hazard including the time dependence (e.g. on attained age) of the baseline rates and the effects of interest. The effects of interest may be described in terms of rate ratios (RR), (the ratio of the rates in groups with different exposures) the excess relative risk (ERR) (which is the proportional increase in the risk in one group—or at a given dose—relative to that in another group—usually those with no exposure—and is equal to the RR minus one), or the rate difference (or excess absolute rate, EAR) models for the exposure associated hazard. The risk models may consider effect modifiers (factors, such as attained age, age at exposure, and sex, that modify the exposure-associated risk). The approach is computationally more efficient than Cox regression modelling, especially when the risk models include time-dependent covariates. ERR and EAR models are particularly useful when considering dose-response functions and the joint effect of two or more continuous risk factors (e.g. radiation and smoking). Maximum likelihood methods based on individual data are alternative ways to analyse cohort data, which avoid the potential loss of information by using only grouped data in Poisson regression [E3, K1].

A88. As noted above, cost is often a limiting factor in the conduct of cohort studies. Since follow-up is essential to cohort studies, those costs are inherent to the conduct of a cohort study. However, in recent years several cohort-based designs have been developed that seek to reduce the (often non-trivial) costs associated with the collection of covariate information (including dose estimation) by limiting the need to collect this information to a subset of the full cohort. These designs include nested case-control and case-cohort designs.

A89. In a nested case–control study, one includes all of the cases in the cohort and a sample of non-cases, typically matched to individual cases on various factors such as sex, vital status and age at the time of diagnosis of the case. The advantage of this type of study is that detailed information on exposure and other risk factors needs to be obtained only for the cases and their matched controls, which almost always comprise only a small fraction of the total cohort. Nested case–control study data are typically analysed using the same methods (conditional logistic regression) that are used for matched case–control studies (see below). These analyses lead to estimates of the (excess) relative risk. A nested case–control study is limited to a specific outcome, which distinguishes “cases” from “controls”. The advantage of a nested case–control study to a (non-nested) case–control study (see next section) is that data of the cohort study can be used, and only data on additional risk factors need to be collected.

A90. As in a nested case–control study, a case–cohort study includes all cases identified in the cohort. However rather than matching non-cases (controls), one selects a subsample of the cohort with a known (possibly stratified) sampling fraction and obtains detailed exposure and risk factor data for all of the cases and all members of the subcohort. Analysis involves a slight modification of standard Cox regression methods [L7] with an adjustment to adjust for the fact that the analysis is using only a subset of the full cohort with oversampling of cases. Although some work has been done on the analysis of case–cohort data using Poisson regression methods, there are not yet any tools or practical methods for carrying out such analyses. Case–cohort studies have an advantage over nested case–control studies in that one can use the same subcohort to analyse the effects of exposure on various outcomes. It has recently been recognized that case-cohort studies are a special case of multi-stage sampling designs [B22] that permit more effective use of available data from the full cohort.

B. Case–control studies

A91. Case–control studies involve the identification of individuals with a specific outcome of interest (cases) and a sample of individuals (controls) from the same population who could have become a case but did not. Case–control studies are best suited for the study of a relatively rare disease (e.g. with prevalence of less than 10%). Analyses involve comparing exposure to a risk factor of interest in the cases and the controls. Case–control studies result in estimates of the odds-ratio for exposure in cases and controls. If the exposures are numerically continuous (e.g. as is usually the case with radiation dose), the odds ratio can be expressed as a function of exposure. Odds ratio estimates from a well-designed case–control study are approximations to the relative risks that one estimates in cohort studies. This approximation is generally quite good for rare diseases.

A92. The primary advantages of case–control studies are that they involve many fewer study subjects than cohort studies and they do not require long-term follow-up. Thus they can be considerably less costly than cohort studies and can often be completed in much less time than cohort studies.

A93. The primary challenge in the design of case–control studies is to ensure that one can obtain useful estimates of the odds ratio. The key issues in designing a good case–control study are (a) inclusion of all cases in a population of interest; and (b) selection of controls from the same population; that is, people who could have developed the outcome (“disease”) of interest and who, had they developed the disease, would have been identified and selected as a case. It is also important that the nature and quality of the information on the exposure(s) of interest be the same for cases and controls. Case–control studies often involve matching on some factors, other than the exposure(s) of

interest and that are known to affect rates (such as sex, race, or being at risk at the age of identification of the corresponding case).

A94. Data from case–control studies are analysed using logistic regression if there is no matching, and conditional logistic regression when there is matching. These methods are discussed in detail in reference [B21]. The results are estimates of the odds ratio as a function of exposure and, as noted above, the odds ratio is approximately equal to the relative risk one could estimate from a cohort study in the same population. It is not possible, without additional—and often unavailable—information on population rates for the outcome of interest, to estimate excess rates from case–control data.

A95. As noted above, case–control studies are generally much less costly and can usually be carried out more rapidly than cohort studies. They are ideally suited to the investigation of a rare outcome. Perhaps the biggest challenge in conducting a case–control study is to obtain comparable exposure information for cases and controls. This is an especially important issue when the characterization of exposure might be different for cases and controls. For example, being a case might prompt one to become more aware of the details of their past exposure or, if cases are deceased or otherwise unavailable to provide information on exposure, information might be more likely to come from proxies rather than the study subjects themselves and this could affect the quality and comparability of the exposure assessment. While it is possible to examine the (joint) effects of different exposures in a case–control study, in contrast to cohort studies, as noted above, the analysis must focus on a single pre-determined outcome that differentiates cases from controls.

C. Geographical correlation studies

A96. Cohort and case–control studies involve the direct observation of outcomes, exposures, and other characteristics in individuals. However in some situations, outcome and exposure data are only available at the population level. For example, one might have only summary information on disease rates or risks in some populations of interest together with information on exposure status (yes/no, proportion exposed, or population mean dose) for these populations. These data are then used to investigate the association between the summary measures of outcome and exposure across groups. Results from geographical correlation (sometimes called “ecological studies”) should be interpreted cautiously, because they are based on proxy summary measures of exposure, which may attenuate the relationship between exposure and the rate (and estimated risk) of the outcome of interest, and because it is generally much more difficult (if not impossible) to control for confounding than in studies based on individual observations.

A97. Issues related to problems of confounding in geographical correlation studies are highlighted in the discussion [L28, P19] of a study of United States county-level lung cancer mortality rates and average radon levels in homes [C14]. Despite their limitations, under some circumstances geographical correlation studies can provide useful descriptive information on health risks when the exposure data are based on relevant direct measurements, or there is good individual data on important potentially confounding risk factors. Examples of useful geographical correlation studies include (a) an analysis of thyroid cancer risks in Ukraine and Belarus following the Chernobyl accident [J2] in which the assigned doses were based on large numbers of age-, village-, and sex-dependent doses and (b) an analysis of lung cancer and residential radon risks in a large United States cohort with individual smoking data and region-dependent radon measurements [T11].

APPENDIX B. SOURCES OF UNCERTAINTY IN RADIOEPIDEMIOLOGICAL STUDIES

I. UNCERTAINTIES IN HEALTH EFFECT INFORMATION	139
A. Selection bias	139
B. Information bias.....	141
C. Confounding	143
D. Changes in information over time.....	143
II. UNCERTAINTIES IN EXPOSURE AND DOSE ASSESSMENT	144
A. Sources of uncertainty in exposure and dose estimation.....	144
B. Reconstruction of external exposure in specific studies	158
C. Reconstruction of internal exposure to radon and its progeny in specific studies.....	168
D. Reconstruction of internal exposure from other pathways in specific studies.....	172
E. Summary.....	178
III. UNCERTAINTIES IN RISK ASSESSMENT	183
A. Impact of uncertainty in health effect information on risk estimates and statistical power of epidemiological studies	183
B. Impact of exposure uncertainty on risk estimates	186
C. Impact of model uncertainties.....	200

I. UNCERTAINTIES IN HEALTH EFFECT INFORMATION

A. Selection bias

B1. A concern that may arise in epidemiology is whether the persons included in the study are representative of the population of interest. In principle, this ought not to be a problem if the study population coincides with this target population; for example, if—in an occupational study—all of the

relevant workers are included. However, whilst this approach might be possible in some cohort studies, there are other study designs such as case-control studies and case-cohort studies that include samples of persons selected, respectively, from the target population or the cohort. If participation were determined purely on the basis of random sampling from the relevant population, then this approach ought not to lead to bias. However, non-random failure to participate may lead to bias, as the following examples will illustrate:

(a) In a cohort study of occupationally-exposed workers, it may not be possible to include all of the workers in the target population because identifying details or information on their radiation exposure is missing. If such information were missing at random, then this ought not to lead to bias, although the reduction in the study population would diminish the statistical power, albeit by a small amount if the level of dropout were low. However, if the health of those workers with missing information tended to differ from that of included workers with similar distributions for factors such as age and sex, then comparisons of disease mortality or morbidity between occupationally-exposed workers and a reference population would be affected. Since record-keeping might sometimes be poorer for workers employed for a very short time than for workers employed for a longer period and because some studies (for example, [G6])—although not all (for example, [C5])—have suggested that workers employed for a very short time might have higher mortality rates, studies of occupationally-exposed workers often define the target population as those employed (or monitored for radiation exposure) for at least six months [M21] or a year [V3];

(b) Persons eligible for participation in an epidemiological study (or persons acting on their behalf) may choose not to take part. For example, in some cohort studies, such as the United Kingdom's National Registry for Radiation Workers (NRRW) [M21], eligible occupationally-exposed workers are given the opportunity to opt out of the study. Provided that—as in this study—the level of dropout is very low (about 1% in the NRRW) and the characteristics of those choosing not to take part (for example, in terms of age and dose distributions) do not differ greatly from those of participating workers, then prospective opting out is unlikely to bias the study. However, if the level of dropout is high—for example, if participation is based on opting into the study rather than opting out—or if participation is influenced by whether or not the person has developed the disease(s) under study, then the results of the study may be unreliable. An example of problems with retrospective decisions on study participation arises in case-control studies, where information is sought on persons with the disease(s) of interest (i.e. the cases) and a sample of non-diseased controls. For non-fatal disease or for disease/mortality in childhood, a case or the case's parents may be more motivated to take part in the study than a healthy adult or the parents of a healthy child. In this situation, participation may be high among potential cases but low among potential controls. Conversely, in a case-control study of mortality, it may be difficult to obtain agreements to include dead cases but easier to enrol live controls. Furthermore, the decision on participation in retrospective studies might be influenced by the level of exposure received. In particular, a person with a non-fatal disease and a relatively high exposure may be more motivated to take part than a healthy person with the same level of exposure.

B2. When the selection of study subjects results in the exclusion of a substantial proportion of eligible persons—and particularly if this proportion differs notably between persons with the disease or condition under investigation and those without this disease or condition—then the potential for bias may be considerable.

B. Information bias

B3. Errors in the information collected in an epidemiological study either on the disease under investigation or on the exposures received by the study population can affect inferences. The impact of uncertainties in exposure and dose assessment is considered in a later section. Here the focus will be on errors in information on disease.

B4. Previous UNSCEAR reports [U11, U12] have given examples of the ways in which errors can arise when assessing disease. “Follow-up bias” can arise if, unbeknown to the investigator, some of the study subjects have left the area under investigation. This may occur if data on mortality or cancer incidence are collected by linking records to regional mortality or cancer registers, but information is not available on whether persons have migrated from the regions covered by these registries. A specific example concerns studies of cancer incidence among the survivors of the atomic bombings in Japan [P14], where information on cancer is available for residents of Hiroshima city and Nagasaki prefecture but not for those survivors who had moved to other parts of Japan. In contrast, information on mortality is available for the whole of Japan. Unless a person was removed from the follow-up at the time of migration from the study area, then he or she would appear “immortal” unless information on later disease or death for that person was collected. This in turn would tend to biased estimates of disease risks towards zero [U12]. In the case of studies of cancer incidence among the survivors, the investigators have adjusted the numbers of person-years to reflect rates of immigration from and emigration to the catchment areas for the cancer registries [P14]. Although information on these patterns is not available for all members of the Life Span Study (LSS) cohort, it is available for a subgroup of these survivors (within the Adult Health Study, AHS) and this was used to make the aforementioned adjustments. Although the person-years calculated in this way would not be exactly the same as that obtained had follow-up information been available for the full cohort, the differences are unlikely to be great.

B5. The ascertainment of disease is often not exact and varies according to the disease in question and whether the focus is on disease incidence or mortality. For example, it is not always easy to establish the underlying cause of death, and the diagnostic tools and criteria available to assess cancer incidence mean that cancer registration data are often preferred to mortality data in epidemiological studies of cancer. For reasons such as this, random or systematic misclassification of disease may arise, which would tend to bias estimates of disease risks towards zero. An example of systematic errors is the finding, from an analysis of death certificate diagnoses among autopsy cases in the LSS cohort studied by the Radiation Effects Research Foundation in Hiroshima and Nagasaki, that cases who had died at home and who were later confirmed at autopsy to have died of lung cancer, frequently had originally received diagnoses of pneumonia as recorded on their death certificates.

B6. Annex A of the UNSCEAR 2006 Report [U12] gave some examples of ascertainment bias. The detection of thyroid and non-melanoma skin cancers in the LSS cohort tends to be more complete for survivors with higher rather than lower doses, because many of the people with higher doses are also in the AHS and hence received biennial medical examinations. In contrast, the follow-up for these diseases was not so intensive for cohort members not in the AHS. Consequently, the study investigators included adjustments in their analyses for participation in the AHS, in order to avoid the over-estimation of risks that would have arisen otherwise [P14]. Ascertainment bias might also arise if comparisons are made between a working population that receives frequent medical examinations and a general population that is not subject to the same degree of surveillance; for example, as previously highlighted by the UNSCEAR 2006 Report [U12] in connection with a study of leukaemia incidence among Chernobyl recovery operation workers [I22]. In this circumstance, it is better to focus on comparisons between workers rather than on comparisons with a population followed in a different manner; for example,

as in a study conducted within the aforementioned cohort of Chernobyl recovery operation workers and which—unlike the earlier study—did not find a raised incidence of leukaemia [I23].

B7. It is better to ascertain information on disease from registers of disease or mortality, rather than from the study subjects or from relatives or friends. In a similar way that—as mentioned earlier—some persons might be more inclined to take part in a study if they have developed the condition under investigation, someone might be better able to recall a past medical event (or mistake this for something else) if they suspect a link to a past exposure. The same point would apply if a proxy were asked about the past health of another person. In such studies, checks with disease information collected from objective sources for a subgroup of individuals are valuable to assess the possible impact of any recall bias. For example, in a study of United States radiologic technologists, Sigurdson et al. [S18] assessed the accuracy of the technologists' personal reports of cancer diagnosis by comparing these reports with information obtained from medical and pathology records. This showed good agreement for some cancers, such as breast, but less so for some others. Consequently, for cancer sites with a high metastatic potential (cancers of the liver, bone or joints, soft tissue and brain) and for uterine cervical cancer (owing to the large numbers recorded with carcinoma in situ), Sigurdson et al. included in their calculations of Standardized Incidence Ratios only those self-reported cancer cases that had been validated with medical records [S18].

B8. Self-reported disease status can often be misleading, especially in situations where there has been a great deal of publicity about cancer risk associated with a controversial exposure, such as to radioactive fallout from nuclear weapons testing. A rather extreme example of information reporting bias is an analysis of cancer incidence data in a cohort of 4,125 members of Mormon families living in three counties in south-western Utah in the United States, plus a relative few in nearby areas in Nevada and Arizona during 1951–1962, as identified from telephone books in selected communities [J15]. “Family” as defined in the study included all persons related by blood or marriage, and the survey, by trained volunteers from the surveyed towns, was filled out by the surveyor and the head of the family working together. Response items included church membership, health effects felt immediately after fallout (such as skin burns, eye burns, hair loss, change in hair colour, nausea, and diarrhoea), and diagnoses of cancer among family members. Respondents reported a total of 288 cancers among 4,125 family members for the combined periods 1958–1966 (chosen to detect leukaemia) and 1972–1980 (for solid cancers), which is 60% higher than the 179 expected according to published cancer incidence rates for all Utah Mormons. This ratio is comparable to that observed in survivors of the atomic bombings in Japan who received over 1 Gy. Rate ratios were extremely high for certain cancers: 5-fold for leukaemia, 8-fold for thyroid cancer, 2-fold for breast and brain cancer, 3-fold for melanoma, and 11-fold for bone cancer. Among those who were reported to have suffered from acute health effects from exposure to fallout, the rate ratios were 45 for leukaemia, 11 for breast cancer, and 5 for all cancers, numbers that are considerably higher than those calculated for atomic bombing survivors with near-lethal doses exceeding 4 Gy.

B9. A partial replication based on Utah county mortality statistics for 1950–1980, was conducted with the rationale that increases in cancer incidence of the magnitudes reported in the interview study [J15] would surely be reflected in mortality statistics for the three Utah counties covered. This study found a significant deficit of overall cancer mortality relative to the rest of Utah. However, the study did find statistically significant evidence of an excess of leukaemia mortality, including 9 childhood leukaemia deaths, in the three counties. The leukaemia mortality finding was consistent with conventional estimates of radiation-related risk, and far smaller than the 5-fold increase reported in the interview study [M1].

C. Confounding

B10. “Confounding factors”, which are correlated both with the disease under study and with an exposure of interest, are discussed in paragraph 8 of UNSCEAR 2006 Report, volume I, annex A [U12]. In a simple example presented as an illustration, incidence of thyroid cancer among patients administered ^{131}I for diagnostic purposes is slightly elevated; the excess incidence was likely related to the fact that diagnostic screening was motivated by concerns about possible existing thyroid cancer [H1]. It is noted that confounding usually is dealt with at the analysis stage, either by incorporating such factors into the regression model or by stratifying the data according to levels of the confounding factor.

B11. It was also noted that cigarette smoking is one of the most serious confounding factors that have to be dealt with in epidemiological studies, especially those dealing with smoking-related diseases [U12]. A recent analysis by Furukawa et al. [F11] found that models assuming generalized interactions of smoking and radiation fit markedly better than simple multiplicative or additive interaction models. The joint effect appeared to be super-multiplicative for light/moderate smokers (that is, excess relative risks were greater than those estimated by a multiplicative interaction model), involving a rapid increase in excess risk with smoking intensity up to 10 cigarettes per day, but additive or sub-additive for heavy smokers smoking a pack or more per day. The estimated sex-averaged excess relative risk (ERR) per unit dose at age 70 after radiation exposure at age 30 was 0.59 (95% CI: 0.31, 1.00) Gy^{-1} for non-smokers, about 1.6 (95% CI: 0.73, 2.4) Gy^{-1} for those who smoked 10 cigarettes (one half pack) per day, but only about 0.1 (95% CI: -0.15 , 0.37) Gy^{-1} for those smoking one pack per day. The impact of smoking on estimates of lung cancer risk from indoor exposure to radon is discussed in appendix D of this annex.

B12. Cigarette smoking is also a confounding factor for lung cancer risk associated with exposure to inhaled radon and radon progeny in underground mines and in dwellings, and individual smoking histories must be taken into account in dose–response analyses. However, a recent pooled analysis of three European case–control studies of uranium miners [L12] of the effects of radon exposure on lung cancer risk including adjustment for smoking found little indication that smoking acted as a confounding factor of the radon risk estimates. The BEIR VI Committee [N18] evaluated the joint effect of radon and smoking on lung cancer risk in six cohorts of underground miners for which smoking data were available. The modelling of joint effects was handicapped by the small number of miners who had never smoked and by limited quantitative information on tobacco smoking; however, the BEIR VI Committee assigned a twofold greater lifetime radon-related ERR for never-smokers compared to that for ever-smokers. The nature of the joint effect of radiation exposure and smoking was also considered in the pooled European miner study mentioned above [L12]. In this analysis it was reported that the data favoured a sub-multiplicative interaction between radon exposure and smoking.

B13. Geographical correlation studies of lung cancer risk based on area-wide estimates of radon and cigarette smoking levels in different geographical areas, which lack individual information on smoking levels and radon exposure, are particularly vulnerable to bias, as discussed in chapter III of annex A to the UNSCEAR 2006 Report [U12].

D. Changes in information over time

B14. Site-specific and age-specific population cancer incidence rates are subject to secular changes, in part because of lifestyle trends involving risk factors such as smoking, diet, and reproductive history, but also because of increased surveillance and improved diagnostic methods. Examples of the latter include mammography screening for female breast cancer and ultrasound screening for thyroid cancer,

which are widely used to diagnose existing cancers early so that treatment may be more successful. Collateral effects include shifting of cancer incidence rates in public health statistics toward younger ages, and diagnosis of indolent cancers that in the absence of screening might never have become clinically significant [N17].

II. UNCERTAINTIES IN EXPOSURE AND DOSE ASSESSMENT

B15. Uncertainties in exposure and dose may influence interpretation of the epidemiological dose response. Uncertainties in individual dose estimation may affect the evaluation of the statistical significance of the dose response, the shape and steepness of slope, and the width of the confidence interval.

B16. The degree to which dose uncertainties affect interpretation of the dose response depend on whether the random errors are due to measurement or assignment error and the nature of any shared errors. In many instances, the uncertainties in dose estimates used to support an epidemiological study may be complex mixtures of multiple sources of systematic and random errors. Methods for evaluating the effect of dose uncertainties on the dose response, including a review of epidemiological studies that have explicitly considered the effect of dose uncertainties, are discussed in section III.B of this appendix.

B17. In general, the radiation dose to specific organs and tissues of the human body cannot be measured directly. Some form of mathematical modelling is required to estimate the dose to specific organs or tissues after measurements are taken from dosimeter readings or bioassay, or are made of radionuclide concentrations in air, water, food, or soil in the location where the individual may have been exposed.

B18. Uncertainty in dose estimation can be expected to increase according to the extent to which mathematical models are used to compensate for an absence of direct measurements of exposure or radionuclide concentrations in the human body or in specific media of the workplace or the environment. The further away from the human receptor that models must be employed to estimate individual exposure and dose, the greater the uncertainty anticipated. These uncertainties may include complex combinations of random and systematic errors [N9, N10, N11]. The following section discusses various sources of uncertainty associated with dose estimation.

A. Sources of uncertainty in exposure and dose estimation

1. Common errors and mistakes

B19. Common errors and mistakes in dose estimation can arise, for example, with measurements, laboratory procedures, record keeping, programming, data input, and computation. Such common sources of errors can invalidate the overall interpretation of a dose response. Thus, it is essential that these common sources of errors be identified and corrected prior to using dose estimates for epidemiological evaluation.

B20. When individual organ doses are estimated with computer models that account for multiple exposure events, numerous contributing pathways of exposure, and time-varying residence and dietary histories for thousands of subjects, rigorous quality assurance/quality control procedures should be followed to identify and correct mistakes. These procedures should include cross-comparison of model inputs, equations, intermediate results and individual dose estimates with independent calculations performed by different persons using independent computational platforms [L31, S20]. All discrepancies identified through these procedures should be resolved and corrections made before estimates of individual doses and their uncertainties are deemed suitable for the evaluation of the dose response.

B21. In the subsequent discussions of this section, it is assumed that all exposure and dose estimates are free of common errors and mistakes. Nevertheless, even after initial dose estimates have been tested by a quality assurance/quality control protocol, the potential for residual errors and mistakes remains. This means that uncertainty in dose estimation may extend beyond the credible intervals and probability density functions specified to represent the states of knowledge about values of dose assigned to individual members of the cohort.

2. Interview data

B22. Often data must be obtained from individual members of an epidemiological study regarding their personal histories of occupation, residence, diet, and lifestyle. These data can be subject to both random and systematic errors. Systematic errors can be the result of numerous causes, including bias inherent in the formulation of interview questions and the conduct of the interview itself [H7, R5, R6, W9]. For epidemiological studies that are of retrospective case-control design, systematic errors are often due to associated recall bias, such as when individuals recall only times when they consumed large quantities of a particular food type, but not times when they avoided the food type completely or when they consumed only smaller portions. Recall bias can also occur when parents or nearest relatives are asked to estimate quantities of specific foods consumed by subjects when these subjects were infants and young children. In general, the amount of recall bias will tend to increase the greater the time between past exposure and the conduct of the interview [R5, R6].

B23. An important type of recall bias occurs when answers given to a questionnaire are correlated with the disease status of the subject. In epidemiological texts, questionnaire information that is correlated with the status of the subject with respect to other variables, including disease status, is referred to as “differential bias.” An example would be subjects with lung cancer who during their interview under-report their past history of smoking. Recall bias that is correlated with disease status can have a profound effect on the dose-response analysis. Differential bias can both exaggerate and suppress the slope of a dose-response relationship [R6]. Recall bias that is not correlated with the status of the individual with respect to exposure or disease, is referred to as “non-differential bias.” In general, but not always, non-differential recall bias will tend to bias the dose response towards the null.

B24. When data are obtained from individual subjects via an interview and systematic errors such as recall bias have been corrected or judged to be of negligible importance, remaining errors in individual responses to questions will tend to have a random error structure that is classical (that is, the variability in individual responses to interview questions will be greater than the true inter-individual variability of true values) [C7]. Removal of recall bias from interview data, however, will be difficult for those epidemiological studies based on a subject’s memory of past exposures in a retrospective case-control design [G18, H7, R5].

3. Uncertainty in estimation of external exposure

B25. Organ doses due to radiation emitted from sources external to the human body are usually estimated from conversion coefficients that are tabulated in terms of kerma in air. The estimates are hence based on values of kerma in air inferred from (a) direct readings of dosimeters worn on the clothing of radiation workers, (b) approximations for individuals without dosimeters made by extrapolating information from those who wore dosimeters and who were present in the same location at the same period of time, or from those who wore dosimeters and had similar occupational assignments, or (c) the measurement or model estimate of the radiation dose rate at the location of human exposure, combined with an estimate of the time over which the individual was exposed and the type and effectiveness of any shielding present [N9]. In general, for exposure to high-energy photons, the uncertainty in the estimation of an individual's organ dose due to external radiation will be less than that in the estimated dose due to internal emitters [N9, N10, N11]. However, depending on the radiation type, and the number of unknown variables, uncertainty in the estimate of the dose from external exposure due to low-energy photons (of <0.03 MeV) can be considerable [N9].

B26. Larger uncertainties will be expected if the kerma in air at the location of exposure is not obtained from a measured value, but instead is approximated using mathematical models of atmospheric dispersion and surface deposition to first estimate the concentration of radionuclides in air, on the ground, and on other surfaces at that location, and from these modelled concentrations, to calculate the corresponding kerma in air and subsequent organ dose [N10].

B27. *Measurement uncertainty.* The major sources of measurement uncertainty in estimating doses from external sources result from imperfect knowledge of the radiation field in which the instrument was used or the dosimeter exposed, owing to differences in energy and angular response between the calibration field and the actual field of radiation. Other important sources of measurement uncertainty include bias in reading and recording the instrument output, finite resolution and sensitivity, inexact calibration standards, and poor precision. The uncertainty can be expected to be greater if the measurement was reported as an operational quantity (for example, as personal or ambient dose equivalent) rather than as a physical quantity (for example, as air kerma or fluence) [N9]. The directional distribution of the field will also contribute significantly to the uncertainty, because some of the dose estimates will be based on isotropic quantities (for example, kerma in air or ambient dose equivalent) whilst others will be based on strongly directional quantities (for example, personal dose equivalent). Organ doses in a given field are strongly influenced by the directional distribution of the field and the orientation of the individual.

B28. In general, the uncertainty for measurements currently made using most personal dosimeters and survey instruments in gamma radiation fields is within limits set by international and national standards organizations [N9]. These standards generally require that a measurement be accurate to within $\pm 30\%$ to $\pm 50\%$ of a true value. However, such a high degree of accuracy was not the case for dosimeter measurements made in the 1950s and 1960s, which are often used for historical dose reconstructions. There may be additional uncertainty associated with changes to the dose quantities that have been used over extended periods, since it will not always be possible to know what quantity was used for some dose estimates. The uncertainty in neutron measurements and mixed field doses is generally greater than for photon and charged-particle exposures. A detailed discussion of the major sources of uncertainty for various instrument systems used to assess external exposure is given in [N9] and summarized in table B1.

Table B1. Summary of major sources of uncertainty for various instrument systems [N9]

<i>Instrument system</i>	<i>Major sources of uncertainty</i>
AREA MEASUREMENTS OF GAMMA AND BETA RADIATION	
Ion chambers	Energy and angular response
GM counters	Energy and angular response
Scintillation detectors	Energy and angular response
Semiconductor detectors	Energy and angular response
Film and TLDs	Energy response, calibration, processing, fading
In situ gamma spectrometry	Calibration, data processing (unfolding spectral data)
AREA MEASUREMENTS OF NEUTRON AND MIXED RADIATION FIELDS	
Tissue equivalent proportional counters	Lower limit of detection, energy and angular responses
Multi-detector neutron spectrometers	Data processing (unfolding), calibration (response matrix)
Scintillation detectors for neutron spectrometry	Data processing, photon–neutron discrimination
Hydrogen and helium proportional counters	Pulse height discrimination
Activation detectors	Calibration, energy and angular response, data processing to infer fluence
PERSONAL DOSIMETERS FOR MONITORING GAMMA AND BETA RADIATION	
Film dosimeters	Calibration, processing, energy response for beta, X-rays, fading
TLDs	Calibration, processing, energy response, fading
OSLs	Similar to TLD but potential fading more important
Electronic dosimeters	Detector-dependent
PERSONAL DOSIMETERS FOR NEUTRON AND MIXED RADIATION FIELDS	
NTA® film	Fading, energy response, track counting
TLD for neutrons	Neutron–gamma partition, energy response, laboratory processing
Track-etch detectors	Track counting, angular response
Neutron bubble detectors	Response varies with temperature

B29. *Uncertainties in conversion of measured quantities to organ absorbed dose.* The true dose to tissues and organs cannot be measured directly, but must typically be calculated by using some type of a model and relevant input data [N9]. Model calculations often require assumptions about conditions that cannot be known with certainty. The model itself may also contribute uncertainty in that it may not perfectly represent the actual exposure scenario and physical situation being assessed. The uncertainty of an estimated dose will be significantly larger than the precision of related measurements because of lack of knowledge about important exposure-related variables. Thus, depending on the circumstances and the state of knowledge about the conditions of irradiation, the evaluation of total uncertainty associated with measurements, models, and the assumptions necessary to estimate the absorbed organ dose may vary from the relatively simple to a highly complex process. The number and relative importance of assumptions necessary to estimate the uncertainty in organ dose can be expected to vary with the exposure situation [N9].

B30. Variations in body size and orientation of the body with respect to the direction of incident radiation contribute to the overall uncertainty. Even if the reported measurement represents an accurate estimate of the exposure rate in air, if the actual incident energy and geometry is not specified, the model estimate of the absorbed organ dose can be highly uncertain, particularly for low-energy penetrating radiations with energy less than 0.03 MeV [N9]. Conversely, even if the model used to convert measurements to absorbed dose is based on the actual energy and geometry of the assessment scenario, if the measurement calibration is conducted in an energy field that differs substantially from the actual energy spectrum, the reported kerma in air can be markedly in error. High uncertainty in the reported kerma in air will translate directly into high uncertainty in the estimate of absorbed dose in an organ [N9].

B31. A comprehensive treatise on uncertainties in the measurement and dosimetry of external sources of radiation has been recently published [N9]. It includes a comprehensive chapter dedicated to the evaluation of the uncertainty in instruments used to measure external exposure, and it includes, in chapter 4, 13 tables of information summarizing the uncertainty in dose conversion factors obtained from mathematical models used to convert measurements of the kerma in air to absorbed organ dose, for various radiation types, energies, organs and tissues, and various irradiation geometries. The analysis is based on published data for 18 different computational phantoms. Table 4.9 in [N9] shows that for higher energy photons (>0.1 MeV) and a known irradiation geometry, the uncertainty in the conversion from air kerma to red bone marrow (RBM) dose is very small, the geometric standard deviation (GSD) varying from 1.01 to 1.12. This small uncertainty can be contrasted with the case where exposure is to low-energy photons (<0.03 MeV) with an unknown irradiation geometry (GSDs vary from <2.0 to >10, depending on the specific situation (tables 4.10 and 4.11)). Tables in [N9] are also given to correlate individual body mass index with estimated values of absorbed organ dose per unit kerma in air, in order to make more precise estimates of individual-specific doses from external exposure.

B32. Table B2, taken directly from [N9], provides estimates of ratios of the maximum to minimum absorbed doses for example organs and radiation spectra when irradiation geometry is unknown. These maximum-to-minimum dose ratios vary from a low of 1.4 for 18 MV bremsstrahlung irradiating the colon and RBM to 38.0 for 60 kV X-rays irradiating the thyroid gland. Maximum-to-minimum ratios for external doses due to deposited radionuclides after the Chernobyl accident or following detonation of a nuclear fission-based weapon vary from 1.5 for the skin to 3.8 for the thyroid gland.

Table B2. Uncertainty arising from unknown irradiation geometry

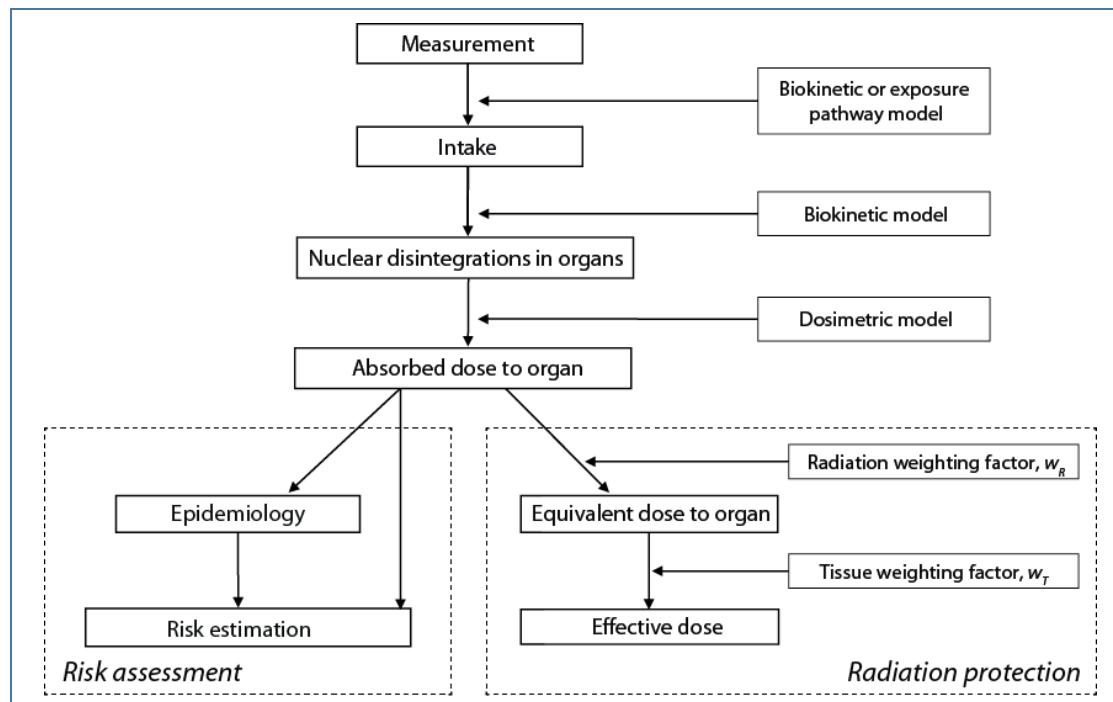
The table lists ratios of maximal/minimal absorbed dose in different organs for a number of irradiation geometries assumed [N9]

<i>Spectrum or source of exposure</i>	<i>Maximal/minimal ratio</i>					
	<i>Breast</i>	<i>Colon</i>	<i>Lung</i>	<i>Red bone marrow</i>	<i>Skin</i>	<i>Thyroid</i>
60 kV X-rays	30.5	11.6	11.8	6.4	2.3	38.0
90 kV X-rays	21.0	7.5	7.8	5.0	2.1	17.2
120 kV X-rays	16.4	6.2	6.5	4.4	1.9	12.3
Radionuclide deposition from Chernobyl accident	3.6	2.6	2.8	2.1	1.6	3.8
Fallout from detonation of fission-based nuclear weapon	3.0	2.1	2.3	1.8	1.5	3.0
Gamma rays (prompt and delayed) from detonation of fission-based nuclear weapon)	2.1	1.6	1.7	1.5	1.9	2.0
18 MV bremsstrahlung	2.4	1.4	1.5	1.4	2.1	1.7

4. Uncertainty in estimation of internal exposure

B33. For radionuclides that have entered the body by inhalation, ingestion, skin absorption, or via wounds, doses must be determined indirectly using appropriate mathematical models that describe the distribution and delivery of dose over time. Biokinetic models are used to describe the distribution, retention and excretion of radionuclides and dosimetric models of organ and tissue structures are used to calculate doses. The most widely used models are those developed by the International Commission on Radiological Protection (ICRP) for the calculation of effective dose coefficients for protection purposes [17, I14]. However, the same models, or adaptations of them, are also often used for scientific purposes, including the calculation of doses for epidemiological studies [H5, S11, S20, V1]. Dose calculations may be prospective or retrospective. Prospective calculations for managing planned or potential exposures include those performed by ICRP to provide dose coefficients (expressed as values of equivalent and effective dose per unit intake of activity). Retrospective calculations are made for epidemiological studies and risk assessments, and also for protection purposes to determine compliance with occupational and public dose limits and constraints. The steps in the calculation of average absorbed organ or tissue doses that are required for epidemiology or risk assessment are shown in figure B-I. The additional steps in the calculation of the protection quantities, equivalent and effective dose, are also shown. This section reviews some of the important sources of uncertainty in the calculation of internal exposure, including: uncertainties in the biokinetic and dosimetric models, and measurement uncertainty. Other uncertainties not discussed here can include the time of intake, the route of intake and uncertainty on the isotopic composition of the incorporated material [N11].

Figure B-I. Steps in the calculation of internal absorbed and equivalent organ dose, internal effective dose and radiological risk



B34. *Measurement to intake.* Intakes of radionuclides incurred by individuals or populations are estimated from measurements. Doses to individuals are often determined from bioassay measurements, which can include whole or partial body counting or measurements of activity excreted in urine or faeces. The estimation of the intake from bioassay measurements requires a suitable biokinetic model

(discussed below). For populations exposed to radionuclides, intakes may be determined from measurements of radionuclides in air, soil, vegetation, food or water, or from an estimation of the amount released by the source, combined with a suitable environmental pathway model to estimate the intake by the population group.

B35. *Intake to dose.* This is a two-stage process: first, biokinetic models, which estimate the uptake and dynamic distribution of radionuclides within the body, are used to calculate the number of nuclear disintegrations that occur in organs and tissues. Then, a suitable dosimetric model, which relies on defined spatial relationships between source and target organs, and on the assumed geometries and masses of these organs, is used to convert the number of disintegrations into the average absorbed dose received by each tissue and organ (figure B-I).

B36. *Biokinetic models.* These are compartment models which follow first-order kinetics and are used to calculate the number of nuclear disintegrations occurring in individual organs and tissues. Specialized models are used to determine the deposition and clearance of inhaled radionuclides to blood from the lungs [I9], the transit and uptake to blood of ingested radionuclides from the alimentary tract [I13], or the uptake to blood of radionuclides deposited in wound sites [N8]. For radionuclides entering blood, element-specific models are used to calculate the distribution of radionuclides in systemic tissues. The most widely used models are those published by the ICRP. These include the Human Respiratory Tract Model (HRTM) which is used to calculate the deposition and clearance of inhaled radionuclides [I9], and the Human Alimentary Tract Model (HATM), which describes the transit and absorption of radionuclides in the alimentary tract [I13]. The ICRP also publishes a range of element-specific models for calculating radioactive disintegrations occurring in systemic tissues after radionuclides have been taken up to blood from the respiratory or alimentary tracts [I8, I10]. Updated systemic models, such as those for plutonium [L10], caesium [L9] and polonium [H5, L10], have been developed based on more recent information. Some of these models are considered for potential use by the ICRP.

B37. *Dosimetric models.* These models estimate the fraction of energy absorbed in every target organ for each disintegration that occurs in a source organ or tissue. The fraction of energy absorbed in a target tissue for a particular source organ/target organ pair and emission type and energy is referred to as the absorbed fraction (AF). For penetrating radiations, AFs have been calculated using Monte Carlo radiation transport algorithms and anthropomorphic phantoms developed at Oak Ridge National Laboratory (ORNL) [C18]. In these, the sizes and positions of the source and target organs are defined by quadratic surfaces in an idealized representation of the human body. More recently, the ORNL type phantoms have been superseded by voxel phantoms which are based on medical imaging data of real people and adjusted to the sizes and proportions of reference males and females [I16, L13]. For non-penetrating radiations, the AF is unity unless the sizes and dimensions of source and target regions prohibit this assumption. Such a situation occurs for walled tissue structures such as the respiratory and alimentary tracts, or for sources in the skeleton. With the exception of the latter, which is represented by a simplified energy-independent model, AFs for the target regions in the HRTM and HATM have been determined using Monte Carlo radiation transport algorithms and three-dimensional models representing source and target cell, or tissue geometries [I9, I13]. The dosimetric model for the skeleton is currently being revised to address a number of simplifications in the ICRP Publication 30 model; these include accounting for electron escape from the trabecular spongiosa to surrounding cortical bone and variations in absorbed fractions with changes in bone marrow cellularity [B17].

B38. Various methods have been used to quantify the uncertainties present at each stage of the dose calculation for internal exposure. The most significant is probably parameter uncertainty analysis, where uncertainties on parameters are propagated through to the calculation of dose using the Monte

Carlo method [T10]. Another popular approach is to directly assign a subjective probability statement to the dose in question [N11].

B39. When quantifying uncertainty it is important to consider the purpose of the dose assessment. For estimating the average risk to populations from radionuclide exposures with a linear model, population mean doses to organs and tissues are of interest. Estimates of these doses are convoluted with appropriate organ or tissue-specific risk coefficients to obtain estimates of lifetime cancer risk (cancer risk per unit intake). For example, the United States government publishes lifetime risk coefficients for exposures to environmental radionuclides [U1]. These coefficients apply to an average member of the United States public, or more precisely, a “hypothetical population whose survival functions and cancer mortality rates are based on recent data for the United States” [P1]. In this case, it is uncertainty on population mean absorbed organ and tissue doses per unit intake that is of interest in estimation of risk using such risk coefficients.

B40. When attempting to quantify uncertainty on population mean absorbed organ dose per unit intake it is important to distinguish between the effects of uncertainty (model parameters that have fixed but unknown values) and variability (model parameter values that vary between individuals), since the misclassification of variability as uncertainty will tend to exaggerate the uncertainty on the mean dose per unit intake. In contrast, if the purpose of the assessment is to estimate the uncertainty on the risk to a specific individual resulting from an internal exposure then it is the distribution of all possible organ doses for the individual in question that is required. Under these circumstances, both variable and uncertain model parameters may be expressed as probability density functions and the one-dimensional Monte Carlo method described in appendix A can be used to calculate the uncertainty on dose. However, if additional bioassay data are available, then Bayesian methods may be used to calculate the conditional distribution of dose given the data. For estimating cancer risk from internal exposures in an epidemiological study, the effects of uncertainty and variability should be separated to account for their differential effects on the estimate of risk. Under these circumstances an appropriate method, such as the two-dimensional Monte Carlo method described in appendix A can be used.

B41. *Uncertainty in measurements.* The type of measurements used for the estimation of internal exposure differs depending on whether the exposure setting is occupational, medical, or environmental. Measurements related to internal exposures in the workplace involve direct and indirect bioassay measurements, workplace measurements in air, water, and on surfaces, and biodosimetry [N11]. The sources of uncertainty in direct measurements of whole or partial body emission of photons include calibration uncertainties that involve unknown distributions of radioactivity in the subject, unknown thicknesses of overlying tissue, and other differences between the subject being measured and the calibration standard. Uncertainties in bioassay measurements of excreta, sweat, or saliva arise from: sampling, the critical issue of which is the representativeness of the sample; storage conditions, which include the duration of storage and variable storage conditions; chemical analysis, the main problem being chemical yield recovery; and counting, for which the critical issue is the calibration of the measurement system [N11].

B42. The calibration of direct bioassay measurements requires the use of anthropomorphic phantoms. Uncertainties may arise because of differences between the amount of shielding provided by overlying tissue of a real person and that provided by the phantom. This is less of a problem for the detection of high energy gamma radiation stemming from the decay of uniformly distributed radionuclides such as ^{137}Cs or ^{60}Co , but much more of a challenge for the detection of lower energy photons that are not uniformly distributed [N11].

B43. Analysis of excreta samples is used to assess intakes of radionuclides that do not emit energetic photons. It is much more sensitive in detecting radioactivity in a sample, with few of the

calibration problems associated with whole body or partial body counting. Radionuclide concentrations in excreta can vary with time for the same individual and from person to person. This inter- and intra-person variability of samples becomes an additional source of uncertainty, which, along with factors associated with proper sample collection, will introduce uncertainty that likely exceeds the uncertainty in the measurement of the sample's activity alone [N11].

B44. The term “workplace measurements” is used to refer to measurements of radioactivity of samples collected from the work environment. These may include, but are not limited to, workplace air samples, or smears of workplace surfaces. For radionuclides that emit no penetrating radiations and that have very low rates of excretion from the body, workplace samples may be the only means available to derive an estimate of intake [N11]. Although the measurement uncertainties may be similar to those encountered with excreta sampling, the uncertainty in the estimate of intake may be greater because it is the worker's environment, rather than the individual worker, that is being monitored.

B45. The term “environmental measurements” is used for measurements of radionuclides in samples taken of air, soil, water, vegetation, and agricultural and non-agricultural food products. Measurement uncertainties are similar to those for bioassay analyses, but a more important source of uncertainty is the representativeness of the sample for estimating the actual exposure or intake of a subject in an epidemiological cohort. When direct measurement of radionuclide concentrations in environmental media at a specific location is absent or sparse, mathematical models are employed using coefficients and algorithms to use measurements and observations made at other locations and time periods. The representativeness of modelled estimates to actual concentrations of radionuclides in the environment is a major source of uncertainty in estimating internal exposure. The uncertainty in the estimation of environmental concentrations in the absence of direct measurements may equal or dominate over the uncertainty in the estimation of the dose per unit intake [A9, A11, N10, N11].

B46. *Uncertainty in intakes.* Exposure to internally-emitting radionuclides can be acute or protracted, and they can be from inhalation, ingestion, skin absorption, uptake from wounds, or from intravenous injection. In occupational settings, intakes can be derived from bioassay analysis and the use of biokinetic models. In addition, estimates of intakes can be made from measurements of radionuclides in the air or the environment.

B47. An important source of uncertainty in the estimation of dose due to inhalation is knowledge of the physico-chemical form of the radionuclide in air. This affects the extent to which the radionuclide is deposited and retained in the airways of the respiratory tract, and the rate at which the material is cleared to blood or the alimentary tract.

B48. The magnitude and uncertainty of intakes estimated from bioassay data depend mainly on the solubility of the inhaled material in the lung. Erroneous assumptions regarding the rate of dissolution and uptake to blood of inhaled aerosols can lead to significant systematic errors in estimated intakes and doses, especially those derived from measurements of radionuclides in urine [B12, D5]. This is especially noteworthy because intake and dose estimates from urine bioassay have been used in epidemiological studies of workers exposed to plutonium and other actinides, including those of the Sellafield workforce [O3] and workers of the Mayak Production Association [G1, S23]. Over the past decade, Bayesian methods have proved useful in identifying true values of intakes and calculating uncertainties on intakes and doses estimated from bioassay data [D4, M14, P16]. The technique has proved a useful tool for incorporating different forms of prior knowledge regarding the exposure. For example, the prior can include workplace measurements of intakes, such as air sampler data, together with plausible ranges of biokinetic parameter values determined from experimental studies.

B49. When measurements of radionuclides in the air or environment are available, intake from inhalation is determined as the product of the time-integrated radionuclide concentration in air, the breathing rate of the individual estimated as an average for the time of passage of the radioactive plume, and any factors accounting for indoor filtration of air compared to outdoors. Rates of inhalation will vary considerably depending on whether the individual is engaged in light or heavy physical activity, or is resting at the time of passage of the plume. To estimate uncertainty in intakes due to inhalation of fallout particles from distant testing of nuclear weapons, the United States National Cancer Institute assigned a geometric standard deviation of 1.3 to age- and sex-specific geometric mean values of inhalation rates [N3]. These log-normal distributions of inhalation rates were to represent uncertainty mostly due to inter-individual variability in breathing rates among individuals of the same age and sex.

B50. Intakes by ingestion are more common in environmental settings where radionuclides released to air and water lead to subsequent radionuclide concentrations in drinking water and terrestrial and aquatic food sources of importance to the human diet. Intakes by ingestion are less common in occupational settings. Intakes from ingestion are derived from the product of the measured or estimated concentration of the radionuclide in water or food, the estimated consumption rate for drinking water and specific food types, and factors that account for radionuclide losses due to water filtration, food preparation, radiological decay during the delay time between food harvest and consumption, and dietary dilution owing to the intake of water and food materials obtained from sources with no radionuclides [N10, N11].

B51. Ingestion rates are obtained from dietary surveys of the individuals, their parents or closest relatives, or from more general dietary surveys of populations composed of individuals of like age and gender. Uncertainties in the estimate of an individual's intake from ingestion will be a combination of the uncertainty in all of the factors mentioned above. As mentioned previously (see section II.A.2 of this appendix), the uncertainty in information obtained from dietary surveys involving an individual's or parent's memory of past intakes of specific food types will be subject to the systematic error of recall bias. Because of the multiple sources of uncertainty affecting the overall estimate of uncertainty for the ingestion of specific radionuclides, the uncertainty in intake via ingestion may often be as great as or greater than the uncertainty associated with the estimate of the absorbed organ dose per unit intake via ingestion [N10].

B52. In a few circumstances, intakes via ingestion for some members of epidemiological cohorts have been determined by direct measurement of radionuclides in food and water combined with bioassay measurements. This has been the case for the estimation of ^{131}I and ^{137}Cs intakes during the aftermath of the Chernobyl accident and ^{90}Sr intakes via ingestion of foodstuffs contaminated by releases to the Techa River [N11].

B53. *Uncertainty in biokinetic models.* There are two sources of uncertainty: uncertainty in how well the structure of the biokinetic model represents the underlying processes that describe the retention and excretion of the radionuclide in question ("model uncertainty"), and uncertainty in the values of the parameters for a given model structure ("parameter uncertainty"). Because biokinetic models are generally constructed for representative members of exposed populations, uncertainty in biokinetic model structure represents a shared error in an epidemiology study. However, uncertainties on biokinetic model parameter values can be shared or unshared. Parameters that describe individual-specific physiological processes (for example, those describing the systemic retention and excretion of radionuclides) have shared and unshared components. The uncertainties in mean and standard deviation of the distribution describing variability are shared among individuals, while the samples from these distributions for a given mean and standard deviation are unshared. Material-specific parameters,

however, such as those describing the deposition and clearance of inhaled materials from the lungs, will usually have shared errors among individuals.

B54. The extent of the uncertainty in the structure of a biokinetic model is dependent on the quality of the data that were used to derive it. Direct measurements of radionuclides of interest in humans are the most representative data in formulating a biokinetic model [L8]. Data expected to be less reliable include measurements of radionuclides of interest in animals, or measurements of chemical analogues in humans or animals. Generally, the most complete data pertain to radionuclides that are of the greatest radiological significance and the best understood biologically. These categories have been used as a tool to derive subjective probability statements regarding the uncertainty in the dose per unit intake for a given exposure pathway [N7]. Quantification of model uncertainty is complicated by the fact that it represents a conceptual uncertainty; however, one approach is to represent model uncertainty in an uncertainty analysis by assigning discrete probabilities to plausible model structures.

B55. The uncertainty on parameter values is more easily quantified than model uncertainty. In many cases it is difficult to measure the value of a biokinetic parameter directly. However, where variation in the parameter value produces an observable change in a bioassay quantity, and suitable data are available, an empirical distribution can be derived that reproduces the observed variation in this quantity in the human population [A10, N11]. For example, rates of uptake of plutonium to skeleton and liver can be varied in the systemic model for plutonium in order to reproduce the observed inter-subject variation in uptake by these organs. It is less straightforward, however, to derive empirical uncertainties for parameters that do not strongly influence bioassay quantities, but may nevertheless significantly impact dose estimates. Under such circumstances, much greater reliance is placed on subjective judgement to assign an uncertainty. The uncertainty assigned to these parameters will significantly affect the uncertainty in the dose for the organ in question. An illustrative example of this is long-term binding of inhaled plutonium to bronchial airways of the lung; here, a small bound fraction (in the order of a few per cent) can increase absorbed doses to bronchial cells from inhaled plutonium by over two orders of magnitude [B12]. However, the inclusion of binding at these levels has a negligible effect on urine bioassay or lung content over time.

B56. For retrospective assessments, bioassay data will generally provide additional information about parameter values that will reduce uncertainties on dose estimates. Bayesian methods have proved useful in this regard by combining existing knowledge with individual-specific data [D4, M20, P18].

B57. *Uncertainty in dosimetric models.* Uncertainties in the absorbed fractions (AFs) calculated using dosimetric models arise because of uncertainty in the positions of source and target tissues, and in the geometry and masses of these tissues. However, quantifying uncertainties in AFs is not straightforward.

B58. To properly account for uncertainties in AFs for penetrating photon emissions it is necessary to perform Monte Carlo radiation transport calculations for a set of phantoms that represent particular combinations of source and target geometries in the uncertainty distribution of interest; such a calculation is computationally very difficult. The variability in the AF values for ^{137}Cs was approximated by Apostoaei and Miller [A10] by quantifying the variation in the ICRP AFs due to the variability in body mass among adult males and females. Estimation of uncertainty in AFs should account for the systematic difference that may exist between the idealized (reference) ORNL phantom and the average individual in the actual population of interest. Voxel-based phantoms offer a means of assessing the likely differences between doses calculated for reference individuals using the ORNL phantom and doses to actual or “true” individuals (a set of AFs that represent the mean of the human population under consideration). Studies show that the biggest discrepancies between the ORNL and voxel phantoms exist for organ cross irradiation (the source and target organs are different) at low

photon energies (<100 keV) [Z1]. On the other hand, the differences in the AFs for self-irradiation of organs (the source and target organ are the same) is small when adjustments have been made for organ mass. As might be expected, the overall effect on absorbed organ doses is less pronounced: doses calculated with the ORNL type phantom are lower than those calculated using the voxel type phantoms, but appear to be typically within 50% [Z1].

B59. For low-penetrating alpha and beta radiation, significant uncertainties in dosimetry exist where the dimensions of source and target regions are small and separated by short distances (a few micrometres). Such situations arise in dosimetric assessments for the respiratory and alimentary tracts and the skeleton. In the lung, the target cells in the bronchial airways are assumed to be the basal and secretory cells in the airway wall. In the formulation of lung dose, the dose to the bronchial region is assigned 33% of the weighted lung dose; however the mass of the bronchial cells constitute around 0.1% of the total lung mass [I9]. Sensitivity analyses of lung doses from radon progeny have confirmed that the dose received by these cells is indeed sensitive to the spatial relationship that exists between them and the low-penetrating alpha-emitting radionuclides that are deposited in the mucus layer of the airway wall [M7]. This sensitivity was comparable to the sensitivity of the lung dose to the assumed physico-chemical form of the inhaled aerosol [M7]. However, for radionuclides with long half-lives that are inhaled in a less soluble form, the uncertainty on lung dose is likely to be dominated by a lack of knowledge of the solubility of the material.

B60. An additional uncertainty is introduced when the location and identity of target cells is poorly defined. In the current bone dosimetry model, for example, it is assumed that the radiosensitive cells that give rise to bone tumours reside in a 10 µm layer of tissue adjacent to the endosteum. However, research by Gössner [G14] and Gössner et al. [G15] indicates that the development of bone sarcomas resulting from irradiation of mesenchymal stem cells is complicated and not dependent on a single cell type. These studies also suggest that the target cells extend at least up to 50 µm from the surface of the endosteum into the active marrow.

B61. *Uncertainties in the dose per unit intake for an unspecified person.* For assessing the risk of internal exposure for a population group, it is the uncertainty in absorbed organ doses per unit intake for an unspecified, but representative or average person, in the population of interest that is required.

B62. An extensive discussion of the various sources of uncertainty associated with the estimate of dose per unit intake for an unspecified person is given in NCRP Report 164 [N11]. This comprehensive report includes tables of uncertainty estimates for specific radionuclides, exposure conditions and organs, when person-specific information from direct or indirect bioassays is not available. Table B3 provides estimates of uncertainty in the absorbed dose to the lung per unit exposure to radon (²²²Rn) and its decay products [N11]. This average dose to the thoracic region of the respiratory tract accounts for the uncertainty in sensitivity to radiation of different regions of the thoracic airways and has a plausible range (defined as the ratio of the upper to lower bound estimate) of a factor of 10. However, for exposure to radon and its decay products in particular, there is evidence that most lung cancers occur in the bronchial and bronchiolar regions (83%) rather than in the alveolar region (16% [S1]), suggesting that a meaningful quantity for epidemiology or risk assessment could be the absorbed dose to the bronchial and bronchiolar regions, as opposed to the average dose to the entire lung.

B63. Table B4 (adapted from [N11]) provides central estimates, together with “likely” upper and lower bound estimates of the associated uncertainties on the central values, of absorbed organ doses for selected radionuclides in which intakes are acute or chronic through ingestion or inhalation, and the intake is of a variety of physico-chemical forms. The uncertainty estimates were largely based on subjective judgements of NCRP. The ratio of upper to lower bound dose estimates varies considerably. For example, for an acute ingestion of ¹³⁷Cs incorporated in food (or as a soluble inorganic form) and

for absorbed dose to the RBM, the ratio of upper to lower bound dose estimates is a factor of 2. This ratio increases to a factor of 5 for the colon. Comparable uncertainties are associated with thyroid doses resulting from chronic intakes of ^{131}I (upper to lower bound dose ratios of 3.4). Higher uncertainties are associated with ingestion of ^{106}Ru in food (upper to lower bound dose ratios ranging from 25 to 40, depending on the organ of interest). Larger uncertainties will be present when the physico-chemical form of the intake is unknown, and if uptake via the alimentary tract is associated with acute, as opposed to chronic, exposure.

Table B3. Central estimates and plausible ranges of absorbed dose to lung tissues per unit exposure to radon (^{222}Rn) and its decay products

Estimates are for intake by a typical healthy adult male and can be applied for residential or workplace exposures [I9, N11, N18]

Tissue	Absorbed dose per unit exposure to radon (^{222}Rn) and its decay products (mGy per WLM)			Ratio of upper to lower bound
	Best estimate	Lower bound	Upper bound	
Lung ^a (D_{lung})	4.5	1.7	17	10
Bronchial region of lung ^b ($D_{\text{BB+bb}}$)	5.6	2.6	12.2	5

^a Detriment-weighted average dose to lung [N11]. Uncertainty range represents a 90% confidence interval and was obtained by Monte Carlo methods for uncertainty propagation. The range accounts for uncertainty in weighting the radiosensitivity of the different tissues (bronchi BB, bronchioles bb, alveolar interstitium and thoracic lymph nodes) considered in the ICRP lung model [I9].

^b Dose to the bronchial region (BB+bb) [N18]. Uncertainty range represents a 90% confidence interval.

Table B4. Central estimates and plausible ranges of 50-year committed doses per unit intake of selected radionuclides

Estimates are for intake by a typical healthy adult male [N11]

Intake	Form	Tissue	Best estimate (Sv/Bq) ^a	Lower bound (Sv/Bq) ^a	Upper bound (Sv/Bq) ^a	Ratio of upper to lower bound ^b
Acute ingestion of ^{131}I	Incorporated in food	Thyroid	4.2×10^{-7}	1.8×10^{-7}	1.0×10^{-6}	5.4
Chronic ingestion of ^{131}I	Incorporated in food	Thyroid	4.2×10^{-7}	2.3×10^{-7}	7.8×10^{-7}	3.4
Acute ingestion of ^{137}Cs	Incorporated in food or soluble inorganic form	Colon	1.3×10^{-8}	6.0×10^{-9}	3.0×10^{-8}	5
		Red marrow	1.4×10^{-8}	8.0×10^{-9}	1.6×10^{-8}	2
Ingestion of ^{106}Ru	Incorporated in food	Colon	5.0×10^{-9}	1.0×10^{-9}	2.5×10^{-8}	25
		Kidney	3.0×10^{-9}	5.0×10^{-10}	2.0×10^{-8}	40
		Liver	1.5×10^{-9}	2.5×10^{-10}	9.0×10^{-9}	36

^a The values for ^{131}I , ^{137}Cs , and ^{106}Ru of equivalent dose per unit intake (Sv/Bq) and absorbed dose per unit intake (Gy/Bq) are equal.

^b The ratio of the upper to lower bound approximates a "likely range", not an absolute minimum or maximum value.

B64. A limited number of studies describe the application of parameter uncertainty analysis to quantify uncertainties on doses per unit intake, some of which have been reviewed by NCRP [N11]. These studies have focused on radionuclides of high radiological importance that are well understood biologically; these including iodine [A10, F8, H3, H23], tritium [H6, M10], caesium [A10] and plutonium and americium [P18]. The studies calculate distributions of absorbed or equivalent organ doses, or effective dose per unit intake. Some of the analyses acknowledge that the doses should be regarded as population mean or central values and interpret their results accordingly [A10, H6, P18]. Generally, however, no attempt was made to distinguish variability from uncertainty in the distributions that were derived for model parameters since many of those studies were not intended for epidemiological purposes. It is therefore likely that the distributions of doses that were calculated overestimate the uncertainty in the population mean absorbed organ doses per unit intake. However, it is possible to infer the uncertainty in the mean values for the exposure pathways that were considered. Approximate ratios of upper to lower bounds of mean dose per unit intake for adult members of the public are:

- (a) Within a factor of 2 for absorbed organ doses resulting from ingestion of ^{137}Cs in food [A10] and absorbed dose to the thyroid from ingestion of soluble forms of ^{131}I [A10, D10, F8, H3];
- (b) Within a factor of 3 for absorbed organ doses from inhalation or ingestion of tritiated water [H6, M10];
- (c) Within a factor of 4 for absorbed dose to the thyroid from inhalation of environmental aerosols bearing ^{131}I [F8, H8];
- (d) Within a factor of 5 for absorbed organ doses from ingestion of organically bound tritium [H6, M10];
- (e) Within a factor of 10 for absorbed doses to liver and bone surfaces from ingestion of ^{239}Pu or ^{241}Am [P18].

B65. Uncertainties in doses for specific individuals. Uncertainties on absorbed organ doses resulting from internal exposures to radionuclides have been calculated for individuals in a number of epidemiological studies. From the standpoint of uncertainties in the internal dosimetry model, these range from the fairly simple (e.g. thyroid doses resulting from ingestion of iodine) to the complex (e.g. lung doses resulting from inhalation of plutonium).

B66. Estimates of dose to the thyroid have been calculated to derive estimates of risk of thyroid cancer in childhood or adolescence following the Chernobyl accident [D8, D9, S28]. In these studies, uncertainties on individual thyroid doses were calculated using Monte Carlo techniques and accounted for uncertainties in the exposure pathway in addition to uncertainty in the dose per unit intake to the thyroid. In both studies uncertainty in the latter was simply taken directly from estimates of the variation in thyroid dose per unit intake estimated by Apostoaiei and Miller [A10] or Dunning and Schwartz [D10]. Thus it was assumed that the range of thyroid dose per unit intake for the subjects in the study groups was comparable to those observed in United States subjects of similar ages. In addition to deriving uncertainties on parameters, Drozdovitch et al. [D8] categorized parameters as shared or unshared, with a view to preserving this error structure in a Monte Carlo analysis of risk. The uncertainties on doses calculated by Stepanenko et al. [S28] were included in a risk analysis by Kopecky et al. [K10]. However, because the uncertainties on thyroid doses were calculated separately for each individual, shared and unshared parameters were not distinguished in the analysis of risk [K10].

B67. The study of nuclear workers exposed to plutonium and other actinides is an invaluable tool for obtaining risk estimates of lung cancer for alpha emitters other than radon progeny. So far, risk

estimates have been derived from point estimates of lung dose that are often estimated from urine or faecal bioassay [G9, S23]. However, such estimates ignore errors in lung dosimetry. As a consequence, there has been significant interest in applying Bayesian inference methods to calculate uncertainties in these estimates. Miller et al. [M15, M16] derived prior distributions of biokinetic model parameters with a view to applying them in a Bayesian analysis of former workers of the Mayak Production Association. This distribution was limited to a small set of biokinetic “types”; each type consisted of a set of parameter values associated with a biokinetic model and was derived by fitting the data to one of 41 sets of worker bioassay and autopsy data. However, representing the prior uncertainty on parameters as a discrete set of sets rather than as continuous distributions may distort the uncertainty on dose and may also make it difficult to distinguish shared from unshared parameters. In a more recent analysis, Puncher et al. [P17] derived uncertainties in the ICRP Human Respiratory Tract Model [19], in the form of a multivariate continuous prior distribution. This was used to calculate uncertainties on lung doses for 2,056 European nuclear workers in a recent European case–control study of lung cancer risk from occupational exposures to actinides [T5]. Although the Bayesian calculation was performed separately for each worker, the sampling regime was implemented so that parameters identified as being shared or unshared would be preserved between workers. Effectively what was calculated was a joint posterior distribution of worker doses conditioned on the matrix of worker bioassay data.

B. Reconstruction of external exposure in specific studies

1. DS02 dosimetry for survivors of the atomic bombings of Hiroshima and Nagasaki

B68. The most recent set of dose estimates for the survivors of the 1945 atomic bombings of Hiroshima and Nagasaki is referred to as DS02 [G23, K4]. Estimates of the external absorbed dose to each organ for each survivor provide the basic foundation for the most recent updates of risk coefficients from the Radiation Effects Research Foundation of Japan (RERF). The absorbed dose estimates from DS02 [G23] provide the basis for the majority of estimates of standardized coefficients of risk per unit dose, including those published by the United States National Research Council [N19], ICRP [I14] and UNSCEAR [U12]. To date, almost all radiation risk coefficients are derived from the Lifespan Study cohort (LSS) of RERF; exceptions are risk coefficients from pooled studies for breast and thyroid, and for lung cancer due to exposure to radon and its decay products [I14, N19, U13]. A detailed analysis of uncertainty in the DS02 dose estimates has been conducted by Kaul et al. [K4]. They evaluated uncertainties in each modular component of the individual dose calculation and compared their calculated total uncertainty estimates with field measurements to test the validity of the results. The computational process for estimating absorbed doses in DS02 is composed of three independent elements: (a) propagation of the radiation leakage from the weapon through air to derive the radiation field above bare, flat ground (referred to as the “flat field”), (b) transmission through and around structures and terrain to produce a “shielded radiation field”, and (c) transmission into the body to compute mean radiation fields and doses in individual organs of each survivor. Calculations are differentiated by neutron and gamma-ray components. The dose uncertainties of each computational element are inferred from input parameters, reaction cross sections, computational methods, computational statistics, assumptions made in creating the computational description of events and on expert judgement. Uncertainties are differentiated into two types: “systematic,” describing the likelihood that doses to all individuals at a given city will increase or decrease together, and “random,” which affect each individual survivor more or less independently.

B69. To evaluate the validity of the computed dose uncertainties, comparisons were made between ensemble uncertainties (computed for individual computational elements and radiation dose components) and field observations, at critical intervals in the computational process for survivor dose estimation. These comparisons included observed and calculated radiation free-field components; the observations included thermal- and fast-neutron activation and gamma-ray thermoluminescence. These comparisons are relevant to the evaluation of systematic uncertainty in DS02. Comparisons were also made between field observations and calculations of survivor shielding, where the observations consisted of biodosimetric measurements for individual survivors. These comparisons were relevant for evaluation of the amount of random uncertainty specified in DS02.

B70. *Systematic uncertainty.* Sources of systematic uncertainty include the yield of the weapon for prompt and delayed radiation, radiation output (that is, radiation leakage from the weapon, describing the disassembly of the bomb as it explodes), height of the burst, air density, air moisture, soil moisture, air transport, nuclear cross sections, fission product radiation uncertainties (including gamma-ray and neutron dose), shielding calculation methodology, and the calculational methodology adopted for estimating organ dose. The total estimated systematic uncertainty for a representative survivor is expressed as a coefficient of variation (CV, also called standard error as a percentage of the central estimate) of 13.6% for the city of Hiroshima and 12.6% for the city of Nagasaki (tables B5 and B6). In this situation, the CV accounts for one standard error about the estimate of the mean, or 64% of the total uncertainty about the mean value.

B71. *Random uncertainty in dose at a known location.* The various factors considered in estimating the random component of total uncertainty are: the distance of the survivor to the hypocentre of the bomb detonation, shielding associated with house modelling, shielding assignment for an individual survivor, shielding histories associated with the use of the 9-Parameter Shielding Model, the use of a variable phantom model and assumptions about the orientation of each survivor to the influence of irradiation, survivor coordinates, survivor recall of location and factors affecting shielding, and recall of posture and orientation (based on re-interviewing 88 survivors of the Nagasaki bombing). The total random uncertainty in survivor dose estimates range between 20% and 41% (coefficients of variation) for the Hiroshima bombing and between 25% and 44% for the Nagasaki bombing.

B72. *Total dose uncertainty.* The uncertainty for each component of the dose calculation for a representative survivor and representative conditions of orientation, shielding and dose at 1,500 m distance from the hypocentre are given in table B5 for Hiroshima and table B6 for Nagasaki. The total uncertainty is dominated by the random uncertainty and ranges in terms of the coefficient of variation from 24.4% to 43.3% for Hiroshima and 27.9% to 45.3% for Nagasaki. These uncertainties appear to be substantiated by limited comparisons for a small number of survivors (22) whose gamma kerma doses could be determined using biodosimetric information [K4].

B73. *Dose uncertainty assumed for LSS risk estimation.* In their evaluation of risk coefficients from the LSS cohort, Preston et al. [P14] assumed a general dose uncertainty (CV) of 35% for survivor dose estimates from both the Hiroshima and Nagasaki bombings. This was assumed to be random and associated with classical measurement error. Pierce et al. [P6] re-evaluated the assumptions used by Preston et al. [P14] and concluded that the total random uncertainty associated with each individual survivor dose estimate ought to be more appropriately expanded to 44%. Of this, a CV of 40% is considered as classical measurement error and a CV of 20% assignment error (referred to in [P6] as “averaging errors”). Of the two types of random errors, classical measurement errors have the most profound effect on introducing a bias in the dose–response analysis (see section III.B of this appendix).

Table B5. Representative DS02 random and systematic uncertainties in total marrow dose at Hiroshima (from [K4])

Factors	Absorbed dose uncertainties (CV, %)			
	Total	Methodology systematic	Methodology random	Input random
Yield	5.8	5.8		
Neutron output	2.6	2.6		
Air density and moisture	2.6	2.6		
Air cross sections	3.3	3.3		
Hydrodynamic model	5.2	5.2		
Fission product source	2.6	2.6		
Air transport calculation method	7.6	7.6		
Burst height	1.2	1.2		
Hypocentre location	1.4		1.4	
Survivor coordinates	14.2			14.2
House materials	5.5		5.5	
Shielding assignment	15.6		15.6	
(Range)	(5.0–35.0)		(5.0–35.0)	
Shielding calculation method	4.5	4.5		
Phantom materials and orientation	4.9		4.9	
(Range)	(5.0–10.0)		(5.0–10.0)	
Organ dose calculation method	3.7	3.7		
Shielding survivor recall	10.8			10.8
Posture and orientation recall	3.6			3.6
Total	28.5	13.6	17.3	18.2
(Range)	(24.4–43.3)		(9.1–36.8)	
Total random				25.1
(Range)				(20.3–41.1)
UNCERTAINTY DUE TO DS02 METHODOLOGY ALONE				
Total	22.0			
(Range)	(16.3–39.3)			

Note of survivor specifications: City: Hiroshima; Distance: 1,500 m.

Conditions of shielding: First floor, external structure within 22.5 degrees to hypocentre, unshielded factor >3, slant penetration from outer surface to survivor 6 metres.

Adult survivor facing hypocentre.

Total dose: 22.7 mGy.

Table B6. Representative DS02 random and systematic uncertainties in total marrow dose at Nagasaki (from [K4])

Factors	Absorbed dose uncertainties (CV, %)			
	Total	Methodology systematic	Methodology random	Input random
Yield	4.5	4.5		
Neutron output	3.5	3.5		
Air density and moisture	2.2	2.2		
Air cross section	3.4	3.4		
Hydrodynamic model	4.1	4.1		
Fission product source	2.1	2.1		
Air transport calculation method	7.5	7.5		
Burst height	0.6	0.6		
Hypocentre location	2.1		2.1	
Survivor coordinates	20.3			20.3
House materials	5.1		5.1	
Shielding assignment (Range)	14.5 (5.0–35.0)		14.5 (5.0–35.0)	
Shielding calculation method	4.3	4.3		
Phantom materials and orientation (Range)	4.9 (5.0–10.0)		4.9 (5.0–10.0)	
Organ dose calculation method	3.9	3.9		
Shielding survivor recall	10.4			10.4
Posture and orientation recall	3.8			3.8
Total (Range)	31.0 (27.9–45.3)	12.6	16.2 (9.0–36.8)	23.2
Total random (Range)				28.3 (24.8–43.5)
UNCERTAINTY DUE TO DS02 METHODOLOGY ALONE				
Total (Range)	20.6 (15.5–38.9)			

Note of survivor specifications: City: Nagasaki; Distance: 1,500 m.

Conditions of shielding: First floor, external structure within 22.5 degrees to hypocentre, unshielded factor >3, slant penetration from outer surface to survivor 6 metres.

Adult survivor facing hypocentre.

Total dose: 44.3 mGy.

2. Occupational exposures

B74. In epidemiological studies of occupationally-exposed people, estimates of absorbed doses to organs of individual workers are used to evaluate dose–response relationships. Procedures must be developed that translate dosimetric data recorded for workers—obtained both from current dosimetry systems designed to estimate the Personal Dose Equivalent (known as $H_p(10)$, the energy absorbed at a depth of 10 mm in tissue), and from older dosimetry systems for which the dose objective was not so clearly defined—into estimates of the absorbed dose in an organ. While translating historical and more recent recorded doses into estimates of organ dose, attention is given to account for systematic and random sources of uncertainty. The following material reviews cohorts occupationally exposed primarily to external sources of high-energy gamma radiation. Individuals exposed occupationally to internal emitters or externally to neutrons or low-energy photons are excluded from consideration.

B75. *Hanford workers.* In a study presenting results of dose–response analyses based on estimated external radiation doses for Hanford workers, Gilbert [G8] corrected for bias in recorded doses to produce estimates of absorbed dose for organs, and they estimated the systematic and random uncertainty in the correction factors. Sources of uncertainty in the bias correction factors were found to include both the random variation of laboratory measurements and the limited ability of the personal dosimeters worn by workers to respond accurately to all radiation energies, as well as the uncertainty arising when measured dose is converted to absorbed dose in an organ. Systematic uncertainty about the overall bias B for specified time periods is represented as a ratio (K_S) between the upper 97.5th percentile of a probability density function for the bias correction factor and the geometric mean value for B for red bone marrow dose and lung dose. The systematic uncertainty in the bias correction factors used in this study were assumed to be perfectly correlated among workers [G7].

B76. The study by Gilbert [G8] of dose–response analyses relied on an earlier study of the same Hanford cohort which evaluated bias and uncertainty in estimates of external exposure derived from measurements using personal dosimeters [G7]. That 1996 study focused on recorded doses as the primary information for estimating absorbed doses to organs, addressing the extent that uncertainties for different workers were correlated. This analysis involved categorizing errors as random (reflecting uncertainties that were independent among individual workers), and systematic or biased (reflecting uncertainty between the mean of the reported dose and the true mean of the absorbed dose to organs for an identified subgroup within the exposure period). The authors assume that uncertainty due to individual sources is described by independent log-normal distributions. Overall uncertainty factors are obtained through propagation of log-normal distributions of uncertainty through a series of multiplicative terms. Data that would allow rigorous determination of uncertainties were not available; thus, the uncertainty factors presented in that paper reflect subjective judgement of the authors.

B77. The evaluation focused on uncertainty resulting from the fact that dosimeters, especially those used in early periods of plant operation, were limited in their ability to respond accurately to all radiation types to which workers were exposed (that is, beta, photon, and neutron) and to radiation coming from different directions (for example, anterior–posterior or rotational). This specific energy and geometry dependence of exposure conditions was a major source of both random and systematic error in the Hanford dose estimates. Because of the different capabilities of dosimeters used in different time periods, separate evaluations were made for the periods 1944–1956, 1957–1971, 1972–1983, and 1984–1993. It was concluded that systematic uncertainties in different dosimetry systems were unlikely to be perfectly correlated, and so the overall systematic uncertainty in cumulative doses that include contributions from more than one of these time periods were likely less than that for uncertainty contributed by individual exposure periods.

B78. The estimated doses follow approximate log-normal distributions, characterized by bias factors B and 95% uncertainty factors K_S (quantifying the systematic uncertainty regarding how well the bias factors are known) and K_R (quantifying the inter-individual variability of true dose among workers, given a possibly true value for B that is without systematic uncertainty). The recorded doses were translated into estimates of deep dose and estimates of absorbed dose to the red bone marrow and lung (see table B7). K_R represents only aleatory uncertainty or assignment error. Classical error resulting from variability of laboratory methods was not considered, because it was only a minor contributor to the total uncertainty of most members of the cohort, especially for those who experienced multiple exposure events over a period of several years.

Table B7. Overall bias and uncertainties in recorded doses of monitored workers as estimates of deep dose, red bone marrow dose, and lung dose [G7, G8]

Source of uncertainty	1944–1956	1957–1971	1972–1983	1984–1989
DEEP DOSE				
Overall bias (B) ^a	1.27	1.02	1.12	1.01
Systematic uncertainty (K_S) ^a				
From energy and geometry	1.2	1.1	1.05	1.05
From other sources ^b	1.4, 1.8	1.3, 1.5	1.2, 1.3	1.2, 1.3
Random uncertainty (K_R) ^c				
From energy and geometry	1.8	1.4	1.2	1.2
RED BONE MARROW DOSE				
Overall bias (B) ^a	1.75	1.41	1.54	1.40
Systematic uncertainty (K_S) ^a				
From energy and geometry	1.3	1.2	1.1	1.1
From other sources ^b	1.5, 1.8	1.3, 1.6	1.3, 1.4	1.3, 1.4
Overall uncertainty ^d	1.6–1.9	1.4–1.7	1.3–1.4	1.3–1.4
Random uncertainty (K_R) ^c				
From energy and geometry	1.9	1.6	1.4	1.4
LUNG DOSE				
Overall bias (B) ^a	1.33	1.07	1.17	1.06
Systematic uncertainty (K_S) ^a				
From energy and geometry	1.2	1.1	1.05	1.05
From other sources ^b	1.5, 1.8	1.3, 1.6	1.3, 1.4	1.3, 1.4
Overall uncertainty ^d	1.6–1.9	1.3–1.6	1.3–1.4	1.3–1.4
Random uncertainty (K_R) ^c				
From energy and geometry	1.6	1.4	1.2	1.2

^a Values of B and K_S define a log-normal distribution representing systematic uncertainty in the central estimate of bias correction that is shared by all members of an exposure period subgroup. B is the geometric mean of the bias correction factor and K_S is the ratio of the upper 97.5th percentile to the geometric mean. K_S is often referred to as a “95% uncertainty factor,” because when it is divided into the geometric mean and then multiplied by the geometric mean, it defines a 95% uncertainty interval for a log-normal distribution.

^b The first entry is uncertainty for the anterior–posterior geometry; the second entry is uncertainty for the rotational geometry.

^c The selection of a possibly true value for systematic uncertainty in bias correction combined with K_R define the inter-individual variability of true doses for each person in the exposure period subgroup.

^d Overall systematic uncertainty reported in [G8].

B79. *A 15-country study of radiation workers.* In order to derive direct estimates of risk of cancer due to chronic exposure to radiation, a 15-country collaborative study of radiation workers in the nuclear industry was conducted, using a common core protocol. An investigation of shared errors in dosimetry was established as part of the study and reported in Thierry-Chef et al. [T2]. One of the main objectives of this investigation was to identify and quantify bias and uncertainties in available recorded dose estimates. Bias correction factors (with their uncertainties) specific for individual recorded doses for each facility and calendar-year period were estimated to correct absorbed doses for organs that would be, on average, unbiased estimates of each subject's organ dose of interest.

B80. Because historical practices for measuring lower-energy photons (<100 keV), very-high-energy photons (>3,000 keV), neutrons, and internal contamination by fission and activation products were less reliable than those for measuring high-energy photons, those workers who had the potential for substantial doses from these radiation types were excluded from the investigation. In addition, independent, unshared (classical) errors due to sampling variation in measurements inherent to different types of dosimeters were not evaluated.

B81. The identified sources of errors in doses associated with high-energy photon irradiation were: exposure conditions in the workplace, dosimetry technology, calibration practices, and administrative practices for recording doses in files. Methods were developed to enable the comparison of recorded doses through time and among different facilities and to quantify identified bias and uncertainties in historical recorded worker doses. Table B8 lists the characteristics of the sources of uncertainty considered by [T2] and identifies which were considered in the quantification of systematic sources of uncertainty.

B82. Thierry-Chef et al. [T2] determined a bias factor B (geometric mean) and its uncertainty factor K ($= \text{GSD}^{1.96}$, where GSD is the geometric standard deviation) to estimate a 95% uncertainty range assuming a log-normal distribution. Doses to colon, lung, and active bone marrow were estimated by dividing the individual recorded doses by a random value selected from the log-normal distribution of the bias factor (as defined by B_i and the uncertainty factor K for a given organ i , see table B9). Once a random value of the bias correction factor is applied for each facility and year, that sampled value is applied for each subject with a recorded dose who worked at the facility and in that year and who was exposed to high-energy photons. The error structure is assumed to be 100% due to assignment (that is, inter-individual variability of true dose varies stochastically and independently about an unbiased mean value that is applied for each cohort subgroup).

B83. Although uncertainties in bias correction factors across different facilities are neither perfectly correlated nor independent. Since common assumptions were used to develop the bias correction factors [G10], the effect of partial correlations in the uncertainty of individual bias correction was not considered.

B84. *Oak Ridge National Laboratory workers.* An illustrative case study by Stayner et al. [S25] developed a method to account for shared errors in exposures within a dosimetry system for a cohort of nuclear workers at the Oak Ridge National Laboratory, United States. Data from this study facility, comprising annual records of external radiation doses from personal dosimeters for all workers, is publicly available from the United States DOE "Comprehensive Epidemiologic Data Resource: A digital collection of public use data sets (CEDR)" website (<https://www.ornl.gov/cedr/>). The ORNL cohort included 5,345 workers, and, following the protocol for the 15-country study [T2], workers who received substantial doses from neutrons and from internal exposures were excluded from the analysis. The bias factors and uncertainties developed for the ORNL facility in the 15-country study were used in Monte Carlo simulations, repeated 10,000 times for each individual in the cohort, to randomly select a set of bias factors from the log-normal distribution for each time period, defined by β and κ in table B10. The bias factors (B) were then used to estimate annual 'corrected' doses for each worker in

the study, by dividing their annual recorded doses by the appropriate sampled bias factor. Workers were assigned the same correction factor for each year of the period, thus sharing a common assignment error and preserving the correlation structure in the errors in doses between individuals in the sampling process. Uncertainty due to classical measurement error was not addressed. Inter-individual variability of recorded dose was assumed to be equal to inter-individual variability of true dose once the recorded dose was divided by the sampled value of B to correct for systematic errors.

Table B8. Characteristic source of errors in dose estimates for the 15-country study of radiation workers [T2]

<i>Sources of errors</i>	<i>Uncertainties in estimated bias factors</i>	<i>Uncertainties resulting from variation in the correct bias factors among workers^a</i>	<i>Potential impact on the dose estimates</i>	<i>Considered in the quantification of errors</i>
CONDITIONS OF EXPOSURE				
Energy	Shared	Assignment	Major	Yes
Geometry	Shared	Assignment	Major	Yes
Other environmental factors (heat, humidity, light)	Shared	Assignment	Negligible	No
DOSIMETRY TECHNOLOGY				
Response to energy	Shared	Assignment	Major	Yes
Response to geometry	Shared	Assignment	Major	Yes
Laboratory practices (dosimeter processing and reading)	Unshared	Classical	Minor	No
CALIBRATION PRACTICES				
Dosimetric quantity	Shared	Assignment	Major	Yes
Radiation source used for calibration	Shared	Assignment	Major	Yes
Backscatter factor	Shared	Assignment	Major	Yes
Factors affecting sources	Shared	Assignment	Minor	Yes
ADMINISTRATIVE PRACTICES				
Frequency of monitoring	Shared	Assignment	Generally minor	No
Criteria for monitoring	Shared	Assignment	Generally minor	No
Rules for below threshold doses and for missing doses	Shared	Assignment	Generally minor	No

^a With the exception of laboratory practices, the errors in the estimated bias factors from each of the sources are shared among workers within a group defined by time period and facility and are due to assignment.

Table B9. Final estimated biases and uncertainties in dose estimates for radiation workers in selected facilities in France and United States [T2]

Facility	Start	End	Lung		Red bone marrow		Colon	
			B_{lung}	K_{lung}	B_{RBM}	K_{RBM}	B_{colon}	K_{colon}
FRANCE								
1	1950	1956	1.62	1.51	1.94	1.33	1.72	1.69
	1957	1960	1.01	1.28	1.21	1.31	1.07	1.22
	1961	1966	1.01	1.17	1.21	1.21	1.07	1.07
	1967	1984	1.00	1.17	1.19	1.30	1.06	1.07
	1985	1994	1.02	1.20	1.22	1.30	1.08	1.07
	1995	1995	1.04	1.20	1.25	1.28	1.10	1.08
2	1968	1978	1.13	1.32	1.36	1.33	1.20	1.26
	1979	1995	1.13	1.22	1.36	1.25	1.20	1.15
3	1955	1960	1.01	1.28	1.21	1.31	1.07	1.22
	1961	1964	1.01	1.17	1.21	1.21	1.07	1.07
	1965	1995	1.03	1.22	1.36	1.25	1.20	1.15
4	1968	1982	1.16	1.21	1.38	1.38	1.23	1.29
	1982	1982	1.11	1.18	1.33	1.20	1.18	1.28
	1983	1997	1.05	1.17	1.26	1.19	1.11	1.18
UNITED STATES								
5	1943	1952	1.93	1.41	2.31	1.72	2.05	1.99
	1953	1979	1.13	1.22	1.36	1.25	1.20	1.15
	1980	1997	1.08	1.23	1.29	1.31	1.13	1.20

B = bias factor (geometric mean).

K = uncertainty (geometric standard deviation^{1.96}).

Table B10. Parameters of the log-normal distribution for bias factors developed for ORNL workers [S25]

Year(s)	Parameters of the distribution for the bias factor	
	Geometric mean (β)	Uncertainty factor (κ) ^a
1943	2.048	1.601
1944–1952	1.353	1.698
1953–1979	1.201	2.464
1980–1997	1.137	1.708

^a κ = the ratio between the upper 97.5th percentile and the geometric mean of a log-normal distribution for the bias correction factor; the ratio represents systematic uncertainty.

3. Medical cohorts

B85. *Thyroid cancer following scalp irradiation. A reanalysis accounting for uncertainty in dosimetry.* In the 1940s and 1950s, scalp irradiation was used as a medical treatment for over 20,000 children in Israel who had ringworm, or tinea capitis, in order to induce epilation. Follow-up studies showed that this radiation exposure was associated with thyroid malignancies, but the individual doses to the thyroid gland estimated in these studies contained probable errors. Schafer et al. [S5] and Lubin et al. [L29] have developed methods to account for the uncertainties in the dose estimates for individuals in this cohort.

B86. Schafer et al. [S5] developed a variant of the multiplicative assignment error model to refine the uncertainties in dose estimates used in the dose–response estimation. Starting from a large data set with health outcomes and imprecisely-determined doses from the tinea capitis cohort, they incorporated data from a separate study of anthropomorphic phantoms exposed to X-rays under similar conditions to formulate and characterize a model for estimating dose. This approach results in assignment error due to using the expected dose from a regression model as a surrogate for the individual’s true dose. Schafer et al. [S5] distinguished between classical measurement errors and assignment errors in their approach, as well as noting that the classical errors in dose estimates for different individuals are correlated.

B87. Schafer et al. developed a model for the distribution of dose on a single course of treatment which included error terms for: (a) intra-individual effects, reflecting the different thyroid doses that would occur if a child were irradiated twice under identical conditions, (from movement during treatment or differences in positioning the body), (b) between-individual effects, reflecting the different doses for different children due to differences in head size and shape, and (c) random errors due to the differences between prescribed and actual skin exposure. These error terms were represented as the standard deviation of logarithms of dose, with the mean of the logarithm of dose assumed to be zero (that is, the uncertainty in dose be unbiased). All three sources of uncertainty are assumed to be associated with 100% assignment error.

B88. The variance of logarithms of the uncertainty variables was considered to be known; moreover, the analysis was conducted with several combinations of values varied within speculated ranges. Values for intra-individual variation of true dose, inter-individual variation of true dose, and random errors due to differences between prescribed and actual skin exposure were assigned standard deviations of logarithms of 0.17, 0.49 and 0.15. The analysis was repeated varying the values of the standard deviation of logarithms to (0.17, 0.25, 0.25) and to (0.5, 0.5, 0.5), respectively.

B89. In analysing the same Israeli tinea capitis cohort, Lubin et al. [L29] present an alternative method to account for uncertainties in dose. They base their analysis on an externally-estimated dose-prediction equation that used results from studies of anthropomorphic phantoms. As with the paper by Schafer et al. [S5], Lubin et al. adjusted for uncertainties inherent in the prediction* of true dose based on studies of phantoms, for random differences in sizes of children of a given age, and for random movements by children during treatment. Additional accommodation was made for uncertainties associated with missing data for ages at subsequent exposure for those receiving multiple treatments. When the prediction equation for individual dose includes uncertainty arising from estimation of the equation parameters, this type of uncertainty also represents a shared error common for all subjects. A second source of uncertainty results from the random deviation of the (log) dose prediction for each subject from the (log) true dose and is called (multiplicative) assignment error [L29].

B90. As was the case with [S5], the intra-individual variability of true dose was estimated as a standard deviation of logarithms of 0.17, based on 13 degrees of freedom, from the data of Modan et al. [M17], in which a phantom was repeatedly repositioned and re-irradiated. The inter-individual

variability of true dose was estimated as a standard deviation of logarithms of 0.49. Additional random uncertainty associated with the difference between actual skin exposure and the amount prescribed by a single X-ray machine was estimated as the standard deviation of logarithms of 0.25. All remaining sources of random uncertainty, such as machine power output, the time the machine was on, and treatment records, were assumed to be minimal. The result was that expected values for true doses were larger than original mean estimates. For example, person-year weighted means for original doses and expected true doses were 94 mGy and 108 mGy, respectively, for treated patients; 101 mGy and 116 mGy for thyroid cancer cases; and 102 mGy and 115 mGy for benign tumour cases. Mean expected true doses are higher than the mean original doses for each category of number of treatments. While the assessment includes most major sources of uncertainty, not all sources of uncertainty are accounted for explicitly. The extent to which the study does not correctly account for random processes generating missing data, or ignores systematic influences, is unknown; however, the authors conclude that any residual random or systematic errors are likely small. Furthermore, the extent of classical error associated with the parameters that define the relationship between added filtration and dose was determined to be small relative to random prediction error from phantom studies.

C. Reconstruction of internal exposure to radon and its progeny in specific studies

1. Occupational exposure (miner data)

B91. *Colorado Plateau uranium miners.* Review of the literature on occupational exposure to radon and radon decay products reveals few epidemiological studies in which exposure uncertainty has been accounted for explicitly. An exception is the paper by Stram et al. [S31], who re-evaluated estimates of individual exposure rates for each of the 3,347 uranium miners of the Colorado Plateau cohort who were exposed for one or more years over the period of 1950 to 1969. Mine-year exposure rate estimation involved averaging measured exposure rates (in working level months, WLM) for each mine-year for which there were measurements, followed by extrapolating those average measured exposure rates to years and mines for which there were no measurements. Measured and extrapolated mine-year estimates were then combined with each miner's history of employment in the industry to produce monthly exposure-rate estimates for each member of the cohort. A crucial aspect of this procedure is the extrapolation of measured exposure rates to years and mines without measurements, taking into account proximity in both time and location.

B92. The authors re-examined the interpolation scheme originally used to create estimates of exposure histories for each of the miners, and computed revised exposure estimates for the large majority of miners in the cohort. Their measurement error correction method was based on the calculation of imputations of mine-year exposure rates for each mine and year of interest. A multi-level analysis of variance model for true average exposure rate as a function of year, mine, locality, and district, was combined with a multiplicative measurement error model for the errors in the actual measurements of exposure rate in that mine-year (if any were taken). Imputations for each mine-year for which at least one cohort member was represented were calculated as the expectation of the true average exposure rate, conditioned on all measurement data specific to a given mine, year, and locality within a given mine district. In the Colorado Plateau miner cohort, errors in exposure estimates come from at least four important sources: (a) from the interpolation process used to estimate dose rates in mines without measurements; (b) from sampling error in the years with measurements owing to the fact

that the mines were not monitored continuously; (c) from within-mine differences in miners' true exposures from the average estimated for that mine-year; and (d) inadequacies in each miner's work history data. Of these four sources of uncertainty, differences in each miner's true exposure from the average estimated for that mine-year was ignored, assuming that if the estimated average is unbiased then all remaining uncertainty is due to assignment error.

B93. A coefficient of variation (CV) of approximately 50% appears to reasonably characterize the variability of measurements within a given mine-year. However, uncertainty about an imputed average exposure to radon (expressed in working level months, WLM) for a given mine-year is a function of how many measurements were taken in the same mine in other years, and in other mines in the same locality or district both in the same year and in other years. For example, in 1950, two years prior to any available measurements, the average imputed value of 74 WLM for exposure rates in a typical mine has a 95% CI ranging from 0.3 WLM to 541 WLM. By contrast, a single imputation of a typical true dose in a mine-year with measurements available was approximately equal to 8.7 WLM with a 95% CI from 5.5 WLM to 13.1 WLM. For years with a single interpolation based only on early exposure-rate estimates obtained from the United States Public Health Service, a typical average mine-year of 13 WLM would have a 95% CI extending from 0.7 WLM to 66 WLM. Further information regarding the calculation of exposure imputations supporting this analysis is available in a supporting technical report [S30].

B94. *French miner cohorts.* The uranium industry in France developed in the aftermath of the Second World War. Prospecting for uranium began in 1946. The last uranium mine in France closed in 1999. The French cohort of uranium miners serves as an important source of information about the risk of lung cancer associated with exposure to low levels of radon and its decay products [A6]. It is recognized that all studies of miner exposure to radon decay products are associated with uncertainty, the nature of which varies with the measurement method. To address uncertainty in the estimate of radon exposure (expressed in Working Level Months, WLM), Allodji et al. [A6] (a) reviewed the uranium extraction process, mining conditions and changes in radiation monitoring methods over time, (b) estimated the overall magnitude of uncertainty in exposure estimates, and (c) characterized the structure of uncertainty in terms of its nature and shape of the uncertainty distribution. This work is a preliminary step towards taking uncertainty into account in the risk models for this cohort and in assessing their impact on the exposure-risk relationship.

B95. The overall size of the uncertainty in the exposure to radon decay products was evaluated using the root sum square (RSS) method. This method is derived by analogy to the statistical calculation that would be used to estimate the variance of a product of independent random variables. The size of each individual source of relative uncertainty was estimated, and the size of the combined relative uncertainty was then calculated as the square root of the sum of the squares of each individual relative uncertainty. In this work, all uncertainties were determined as Type B (characterizing uncertainty about unknown fixed values of the quantity of interest using methods other than a statistical summary of the variability of direct measurements). All sources of uncertainty were separated into two categories: random unshared uncertainties and systematic (shared) bias. It is recognized that random uncertainty can be composed of combinations of assignment errors and classical measurement errors. Measurements were not available for the years 1946–1955, and exposures were retrospectively reconstructed by an expert group. However, because of the likelihood of significant correlations among the sources of uncertainty, it was not possible to determine all of the characteristics of uncertainty for this early period. For this reason, the analysis of uncertainty was restricted to the period of 1956–1999 [A6].

B96. Six primary sources contributed to the overall uncertainty in exposure to radon decay products in French uranium mines: (a) natural variations of airborne gas concentrations; (b) precision of the measurement device; (c) approximation of the equilibrium factor to estimate the proportion of radon

decay products to radon gas in air; (d) human error; (e) estimation of working time; and (f) record-keeping and data transcription. The combined relative uncertainty (expressed as a relative standard error) ranged from 46.8% during the period of 1956–1974 to 10.1% during the period of 1983–1999. Uncertainty in the natural variation of radon gas concentrations, precision of the measuring devices, and equilibrium factor dominated the overall uncertainty from 1956 to 1982. For the time period of 1983 to 1999, only the uncertainty in the precision of measuring device dominated the overall uncertainty in the estimate of radon exposure because of an improved system of continuous monitoring of each individual miner. These results do not address the issue that shared errors can lead to a bias in the central estimates of exposure. Prior to 1983, the overall annual mean exposures ranged from 21.3 to 1.4 WLM from 1956 to 1982. From 1983 to 1999, the annual mean exposure was 0.4 WLM. From 1956 to 1982, the overall uncertainty was assumed to be 100% assignment error. From 1983 to 1999, the uncertainty was assumed to be composed of 100% classical measurement error. The presence of shared sources of uncertainty, and how this potential source affected possible bias in the estimates of the overall mean annual exposure was not addressed.

2. Residential exposure to radon

B97. *Residential radon exposure in south-west England.* In a 1998 case–control study of lung cancer in south-west England, Darby et al. [D1] used measured radon concentrations at the addresses where subjects had lived for 30 years, in a period ending five years before the study. For each residence in which measurements had been taken, an average annual radon concentration in indoor air was estimated. Each subject’s time-weighted average indoor radon concentration was calculated over the 30-year period of interest, the weights being equal to the number of years living at each address. When the measured radon concentration at a specific address of a subject was available, its value was used. For estimating missing values of radon concentrations, a method of analysis was developed that accounted for uncertainty due to measurement error associated with the estimate. The mean time-weighted average radon concentrations, adjusted for uncertainties, are the average values for the subjects in question. For each subject, this quantity is the expected value of the true time-weighted average radon concentration given the observed value, conditional on current residence. All remaining uncertainties are assumed to be due to assignment.

B98. *Residential radon exposure and lung cancer—a collaborative analysis of 13 epidemiological studies in Europe.* In a 2006 collaborative analysis by Darby et al. [D3], data from studies of residential radon exposure from 13 European countries were assembled in a uniform manner in order to investigate any association between radon exposure and lung cancer. The major source of uncertainty in exposure originated from variability associated with repeated measurements in the same dwelling. Analyses were first carried out using the observed radon concentration without making any adjustment for the effect of random uncertainties in the assessment. The major analyses were then repeated with an approximate adjustment to take these uncertainties into account. Long-term measurements (of at least two months) of radon gas concentrations in the residences were made, which were expected to be representative of the levels experienced by the study subjects during the time in which they lived there. A weighted average was calculated to give a single representative value for each dwelling. A time-weighted average (TWA) of the observed radon concentrations was calculated for each subject. In order to correct for the biases caused by both assignment and classical error, it was assumed that the “true” radon concentrations had a log-normal distribution. It was also assumed that, on a log scale, the variability associated with repeated measurements in the same dwelling was normally distributed about the true radon concentration for that dwelling. The TWA of the radon concentrations were corrected by assuming that every measured or estimated radon concentration was equal to the expected value of the corresponding distribution of the true radon concentrations given the observed value, using the

distribution for the logarithm of the true radon concentration. These corrected values were used to derive the mean corrected radon concentrations for groups of persons. The main analyses were then repeated. Using the corrected TWA of the radon concentrations rather than the observed ones in a regression calibration assumes that any remaining error is 100% due to assignment.

B99. *Residential radon exposure in a high-exposure area of Gansu Province, China.* In a 2002 case-control study of lung cancer in a predominantly rural area of China with low mobility and high radon levels, Wang et al. [W5] identified three important sources of error in assessing radon exposure: (a) detector measurement error; (b) use of contemporary measurements to estimate radon levels throughout the house and in prior years; and (c) missing radon values. The authors restricted data to subjects for whom data were nearly complete in order to reduce the effect of missing radon values, thus minimizing assignment error. Classical error from the estimation of radon levels was the predominant form of uncertainty affecting the study. A sub-study, in which six alpha-track detectors were placed for one year in each room of 55 houses over three consecutive years, was conducted to provide data to adjust for exposure variability. Uncertainties were assumed to have resulted from random variations in radon concentrations within houses and over time, and residential mobility was assumed to be unrelated to radon level. Use of a component of variance analysis estimated a GSD of about 1.5 for the error distribution. A Monte Carlo approach was used to evaluate error, in which a randomly-sampled value was chosen for each subject's house in order to compute a "true" time-weighted average radon concentration. Later measurements of Yamada et al. in the same homes in Gansu, with a discriminatory radon detector measured both radon (^{222}Rn) and thoron (^{220}Rn) [Y1]. Thoron was a significant fraction of the total measurement signal, suggesting additional bias and uncertainties in the exposure estimates.

B100. *Adjusting lung cancer risks for temporal and spatial variations in radon concentration in dwellings in Gansu Province, China.* In a 2005 re-analysis of the Wang et al. [W5] study of residential radon exposure in Gansu Province, China, Lubin et al. [L31] used a three-year sub-study to model the temporal and spatial variations in radon levels. Their error model specified random variation about a true mean radon concentration (Bq m^{-3}) for each dwelling type and random variation common to all homes. Bootstrap sampling accounted for the usual sampling variability of the data, the uncertainty in estimating mean and variance from the control data, and the imputation of gaps in the exposure-time window. Regression calibration shrank exposures toward the mean of the true distribution and reduced the range of exposures. The study's estimate of uncertainties in adjusted mean radon concentration was expressed as a GSD of 1.50, corresponding to a CV of 0.43 (95% CI: 0.40, 0.46).

B101. *Residential radon exposure assessment in Sweden.* In a re-analysis of an epidemiological study of residential radon exposure and lung cancer in Sweden, Lagarde et al. [L1] attempted to refine the quantification of random error in the exposure assessment. Radon measurements were made in 8,992 dwellings over a period of 3 months during the heating season. In the original study [P2], information on imprecision in exposure assessment [B3] was used to evaluate possible bias in risk estimates related to random error in the retrospective assessment of time-weighted average radon concentrations. Simulated "true" exposures and corresponding "estimated" exposures were modelled, using the square of the correlation coefficient (R^2) between the "true" and "estimated" exposures, to show a measure of the discrepancy between "true" and "estimated" exposures related to the sources of errors modelled in the simulations. A coefficient of variation (CV) of 35% was used in the original study to represent the combined error due to radon measurement and extrapolation to a long-term average concentration, in accordance with the findings of Bäverstam and Swedjemark [B3]. However, subsequent simulations in the re-analysis, which reflected more of the error conditions from the original study, showed a CV of 53%. A value for R^2 of 0.55 as observed in the simulations involving multiple error components was then chosen to reflect the more appropriate size of the CV and used in the re-analysis of the data [L1]. Some underestimation of error is still expected because uncertainties associated with choices for placement of detectors in rooms and incorrect address information were not taken into account.

Individual “corrected” exposures were based on the use of imputed values of the expectation of the true time-weighted average exposure as a surrogate for the observed time-weighted average. Once corrected exposures were obtained, all remaining uncertainty was assumed to be 100% assignment error.

D. Reconstruction of internal exposure from other pathways in specific studies

1. Hanford

B102. The Hanford Nuclear Site in south-eastern Washington State, United States, was established in 1943 to produce plutonium for atomic weapons. From 1944 through 1957, approximately 27 PBq of ¹³¹I were released to the atmosphere [K8]. The potential impact of these releases on children off-site consuming milk containing ¹³¹I was addressed by the Hanford Thyroid Disease Study (HTDS) [D6]. Individual dose estimates were made for 3,191 participants who made up a retrospective cohort study [D6, K8, K9].

B103. Individual doses were calculated for HTDS using the computer program, Calculation of Individual Doses from Environmental Radionuclides (CIDER), developed by the Hanford Environmental Dose Reconstruction Project [F1]. CIDER provided 100 alternative sets of 3,191 dose realizations, an early version of a two-dimensional Monte Carlo uncertainty propagation. The CIDER uncertainty analysis addressed both inter-individual variability of possibly true doses and uncertainty in individual doses.

B104. Point estimates of individual doses, composed of the median of the 100 Monte Carlo dose realizations for each individual were used for the primary dose–response analysis performed by HTDS. Individual median doses ranged from 0.0029 mGy to 2,823 mGy. The arithmetic mean of all individual median dose estimates was 174 mGy, with a standard deviation of 224 mGy. These statistics provide an indication of inter-individual variability of dose. They do not address uncertainty in dose estimation.

B105. The uncertainty of each individual’s dose estimate was characterized as the ratio of the individual’s upper 95th percentile to the 50th percentile (median) of the 100 alternative dose realizations produced by CIDER for each person. These uncertainty ratios ranged from 1.8 to 13.7. Of these individual dose uncertainty ratios, 80% ranged from 2.7 to 5.3. The GSD (exponential of the standard deviation of log-transformed values) of the uncertainty in the individual dose estimate ranged from 1.56 to 5.42. A total of 890 participants had dose estimates with uncertainties expressed by GSDs of less than 2.0.

B106. The primary dose–response analysis was based on the individual median dose. All uncertainty was assumed to be due to stochastic inter-individual variability of true dose. Thus the dose uncertainty was assumed to be associated with pure assignment error. It was further assumed that there were no important systematic sources of bias [D6, H19, K8].

B107. Hoffman et al. [H19] reviewed the dose estimates of HTDS and concluded that the dose uncertainties were likely larger and more complex than originally estimated and reported. HTDS individual dose uncertainties were composed of mixtures of shared and unshared assignment errors, classical errors, and uncertain degrees of systematic bias in the estimate of the centre and spread of

model coefficients used to simulate stochastic inter-individual variability of true dose. For example, the central value of the transfer coefficient for ^{131}I in the milk of commercial dairy cows may have been overestimated by as much as a factor of five, resulting in a systematic bias towards large overestimation of the thyroid dose for individuals consuming dairy milk from commercial sources. Data obtained from personal interviews of a subject's parent or other relative were assumed to be without random or systematic error, even though information was obtained from memory recall of events that occurred more than four decades previously. Assumptions about dietary sources, dairy management practices, and participant and residence histories were assumed to be known without error. Concomitant exposure to significant amounts of ^{131}I from 1950s fallout from the Nevada Test Site was treated as a general confounding variable, but these additional exposures were not included in estimating individual doses. Hoffman et al. [H19] concluded that underestimation of the magnitude and complexity of dose uncertainty affected the overall interpretation of the HTDS findings, namely increasing the magnitude of uncertainty on risk estimates and decreasing the power of the study to detect a statistically significant dose response for thyroid cancer and other thyroid neoplasms.

2. Weapons fallout studies

B108. *Exposure to fallout from detonation of nuclear weapons at the Nevada Test Site.* Nuclear weapons were tested above ground at the Nevada Test Site (NTS) from 1951 to 1958. Additional releases continued on occasion through 1968 as the result of venting from underground tests. In the 1980s, individual thyroid doses and uncertainties were estimated for a retrospective study cohort of 2,473 subjects who were children at the time of exposure [K5, S29]. In a recent effort to restore the databases and computer codes used to estimate doses reconstructed in the 1980s, various deficiencies were found in the estimated doses owing to improperly operating computer codes, corruption of secondary data files, and lack of quality control procedures [S20]. From 2001 through 2004, the dosimetry system was restored and corrected, and individual doses were recalculated for 2,497 subjects. Although the arithmetic means of all individual mean dose estimates were not changed significantly, many individual mean doses were revised by more than an order of magnitude [S20].

B109. As the result of this revised dose reconstruction with improved quality control procedures, individual mean doses varied from 0.0011 mGy to 1,400 mGy. The arithmetic mean of individual mean dose estimates was 120 mGy with a standard deviation of 167 mGy, indicating inter-individual variability of thyroid doses among individuals in the cohort.

B110. Uncertainty in individual doses was represented by the GSD, which ranged from about 1.5 to 8.5, with 90% of the cohort GSDs ranging from about 2.0 to 4.0. Assuming a log-normal distribution of individual dose estimates, these GSDs would translate into a ratio between the upper 95th percentile of individual dose to the median of individual dose ranging from about 1.9 to 34, with 90% of the cohort ranging from 3.1 to 9.8. These uncertainties were estimated using algebraic solutions to the propagation of uncertain terms in multiplicative and additive series [S20].

B111. The initial dose–response analysis performed by Lyon et al. [L34] used regression calibration and point estimates of individual doses based on the individual mean dose, assuming 100% unshared assignment error. Subsequent analysis by Li et al. [L14] evaluated the uncertainty in dose accounting for mixtures of shared and unshared assignment errors and classical errors. Individuals were classified into 40 strata depending on the type of exposure, the location of exposure, and the source of milk consumed. Ranges of 50% to 70% were set for the shared assignment correlation of Washington county residents who consumed milk from local commercial sources, 40% to 60% for local backyard sources of milk, and roughly 20% to 40% for other sources of exposure. For residents from other Utah counties,

lower ranges of shared assignment correlations were specified. It was also estimated that 30% to 50% of the total uncertainty assigned to each individual's dose was composed of random classical measurement error. Mixtures of assignment and classical uncertainty were accounted for explicitly in the dose–response analyses performed by Li et al. [L14] (see section III.B of this appendix).

3. Other environmental exposures

B112. *Chernobyl accident cohorts.* In a study supporting the Kopecky et al. [K10] case–control epidemiological study of childhood thyroid cancer in Bryansk oblast after the Chernobyl accident, Stepanenko et al. [S28] estimated individual thyroid doses for 26 cases and 50 controls, all of whom were children born before 26 April 1986 and diagnosed with thyroid cancer before October 1997. The children were all present in one of the most contaminated areas of the oblast on 26 April 1986. In the months May–June 1986, thousands of measurements were taken of the radiation emitted from the necks of residents of the contaminated areas, in order to estimate the ^{131}I activities in their thyroids. These direct measurements served as the basis for thyroid dose estimates for samples of the population, but such data were not available for all affected individuals. Because the epidemiological study required that thyroid doses should be estimated using the same method for all study subjects, a semi-empirical model was selected that could be applied uniformly to all cases and controls. Using this method, modelled doses for all study subjects were calibrated using direct measurements available for sample individuals. Uncertainty in individual thyroid doses comes from a variety of sources: the unknown coefficients of empirical regression models (derived using data from settlements in reference territories), the isotopic ratios (^{131}I to ^{137}Cs , which ranged from 10 to 45 with an average of 24, and GSD of approximately 1.4), and the ^{137}Cs deposition densities (measured in nine locations, with substantial variation among the average doses for the same settlement contamination level). The uncertainty in individual thyroid doses was estimated using a Monte Carlo calculation procedure, with uncertainty distributions of all of the variables in the thyroid dose calculations sampled repeatedly and used to compute 10,000 estimates of the thyroid dose for each person. The distributions of individual dose estimates were typically log-normal, and the overall uncertainties were characterized by the GSDs of the log-normal distributions of dose estimates. The GSD representing the uncertainty characteristic of reference individual thyroid dose estimates ranged from 3.0 to 3.9, depending on the type and source of milk consumed and the time interval between consumption and cessation of ^{131}I uptake [S25]. The mean ratio of the thyroid doses between those estimated using the semi-empirical model and those estimated using direct thyroid measurements was 1.2 ± 0.99 (sample standard deviation); the geometric mean ratio was 0.77 (GSD = 2.9); the distribution of model-to-measurement ratios was approximately log-normal. The investigators found no evidence of a systematic bias in the individual dose estimates. All sources of uncertainty in this study are assumed to be random classical measurement error, although it is recognized that uncertainties are likely complex, composed of classical and assignment error. To the extent that uncertainties are shared, systematic uncertainty affecting multiple groups of individuals simultaneously remains to be investigated.

B113. Supporting an epidemiological study for Astakhova et al. [A14], Gavrilin et al. [G1] conducted an extensive evaluation of thyroid dose for individuals, considering the contribution of ^{131}I , short-lived radioiodines (^{132}I , ^{133}I , and ^{135}I) and short-lived radiotelluriums ($^{131\text{m}}\text{Te}$ and ^{132}Te). The model was based on three “reliability groups” originally developed by Gavrilin et al. [G2], in which doses were (a) derived from direct measurement of the thyroid gland; (b) derived by affinity (for example, when milk consumption accounted for most of the thyroid doses in a village, it was assumed that the ^{131}I concentrations in milk were relatively uniform throughout the village and therefore that the thyroid doses for individuals of a given age was a linear function of their milk consumption; for every village with a sufficient number of residents with measured thyroid doses, individual thyroid-dose

distributions—“passport doses”—were determined for several age groups and levels of milk consumption); or (c) empirically derived (“inferred” from measurement of ^{137}Cs deposition). The overall method selected for individual dose assignment was the “inferred” methodology, as this method was available for all cases and controls. This “inferred” method was used in estimating doses due to ^{131}I , making use of the observed relationships between the ^{137}Cs deposition density and the mean adult thyroid doses derived for the people with direct thyroid measurements in the areas considered. Although this method provides dose estimates that are more uncertain than other methods, only the place of residence of the subjects within a few weeks of the accident and the ^{137}Cs deposition density at those locations were available for all subjects. Overall uncertainties attached to the estimates are characterized by GSDs of 2.2 to 2.8 if the milk consumption rate is relatively well known, and 2.5 to 3.1 if the milk consumption rate is unknown. For a number of cases and controls, “measured” and “passport (derived by affinity)” doses could be compared to the “inferred” doses. The results of this comparison are illustrated in figure B-II.

B114. In a supporting study for the International Agency for Research on Cancer (IARC) a population-based case-control study described by Cardis et al. [C2], Drozdovitch et al. [D9] reconstructed thyroid doses for young people aged 0–18 who resided in the areas of Belarus and Russia that were heavily contaminated after the Chernobyl accident. They estimated doses derived (a) from internal ingestion of ^{131}I ; (b) from the short-lived radioisotopes of iodine, ^{132}I , ^{133}I , and ^{135}I and of tellurium, $^{131\text{m}}\text{Te}$ and ^{132}Te ; (c) from internal exposure to long-lived radionuclides such as ^{134}Cs and ^{137}Cs ; and (d) from the external irradiation of the thyroid resulting from deposition of radionuclides on the ground. In general, the fraction of the thyroid dose due to exposure to the short-lived iodine and tellurium isotopes, from external exposure, or from radiocaesium ingestion, was found to be nearly 1% for each pathway mode. Because a single uniform method for the dose reconstruction was required for all individuals in the study, Drozdovitch et al. [D9] conducted an inter-comparison evaluation of four dosimetric models previously developed for use with Chernobyl cohorts who had not had their thyroids directly measured in order to select the model with which to estimate individual thyroid doses (figure B-III).

B115. An uncertainty analysis was performed on the estimates of thyroid dose due to ^{131}I intake, as this was the dominant pathway for thyroid exposure for the majority of study subjects [D8]. A Monte Carlo method was used to obtain the stochastic distribution of individual dose estimates for each study subject, simulating 1,000 possible dose realizations for each person in each trial, with a probability density function assigned to each uncertain model parameter. The values of some model parameters were common to groups of subjects (shared), for which inter-individual correlations were also defined to account for the shared errors. For other uncertain subject-related model parameters, the values were independent from subject to subject (unshared), and different levels of uncertainty were associated with these unshared errors. Characteristics of the distributions were evaluated using a maximal-likelihood method, and a mean or median of distribution and CV or GSD were used to describe the parameters. Around 70 parameters were used in the dose reconstruction and considered in the uncertainty analysis. The GSD of the thyroid doses varies from 1.7 to 3.7 among study subjects with a mean GSD over all subjects of 2.3 (figure B-IV). The extent to which shared uncertainties are associated with unique conditions of systematic error and to which random uncertainties can be separated into classical and assignment errors is a subject that requires further investigation.

Figure B-II. Comparison of the “inferred” thyroid dose estimates and (a) the “measured” thyroid dose estimates for the 12 cases with direct thyroid measurements, (b) the “passport” thyroid dose estimates available for 51 cases, and (c) the “passport” thyroid dose estimates available for 58 controls

The error bars represent 95% confidence intervals (adapted from [G1])

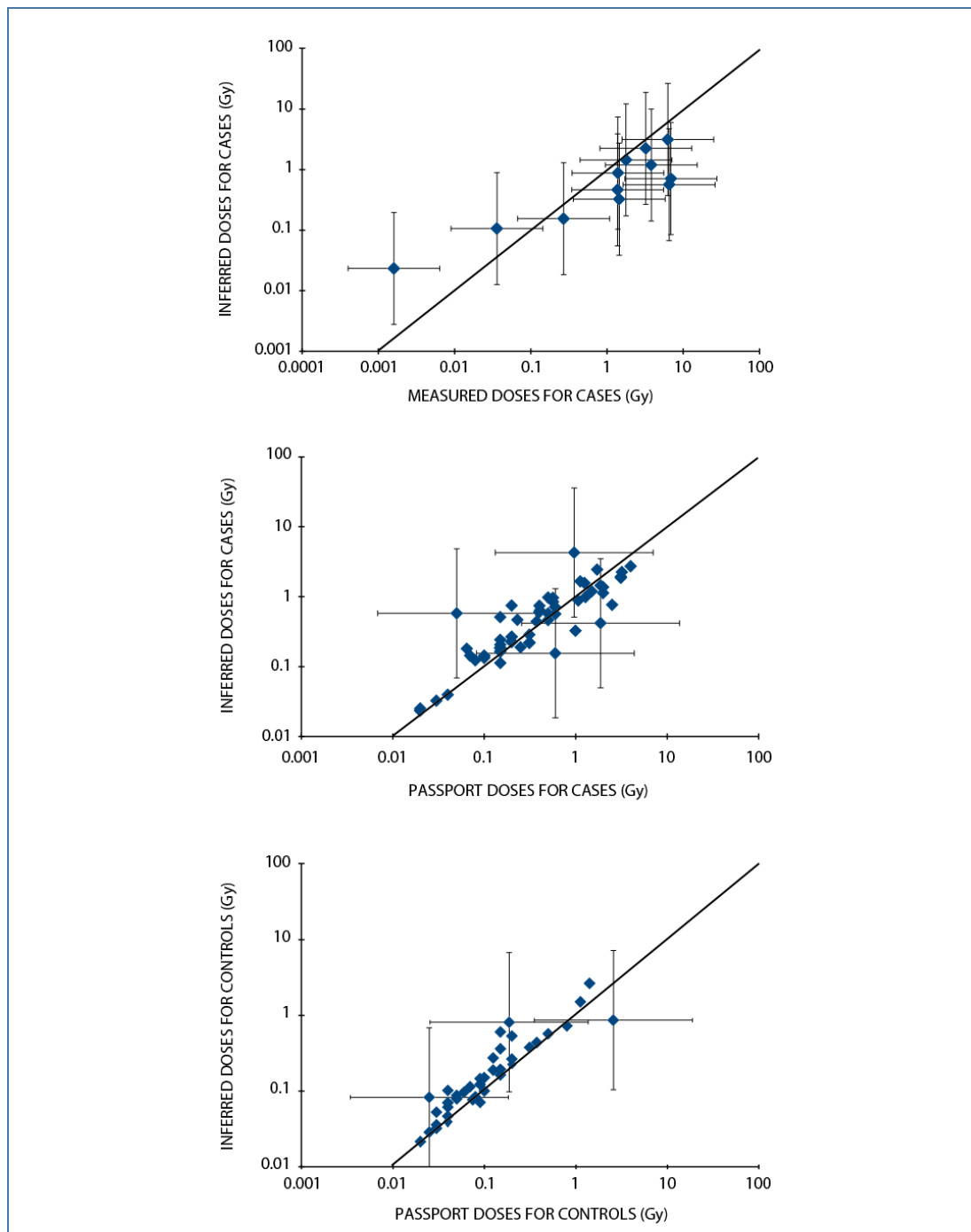


Figure B-III. Comparison of estimates of individual thyroid doses due to ¹³¹I for 81 study subjects calculated using the model with doses derived from direct thyroid measurements

The error bars represent 95% confidence intervals (adapted from [D9])

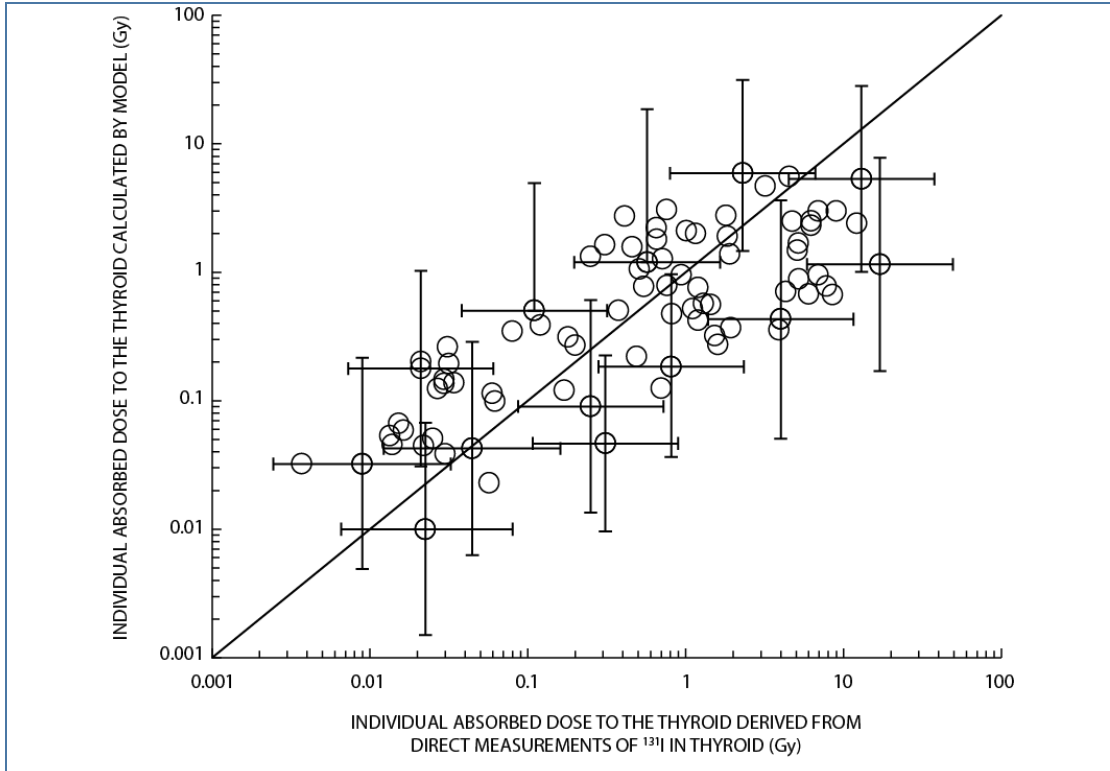
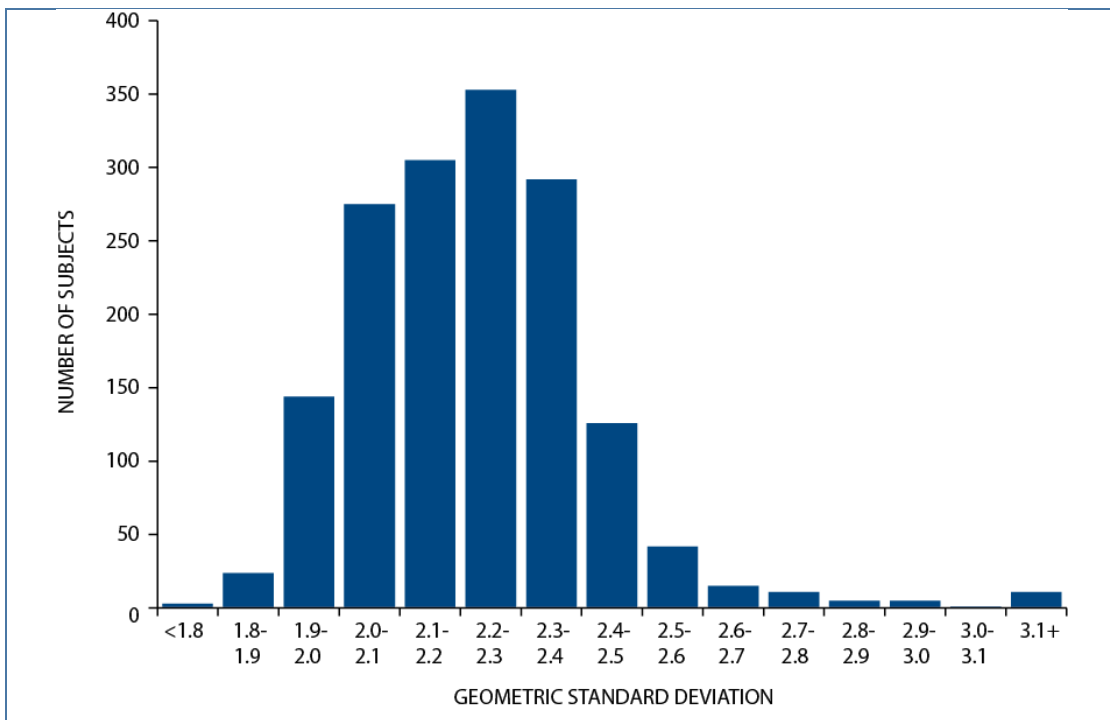


Figure B-IV. Distributions of the geometric standard deviation (GSD) of the estimates of individual thyroid dose due to ¹³¹I for the subjects of the case-control study (adapted from [D9])



E. Summary

B116. A summary of the uncertainties in the estimation of absorbed dose to organs is given in table B11 for external exposure, table B12 for internal exposure to radon and its progeny, and table B13 for internal exposure to other radionuclides. To enable a comparison of dose uncertainties in tabular form, all reported uncertainties in specific studies (with the exception of table B12) were converted to a 95% uncertainty factor, assuming an underlying log-normal distribution. For example, where uncertainties are reported as a geometric standard deviation (GSD), the 95% uncertainty factor (UF_{95}) is calculated as

$$UF_{95} = GSD^{1.96} \quad (\text{B.1})$$

In the case where uncertainties are reported as a coefficient of variation (CV), the 95% uncertainty factor is calculated as

$$UF_{95} = \exp\left[1.96\sqrt{\ln(1+CV^2)}\right] \quad (\text{B.2})$$

For occupational exposures based on recorded doses, the recorded dose is divided by a bias correction factor to obtain an estimate of the absorbed dose to a specific organ. The 95% uncertainty factor or the bias correction factor represents systematic uncertainty that is applied to the correction of each individual's recorded dose. Additional uncertainty associated with the inter-individual variability of true dose is assumed to be associated with 100% assignment error. The uncertainty associated with inter-individual variability of true dose in occupational exposures is only quantified in the study of Hanford workers [G7, G8]. Among the studies of external exposure reviewed, only Pierce et al. [P6] make an explicit distinction between the amount of total uncertainty that is composed of assignment error and the amount of total uncertainty that is classical.

B117. For the studies on internal exposure (table B13), the 95% uncertainty factor refers to the uncertainty associated with dose estimation for specific organs of particular or representative individuals. The uncertainty factors for estimation of internal exposure (which range from 2.21 to 66.3) are markedly higher than the uncertainty factors for external exposure given in table B11 (which range from 1.07 to 2.61). Among the studies on internal exposure, only the study by Li et al. [L14] made an explicit distinction between the amount of total uncertainty that is shared and unshared assignment error and the amount that is classical.

B118. For the radon exposure studies summarized in table B12, all studies that address exposure uncertainties use a form of a regression model to impute an expected value of a true time-weighted average radon exposure for groups of individuals occupying the same mine or residential dwelling, respectively, conditioned on information obtained from measurements and data about occupation or residence history of study participants. This imputed expected value of a true time-weighted average radon exposure is used as a surrogate for observed or measured values of time-weighted averaged exposure assigned to the individual. All remaining uncertainty is associated with inter-individual variability of true exposure rates, and thus the remaining uncertainty is assumed to be composed of assignment error. Uncertainty associated with the imputed true time-weighted average value of radon exposure varies as a function of the number of measurements and other information available for a given mine or dwelling, and with the data available about the working or residence history of each study participant.

Table B11. Epidemiological studies of external exposure that discuss uncertainties

Name of study	Size of uncertainty		Accounts for		
	Bias correction factor ^a	95% uncertainty factor ^b	systematic error?	assignment error?	classical error?
DS02					
Kaul et al. 2005 [K4] ^{c, d}	n/a	Hiroshima 1.6–2.25 Nagasaki 1.71–2.33 ⁱ	Yes - Hiroshima 1.3 Nagasaki 1.28	Total random ^e - Hiroshima 1.48–2.17 Nagasaki 1.61–2.26	
Preston et al. 2007 [P14] ^{c, f}	n/a	1.95	No	No	Yes
Pierce et al. 2008 [P6] ^{c, f}	n/a	2.28	No	95% uncertainty factor Assignment error: 1.47 Classical error: 2.13	
OCCUPATIONAL EXPOSURES					
Hanford workers					
Gilbert 1998 [G8]			Yes	Yes	No
Red bone marrow ^d	1.40–1.75	1.3–1.9 ^g		1.4–1.9 ^h	
Lung ^j	1.06–1.33	1.3–1.9 ^g		1.2–1.6 ^h	
15-country study					
Thierry-Chef et al. 2007 [T2]			Yes	Yes	No
Red bone marrow ^k	1.19–2.31	1.19–1.72 ^g			
Lung ^k	1.00–1.93	1.17–1.41 ^g			
Colon ^k	1.06–2.05	1.07–1.99 ^g			
ORNL workers					
Stayner et al. 2007 [S25] (specific organs not given) ^j	1.14–2.05	1.60–2.46 ^g	Yes	Yes	No

Name of study	Size of uncertainty		Accounts for		
	Bias correction factor ^a	95% uncertainty factor ^b	systematic error?	assignment error?	classical error?
MEDICAL COHORTS					
Israeli tinea capitis					
Schafer et al. 2001 [S5] ⁱ			No	Yes	No
Within-person variation of true dose	n/a	1.40			
Between-person variation of true dose	n/a	2.61			
Differences between prescribed and actual skin exposure	n/a	1.34			
Lubin et al. 2004 [L29] ⁱ			No	Yes	No
Within-person variation of true dose	n/a	1.40			
Between-person variation of true dose	n/a	2.61			
Differences between prescribed and actual skin exposure	n/a	1.63			

^a Bias correction factor is divided into recorded dose to estimate absorbed dose to a specific organ.

^b Ratio of 97.5th percentile to the 50th percentile.

^c 95% uncertainty factors derived from coefficient of variation (%), assuming a log-normal distribution.

^d Total marrow dose for representative individuals, for both Hiroshima and Nagasaki.

^e Assignment vs. classical errors are not specifically identified within the general uncertainty category designated as random uncertainty.

^f Hiroshima and Nagasaki bombing survivors are assigned the same dose uncertainty.

^g Systematic uncertainty about a central estimate (geometric mean) of the bias correction factor.

^h 95% uncertainty factors that account for random inter-individual variability of true dose.

ⁱ Total systematic and total random uncertainty for a representative individual located at 1,500 m from the hypocentre.

^j Bias correction factor and its uncertainties are dependent on the time period of exposure.

^k Bias correction factor and its uncertainties are dependent on the specific facility and the time period of exposure.

^l Classical error assumed to be inconsequential.

Table B12. Epidemiological studies of radon exposures that discuss uncertainties

<i>Name of study</i>	<i>Remarks</i>
MINER COHORTS	
Colorado Plateau	
Stram et al. 1999 [S31]	<p>Typical variability of measurements (CV = 50%) within a mine-year</p> <p>Uncertainty about imputed average radon exposure for a given mine-year varies considerably depending on the number of measurements available in the same and nearby mines for the same and other mine-years</p> <p>Imputation of monthly average values of radon exposure for each miner assumes all remaining uncertainty is 100% assignment error</p>
RESIDENTIAL COHORTS	
South-west England	
Darby et al. 1998 [D1]	The mean time-weighted average radon concentrations, adjusted for uncertainties, is used as the expected value of the true time-weighted average radon concentration given the observed value, conditional on each subject's residence history. All remaining uncertainty is assumed to be 100% assignment error
European collaborative study	
Darby et al. 2006 [D3]	To correct for biases caused by assignment and classical error, it was assumed that the "true" radon concentrations had a log-normal distribution and that the variability of repeated measurements was log-normally distributed about the true radon concentration for each building. Corrected time-weighted average concentrations were substituted for observed values for each subject, assuming all remaining uncertainty was 100% assignment error
Gansu Province, China	
Wang et al. 2002 [W5] and Lubin et al. 2005 [L31]	<p>The estimate of uncertainties in adjusted mean radon concentration was expressed as GSD equal to 1.5</p> <p>All remaining uncertainty assumed to be 100% assignment error once corrected mean radon concentrations were assigned to each subject, conditional on dwelling type, location, and residence history</p>
Sweden	
Lagarde et al. 1997 [L1]	<p>Simulated "true" and corresponding "estimated" exposures were modelled and showed CV of 53% representing the combined error from radon measurements and extrapolation to a long-term average concentration in homes</p> <p>Once the adjusted expected value of a time-weighted average exposure is obtained for each study participant, all remaining uncertainty is assumed to be 100% assignment error, although additional sources of uncertainty due to placement of detectors and the presence of errors in addresses were not addressed</p>

Table B13. Epidemiological studies of internal exposure that discuss uncertainties

Name of study	Size of uncertainty		Accounts for		
	Bias correction factor ^a	95% uncertainty factor ^b	systematic error?	assignment error?	classical error?
HANFORD					
Davis et al. 2004 [D6] and Kopecky et al. 2004 [K8]	n/a	2.39–24.5 ^c	No	All uncertainty assumed to be 100% assignment	
WEAPONS FALLOUT STUDIES					
Nevada Test Site					
Simon et al. 2006 [S20] and Lyon et al. 2006 [L34]	n/a	2.21–66.3 ^d	No	All uncertainty in [L34] assumed to be 100% assignment	
Li et al. 2007 [L14]	n/a	Total individual dose uncertainty same as in [S20]	No	Assumed 20–70% of total uncertainty was shared assignment error ^e	Assumed 30–50% of total uncertainty was classical ^e
CHERNOBYL ACCIDENT					
Kopecky et al. 2006 [K10] and Stepanenko et al. 2004 [S28]	n/a	8.6–14.4 ^f	No	All uncertainty in [K10] assumed to be 100% classical	
Gavrilin et al. 2004 [G1]			No	No	No
Milk consumption rate relatively well known	n/a	4.69–7.52 ^g			
Milk consumption unknown	n/a	6.03–9.18 ^h			
Drozdovitch et al. 2010 [D9]	n/a	2.83–13.0 ⁱ	No	No	No

^a Bias correction factor is divided into recorded dose to estimate absorbed dose to a specific organ.

^b Ratio of 97.5th percentile to the 50th percentile.

^c Obtained from individual dose GSDs ranging from 1.56–5.42.

^d Obtained from individual dose GSDs ranging from 1.5–8.5.

^e The degree of shared assignment versus classical measurement error depends on location and individual diet.

^f Uncertainties characteristic of reference individuals, depending on diet, milk source, and duration of ¹³¹I uptake.

^g Obtained from individual dose GSDs ranging from 2.2–2.8.

^h Obtained from individual dose GSDs ranging from 2.5–3.1.

ⁱ Obtained from individual dose GSDs ranging from 1.7–3.7.

III. UNCERTAINTIES IN RISK ASSESSMENT

A. Impact of uncertainty in health effect information on risk estimates and statistical power of epidemiological studies

1. Impact of uncertainty in health effect information on risk estimates

B119. Section I summarizes four types of uncertainty in health effect information, namely, selection bias, information bias, confounding and changes in information over time. These uncertainties may lead to systematic errors in the estimates of risks from radiation exposure and/or affect the precision of these risk estimates. Section I provides examples of how each of these types of uncertainty may affect the risk estimates.

B120. As mentioned in annex A (section I.D) of the UNSCEAR 2006 Report [U12], statistical methods have been developed to deal with multiple sources of bias, such as those listed above (for example, [G16]). However, concerns have been raised about the methodological basis for such approaches (see discussion in [G16]). To date, these methods have been used infrequently in epidemiological analyses.

2. Statistical power and aggregation of epidemiological studies

B121. Low statistical power, associated with studies of small sample size and/or low radiation doses, typically will result in non-significant results whether or not there is a true underlying association between radiation dose and the disease of interest. Such a finding, in isolation, has very little informational value, since the same result is to be expected under the null hypothesis of no association or the alternative hypothesis of a positive association. However, the statistical inference process, in order to allow for the possibility of a statistically significant finding under the alternative hypothesis, requires the possibility of an occasional statistically significant finding when there is no association between exposure and disease occurrence as the price of being able to detect a true association. At the 5% significance level, for example, over the long term it can be expected that one in twenty well-conducted studies will reject the null hypothesis, regardless of whether or not there is a true underlying association. Moreover, if a study of low statistical power results in a significant finding, then by definition the point estimate of risk likely will be exaggerated [L3]. In such cases the confidence intervals on the risk estimate are likely to be very wide (although by definition the limits will not include zero). Thus, the body of evidence regarding radiation-related risk relies heavily on a combination of studies of high statistical power and replications of study findings in different exposed populations.

B122. Aggregating findings from different studies that address the same topic increase the statistical power and ought to give more precise estimates of risk. Furthermore, as described below, this approach

may provide insights into how the risks of radiation exposure vary according to possible modifying factors such as age, time and smoking status. However, care is required to ensure that the process of data aggregation does not lead to invalid findings.

B123. *Meta-analyses of published findings.* An approach that is sometimes adopted involves combining published findings from several studies. For example, estimates of relative risks or absolute rates for specific exposure categories or estimated linear or log-linear trends in relative risks or absolute rates with some measure of radiation exposure—together with the corresponding confidence intervals—may have been cited in the publications giving the results from these studies. It may then be possible for each exposure category to calculate average values of the risks, weighted according to the reciprocals of the corresponding variances. Alternatively, an overall estimate of the trend in risk could be calculated, either as a weighted average of the estimated trends from each study or via weighted regression of the average risks for each exposure category. For example, in examining the risk of lung cancer following exposure to radon in homes, Lubin and Boice [L27] fitted—for each of eight studies—a weighted linear regression model to the published estimates of the logarithm of the relative risk for each exposure category. A weighted average of the estimated trends from each study was then calculated.

B124. In principle, conducting a meta-analysis is fairly straightforward, provided that the necessary information has been published. However, this condition is not always met, because, for example, different exposure categories might be used in different studies, the measures of risk used might vary or the confidence intervals or standard errors might not be given for all of the relevant quantities. A further concern is whether the variations between studies, either in the control for confounding or in modifying factors that influence the risks from radiation exposure, could lead to incompatibility in the results across the studies. A statistical approach that is often used in meta-analyses is a “random-effects” model. Unlike a “fixed-effects” model, where the underlying risk is assumed to be constant across studies, the random-effects model assumes that the underlying study-specific risks vary between studies according to, say, a normal or a log-normal distribution. In this instance, it is possible to calculate an overall risk estimate and confidence interval using an approach that takes account not only of uncertainties within the studies, but also between the studies. Lubin and Boice [L27] describe the application of this technique to the aforementioned analysis of radon exposure and lung cancer. Typically, the confidence interval for the overall risk estimate is wider under a random-effects model than under a fixed-effects model, particularly if there is strong evidence of heterogeneity in the findings between the studies.

B125. While the random-effects model provides a statistical means of allowing for differences between studies, care is required in its use. Without a clear understanding as to why risk estimates might vary between studies, the computation of an overall estimate may have little meaning. Furthermore, if it is clear from the description of the individual studies that some studies were much better conducted and/or made better allowance for confounding than other studies, then it is questionable as to whether the findings from all of these studies should be combined. Rather, there would be a case for combining those studies that are judged—based on criteria defined a priori—to be methodologically superior.

B126. If the impact of modifying factors could differ between studies, then it would be better to combine studies with similar values for these factors, rather than to combine all studies. For example, it would be more sensible—at least in the first instance—to look at studies of childhood exposure separately from those of exposure in adulthood. A more sophisticated approach is taking into account differences in modifying factors by scaling the results to a comparable quantity before combining them in a meta-analysis (see, e.g. [J5]).

B127. *Combined analyses using original data.* On occasion, investigators who have been studying the same topic in, say, different countries or regions may collaborate in a combined analysis of their individual-level data. For example, combined analyses of radon exposure in homes and lung cancer have been conducted in Europe [D2, D3], North America [K14, K15] and China [L30]; these analyses are discussed further in appendix D. This approach has several advantages over meta-analyses of published findings:

(a) By bringing together their data, the investigators ought to be able to recognize any differences in the way in which the data had been collected or in which exposures had been assessed. This ought to inform decisions about how the data might be combined. For example, data from cohort studies and those from case–control studies might be pooled separately in the first instance, because of the differing potential for bias between study designs. Alternatively, analyses may be restricted to persons with a specific form of radiation exposure (for example, by excluding persons with high-LET irradiation in an analysis of low-LET irradiation). More generally, since a combined analysis is easier to perform if the individual studies are of a similar design, a prospective approach whereby studies are constructed around a common protocol may be more advantageous than a retrospective pooling exercise. This approach was advocated for an international study of cohorts of occupationally-exposed workers in the nuclear industry [C1] and for case–control studies of lung cancer and residential radon exposure [S2];

(b) In contrast to meta-analyses, it is possible in a combined analysis of original data to use the same approach to analyse all of the data; for example, in using common exposure categories and in applying the same form of adjustment for confounding factors. This should enhance the compatibility of the findings across studies. In the case of radon exposure in homes and lung cancer, a key advantage of the combined analyses was the ability to adjust for smoking (the leading cause of lung cancer) in a uniform way across studies, whereas the published findings from individual studies had used differing adjustments. It is notable that whereas the earlier meta-analysis of Lubin and Boice [L27] found statistically significant heterogeneity between studies in the radon-related lung cancer risk, this was not the case for the combined analyses in Europe [D2, D3], North America [K14, K15] and China [L30] which used individual-level data;

(c) In general, the published findings are not sufficiently detailed to allow for a full examination in a meta-analysis of how risks might be modified by factors such as age, time and smoking. In contrast, this topic can be addressed using the original data from the studies. For example, Darby et al. [D2, D3] were able to look at how radon-related risks varied between continuing smokers, ex-smokers and never-smokers. Furthermore, the sensitivity of the findings, for example, to the form of adjustment made for confounding or the exposure metric used, may be addressed using the original data but not through the published findings.

B128. Thus, in addition to increasing statistical precision, combined analyses may be able to resolve apparently conflicting results from different studies. By aligning the studies in a parallel fashion and analysing them using a common approach, it may be possible to explain such differences on the basis of, for example, different categorizations of the exposure data. Although there is a greater opportunity to address this topic in combined analyses of original data than in meta-analyses, it is important in both types of analysis to consider the compatibility of data from different studies before combining findings across studies. If there is statistically significant heterogeneity in estimates of risk between studies, then it is not sufficient simply to report findings based on a random-effects model; rather, careful examination is required of the possible reasons for this heterogeneity and, based on this, then to decide whether it is sensible to pool all or even part of the data.

B129. Another difficulty that may affect attempts to pool findings across studies is publication bias, that is, the selective reporting of results depending on whether the outcome was judged to be positive or negative. However, this tends to arise for small or ad hoc studies, which would carry less weight in a pooled analysis if a number of large studies with clear, predefined objectives were included. Furthermore, in contrast to meta-analyses, it is possible in combined analyses to address a wider range of questions than were addressed in the original publications, thereby reducing the impact of any selective reporting within studies.

B. Impact of exposure uncertainty on risk estimates

B130. The impact of exposure uncertainty on risk estimates was considered briefly in the UNSCEAR 2006 Report (annex A, section I.D) [U12]. Key distinctions were made between the effect of random errors and systematic errors, and whether or not these errors were differential, that is, related to the disease outcome.

B131. Systematic errors in exposure assessment could arise, for example, from incorrect calibration of a dosimetry badge reader or from incorrect assumptions or coefficients in an algorithm to reconstruct doses [U12]. The impact of systematic errors depends on the particular context and it is not possible to make a general statement on how such errors would bias dose–response relationships. There are some exceptions to this. For example, if all doses had been underestimated by a given fixed factor and a linear dose response had been used to model the relationship between disease risk and dose, then the effect of these systematic dose errors would be to overestimate the slope of the dose response by the same factor.

B132. In practice, the magnitude of systematic errors—expressed either as a proportion or an absolute value—may vary according to the level of dose, possibly in a complex fashion. Consequently, the impact of these errors would need to be evaluated on a case-by-case basis. Generally this involves sensitivity analyses, in which different assumptions are made about the form and magnitude of the systematic errors. For example, in analysing the United Kingdom National Registry for Radiation Workers, Muirhead et al. [M21, M22] explored the impact of dose recording practices by conducting sensitivity analyses that excluded some or all of the correction factors applied to recorded doses. Here—and in many other examples where investigations of systematic errors indicated little impact on the dose–response analyses—no adjustments were made to estimates of risks from radiation exposure or their confidence intervals to reflect the possible impact of systematic errors. This contrasts with the situation regarding random errors where—as will be described below—more sophisticated approaches have been used to quantify the impact of these errors on dose–response analyses. However, in some analyses of nuclear industry workers, including of workers at Oak Ridge National Laboratory [S25] and at Hanford [G8] in the United States, account was taken not only of correction factors to allow for differences between recorded doses and organ doses, but also for the uncertainty in these correction factors [T2]. In essence, these analyses took account of shared errors that arose from applying the same correction factors to doses for groups of people.

B133. Differential measurement errors, such as when greater efforts are made to determine the dose for persons with the disease of interest than for persons without it, can introduce serious and unpredictable bias. Whilst it may be possible to assess whether risk estimates have been underestimated—or overestimated—as a consequence of differential errors, quantifying the impact on dose–response analyses is almost impossible without a detailed understanding of the structure and magnitude of these errors. Avoiding such errors is a major concern in study design.

B134. Non-differential random measurement errors, which are not influenced by disease status, affect virtually all quantitative epidemiological studies to some degree and can introduce bias. However, such bias can often be addressed and corrected in the analysis, based on information about the statistical structure of the errors. These errors form the focus of much of the research undertaken into the impact of exposure uncertainty on risk estimates, as described below.

B135. In epidemiology, measurement errors of true exposure will generally result in a bias of a dose–response function towards the null [C7, H18, S6, U12]. Thus, what appears to be a source of random measurement error will actually lead to a systematic bias towards overestimation of the statistical power of an epidemiological study and an underestimation of risk [C7, H16, H17, H18, S6]. An example of measurement error occurs when individual dosimeter readings are used to estimate individual doses to occupationally-exposed workers over a certain period; the error reflects a (random) lack of precision in each of the individual measuring devices. Here, assuming a multiplicative error model for dose and a linear dose–response model, the effect of error in the estimated dose is to flatten the fitted dose response gradually with increasing dose, creating an apparent negative curvature and a bias toward reduced slope [C7]. Similarly, if the true dose–response relationship were linear–quadratic with positive curvature, the fitted curve might show a reduced, zero, or even negative curvature. Another example is with the reconstructed gamma-ray doses from the atomic bombings of Hiroshima and Nagasaki, which were affected by uncertainties about the locations of individual survivors and the shielding provided to them by buildings and other structures. In addition to inducing bias, classical error reduces statistical power, but bias correction typically does not involve a further decrease in statistical power [S6].

B136. Virtually all epidemiological studies of the radiation dose response for cancer or other disease outcomes rely on individual dose estimates derived largely from idealized dosimetry systems that were based on few, if any, direct measurements of the relevant doses. Even in nuclear worker studies for which there might be individual film badge readings, numerous models and assumptions must be made to develop the (organ) dose estimates needed for risk assessment. In studies of environmental exposures (including, for example, survivors of the atomic bombings or populations exposed as a result of accidental releases of radioactive material) there are often few, and in many cases no, measurements of individual dose.

B137. Traditionally dosimetry systems have provided point estimates of the dose for individual (or representative individual) members of the population of interest. However, as awareness of the potential effects of uncertainty in individual doses (including biased risk estimates and underestimation of the uncertainty in these estimates) has increased, efforts are being made to provide more information on the magnitude and nature of the uncertainty in individual dose estimates. When information about the uncertainty of individual dose (component) estimates is available, it comes in many forms. Some examples are:

- (a) A statement that estimated doses have an uncertainty of x %;
- (b) An uncertainty associated with each individual dose (component);
- (c) A set of realizations of dose (component) estimates for each person based on a complex dosimetry system; uncertainties associated with measurements, model parameters, individual characteristics (such as age or residence location) and other factors affecting dose are described in terms of (generally subjective) distributions; and dose realizations are determined using a Monte Carlo-based system to determine specific values for the parameters associated with an individual dose (component).

B138. Methods for quantifying the impact on risk estimates of exposure uncertainties will now be described in more detail, together with summaries of radiation epidemiology studies in which these methods have been applied.

1. Regression calibration

B139. The basic idea of regression calibration is as follows. If the true values of an explanatory variable (referred to here as “dose”) are unknown, then these values are replaced in a regression analysis by the expected values of dose given the observed values [C7]. In other words, “observed dose” is replaced in the regression analysis by “ $E(\text{true dose}|\text{observed dose})$ ”. If the expected value of the dependent variable in the regression analysis (in this context, a disease rate or an indicator of whether or not an individual has the disease under investigation) were to vary as a linear function of “true dose”, then this linear relationship would be preserved—with the same slope—if $E(\text{true dose}|\text{observed dose})$ were used instead. In contrast, if the relationship based on “true dose” were non-linear, then this relationship would not be preserved if $E(\text{true dose}|\text{observed dose})$ were substituted into the regression analysis. However, in practice this approach appears to work well in a range of non-linear regression models [C7].

B140. A complication is that $E(\text{true dose}|\text{observed dose})$ may not be known exactly. For additive assignment errors as defined in appendix A, the situation is simple, because in this situation $E(\text{true dose}|\text{assigned dose})$ is equal to the “assigned dose”. Thus, the regression analysis would proceed based on the observed doses. However, for measurement errors, the calculation of $E(\text{true dose}|\text{measured dose})$ would require knowledge of the distributions of the measurement error and of true dose. If, for example, these latter two variables are distributed independently as normal, with variances σ_c^2 and σ^2 respectively, and if the measurement errors were unshared, then:

$$E(\text{true dose}|\text{measured dose}) = [\sigma^2 \times \text{measured dose} + \sigma_c^2 \times E(\text{true dose})] / (\sigma_c^2 + \sigma^2) \quad (\text{B.3})$$

which is a weighted average of the measured dose and the expected true dose. Thus, in this situation, measured dose is replaced by a value that is closer to the expected value for true dose. The spread in the values of $E(\text{true dose}|\text{measured dose})$ is narrower than that in measured dose, by an amount that depends on the ratio of the variance of the measurement errors to the variance of the true doses. If this ratio were much smaller than 1, then the values used in the regression analysis would be similar to the measured doses. Conversely, if this ratio were larger than 1, indicating that much of the variation in the measured doses is due to classical measurement errors, then the values used in the regression analysis would be “shrunk” towards $E(\text{true dose})$. For linear regression under the assumptions outlined above, correction for unshared non-differential classical measurement errors would increase the slope of the dose–response curve by a factor of $1 + \sigma_c^2 / \sigma^2$, which corresponds to the ratio of the variance of measured dose to that of true dose. In order to implement this approach, estimates of these two variances are required.

B141. In practice, the situation may be more complicated. First, if there were assignment errors, but they were multiplicative rather than additive, that is if

$$\log(\text{true dose}) = \log(\text{assigned dose}) + \text{individual peculiarity}, \quad (\text{B.4})$$

then $E(\text{true dose}|\text{assigned dose})$ would not be equal to “assigned dose”. As shown by Schafer and Gilbert [S6], multiplicative assignment errors would lead to an overestimation of the slope of a linear dose–response model and would overstate the degree of curvature in a linear–quadratic dose–response

model, unless account were taken of these errors. Secondly, if there were multiplicative rather than additive classical measurement errors, that is if

$$\log(\text{measured dose}) = \log(\text{true dose}) + \text{measurement error}, \quad (\text{B.5})$$

then $E(\text{true dose}|\text{measured dose})$ could not be calculated using the simple expression given in the preceding paragraph. Unless these errors are taken into account, they may induce downward curvature in the observed dose–response relationship and understate the evidence for any upward curvature [S6]. Thirdly, if the errors were of a more complex form—for example, containing a mixture of assignment and classical measurement errors, either or both of which may be multiplicative, and possibly including shared errors—then it would not be possible to make general statements about the impact of these errors and the calculation of $E(\text{true dose}|\text{observed dose})$ might be more difficult than in the preceding situations.

B142. In situations where $E(\text{true dose}|\text{observed dose})$ cannot be calculated analytically, an alternative is to use simulation. This has the advantage that shared errors can be handled automatically as part of the simulation process. However, it is important to be aware of the importance of specifying the relevant probability density functions correctly. In particular, Schafer and Gilbert [S6] highlighted the potential for confusion between the population distribution of “true dose given observed dose” and the hypothetical distribution of “true dose given observed dose” for a particular individual. Otherwise, shared errors might not be handled correctly, for example. Furthermore, the parameters used to specify these distributions are themselves unknown and the use of estimates rather than the true values of these parameters may have some impact on the effectiveness of regression calibration [S6], although the magnitude of this impact would vary according to the situation under study.

B143. In some instances, regression calibration implies the same—not only in terms of best estimates of the risks from radiation exposure, but also in terms of measures of uncertainty such as confidence intervals—as an approach based on the probability density function for the disease outcomes conditional on the observed doses. For example, through the use of maximum likelihood under a frequentist approach or combining the likelihood function with a prior distribution under a Bayesian approach. This equality will hold if the expected value of the dependent variable (that is, a disease rate or an indicator of whether or not an individual has the disease under investigation) varies as a linear function of “true dose”. However, if this relationship is non-linear, then regression calibration and methods based on the likelihood function may give different answers. Consequently, other statistical methods have been developed to deal with such situations. These methods and their application in radiation epidemiology are described in subsection 2 below.

B144. The principal applications of regression calibration in radiation epidemiology will now be described.

B145. *Life Span Study*. Recent analyses of the Life Span Study (LSS) of Japanese atomic bombing survivors (e.g. [P14]) have routinely incorporated corrections for additive measurement errors using regression calibration. The foundation for these corrections was an analysis by Jablon [J1], in which he concluded that the errors in the dosimetry were most likely to be distributed log-normally, with a coefficient of variation of about 30%. Pierce et al. [P4] examined the impact of such errors on analyses of cancer in the LSS, based on linear dose–response models. Using regression calibration, Pierce et al. [P4] concluded that risk estimates would be increased by 6% to 17%, once adjustment was made for measurement errors with a coefficient of variation in the range 30% to 40%. However, the increase was only 4% to 11% if, as in some analyses of LSS, survivors with dose estimates above 4 Gy were excluded from the analysis. Pierce et al. [P4] did not quantify the impact of these errors on the width of confidence intervals. A later analysis by Pierce et al. [P6] considered both classical and assignment

error models. They presented formulae for $E(\text{true dose}|\text{observed dose})$, based on log-normally distributed classical and assignment errors and applied this approach to data on solid cancer mortality in the LSS. Having excluded survivors with dose estimates above 4 Gy, allowing for measurement errors with GSDs in the range 35% to 40% increased estimates of the risk per unit dose by 12% to 14%. Additional adjustment for assignment errors had little impact on the risk estimate. Pierce et al. [P6] also found that adjustment for classical errors increased the evidence for curvature in the solid cancer dose–response, such that the risk per unit dose increased with increasing dose. Again the impact of these adjustments on the precision of risk estimates was not quantified.

B146. *Medical exposures.* Lubin et al. [L29] analysed data on thyroid neoplasms in a cohort of 10,834 Israeli patients who were treated with X-rays for tinea capitis, together with unexposed comparison groups. In so doing, they took account of uncertainties in dose estimates that arose from: (a) modelling of phantom data and extrapolating this to all ages of exposure; (b) applying the prediction model for a given age, filtration and beam exposure; and (c) adjusting for missing patient information. First, the relationship between dose to the thyroid and various predictor variables was modelled. Secondly, because the patient data were complete, missing values of the predictor variables were imputed based on the data that were available. Having estimated the expected values for true individual dose given the predictor variables, these expected values were then inserted into the regression model linking radiation dose to the risk of thyroid neoplasms. The expected true doses were generally larger than the original doses, particularly for those persons who received only one treatment. In contrast, for persons with two or more treatments, the ratio of original dose to expected true dose was generally less than one, because of the adjustments made for age of exposure and the failure of the original doses to account for ages at second or later treatments. The estimated excess relative risk (ERR) of thyroid cancer per unit absorbed dose, based on a linear dose–response model, was slightly smaller (by 12%) based on the expected true doses, compared with the original doses, reflecting the tendency for the former doses to be greater than the latter doses. The impact of using expected true doses on the modifying effects on the ERR per unit dose of factors such as age at exposure and time since exposure was minimal.

B147. In this study, there were both shared classical measurement errors, associated with the estimation of parameters in the prediction equation, and assignment errors, resulting from random deviations between the predicted and true doses. Although the confidence intervals for the ERR per unit dose calculated by Lubin et al. [L29] based on the expected true doses were similar to those based on the true doses, they cautioned that regression calibration would not have accounted for the variability arising from measurement errors. However, an earlier analysis of these data using a likelihood-based approach that took account of measurement errors [S5] suggested that the upper and lower confidence limits for the ERR per unit dose should be multiplied and divided by a factor of about 1.06, respectively; this means that the impact on the confidence interval should be small.

B148. *Residential radon exposure and lung cancer.* In a combined analysis of case–control data from European studies of radon exposure in homes and lung cancer, Darby et al. [D2, D3] calculated risk estimates and associated confidence intervals that were adjusted for classical and assignment errors. Classical errors are particularly important in studies of this topic, because measurements made in the same dwelling in different years show considerable variability, with a coefficient of variation that may be of the order of 40% [D2]. Thus, representing the long-term average radon concentration in a dwelling by a measurement made in a single year is a major source of uncertainty. This uncertainty is likely to be due not only to the measurement process, but also reflects variation in the true radon concentration arising from year-on-year changes in weather, changes in the habits of the occupants of the dwelling and structural changes to the dwelling. In addition to classical errors, assignment errors arose through the need to input values for dwellings where no measurement of radon levels could be made. In these situations, the arithmetic mean of the concentrations measured for controls was used,

either for all of the controls in the study in question or—for those studies where the mean square error of prediction was improved by more than 10%—by using solely data for those controls within the same area [D2].

B149. In order to allow for classical measurement errors, Darby et al. [D2, D3] assumed that within each geographical district, the “true” (i.e. long-term average) radon concentration followed a log-normal distribution. It was also assumed that the variability associated with repeated measurements of radon concentrations in the same dwelling followed a log-normal distribution about the true concentration for that dwelling. For those countries where repeated radon measurements had been made, these data were used to estimate a country-specific coefficient of variation for the classical measurement errors. For the remaining countries, a coefficient of 40% was assumed, based on the median of the variances for the logarithm of measured concentrations for those countries where data were available. Having used regression calibration to replace the measured radon concentrations by their expected values, the mean radon concentration for the lung cancer cases fell from 104 Bq m⁻³ to 90 Bq m⁻³, whilst the corresponding values for the controls were 97 Bq m⁻³ and 86 Bq m⁻³, respectively. As expected, regression calibration “shrank” the range of concentrations: for those persons (cases and controls combined) associated a measured concentration of more than 800 Bq m⁻³, the mean measured value was 1,204 Bq m⁻³, whereas the mean corrected value was 678 Bq m⁻³. Similarly, for those persons (cases and controls combined) associated with a measured concentration of less than 25 Bq m⁻³, the mean measured value was 17 Bq m⁻³, whereas the mean corrected value was 21 Bq m⁻³.

B150. Based on a linear model, the excess relative risk was estimated to be 0.084 (95% CI: 0.03, 0.16) for 100 Bq m⁻³ without adjustment for classical measurement errors and 0.16 (95% CI: 0.05, 0.30) when adjustment was made for these errors using regression calibration [D2]. Adjustment for these errors using a more sophisticated approach, namely Monte Carlo integration of the likelihood gave a very similar result to that from regression calibration, specifically an ERR of 0.16 (95% CI: 0.05, 0.31) for 100 Bq m⁻³. Analyses of effect modification by sex, age, smoking status and histological type of lung cancer gave similar results with and without correction for classical measurement errors, although the correction gave a proportionately greater impact on the ERR estimate for ex-smokers and lifelong non-smokers than on the corresponding estimate for current smokers. Nevertheless, there was no statistically significant heterogeneity in the ERR between smoking categories, either with or without adjustment for measurement errors. Furthermore, the ERR estimates and confidence intervals from the analyses of effect modification were similar using the regression calibration and integrated likelihood approaches. In a related methodological paper, Fearn et al. [F2] suggested that regression calibration ought to perform very well in adjusting for measurement errors in studies of residential radon exposure and lung cancer and that more sophisticated approaches are not required.

B151. *Uranium miners.* Stram et al. [S31] analysed data on lung cancer among the United States Colorado Plateau uranium miners, with corrections for errors in the measurement of radon exposures. This involved the development of a multi-level model for the “true” average exposure rate (expressed in Working Levels, WL, of radon progeny) in a given year, mine, locality and district, combined with a multiplicative measurement error model that described the variability in measurements that were made of exposure rates, classified by year and mine. According to the fit of the multi-level model to the exposure rate measurements, the “true” average exposure rate decreased by about 11% per year over the period 1950–1969, which is of particular relevance to the miners in the study. For each mine and year in which at least one cohort member was exposed, the measured exposure rate was replaced in the epidemiological analysis by the expected value of this exposure rate, given all of the measurements made in that district.

B152. Adjustment for measurement errors provided a statistically significant improvement in the fit of models to these data. The estimated slope of a linear exposure–response model increased by about

60% and the standard error of the estimated slope was nearly doubled as a consequence of this adjustment. Both with and without adjustment of measurement errors, the data indicated a sub-multiplicative relationship for the joint effect of radon and smoking on the risk of lung cancer. Similar patterns in the modifying effects of time since exposure and age at exposure were seen with and without adjustment for measurement errors, although again the estimates and their standard errors were larger when this adjustment was made. There was less evidence for an inverse exposure rate (i.e. a higher risk per unit exposure at lower rather than higher exposure rates) with adjustment for measurement errors. This adjustment had little impact on the estimated risk per unit exposure at relatively low exposure rates (below 15 WL) but increased the corresponding estimate at higher exposure rates, to bring it closer to the value for lower exposure rates. This change was particularly pronounced when miners who started work prior to 1952—and whose early exposures are highly uncertain—were excluded from the analysis. However, it is unclear whether the lack of evidence for an exposure–rate effect in the restricted cohort is a reflection of low statistical power rather than of errors in the assessment of exposures before 1952.

B153. *Fallout from nuclear weapons testing.* Lyon et al. [L34] conducted a re-analysis of thyroid disease in a cohort of persons exposed to radioactive iodine in childhood as a consequence of nuclear weapons testing at the Nevada Test Site in the United States. This analysis included corrections to dose estimates and to information on disease classification. When fitting dose–response models, the authors used the arithmetic mean of the dose for each person, assuming a log-normal distribution for alternative realizations of that person's dose. Because a multiplicative rather than an additive error model was used, the arithmetic mean of the dose realizations was not equal to the output from the dosimetry model. Whilst the focus of this analysis was not on the use of regression calibration to allow for dose uncertainties, Lyon et al. commented on the impact of assuming, as here, that these uncertainties are purely due to assignment. They referred to an earlier methodological paper by Mallick et al. [M6] that analysed earlier data from this study accounting for a mixture of assignment and classical measurement errors. Mallick et al. showed that as the ratio of classical to assignment errors increases, the estimated ERR per unit dose increases, as do the length and upper end of the corresponding 95% confidence interval. For example, if 50% of the measurement errors are assumed to be classical and the remainder to be due to assignment, rather than all of the errors being due to assignment, the estimated ERR per unit dose for thyroiditis increases from 4.2 (95% CI: 1.4, 9.6) mGy⁻¹ to 7.2 (95% CI: 2.9, 14.9) mGy⁻¹.

2. Other methods

B154. *Generalization of regression calibration.* Reeves et al. [R1] develop a simple error model, originally suggested in [T6], that includes classical measurement error and assignment errors. The additive version of the model describes the true (X_t) and observed/surrogate (X_s) value as functions of an unobservable latent variable (\tilde{X}) with $X_t = \tilde{X} + e_t$ and $X_s = \tilde{X} + e_s$, where \tilde{X} , e_t and e_s are independent random variables with means μ , 0 and 0, and variances $\tilde{\sigma}^2$, σ_t^2 and σ_s^2 , respectively. If, as is often the case for radiation doses, the measurement uncertainty is assumed to be proportional to the magnitude of the true dose, then the error model can be written in terms of the logarithms of the latent variable and the true and surrogate doses: ($\tilde{Z} = \log(\tilde{X})$, $Z_t = \log(X_t)$, and $Z_s = \log(X_s)$). This model can be used to develop the likelihood for a linear regression model ($Y = \alpha_t + \beta_t X_t$) and, an approximate likelihood for the standard logistic ($\Pr(Y = 1 | X_t) = e^{\alpha_t + \beta_t X_t} / (1 + e^{\alpha_t + \beta_t X_t})$) regression model that depends on true dose–response parameters (α_t and β_t) and four parameters (which are referred to here as “nuisance parameters”) not directly related to the dose response (μ , $\tilde{\sigma}^2$, σ_s^2 , σ_t^2). The authors show that it is possible to obtain good estimates of the dose–response parameters and their uncertainties using

relatively simple methods that do not require difficult computations based on the full likelihood of all of the parameters.

B155. Fearn et al. [F2] extend the method developed by Reeves et al. [R1] for use with a linear odds model $\alpha(1 + \beta x) / (1 + \alpha(1 + \beta x))$. They compare the results of this generalized regression calibration approach to a more precise but computationally more demanding method involving Monte Carlo integration of the full likelihood (discussed below) in a pooled analysis of 13 European studies of the effects of residential radon exposures on lung cancer risks [D2, D3]. It was found that not only did the simpler regression calibration approach give virtually the same point estimates as the integrated likelihood method, but that the adjusted confidence intervals were also virtually identical for the two methods.

B156. Regression calibration as described in this document requires computation of the expected value of the true dose (X_t) conditional on the observed dose (X_s) and, possibly, other relevant information. Unless information about the distribution of the observed dose given the true dose, $f(X_s | X_t)$, is available from a validation study in which the distribution of true doses is approximately the same as in the study population, $f(X_t)$, the determination of $E(X_t | X_s)$ can be quite complicated. Pierce and Kellerer [P5] have proposed a relatively simple method for the estimation of $E(X_t | X_s)$ when it is reasonable to assume that the distribution of the observed dose given true dose, $f(X_s | X_t)$, is log-normal with a constant coefficient of variation and that the distribution of true doses is reasonably smooth. The method involves approximating the empirical density of the observed doses using a smooth function with at least two continuous derivatives and then using simple Laplace transformations [B1] to estimate correction factors that can be used to approximate $E(X_t | X_s)$.

B157. In addition to providing adjusted estimates of dose (and powers of dose) for use in simple regression calibration, Pierce and Kellerer [P5] extend their approach for use in situations in which the uncertainty in individual dose estimates arises because of a combination of classical measurement error and assignment error when one has information about both the coefficient of variation in the observed doses associated with classical error and that associated with assignment error. The computation of the adjustment factors to be applied to the observed doses is no more difficult when the dose uncertainty reflects a mixture of classical and assignment error than in the case in which the dose uncertainty arises solely due to classical error. As noted above, Pierce and Kellerer [P5] have used these methods to analyse the atomic bombing survivor data. Their results suggest that even fairly large dose uncertainties (coefficients of variation of 40% for classical error and 20% for assignment error) have a relatively small effect on estimates of cancer risk that are assumed linear with dose (increasing them by 10% to 15%), but tend to increase the evidence for upward curvature in the dose response for doses less than 2 Gy. It was also found that allowing for dose uncertainty has little impact on the precision of the estimates of cancer risk since the effect of the over-dispersion (see below) arising from this uncertainty is much smaller than the uncertainty inherent in the cancer data.

B158. As discussed thus far regression calibration involves determination of an expected value of the true dose given the observed dose and possibly other relevant information, and the use of this expected true dose in standard, often maximum-likelihood-based, risk analyses for the outcome of interest (y) with, possibly, some adjustment to allow for the uncertainty in the expected true dose. This is a relatively simple approximation to a full likelihood analysis. The likelihood of interest can be written as $f(y | X_t, z, \theta)$, where z are other factors that affect the risk of the outcome and θ is a set of unknown parameters. However, X_t is not known and in its place we have an observed surrogate, X_s . Assuming that the outcome is independent of X_s if X_t is known then the likelihood of interest is:

$$f(y, X_s | z, \theta) = \int f(y, X_s, X_t | z, \theta) dX_t \propto \int f(y | X_t, z, \theta) f(X_t | X_s) dX_t \quad (\text{B.6})$$

Since risk modelling generally requires some specification of the likelihood in terms of the true dose and since any form of regression calibration involves some characterization of $f(X_t | X_s)$, it is possible, at least in principle, to directly maximize this likelihood. This general form of regression calibration is discussed in detail by Carroll et al. [C7]. In practice, direct evaluation of the integral in the above expression is infeasible for all but the simplest problems. However for some problems the integral can be evaluated using Monte Carlo methods especially if conditioning can be used to reduce the problem to one involving only a single parameter.

B159. Regression calibration is an attractive method since after computing $E(X_t | X_s)$ (which can be challenging) the analyses generally proceed using standard methods with, possibly, some adjustment of the variance of the parameter estimates to allow for the additional uncertainty associated with the estimation of the expected true dose. Pierce and Kellerer [P5] argue that when dealing with analyses of rare events, such as cancer cases, the adjustment for this additional uncertainty will have little impact on inference unless it is large relative to the uncertainty that is inherent in the basic statistical model for the outcome. If a simple linear model is considered for (say) cancer incidence data of the form $y = \alpha + \beta X_t + \varepsilon$, where ε is an error term with variance σ_ε^2 determined by the nature of the data, the regression calibration model can be written as:

$$y = \alpha + \beta E(X_t | X_s) + \beta(X_t - E(X_t | X_s)) + \varepsilon = \alpha + \beta(E(X_t | X_s) + u) + \varepsilon \quad (\text{B.7})$$

where $u = \beta(X_t - E(X_t | X_s))$ is an unobserved random effect with variance $\sigma_u^2 = \beta^2 \text{var}(X_t | X_s)$, and $\text{ERR} = \beta/\alpha$. Thus the regression calibration model is said to be over-dispersed relative to the model in true dose since the error variance of the regression calibration model is $\sigma_\varepsilon^2 + \sigma_u^2$. While this over-dispersion will increase the variance of the estimate of the ERR ($= \beta/\alpha$) (or the other parameters), this effect will be small provided that $\sigma_u^2/\sigma_\varepsilon^2 \ll 1$. For data following a Poisson distribution $\sigma_u^2/\sigma_\varepsilon^2 = \beta^2 \text{var}(X_t | X_s) / (\alpha(1 + \text{ERR} X_t)) = \alpha \text{ERR}^2 \text{var}(X_t | X_s) / (1 + \text{ERR} X_t)$ and $\sigma_\varepsilon^2 = \alpha + \beta X_t$ will be much less than 1 even for relatively large dose errors, such as those seen in the LSS. Therefore in cancer risk analyses there is little need to adjust the variance estimates in regression calibration. However, in analyses of binomial outcomes, such as the proportion of chromosome aberrations in (say) 100 or 1,000 cells per subject, dose errors can lead to substantial over-dispersion, and adjustment of the variance using methods such as those given in [R1] is important.

B160. *Simulation-extrapolation (SIMEX) methods.* In 1994, Cook and Stefanski [C15] proposed a simple Monte Carlo-based method for estimating and reducing bias in regression estimates arising from measurement error. The method is easiest to describe for the case of normal, additive measurement error but is readily generalized to handle multiplicative or many other types of non-additive errors. It is also assumed that the variance of the measurement is known (or that an estimate is available). The observed data consist of the outcome of interest (Y_i) together with measures (surrogate) doses such that $X_{s,i} = X_{t,i} + u_i$ with u_i having a normal distribution with mean 0 and variance, and other variables, Z_i , that affect the risk. The dose-response model can be taken as $Y_i = f(X_{t,i}, Z_i | \beta, \theta)$ where β represents the dose-response parameters and θ are additional parameters. It is also assumed that we have some method, such as the maximum likelihood method, that can be used to provide estimates of β and θ given dose estimates and values of the other variables. The basic idea is that by adding fixed amounts of additional variability to the doses and then examining the relationship between the parameter estimates and the amount of additional variability in the doses, it is possible to obtain information that allows one to extrapolate to the situation in which there is no dose error. In particular, SIMEX uses simulation methods to examine how the parameter estimate changes as a function of an error variance inflation factor, $\xi \geq 0$, chosen such that measurement error variance is $\sigma_u^2(1 + \xi)$ and then extrapolates

this relationship back to the hypothetical value of $\xi = -1$ for which, in principal, the measurement error variance is 0.

B161. While SIMEX is a simple, attractive, alternative to the regression calibration method for dealing with the effect of dose errors on risk estimates, it has some limitations that restrict its applicability in realistic situations that involve complex dosimetry systems. It was designed for situations in which the uncertainty arises primarily as a result of independent measurement errors and it requires some knowledge of the measurement error variance. SIMEX can be used in situations where the relevant dose is a function of a number of components (such as annual dose estimates or doses arising from internal and external exposures), but the number of replications necessary to obtain reliable estimates for each variance inflation factor value increases. It is possible to apply SIMEX to situations involving a mixture of measurement (classical) error and assignment error if the magnitude of the different types of error is known (see [B5, F10]).

B162. Kopecky et al. [K10] used SIMEX to adjust for the effect of dose uncertainty in an analysis of childhood thyroid cancer risks in a Russian population exposed as a consequence of the Chernobyl accident. Assuming that all of the error in the doses was measurement error, the dose uncertainty adjustment increased the point estimate of the ERR per unit dose by a factor of three. However, as noted by the authors, the adjusted estimate is almost certainly too large since it is unlikely that all of the dose uncertainty arose from measurement error.

B163. More recently, Kukush et al. [K17] have compared the performance of various approaches to estimating risks from radiation exposure for a binary outcome (such as cancer incidence) when doses are estimated as a ratio of two quantities determined with error, one of which (^{131}I activity in their example) is measured with classical error and the other (thyroid mass) is subject to assignment error. The analysis was motivated by studies of thyroid cancer incidence in the Ukraine following the Chernobyl accident [L15, T8].

B164. They used a simulation study to examine the bias and uncertainty in estimates of the baseline rate and excess absolute risk per unit dose for seven approaches to error adjustment for a broad range of uncertainties in the two values used in dose estimation. The methods used were the naive analysis (in which the measured doses are used without adjustment), two full maximum-likelihood methods (one of which assumes that the error in the activity measurements is log-normal while the other uses a categorical model to describe the measurement error), regression calibration methods (assuming either log-normal or categorical models for the measurement error), and a pair of SIMEX methods (one of which uses the ordinary method for parameter estimation and the other uses an efficient estimation method developed specifically for the problem of interest). For each method they consider two measurement area scenarios. In one of these the activity measurement errors follow a log-normal distribution, while in the second scenario the measurement errors are from a truncated log-normal distribution.

B165. The authors found that the full maximum likelihood and regression calibration methods exhibited little bias when the measurement error distribution was characterized non-parametrically and that the computationally efficient SIMEX method performed quite well for a broad range of errors. They concluded that while the categorical full maximum likelihood or efficient SIMEX methods were somewhat more accurate than simple regression calibration using a categorical measurement error model, the latter method was much easier to apply and has the advantage that risk estimates can be carried out using standard computer programs for risk estimation.

B166. *Bayesian methods.* The regression calibration methods described above deal with measurement error and have all relied on frequentist methods. Bayesian methods provide a conceptually simple and

attractive approach to characterization of the nature of the dose error on risk estimates. In the following paragraphs a Bayesian framework for risk estimation is outlined in the context of dose uncertainties that involve classical, and shared and unshared assignment error. Following this discussion some published applications of these methods are described.

B167. An assumption is made that there is a dose–response model for an outcome (y) of interest (such as an ERR or an EAR model for cancer incidence rates) that depends on the true dose (X_t) and some other covariates (Z) with unknown dose response (and possibly effect modification) parameters (β) and additional parameters (θ) related to the dependence of the outcome on the other covariates. The likelihood of outcome y given the covariates and model parameters is represented by $p_y(y | X_t, Z, \beta, \theta)$. A Bayesian analysis involves specification of a prior density, $\pi(\beta, \theta)$, for the model parameters and the combination of the likelihood and the prior density to compute the posterior density for the parameters given the observed data, $\pi(\beta, \theta | y, X_t, Z)$.

B168. Inference about the dose–response parameters can then be based on the (marginal) posterior density for β . In general, determination of a posterior density for all but the simplest problems requires evaluation of multi-dimensional integrals. However readily available Markov Chain Monte Carlo (MCMC) software [L33] can provide samples from posterior (marginal) densities for many fairly complex problems. Given a sample of the posterior density for a parameter (or parameters) of interest it is possible to present representative values (such as mode, mean, or median), credible (or Bayesian confidence) intervals, or other quantities of interest for a specific parameter or for functions of parameters of interest.

B169. The basic Bayesian inferential framework described above can readily (if not always easily) be extended to address inference about dose–response parameters when there are uncertainties in dose. In this case, in addition to the likelihood function and prior distribution noted above, a model (density function) for distribution of the measured dose (X_s) given X_t , $p_s(X_s | X_t, \gamma)$, is needed, as well as for the distribution of true doses in the population of interest, $p_t(X_t | \eta)$ and a prior density ($\pi_x(\gamma, \eta)$) for the parameters of these densities. Given this setup, the complete probability function used in determining the posterior density can be written as

$$p_y(y | X_t, Z, \beta, \theta) \times p_s(X_s | X_t, \gamma) \times p_t(X_t | \eta) \times \pi(\beta, \theta) \times \pi_x(\gamma, \eta) \quad (\text{B.8})$$

B170. A somewhat more specific formulation considers a Reeves-type [R1] error model for log-dose (indicated by the * superscript) in which the true and surrogate log-doses for person i are defined as $X_{i,t}^* = \tilde{X}_i^*(Z_i) + \varepsilon_{i,c}$; $X_{i,s}^* = \tilde{X}_i^*(Z_i) + \varepsilon_{i,b}$, respectively. If the classical and assignment error components are assumed to be normal with mean 0 and variance σ_c^2 and σ_b^2 , respectively, the latent variable taken as normal with mean $\mu_L(Z_i)$ and variance σ_L^2 , and some correlation (ρ) between the \tilde{X}_i^* then we have a model with some shared error. The posterior density for this situation is

$$p_y(y | X_t, Z, \beta, \theta) \times \phi(X_s, X_t | \tilde{X}^*, \sigma_c^2, \sigma_b^2) \times \phi(\tilde{X}^* | \mu_L, \sigma_L^2, \rho, Z) \times \pi(\alpha, \beta) \times \pi(\sigma_c^2, \sigma_b^2, \mu_L, \sigma_L^2, \rho)$$

where $\phi(\dots)$ are normal densities.

B171. This Bayesian framework is similar to that used in an analysis of data on the effects of exposure to fallout from the Nevada test on thyroiditis and thyroid neoplasm risks in a cohort of about 2,500 people carried out by Li et al. [L14]. In this dataset the information on dose uncertainty had the fairly common form of an estimate of the total (classical plus assignment) geometric standard deviation for each individual dose and with no explicit information on the magnitude of the correlation induced

by the shared error. To address the limited information on the nature of the dose uncertainty, the authors used informative priors for the between-subject correlations (uniform on the range 0.3 to 0.5) and assumed a constant, but unknown fraction of the total uncertainty was due to assignment error with prior distributions that were uniform on region-specific ranges. A custom MCMC algorithm was used to obtain samples from the posterior parameter densities, and inference about the parameter of interest (the ERR per unit dose) was based on the posterior marginal densities resulting from two different priors for the ERR. The first of these was a normal distribution truncated at 0 with a mean chosen as “a plausible point estimate” and a “reasonably large variance”. The second was a scale-invariant prior called a Jeffrey’s prior [J12]. The data were also analysed using simple regression calibration and using a non-Bayesian approach in which the full likelihood was maximized using a complex Monte Carlo estimation maximization (MCEM) algorithm [M9]. The Bayesian posterior mode and the MCEM estimates of ERR were similar for each outcome. However, for the rarer outcome (neoplasms) the posterior density for the ERR was skewed to the extent that posterior mean or median values were much greater than the non-Bayesian estimates. In comparison to estimates that allow for a mixture of classical, and shared and unshared assignment error, regression calibration estimates were considerably less than estimates based on either Bayesian or MCEM estimates using general dose error models that allowed for a mixture of shared and unshared assignment and classical error. Allowing for shared errors had little impact on either the risk estimates or the width of the Bayesian credible or confidence intervals.

B172. Mallick and colleagues [M6] use earlier data on thyroid cancer in the Nevada test site fallout cohort to illustrate a Bayesian risk analysis allowing for uncertainty in dose estimates. Except for some brief comments in the discussion they do not consider shared errors but in other respects their analysis is similar to that of Li et al. [L14]. A primary feature of this analysis is the consideration of both parametric and rather complicated semi-parametric models for the distribution of the latent log-dose variable (\tilde{X}^*) in a Reeves-type measurement error model and the dose–response function. They find that a model that allows for a mixture of classical and assignment error provides the best description of the dose uncertainty and that while allowing for dose uncertainty leads to some increase in the risk estimate, the main effect is a marked increase in the width of the confidence interval for the excess risk parameter owing mainly to an increase in the upper bound.

B173. Even with the availability of software that can greatly simplify the conduct of MCMC analyses, conducting full Bayesian risk analyses that incorporate dose uncertainty remains challenging, especially if one wants to consider the impact of systematic uncertainties arising from the uncertainties about the nature of the doses or the models used to estimate the doses. In addition, at this time, carrying out such analyses is difficult in large cohorts (such as the LSS) because of the intensity of computation involved. However, since Bayesian analyses and the MCMC methods used to implement them provide a natural way of looking at the impact of complex dose uncertainties on risk estimates, further research and development of these methods is extremely important.

B174. *Risk analyses using data from multi-realization dosimetry systems.* In both of the analyses discussed above, the data on dose uncertainty were limited to a single value for the uncertainty in individual dose estimates. Ideally one would like to have more detailed information on, for example, the nature and magnitude of classical and assignment errors and of the relative importance of shared errors on individual dose estimates. However, except possibly for the simplest dosimetry systems, it is neither feasible nor, in most cases, possible to characterize this information in any simple way. In order to deal with this issue dosimetrists are developing increasingly complex systems that provide multiple realizations of individual dose (or dose component) estimates based upon an assessment of the nature and magnitude of uncertainties in various aspects of the dosimetry system.

B175. These systems are often two-dimensional Monte Carlo systems (see appendix A) that attempt to take into account systematic uncertainties in factors that affect all relevant individuals in a

predictable manner (such as the values of parameters in a model for the source term or transport of radiation from some environmental exposure) and uncertainties in individual doses that arise as a consequence of assigning representative (but not necessarily correct) doses to members of specific groups (such as when all residents of an exposed village are assigned the estimated mean dose for the village). A proper Monte Carlo dosimetry system provides alternative realizations of values of the expected true dose for individuals conditional on what is known (or uncertain) about the individual's exposure situation and model uncertainties. It is important to understand that these systems should not provide alternative realizations of surrogate doses. That is, Monte Carlo uncertainty systems are intended to capture variability arising from systematic and assignment errors but individual measurement (classical) errors must be addressed independently. For example, if dose estimates depend on individual values measured with error then a Monte Carlo dosimetry might make use of an error-corrected (such as regression calibration) estimate of the measured value for that individual in each realization. A better, but more challenging, approach would be to characterize the distribution of the true values given the measured values and then incorporate sampling from this distribution into the dosimetry system.

B176. Hofer [H18] has highlighted the importance of removing effects of classical error in Monte Carlo dosimetry systems. It would be useful if the documentation of Monte Carlo dosimetry systems included some discussion of sources of classical error and how these were addressed in the development of the system.

B177. As indicated above, a properly specified Monte Carlo dosimetry system provides a sample from the distribution of true dose given knowledge of the nature of the dosimetry system for each study subject (including the value of dose surrogates if they exist). Given this information one could then carry out a standard regression calibration analysis using the mean dose and any non-linear functions of dose (such as dose-squared) that enter into the dose–response modelling for each subject. The main limitations of this simple and straightforward approach are that it fails to allow for the effect of inter-subject correlations arising from shared errors and it assumes that the uncertainties in the dosimetry system were properly characterized in the sense that the system leads to unbiased estimates of mean individual doses. As noted in [S32] ignoring shared errors will have little effect on testing of the hypothesis of no dose response, but will tend to result in confidence intervals that are too narrow primarily because of underestimation of the upper bound.

B178. More comprehensive analyses would make direct use of the information from all of the dose realizations for each subject. A naive approach to doing this would be to carry out a separate risk analysis for each dose realization, and describe the risk based on the distribution of the risk estimates resulting from these analyses. However, this naive method will lead to risk estimates that are biased toward zero. This is because the variability in individual dose estimates across realizations is an instance of classical error in which the distribution of the differences between a dose realization for an individual and the true dose for an individual is independent of the true dose for that individual.

B179. Stram and Kopecky [S32] describe complex “Monte Carlo dosimetry” systems based on a generalized assignment error model that includes shared and unshared additive and multiplicative errors. They then outline a Monte Carlo maximum-likelihood method to obtain estimates and confidence bounds for dose–response parameters when one has a set of realizations from the distribution of true dose conditional on what is known (or uncertain) about the dosimetry system and individual characteristics (Z), (such as those provided by a “Monte Carlo dosimetry” system).

B180. If the likelihood for the data given the true dose and some parameters is $p_y(y|X_t, \alpha, \beta)$, where β represents parameters describing the dose response and α represents other parameters (such

as those related to the risk in the absence of exposure), then the likelihood ratio test (LRT) of the hypothesis that $\beta = \beta_1$ against the alternative that $\beta = \beta_0$,

$$l_0(\beta) = \log \left(E \left(\frac{p_y(y | X_t, \alpha(\beta), \beta)}{p_y(y | X_t, \alpha_0, \beta_0)} \mid y, Z, \alpha_0, \beta_0 \right) \right) \quad (\text{B.9})$$

can be approximated by the average of the LRTs over realizations of the expected true dose, that is

$$\hat{l}_0(\beta) = \log \left(\frac{1}{n} \frac{p_y(y | X_{t,r}, \alpha(\beta), \beta)}{p_y(y | X_{t,r}, \alpha_0, \beta_0)} \right) \quad (\text{B.10})$$

The approximation has some limitations. First, when β is far from β_0 the approximation can require a large number of dose realizations. Second, the exact expression involves conditioning on the outcome variable, y , while the dosimetry system provides estimates of X_t conditional only on Z . Since the likelihood of the outcome does not depend on X_t when there is no dose response ($\beta_0 = 0$), using this approach works best when testing the null hypothesis of no response. However, if there is a strong dose response then it can take a large number of dose realizations to obtain a good approximation to the LRT. Nevertheless, if these limitations can be overcome the above expression can be used to find point maximum-likelihood estimates of the dose–response parameters and likelihood-based confidence bounds for these estimates.

B181. Stayner et al. [S25] use data on cancer mortality in the Oak Ridge National Laboratory nuclear worker cohort to illustrate the use of the Monte Carlo maximum-likelihood method to adjust for shared uncertainties. In their example the only uncertainty is a period-dependent bias-factor that is applied to individual annual doses. For each of the 10,000 realizations of dose the dosimetry system chooses a multiplicative bias factor for each of four periods by sampling from period-specific log-normal distributions, and all individual doses are adjusted by the same set of bias factors without allowance for any other dosimetric uncertainties. Radiation-induced health effects were modelled using a simple linear ERR model without effect modification with age-dependent baseline rates. Even in this simple, and relatively small (5,345 workers with 225 cancer deaths over 136,673 person–years), the authors noted some computational challenges in dealing with 10,000 dose replications. In comparing the results from analyses that used average bias correction factors (unsimulated analyses) with the Monte Carlo maximum likelihood estimates based on 10,000 dose realizations (simulated analyses) they found small changes in the point estimate of the risk and only a slight increase in the confidence interval width. Because of the simple shared assignment error structure used in this analysis, one would not expect a substantial difference between the risk estimates in the unsimulated and simulated analyses. However, the simulated analyses ought to lead to wider confidence intervals, as was the case here. Nevertheless, even these differences were small. The authors speculate that this is a consequence of the fact that the bias factors were of similar magnitude for all four periods and that the effect on the width of the confidence interval would be greater if the period-specific biases were more heterogeneous.

B182. As noted above, with considerable effort Stayner et al. [S25] used the results from a simplistic Monte Carlo dosimetry system in which dose uncertainty arose owing to variability in a single bias factor affecting a simple measure of total dose and one was interested in a single risk parameter (such as the ERR per unit dose). However, in real-world problems there are a large number of sources of uncertainty affecting dose estimates; the doses of interest are often time-dependent lagged values that combine doses to the (presumably) relevant organ or tissue received from various sources (such as doses to different organs or tissues arising from a combination of external occupational or environmental exposures, internal occupational or environmental exposures and possibly even from

medical diagnostic procedures). Furthermore, risk is almost certainly not adequately estimated from simple ERR or excess rate parameters but depends on factors such as sex, age, or time since exposure. Thus, there is a need to consider other methods for making use of the often vast amount of dosimetry data that arises from a complex, multi-realization, Monte Carlo dosimetry system.

B183. One possibility that seems useful to explore involves the use of multiple dose realizations in a Bayesian risk analysis. This might be done through the implementation of an MCMC analysis in which sampling is from suitable prior densities for the risk model parameters and a (discrete) uniform prior density over the dose realizations. The result of the analysis would be samples from the posterior densities of the risk parameters and a set of unequal weights for the dose realizations. If this method were carried out for a relatively simple risk model, it might be possible to use the posterior dose realization weights to compute weighted mean doses that could be used in some relatively straightforward regression calibration-like analyses for more complex risk models.

B184. While there is considerable interest in complex dosimetry systems and efforts are being made to develop such systems for a number of populations, including X-ray technologists in the United States, Chernobyl emergency and recovery workers, people exposed along the Techa River, and Mayak workers, there has been remarkably little progress in the development of methods that make effective use of the resulting individual dose distributions. A primary reason for this is that, as challenging as it can be to develop Monte Carlo dosimetry systems that adequately capture the nature of the uncertainties in individual dose components, using the resulting information about individual dose component uncertainties in risk estimation is even more challenging. Except for the simplest problems, the estimation of risks from radiation exposure is an iterative, exploratory process. Increasing the computational burden significantly by allowing for the effects of dose uncertainty, when fitting even the simplest risk models, tends to push investigators towards analyses that largely ignore the effects of dose error or that focus on a single risk summary that may fail to capture adequately the nature of the radiation-associated risk. There is clearly a need for considerably more effort to develop practical methods that account for the impact of dose uncertainty in realistic dose–response models.

C. Impact of model uncertainties

B185. Models are designed to give a simplified description of the main processes or an assessment of key parameters of complex processes. Thus, in the sense of giving a complete picture of reality “all models are wrong, but some are useful” [B19]. Various models may approximate a data set equally well but give different results for some quantities of interest. An evaluation of the results from several models is a tool of clarifying the messages contained in the data and, possibly, the artefacts introduced by the use of specific models. Evaluation of several models will increase the confidence in the results that are obtained commonly by those models that exhibit a good quality of fit. If differences between two model estimates are not statistically significant, then this is often considered as a confirmation of the result. Nevertheless, this difference will have an impact on the uncertainty range. Taking both models into account will generally result in an uncertainty range wider than each of the uncertainty ranges of the two models. This may imply, for example, that a risk estimate, which is significant in a preferred model, does not remain significant, if other models are taken into account.

B186. There is a large body of publications on model uncertainties (for summaries, see [B25, C10, H15]). Fields of applications are manifold including ecology [W11], econometrics [L12], analysis of microarray data [A8], phylogenetics [P8], and applications in meta-analyses [B9].

B187. In the frame of estimates of risk from radiation exposure, only initial approaches to the application of formal procedures for model selection and derivation of model uncertainties, for example, by multi-model inference, have been reported. Consequently, most evaluations of results, for example, on excess risks from radiation exposures, are overconfident. A number of reports, including previous reports of the Committee, acknowledged model uncertainties but studies that quantified them had not been conducted (such as NCRP and UNSCEAR [N9, U11]).

B188. In general, radioepidemiological data are obtained for a range of variables, such as age at exposure, dose, or age at diagnosis of, or death due to, a disease. In most cases, central estimates are relatively insensitive to the choice of the model [E3, J4, P14, W3]. However, model uncertainties are greater in the border zone of the observed ranges of variables, for example, at young or old age at exposure, at low dose, or young age attained.

B189. The Committee noted in the UNSCEAR 2000 Report that the outcome of cancer risk modelling is often dependent on the initial biological assumptions made. This is clearly a source of model uncertainty ([U11] annex G). Key questions concerning model uncertainties are how to select models that have to be considered, and how the variability of results produced by different models can be taken into account. One method of dealing with such model uncertainties is multi-model inference of risk quantities, which is also called in the statistical literature “model averaging”. Before addressing these questions, this section summarizes types of models considered in the risk analyses, and the evidence for model uncertainties in the estimates of cancer risks after exposure to ionizing radiation.

1. Model types

B190. Radioepidemiological data can be analysed with a variety of models. For the discussion below, model types are subdivided into two major groups: empirical models and mechanistic models.

B191. Empirical models use simple mathematical terms to describe baseline morbidity or mortality rates and excess risks associated with radiation exposure. Baseline rates can be modelled by allowing for different baseline rates in a number of strata (groups) defined, for example, by sex and ranges of birth year and age. Conventionally, such models are called stratified. Other models use parameters for relative risks in different dose categories (categorical models). Alternatively, functions of the variables are used in so-called parametric models. Excess rates are expressed as excess relative risk (ERR) or excess absolute rate (EAR) depending on dose and possibly further variables [U12]. Empirical models have two advantages: (a) mathematical simplicity; and (b) often an estimate of a quantity of main interest, for example, in a linear model, the ERR per unit dose and its uncertainty distribution are obtained directly by the fit of the model to the data.

B192. In cohort studies, such as the Life Span Study (LSS) of atomic bombing survivors [P14], baseline cancer rates and dose-specific EAR or ERR can be estimated as parametric functions of age at exposure, attained age, sex, and other variables of interest, whereas in matched case-control studies, absolute rates can be estimated only if the baseline rates can be estimated from other data sources. In a cohort study, a typical rate model where the rate is assumed to vary linearly with dose might have the form:

$$\text{Total rate} = \exp(\alpha_0 + \sum \alpha_i x_i) + \beta D \times \exp(\sum \delta_j y_j), \quad (\text{B.11})$$

while a typical excess relative risk model has the form:

$$\text{Total rate} = \exp(\alpha_0 + \sum \alpha_i x_i) \times [1 + \gamma D \times \exp(\sum \varepsilon_j y_j)]. \quad (\text{B.12})$$

Here, in these models β , γ , α_0 , α_1 , α_2 , ... , δ_1 , δ_2 , ... , and ε_1 , ε_2 , ... are unknown parameters and x_1 , x_2 , ... , and y_1 , y_2 , ... represent possible modifiers of baseline and dose-specific rates or relative risks, respectively. For example, the baseline rate of female breast cancer might be represented by the exponential function $\exp(\alpha_0 + \sum \alpha_i x_i)$, where x_1 has value 1 for Hiroshima and value -1 for Nagasaki, x_2 is the attained age in years and x_3 is age at first full-term pregnancy; D might be breast tissue dose in grays; and $\exp(\sum \delta_j y_j)$, representing possible modification of dose-related excess rate, might have y_1 as age at radiation exposure, y_2 as attained age in years, and y_3 as age at first full-term pregnancy (often the same variables can be modifiers of both baseline and excess rate). More complex dose dependences as, for example, linear–quadratic, linear–quadratic–exponential or threshold-type dose dependences, are typically considered as well.

B193. In the field of risks from radiation exposure, the main use of mechanistic models is related to cancer induction and development. These models were initially developed to describe the age dependence of cancer [A12, M18, M19]. Although more recent models are quite complex (such as [L19]), they still represent a huge simplification because not all of the many processes leading to cancer induction and development are well understood. The relevant molecular pathways, cellular processes, tissue reactions* and influences of the immune system depend on the site and the type of cancer. Because of insufficient knowledge of these processes and to the limited statistical power of epidemiological studies, it is generally not possible to identify uniquely one mechanistic model of carcinogenesis that is superior to others. Nevertheless, a main advantage of mechanistic models is that they provide the possibility of integrating knowledge on radiobiological processes in the evaluation of radioepidemiological data [J6]. For example, Eidemüller et al. [E3] concluded that the age dependence of the radiation-related excess incidence of breast cancer among the Swedish haemangioma patients may be related to a radiation-induced genomic instability,* which causes a lifelong increase of the (otherwise spontaneous) initiation rate of carcinogenesis. Shuryak et al. [S16] related the limitation of the growth of pre-neoplastic lesions to age and dose dependencies of cancer after exposure to ionizing radiation. Brugmans et al. [B23] incorporated the effects of decreased cellular proliferation at very advanced age for improving the description of the baseline lung cancer risk among miners.

B194. An attempt has been made to assess the impact of individual radiation sensitivity on the estimation of risk factors for population groups [M13].

B195. The Committee recommends applications of empirical and of mechanistic models to the same radioepidemiological data in order to explore model uncertainties.

2. Evidence for effect of model uncertainties on estimates of risk from radiation exposure

B196. A study by Preston et al. [P14] of solid cancer incidence was based on 17,448 first primary cancers (including non-melanoma skin cancer) diagnosed from 1958 to 1998 among 105,427 survivors of the atomic bombings in Japan. In their standard model with an ERR decreasing exponentially with age at exposure, the ERR at age 70 after an exposure of 1 Gy at age 60 was 0.27. Describing the age-at-exposure dependence by a log–quadratic spline with a single knot at age 40 improved the quality of fit ($P = 0.02$) and resulted in an ERR estimate that was higher by a factor of 2.5.

B197. Lung cancer mortality risk was studied by Jacob et al. [J3] for male Mayak workers, for whom lung doses were estimated from the measured plutonium content of urine and for whom additional information was available on external exposure and smoking behaviour. Among 6,293 workers, 301 lung cancer cases were registered in the follow-up period until the end of 2002. At age 50, after a

plutonium exposure of the lung during the age period of 20–40 years with a cumulative dose of 0.1 Gy, an ERR of 0.12 was obtained with the preferred model of carcinogenesis. With an empirical model, however, the value was larger by a factor of four.

B198. Richardson et al. [R2] analysed leukaemia mortality among Japanese atomic bombings survivors. The analysis included 310 deaths due to leukaemia during the period 1950–2000 among 86,611 people in the LSS. In their preferred model, the dependence of the ERR on time after exposure was a cubic spline function with a knot at 30 years. For a bone marrow dose of 1 Gy, a best estimate of the ERR of 0.8 was found for 30 years after an exposure that occurred at age 10. BEIR VII [N19] obtained for the same specification with a simpler model, an ERR of 4.5. Thus, based on very similar data, the two risk estimates differ by more than a factor of five.

B199. The three examples discussed above demonstrate that considerable model uncertainties have been observed for estimations of cancer risk after exposure to ionizing radiation in specific circumstances. A first step to dealing with the problem is to select models that are appropriate for analysing the epidemiological data.

3. Selection of a preferred model

B200. Plausibility considerations are an important part of model selection. For example, fits of mechanistic models may result in biologically implausible parameter values; thus parameter values need to be restricted to plausible values.

B201. An important quantity in model selection is the likelihood, L , of the data given a model, \mathcal{M}_k , and the maximum likelihood estimator, $\hat{\theta}_k$, of the parameters. Because of technical reasons, the logarithm of the likelihood multiplied by -2 is used, which is for generalized linear models, apart from a constant, the deviance:*

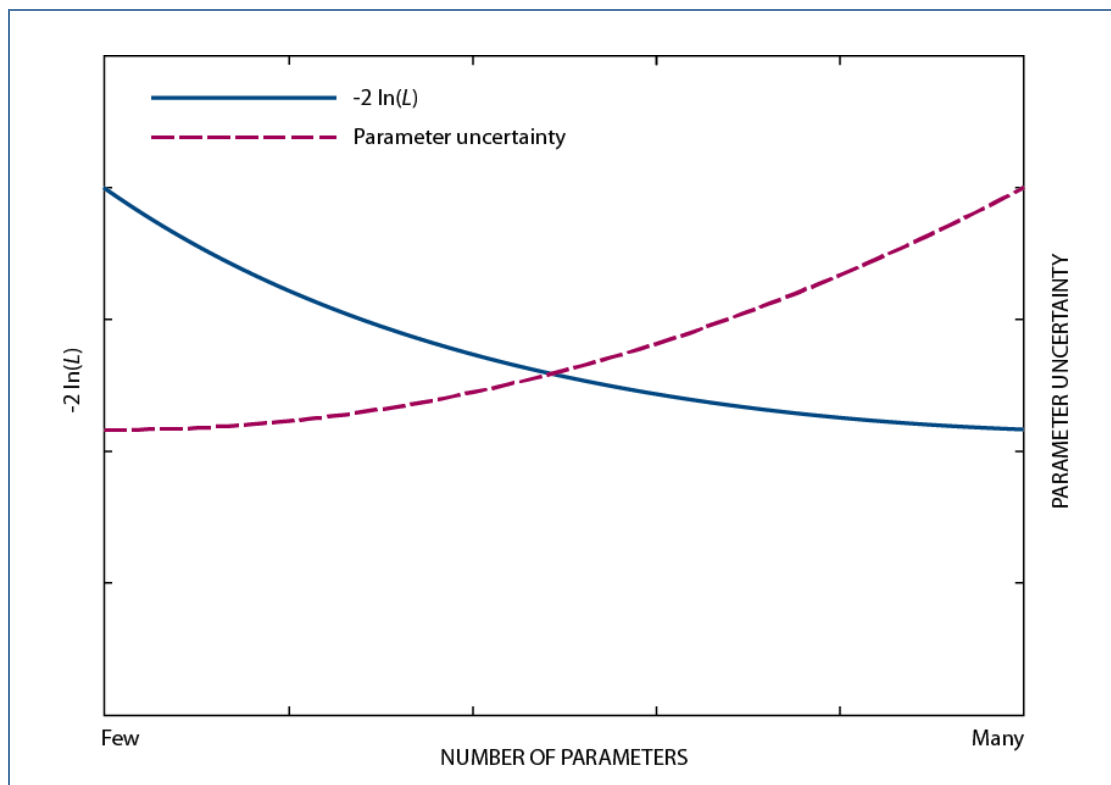
$$\text{dev}_k = -2 \ln[L(\text{data}|\mathcal{M}_k, \hat{\theta}_k)] \quad (\text{B.13})$$

In analyses with a large number of degrees of freedom, as is normally the case in analysing epidemiological data, generally only differences of the deviance are considered so that the constant term does not play a role. The term “deviance” is also used for other models than generalized linear models as a convenient abbreviation for minus twice the logarithm of the likelihood (plus an unknown constant).

B202. The addition of more terms to a model generally increases the likelihood and thus reduces the deviance. However, the resulting more complex model is not necessarily an improvement, because a model with many parameters may result in over-fitting of the data. The relevance of various possible parameters for a description of the data can be tested by calculating measures of the quality of fit as, for example, the deviance. Generally, the uncertainty of parameter estimations increases with the complexity of the model (see figure B-V). As a consequence only parameters that really matter ought to be included in the selected model [C10]. Already in the fourteenth century, this has been expressed by the principle of parsimony (the so-called “Occam’s razor”) (Occam, ca. 1320, referenced by Posada and Buckley [P8]). Methods for model selection aim at avoiding too large deviances by oversimplification and too large uncertainties by over-fitting.

Figure B-V. Deviance and parameter uncertainty as a function of the number of parameters

Generally, the deviance (more generally expressed by minus twice the logarithm of the likelihood) decreases and the uncertainty of parameter estimates increases with the number of parameters in a model [P8]. Methods for model selection aim at finding a balance between these two trends



B203. Methodologies for model selection depend on whether the models considered are nested or non-nested. Model selection may also depend on the procedure for adapting the models to the data [C10]. The Committee emphasizes the importance of defining the criteria for model selection before a study is performed and of making the criteria transparent in the publications.

B204. Two models are called “nested”, if the simpler model can be obtained from the more complex model by deleting one or several terms in the model equations. Thus, deletion of one term $\delta_j y_j$ in equation (B.11), where y_j is, for example, the risk modifier “age at exposure”, in a model, \mathcal{M}_1 , results in a model \mathcal{M}_2 , which is nested in \mathcal{M}_1 . An approach to selecting one of the two models is based on the likelihood ratio test. This test is based on the fact that the difference of the deviances of two nested models in Poisson regressions is approximately chi-square distributed [H4, N14]. If the deviance of the more complex model is according to the chi-square statistics significantly lower than the deviance of the simpler model, then the more complex model is selected, because it is considered to have an improved quality of fit. Otherwise, the additional terms in the more complex model are dropped and the simpler model is retained. Table B14 gives the limiting values for the difference in deviance for an improvement of the fit at the 95% confidence level [W2]. Thus, if the two models differ by a term with one additional parameter, then the model including this term will be selected if its deviance is smaller than the deviance of the simpler model by more than 3.84. The likelihood ratio test is not only applied to Poisson regression but also to analyses of individual data.

Table B14. Difference in deviance indicating an improvement of fit of nested models at the 95% confidence level [W2]

For example, if two nested models differ by terms with two additional parameters, then the more complex model will be selected if its deviance is smaller than the deviance of the simpler model by more than 5.99

Δ number of parameters	Δ deviance
1	3.84
2	5.99
3	7.81
4	9.49

B205. A criterion for the relative quality of fit of non-nested models has been derived by extension of the maximum likelihood principle using information theory [A3, A4, B25, C10, W2]. Akaike used the Kullback-Leibler information as the fundamental basis for model selection [A3, A4]. The Kullback-Leibler (K-L) information, $I(f, k)$, is the information lost, when the model \mathcal{M}_k is used to approximate full reality, f [A7, K3]. Akaike's major invention was the idea to calculate not the K-L information itself, but the expectation of the K-L information and linking it to the log-likelihood function at its maximum. The complex mathematical analysis yielded a simple expression, the Akaike Information Criterion, AIC, as a measure of the "distance" in information between a model and full reality.

B206. In its first approximation, the AIC is defined by twice the difference of the number of parameters and the natural logarithm of the likelihood:

$$\text{AIC}_k = 2(n_k - \ln(L_k)) \quad (\text{B.14})$$

where n_k is the number of parameters of a model \mathcal{M}_k . The model with the lowest value of AIC is selected as the one with the highest probability. In this algorithm, a model is preferred to one with Δn fewer parameters, if twice the logarithm of its likelihood is larger by at least $2\Delta n$. Unlike the likelihood ratio test for nested models, the Akaike approach prefers more complex models. The term $2n_k$ is often called the "penalty term", because the more parameters there are, the more the model is weighed down by the information criterion.

B207. In the approach of Akaike, the probability for a model improvement is given by:

$$p = 1 - \exp(-0.5 \Delta \text{AIC}) / (1 + \exp(-0.5 \Delta \text{AIC})) \quad (\text{B.15})$$

where ΔAIC is the difference of the AICs for the two models under consideration [W2]. Under these conditions, a model has a 95% probability of improvement if the difference in the AICs amounts to 5.9.

B208. Based on Bayesian statistics, an alternative criterion for the relative quality of fit of non-nested models has been proposed by Schwarz and Yang [S10, Y2]. The Bayesian Information Criterion is defined by:

$$\text{BIC}_k = n_k \ln(N) - 2 \ln(L_k) \quad (\text{B.16})$$

where N is the sample size [C10, P8]. Again the model with the lowest BIC is selected. Compared to the AIC, the BIC prefers simpler models for sample sizes larger than 7. Most authors in the field of radioepidemiology have tended to favour the use of the AIC [K2, L19, W4]. The BIC, however, has been used for the selection of a model describing lung cancer risk after exposure to radon and cigarette

smoke in a joint analysis of three European case–control studies among uranium miners [L12]. Some papers include both indices in their model selection procedure [J3, J6, W3]. None of the papers state, however, why the AIC or the BIC has been chosen for model selection.

B209. The Deviance Information Criterion, DIC, is specifically designed for model adaptations to data based on Bayesian MCMC methods [S24]. In these methods, the prior information may be considered to reduce the degrees of freedom. Correspondingly, the number of parameters, n_k , in the penalty term in the definition of the AIC for a model \mathcal{M}_k (see equation (B.14)) is replaced by the number of “effective parameters”, p_D . The number of effective parameters is defined by the difference between the posterior average of the deviance and the deviance evaluated at the average of the posterior parameter distribution. Little et al. [L17] have calculated the DIC for some models, which they considered for the evaluation of radiation-induced lifetime cancer risk and its uncertainty employed in the UNSCEAR 2006 Report [U12].

B210. Besides AIC, BIC and DIC, other criteria have been developed that are designed for special purposes or small-size data sets [C10].

B211. Model selection techniques as described above generally reject stratified or categorical models in favour of parametric models [C10], because the number of parameters that have to be determined from the data is considerably larger for the parametric models. Walsh et al. [W3] used additional tests to select between parametric and semi-categorical models (models that described some variables by functions and other variables by parameters for different categories). They analysed thyroid cancer incidence after the Chernobyl accident. The results on the time and age dependences of the excess relative risk estimates of the parametric and non-parametric models were significantly different. Quality-of-fit tests based on the AIC and on the BIC favoured modelling of the baseline incidence by continuous functions, because the number of parameters in the semi-categorical model is considerably larger. The authors finally preferred the model with a parametric description of the baseline risk*, because the number of thyroid cancer cases in various age and time-after-exposure classes was better predicted than by the semi-categorical model.

B212. Posada and Buckley [P8] noted that model selection techniques may not result in one optimal model. A possible way of overcoming this problem is to use multi-model inference.

4. Multi-model inference

B213. In order to take into account more than just one preferred model, a strategy is needed to select those models that are to be considered in the assessment of model uncertainties. In principle, there are an infinite number of models that could be tested. For example, one may start with the model in equation (B.11). There is already an infinite number of new models with one additional parameter, ε , obtained by adding a term with one of the covariates, x_i , to the power of k , that is $\varepsilon(x_i)^k$. Multi-model inference strategies based on an infinite or very large number of models are dealt with shortly in the following paragraph, whereas the focus of this section is on strategies that base the inference on a more limited selection of models.

B214. An approach based on a very large number of models is the MCMC model composition, MC³ [H15, M4]. The Markov chain starts with some model M and constructs a neighbourhood to the model. For example, if the model represented by equation (B.11) is the starting point, then models as constructed in the last paragraph (such as up to a specified power, k_{spec}) can be defined to be part of the neighbourhood of \mathcal{M} . A model \mathcal{M}' is sampled from the neighbourhood of \mathcal{M} . If the conditional

probability of \mathcal{M}' , $p' = p(\mathcal{M}'|\text{data})$, is larger than the conditional probability of \mathcal{M} , $p = p(\mathcal{M}|\text{data})$, then \mathcal{M}' is accepted as the next model in the Markov chain. If the conditional probability of \mathcal{M}' is smaller than the conditional probability of \mathcal{M} , then \mathcal{M}' is accepted with probability p'/p . Otherwise, the chain remains in state \mathcal{M} . The approach is known in physics as the Metropolis-Hastings algorithm of importance sampling [C8]. The Committee is not aware of any application of this approach in evaluating the risks from radiation exposure.

B215. An approach with a more limited selection of models has been proposed by Madigan and Raftery [M3]. This approach corresponds to discarding all models that are less supported—to 95% probability—by the data than the model with the highest probability. Applying the approach to models, as they have been constructed in the first paragraph of this subsection, would result in an infinite number of selected models.

B216. A simple approach to selecting models is to analyse only models that have been defined in the literature as preferred models, and to apply model selection approaches to such a set of models [P8].

B217. Jacob et al. [J4] discussed model uncertainties in estimation of risk from radiation exposure for solid cancer among the survivors of the atomic bombings in a three-step procedure:

- (a) Definition of four groups of models: (i) empirical models; (ii) two-step clonal expansion, TSCE, models with a radiation action on the promotion rate of precancerous cells; (iii) TSCE models incorporating a classical cell-killing term for precancerous cells; (iv) TSCE models incorporating low-dose hypersensitivity in cell killing of precancerous cells;
- (b) Application of the likelihood ratio test within each group of models to select for each group of model with the best quality of fit;
- (c) Comparison of the risk estimates obtained by the four selected models.

The TSCE model was found to represent the data more economically than the empirical risk model: a similarly good description of the data was achieved with a smaller number of parameters. However, the statistical power of the data was sufficient to give a clear preference to one of the four selected models. Central ERR and EAR estimates (at 1 Sv, for age at exposure 30 y and age attained 70 y) were similar in all of the four selected models. The TSCE models with radiation-induced cell killing tended to give for young ages at exposure lower risk estimates than the empirical model.

B218. Various approaches to multi-model inference are discussed in the statistical literature [C10, H15, P8]. An estimator of a quantity, $\hat{\mu}$, is calculated by a weighted average of estimators, $\hat{\mu}_k$, obtained with model \mathcal{M}_k :

$$\hat{\mu} = \sum_k w_k \hat{\mu}_k \quad (\text{B.17})$$

Generalizing equation (B.15) to a number of k models, and choosing the weights of the models according to the probability of the data in the Akaike approach, results in:

$$w_k = \exp(-0.5\text{AIC}_k) / \sum_i \exp(-0.5\text{AIC}_i) \quad (\text{B.18})$$

where AIC_i is the AIC for model i . In a Bayesian approach to multi-model inference, a similar result is obtained, in which the AIC in equation (B.18) is replaced by the BIC. Again, other information criteria are used for special purposes or if the data set has a limited size [C10].

B219. Analytical approaches have been developed to derive parameters of the distribution of a quantity of interest, μ [C10, H15]. Alternatively, a straightforward Monte Carlo procedure can be applied [W4]. The procedure is based on probability density functions for a quantity of interest as derived from the various models under consideration. The probability density function of the quantity of interest according to multi-model inference is then obtained by sampling with probability w_k from the probability density function according to model M_k .

B220. Walsh and Kaiser [W4] included nine recently published relative risk models (see equation (B.12)) in a multi-model inference study of leukaemia mortality among the Japanese atomic bombing survivors. Walsh et al. fitted all models to the same data set (DS02CAN.DAT from www.rerf.or.jp). The model selection and weighting procedure was based on the AIC. The lowest AIC was obtained by the model published by the Committee in 2006 [U12]. According to the weighting procedure in equation (B.18), 51% of the samples in the pdf for the multi-model inference were drawn from the pdf produced by the model of the Committee. Corresponding results are summarized in table B15 for all nine models considered. The different models give similar results for ages attained and ages at exposure that are in the central regions of the data set (see table B16 for $a = 55$ and $e = 30$). In this central data region, best estimates and confidence intervals in the multi-model inference are close to those in the model with the highest weight. Larger variability is observed, however, for ages that are not in the central region of the data. For attained age 17 after an exposure at age 7, for example, best estimates of the nine models for the ERR at 1 Gy range from 11.3 to 86.4. Multi-model inference resulted in an ERR of 18.4 (95% CI: 0.6, 35.6) [W4]. The best estimate is close to the best estimate of the model of the Committee [U12]. The confidence interval, however, is wider. The ratio of the upper and lower bounds of the 95% confidence interval is 38 in the model of the Committee and 59 according to multi-model inference [W4]. The impact of dose uncertainty on the width of the uncertainty ranges for the risk estimates has not been considered in the analysis.

B221. Kaiser et al. [K2] analysed breast cancer incidence in the LSS cohort of Japanese atomic bombing survivors. Applying a formal selection procedure to a large number of models, one empirical model and three versions of the TSCE model of carcinogenesis were selected for multi-model inference. Carcinogenesis of baseline cases in the TSCE models was characterized by an initiation rate increasing with age from birth up to about 25 years, and a growth rate of preneoplastic lesions that dropped for those in their forties. Multi-model inference resulted in uncertainty ranges of values for the ERR per unit dose that were larger than uncertainty ranges of the preferred empirical model, especially for young ages at exposure. For aged 10 at exposure and age 70 at diagnosis, for example, ratio of the 95th to 5th percentiles increased from 2.5 to 5.9 (see table B17).

B222. The Committee notes that neglecting model uncertainties may lead to a considerable underestimation of the total uncertainty of risk estimates, and recommends the application of multi-model inference techniques in future risk evaluations. This will allow more realistic assessment of the uncertainty of risk estimates than in most analyses up to now.

Table B15. The number of parameters, minus twice the logarithm of the likelihood, the AIC_k and the sampling weight w_k applied in multi-model inference for leukaemia risk among the Japanese atomic bombing survivors [W4]

<i>Model</i>	n_k	$-2 \ln(L_k)$	AIC_k	w_k
Preston et al. [P13] ^a	22	2 258.7	2 302.7	<0.0005
BEIR VII, phase 2 [N19]	19	2 255.2	2 293.2	0.001
Richardson et al. Model 2, table A1 [R2]	21	2 250.1	2 292.1	0.001
Schneider and Walsh LQ model [S9]	13	2 258.0	2 284.0	0.069
Schneider and Walsh LQ-exp model [S9]	14	2 253.9	2 281.9	0.198
Little et al. [L17]	11	2 259.7	2 281.7	0.219
UNSCEAR [U12]	10	2 260.0	2 280.0	0.512
Richardson et al. Main model [R2]	448	1 915.5	2 811.5	<0.0005
Richardson et al. Model 3, table A1 [R2]	1 086	1 560.3	3 732.3	<0.0005

^a The functional form of the EAR model of [P13] has been used to construct a corresponding ERR model.

Table B16. Best estimates with 95% confidence intervals of the ERR for leukaemia mortality among Japanese atomic bombing survivors at attained age a after exposure at age e following a bone marrow dose of 1 Gy [W4]

<i>Model</i>	$e = 7; a = 17$	$e = 30; a = 55$
Preston et al. [P13] ^a	11.3 (4.3, 21.9) ^b	2.72 (1.21, 4.24)
BEIR VII, phase 2 [N19]	19.9 (−12.2, 37.9)	2.11 (−0.09, 2.98)
Richardson et al. Model 2, table A1 [R2]	22.7 (−12.1, 43.8)	2.50 (−0.10, 3.59)
Schneider and Walsh LQ model [S9]	19.2 (−0.6, 38.8)	2.73 (1.60, 4.03)
Schneider and Walsh LQ-exp model [S9]	19.3 (2.0, 36.5)	2.95 (1.51, 4.06)
Little et al. [L17]	18.5 (0.2, 35.6)	2.78 (1.53, 4.04)
UNSCEAR [U12]	17.9 (0.9, 34.6)	2.71 (1.49, 3.88)
Richardson et al. Main model [R2]	86.4 (12.1, 582)	2.55 (1.12, 4.18)
Richardson et al. Model 3, table A1 [R2]	31.0 (−32.6, 66.6)	2.72 (1.12, 4.18)
Multi-model inference	18.4 (0.6, 35.6)	2.77 (1.43, 3.84)

^a The functional form of the EAR model [P13] has been used to construct a corresponding ERR model.

^b Results for the age group 0–19 years were taken.

Table B17. Best estimates with 90% confidence intervals of the ERR for breast cancer incidence among Japanese atomic bombing survivors at attained age a after exposure at age 10 following a breast dose of 1 Gy [K2]

<i>Model</i>	$a = 30$	$a = 70$
Empirical, linear dose response modified by age attained	5.2 (2.6, 9.8)	1.1 (0.60, 1.5)
TSCE, lifelong effect of acute exposure on growth rate of pre-neoplastic lesions	8.9 (4.2, 20)	1.2 (0.91, 1.5)
TSCE, immediate initiation of pre-neoplastic lesions by acute exposure	3.2 (2.4, 4.1)	0.44 (0.14, 0.96)
Multi-model inference	5.1 (2.6, 14)	1.1 (0.27, 1.6)

APPENDIX C. UNCERTAINTY IN TRANSFERRING RISK QUANTITIES FROM GIVEN STUDIES TO OTHER EXPOSURE SITUATIONS OR POPULATIONS OF INTEREST

I. TRANSFER TO ANOTHER POPULATION	213
II. EXTRAPOLATING RISKS OVER LIFETIME.....	219
III. TRANSFER TO LOW-DOSE AND LOW-DOSE-RATE EXPOSURE WITH LOW-LET RADIATION	221
A. Statements of various bodies up to the UNSCEAR 2006 Report	222
B. New radiobiological information.....	224
C. New epidemiological information	225
D. Evaluation of the uncertainty of the DDREF	226
E. Uncertainty associated with the projection of risk to the region of low and very low doses.....	227
IV. TRANSFER FOR EXPOSURES TO OTHER TYPES OF RADIATION.....	228
A. Modifying factors to estimate risks of cancer for different radiation types	228
B. Quantification of modifying factors up to UNSCEAR 2006 Report	229
C. Modifying factors for neutrons.....	229
D. Modifying factors for alpha particles.....	230
E. Modifying factors for lower-energy photons	233
F. Modifying factors for low-energy electrons.....	236
G. Summary of modifying factors	239
V. INTEGRATIVE APPROACHES FOR QUANTIFYING THE OVERALL UNCERTAINTY IN RISK ESTIMATES.....	239

I. TRANSFER TO ANOTHER POPULATION

C1. The UNSCEAR 2006 Report (annex A, I. Features of Epidemiological Studies, H. Transfer of radiation risk estimates between populations, and interactions of carcinogens, paragraphs 39–48) [U12] considered that the question of how to transfer risk estimates derived from one population to a different population remains unanswered, and that available data suggest that there is no simple solution to the problem. The question is related to the issue of how one should model interactions between radiation and other agents in relation to cancer risk, as extensively reviewed in annex H of the UNSCEAR 2000 Report [U11]. It was concluded, however, that for the foreseeable future, the most useful information relevant to transferring radiation-related risk coefficients from one population to another will come from multinational comparisons of site-specific, radiation-related risk, rather than from investigations of underlying cancer risk factors and their interactions with radiation dose.

C2. *Baseline and excess risk.* Epidemiological information about radiation-related cancer risk is obtained by studying population groups characterized by individual demographic data such as sex, birth year, nationality, lifestyle factors, history of exposure to ionizing radiation, site-specific cancer incidence and/or mortality, and other factors that conceivably might be informative about “baseline” cancer risk unrelated to radiation dose, and by dose-related “excess” cancer risk. Useful site-specific data on baseline cancer risks as functions of attained age are readily available for many populations, as published periodically by the International Agency for Research on Cancer [I5]. Dose–response analyses of data from a particular population of interest are conducted to determine the extent to which cancer risk in this population may depend upon radiation dose, and the extent to which baseline and excess risk may vary according to factors other than radiation dose. In particular, evidence about modification of baseline risk and/or radiation dose response by demographic factors such as sex, age at exposure, and attained age, and by lifestyle factors such as tobacco use, diet, and reproductive history, is of interest because such findings might lead to more useful risk estimates and, ultimately, to better understanding of the biological processes of radiation carcinogenesis in man.

C3. *Additive and multiplicative expressions of risk.* It is computationally and cognitively convenient to express excess risk in absolute terms, as an addition to baseline risk:

$$\text{additive risk} = \text{baseline risk} + \text{excess absolute risk (EAR)} \quad (\text{C.1})$$

and in relative terms as a multiple of baseline risk:

$$\text{multiplicative risk} = \text{baseline risk} \times (1 + \text{excess relative risk (ERR)}) \quad (\text{C.2})$$

“Baseline” risk, by definition, is not influenced by radiation dose and therefore its estimate would be expected to be essentially the same whether the excess risk is expressed in absolute terms using an additive model or relative terms using a multiplicative model as in equations (C.1) or (C.2). An immediate practical problem concerns the portability of radiation-related, site-specific risk estimates from one population to another. If the two populations have distinctly different age-specific baseline rates for a given cancer site, additive and multiplicative projections of risk from one population, such as the LSS cohort of atomic bombing survivors [P14], to another, for example, to the population of another country, will yield discordant risk estimates in the second population. Additive and multiplicative projections will not differ much if the two populations have similar baseline rates,

although of course it does not necessarily follow that the projection to the second population will be accurate.

C4. *Breast cancer example: Projection of radiation-related risk between Japanese and American populations.* Baseline rates for female breast cancer are substantially different between Japan and the United States, which historically have had among the world's lowest and highest breast cancer rates, respectively [I5, M2]. Table C1 shows linear model estimates, with 90% confidence intervals, of ERR and EAR per unit dose for LSS female breast cancer at age 70 following exposure at age 30 (i.e. in 1985) ([P14] table 29). Under the reasonable assumption that the ERR and EAR estimates are consistent in describing the same phenomenon, the relevant LSS baseline risk for breast cancer at age 70 in 1985 can be estimated as the ratio of the EAR and ERR per unit dose estimates, i.e. 9.2 per (10^4 PY Gy) divided by 0.87 Gy^{-1} resulting in 10.6 per 10^4 PY (table C1). A recent estimate of the United States baseline female breast cancer rate at age 70, based on data from the 14-centre SEER Registry tumour registry [I5], is 41.4 per 10^4 PY; or 3.9-fold higher than the corresponding estimate for the 1985 LSS baseline. Multiplying the contemporary United States baseline rate by the LSS-based estimate of ERR per unit dose gives a multiplicative projection of 36.0 (90% CI: 22.8, 53.8) per (10^4 PY Gy), which is 3.9 times the estimated additive projection of 9.2 (90% CI: 6.8, 12.0) per (10^4 PY Gy) as provided by the LSS estimate of EAR per unit dose.

C5. *Female breast cancer: International pooled analysis of radiation-related risk.* In a pooled analysis of female breast cancer incidence data from the LSS cohort and from seven western populations exposed to medical X-rays, Preston et al. [P11] found that age-specific EAR estimates per unit tissue dose to the breast were consistent among the LSS cohort of Japanese atomic bombing survivors, two United States cohorts of tuberculosis patients given multiple chest fluoroscopies during lung collapse therapy [B16], and a cohort of United States children given X-ray therapy for what was at one time considered to be enlarged thymus glands [H13]. As discussed in the previous paragraph, ERR estimates differed significantly between the LSS and United States cohorts. Therefore the "restricted pooled-analysis" EAR estimate based on these four populations was adopted for the United States population as a whole by the BEIR VII committee [N19], after including more recent LSS breast cancer data [P14]. Despite the large United States–Japan difference in baseline rates, this estimate is very close to the additive projection estimate discussed in the previous paragraph and in part 1 of table C1.

C6. *Female breast cancer: Inconsistencies among irradiated study populations.* Data from each of four additional study populations (comprising United States women treated for acute post-partum mastitis [S15], Swedish women treated for benign breast disease [M8], and two populations of Swedish women treated with radium plaques for skin haemangioma in infancy [L16, L32]) were found to be statistically inconsistent with a common model for EAR per unit dose as discussed in the previous two paragraphs or indeed with each other [P11]. Thus, the Preston et al. [P11] analysis supports the use of an additive projection of radiation-related breast cancer risk from the LSS cohort to the general United States population, or (equivalently) of the "restricted pooled-analysis" risk model discussed in the preceding paragraph. However, the additive models may not be appropriate for populations with benign breast disease such as acute post-partum mastitis, or for infants treated with radium plaques for haemangioma.

Table C1. Best estimates and 90% confidence intervals (CI) of risk for specific cancers at age 70 per unit dose of low-LET radiation at age 30 using a linear model

<i>Risk quantity on which transfer is based</i>	<i>LSS coefficients (90% CI)</i>	<i>LSS baseline^a</i>	<i>Estimated LSS excess rate per unit dose (90% CI)^b</i>	<i>United States (SEER) baseline^c</i>	<i>Extrapolated excess rate per unit dose (90% CI) for US population</i>
Female breast cancer risk per unit dose (Gy⁻¹) [P14], table 29					
ERR per unit dose	0.87 (0.55, 1.3) Gy ⁻¹	10.6 per 10 ⁴ PY	9.2 (5.8, 13.7) per (10 ⁴ PY Gy)	41.4 per 10 ⁴ PY	^d 36.0 (22.8, 53.8) per (10 ⁴ PY Gy)
EAR per unit dose	9.2 (6.8, 12.0) per (10 ⁴ PY Gy)				9.2 (6.8, 12.0) per (10 ⁴ PY Gy)
Gastric cancer risk per unit dose (Gy⁻¹), sex averaged [P14], table 16					
ERR per unit dose	0.34 (0.22, 0.47) Gy ⁻¹	27.9 per 10 ⁴ PY	9.5 (6.1, 13) per (10 ⁴ PY Gy)	3.63 per 10 ⁴ PY	^d 1.2 (0.80, 1.70) per (10 ⁴ PY Gy)
EAR per unit dose	9.5 (6.1, 14.0) per (10 ⁴ PY Gy)				9.5 (6.1, 14.0) per (10 ⁴ PY Gy)
Colon cancer risk per unit dose (Gy⁻¹), sex averaged [P14], table 18					
ERR per unit dose	0.54 (0.30, 0.81) Gy ⁻¹	14.8 per 10 ⁴ PY	8.0 (4.4, 12) per (10 ⁴ PY Gy)	15.2 per 10 ⁴ PY	^d 8.2 (4.6, 12.3) per (10 ⁴ PY Gy)
EAR per unit dose	8.0 (4.4, 12.0) per (10 ⁴ PY Gy)				8.0 (4.4, 12.0) per (10 ⁴ PY Gy)

^a Estimated as the LSS ratio of site-specific EAR to ERR coefficients.

^b LSS ERR × LSS baseline.

^c Baseline incidence at age 70 from SEER 14-registry data [15].

^d LSS ERR × SEER baseline.

C7. *Gastric cancer: Baseline rates in Japan and the United States.* For gastric cancer, age-specific population incidence rates in Japan are roughly an order of magnitude higher than those in the United States [I5], and there is strong evidence of a radiation dose response over the dose range 0–4 Gy among members of the LSS cohort [P14]. Along with the LSS breast cancer estimates just discussed, table C1 presents sex-averaged, linear model estimates of ERR per unit dose and EAR per unit dose for gastric cancer at attained age 70 following exposure at age 30, with 90% confidence intervals ([P14] table 12). As is the case with breast cancer, the relevant LSS baseline risk for gastric cancer at age 70 in the year 1985 can be estimated as the ratio of the EAR to the ERR per unit dose estimates, i.e. 9.5 per (10^4 PY Gy) divided by $0.34 = 27.9 \text{ Gy}^{-1}$. According to [I5], the current sex-averaged gastric cancer rate at age 70 in the United States, as represented by the 14-centre SEER Registry, is 3.63 per 10^4 PY, or 7.7-fold less than the corresponding LSS rate. Multiplying the LSS estimate for ERR per unit dose, 0.34 (90% CI: 0.22, 0.47) Gy^{-1} , by this baseline rate yields a multiplicative model projection of the LSS estimate for the United States population, EAR per unit dose of 36 (90% CI: 23, 54) per (10^4 PY Gy) that is 4-fold higher than the corresponding additive model projection given by the LSS EAR per unit dose estimate, 9.2 (90% CI: 6.8, 12) per (10^4 PY Gy).

C8. *Gastric cancer: United States cervical cancer study.* Unlike breast cancer, very few published estimates of radiation-related gastric cancer risk are available for comparison with the LSS ERR and EAR estimates in table C1. One source is a large case–control incidence study of women treated for cervical cancer, mostly by radiotherapy [B16]. Cases (i.e. patients who developed a second cancer) and their matched controls were identified based on records from 20 clinical centres and 19 tumour registries in Canada, Europe, and the United States. Stomach doses averaging 2 Gy were associated with a borderline elevated gastric cancer risk (ERR at 1 Gy = 0.69 with 90% CI: 0.01, 2.25). As in most epidemiological studies, the confidence interval is just based on statistical fluctuations and does not take into account other sources of uncertainty, such as uncertainties of the dose estimates. A “crude” approximate estimate of EAR per unit dose, 3.16 (90% CI: 0.05, 10.4) per (10^4 PY Gy), was calculated from the estimated ERR at 1 Gy multiplied by an estimate of baseline gastric cancer incidence based on previous cohort analyses for the appropriate person-years of observation [B16]. That estimate is statistically consistent with both the LSS multiplicative and additive gastric cancer projections in table C1 part 2, but is closer to the multiplicative projection. However, the authors cautioned that a relatively large number of the second cancers identified in the stomach were without pathological confirmation [B16]. An additional, somewhat minor consideration is that women with cervical cancer might not have the same baseline gastric cancer risk as the general population.

C9. *Gastric cancer: United States peptic ulcer study.* A long-term follow-up study of American peptic ulcer patients given multiple therapeutic doses of 250 kVp X-rays to the stomach found a statistically significant overall excess of gastric cancer mortality in 1,860 patients irradiated between 1937 and 1965 compared to 1,859 non-irradiated patients treated between 1929 and 1959 [C6, G19]. Cumulative radiation doses, averaged over the entire stomach (mean 14.8 Gy, standard deviation 5.6 Gy, and range 1–42 Gy) and delivered in one or two 6- to 14-day courses of treatment, were far higher among the irradiated patients than those estimated for any members of the LSS cohort. The estimated ERR per unit dose over the entire dose range, based on 1,475 patients with more than 10 years of follow-up and an approximately equal number of non-exposed patients, was 0.06 (95% CI: 0.02, 0.10) Gy^{-1} , significantly lower than the LSS estimate of 0.34 (90% CI: 0.22, 0.47) Gy^{-1} [P12]. However, the estimated ERR per unit dose based on the 309 patients who received stomach doses of 10 Gy or less (mean dose 8.9 Gy) was 0.20 (95% CI: 0.0, 0.73) Gy^{-1} , which is statistically consistent with the LSS estimate based on radiation doses under 5 Gy.

C10. *Gastric cancer: implications for projection from the LSS cohort.* The estimated values of ERR per unit dose obtained from the peptic ulcer study [C6, G19] for different dose ranges are consistent

with the LSS estimate of 0.34 (90% CI: 0.22, 0.47) Gy⁻¹ and inconsistent with estimates an order of magnitude higher, as would be implied by an additive model projection from the LSS to the United States SEER population. The cervical cancer study results [B16] are also consistent with multiplicative projection from the LSS but, because of wider confidence bounds for the ERR per unit dose, they are not significantly different from the LSS additive projection.

C11. *Colon cancer.* The third analysis shown in table C1, for sex-averaged colon cancer, is methodologically similar to those for female breast cancer and for gastric cancer. In the case of colon cancer, however, baseline rates at age 70 are similar between the LSS cohort and the SEER registry, and consequently there is little difference between additive and multiplicative projections from the LSS cohort to the United States SEER population. Risk estimates based on populations other than the LSS cohort pertain mainly to patients receiving radiotherapy directed at nearby organs, and are generally consistent with the LSS cohort findings, for example, an ERR per unit dose of 0.5 Gy⁻¹ for colon cancer mortality among women who received colon doses under 5 Gy following irradiation with intra-uterine radium (²²⁶Ra) capsules (used for treating benign gynaecological bleeding disorders) [I21]. In this case there is some support for multiplicative projection, but with essentially no consequences in terms of projected risk.

C12. *Possible relevance of biological mechanisms for radiation-related cancer.* Both additive and multiplicative projections are plausible in terms of biological mechanisms. For example, to the extent that different baseline rates in the two populations reflect differential exposure to cancer initiators, and assuming that ionizing radiation acts mainly as a cancer initiator, one might expect the dose-specific EAR to be the same regardless of baseline rate while, to the extent that the difference in baseline rates reflects differential population exposure to cancer promoters, the dose-specific EAR might be expected to increase or decrease proportionally to the baseline rate [N7]. Probably, both kinds of interaction are involved to some extent and, in the absence of more detailed information on competing initiators and enabling or disabling promoters, it may be useful to model the process as a random mixture of interactions of radiation with such baseline risk modifiers. Thus, additive projection would seem to be strongly supported by the analytical results for the pooled breast cancer analysis involving only the LSS, pneumothorax, and thymic irradiation cohorts, but not by the results for women therapeutically irradiated for benign breast disease in general, acute post-partum mastitis in particular, or skin haemangioma. The gastric cancer dose–response comparisons are more consistent with multiplicative projection from the LSS compared to the additive projection. However the support from these comparisons is not as clear-cut as that provided for breast cancer by the data on the atomic bombing survivors, pneumothorax patients and thymic irradiation patients. Both analyses, and particularly the gastric cancer example, leave room for uncertainty about the appropriateness of choosing either of the two simple projection models.

C13. *Expressing uncertainty about the relationship between excess and baseline risk: the interactive NIH radioepidemiological tables program (IREP) and NRC BEIR VII committee examples.* In cases where baseline risk differs between two radiation-exposed populations, as it does in the breast cancer and gastric cancer examples given above, it is certain that multiplicative and additive projections of radiation-related risk from one of the populations to the other will differ, and thus there is a very real possibility that whatever projection is chosen will be wrong if it is not supported by comparisons of dose–response data from both populations. In general, it seems reasonable to incorporate subjective expressions of the uncertainty about the choice of projection model into the estimate of radiation-related risk for the population of interest. This is particularly so when the choice of estimate has consequences for public policy such as radiation protection or adjudication of compensation claims for radiation-related cancer as was the case for the 2003 NIH radioepidemiological tables report [L5]. This is also the case for the 2006 BEIR VII report [N19], which is an important information resource for lifetime risk projections developed at the National Cancer Institute [B7].

C14. For most cancers, the 2003 NIH working group [L5] used a subjective, uncertain mixture of additive and multiplicative projection models for transferring cancer risk from the LSS cohort (based mainly on LSS Tumor Registry data [T4]) to the United States population, as follows:

$$\text{Projected risk} = X \times (\text{additive risk}) + (1 - X) \times (\text{multiplicative risk}) \quad (\text{C.3})$$

where X is a Bernoulli (p) random variable with uncertain parameter p uniformly distributed over the unit interval (0, 1) with probability 0.95, triangular (-0.1, 0, 0) with probability 0.025, and triangular (1, 1, 1.1) with probability 0.025 to express complete uncertainty between the two simple projection models and to allow for the possibility that the truth might lie outside the additive-multiplicative domain. For breast cancer, the uncertain Bernoulli distribution parameter was assigned the value $p = 1$ with probability 0.5, and the model described by equation (C.3) was uniformly distributed with probability 0.5. For stomach cancer the IREP task group assigned probability 0.5 to the value $p = 0$ and 0.5 probability to model (C.3).

C15. Like the 2003 NIH working group, the BEIR VII committee [N19] expressed radiation-related risk as a stochastically weighted average of an addition (EAR) to and a multiplier (ERR) of baseline risk. EAR and ERR were formulated as sex-specific functions of radiation dose (D), age at exposure (e), attained age (a), and time (t) between exposure and observation for risk (essentially, $t = a - e$):

$$\text{Risk}(\text{pop}, D, e, a, t) = \text{baseline}(\text{pop}, a) + \text{EAR}(D, e, a, t) \quad (\text{C.4})$$

and

$$\text{Risk}(\text{pop}, D, e, a, t) = \text{baseline}(\text{pop}, a) \times (1 + \text{ERR}(D, e, a, t)) \quad (\text{C.5})$$

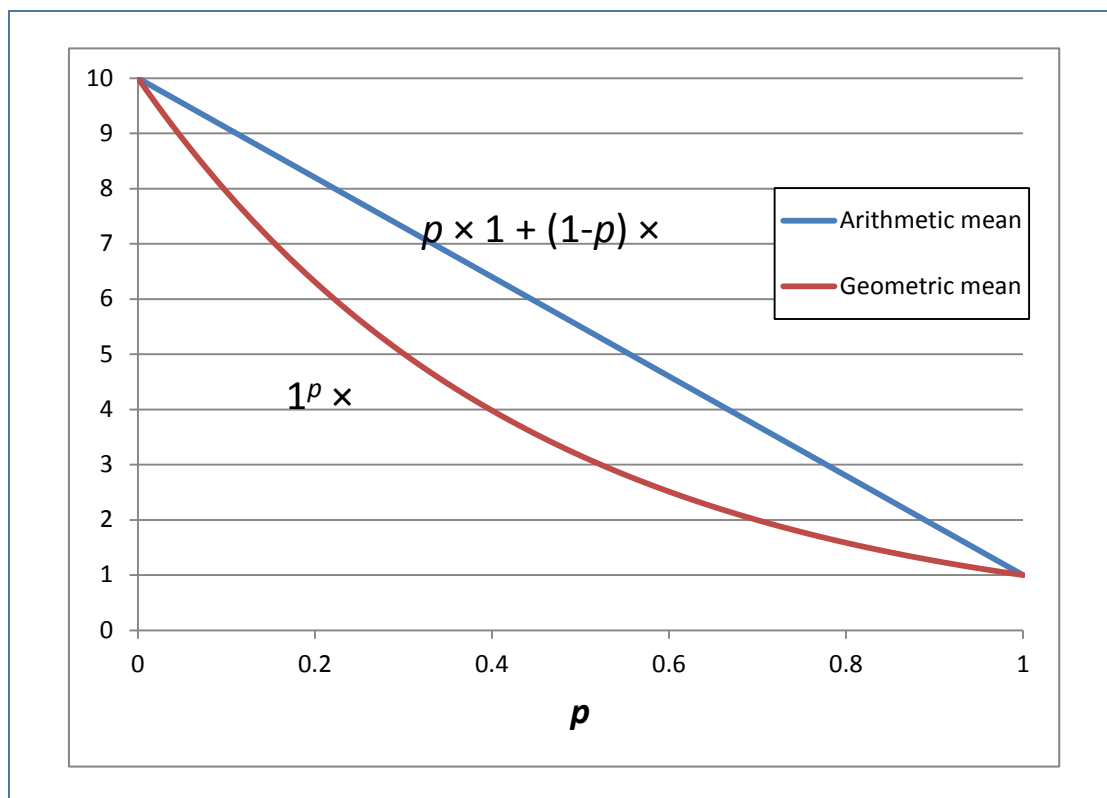
Most site-specific formulations of EAR and ERR for solid cancers were based solely on analyses of incidence data from the LSS cohort of atomic bombing survivors studied by the Radiation Effects Research Foundation [P14]. One exception was the female breast, for which the approach of [P11], as discussed above, was used with the 1958–1984 LSS tumour registry data replaced by then unpublished 1958–1998 data [P14]. Another exception was thyroid [R3], also used by NIH IREP, for which the formulations were based on pooled analyses of site-specific dose–response data from several different study populations, including the atomic bombing survivors; and another was leukaemia (all types combined except CLL) which was based on mortality data from an earlier LSS analysis [P13].

C16. *Comparison of IREP and BEIR VII.* For most cancer sites, the BEIR VII algorithm is based upon more recent data than the earlier NIH (IREP) algorithm, and is to be preferred for that reason. However, there are other differences that may favour the IREP approach. Both committees assumed that thyroid cancer risk was multiplicative and that leukaemia risk was additive with respect to site-specific population baseline risk. BEIR VII used additive risk for breast cancer, with no probability assigned to multiplicative risk, whereas the NIH IREP committee [L5] used a random mixture of additive and multiplicative risks, strongly weighted toward additivity. For all other cancers addressed except lung cancer, the BEIR VII mixture between additive and multiplicative interaction was on a logarithmic scale with weights of 0.7 for a multiplicative projection and 0.3 for an additive projection. For lung cancer this weighting was reversed: 0.3 for the multiplicative and 0.7 for the additive projection. Compared to arithmetic averaging, as in IREP, the BEIR VII multiplicative averaging scheme is biased towards lower estimated risk because the geometric mean (weighted or unweighted) of two positive numbers is never greater than the arithmetic mean (figure C-I), that is:

$$x^p \times y^{1-p} \text{ is always less than or equal to } p \times x + (1 - p) \times y \text{ for } 0 < p < 1, y > 0 \text{ and } x > 0. \quad (\text{C.6})$$

Figure C-I. Comparison of p -weighted arithmetic and geometric means of 1 and 10 for fixed values of the parameter p between 0 and 1

Given p , the arithmetic mean is $p \times 1 + (1-p) \times 10$ and the geometric mean is $1^p \times 10^{1-p}$



C17. *Summary.* The comparison of the IREP and BEIR VII approaches to transfer between populations of risk estimates when additive and multiplicative risk projections differ, show that choice of a mixture algorithm can make a substantial difference. The geometric and arithmetic mixture algorithms agree at the extremes, where $p=0$ or $p=1$, but as shown by the ratio of arithmetic to logarithmic mixtures, the geometric mixture always gives a smaller risk estimate for intermediate values of p . When the two projections differ substantially, and when the mixture algorithm is more or less evenly weighted between additive and multiplicative mixtures, (e.g. for $p=0.5$), the difference can be substantial. In this case, a choice made for computational convenience may unduly influence the conclusions.

II. EXTRAPOLATING RISKS OVER LIFETIME

C18. Typically, for epidemiological studies of cancer risk in irradiated populations which have been followed over time following a single exposure, accumulated information on radiation dose will be specific with respect to age e at exposure and information on subsequent disease events will be specific with respect to age a at observation or (equivalently) time $t = a - e$ following exposure, assuming survival until age a . In the BEIR VII report [N19] site-specific, radiation-related solid cancer risks and

leukaemia risks in the LSS cohort were modelled as uncertain parametric functions of sex s , neutron-weighted radiation dose D , exposure age e , and attained age a . Both additive and multiplicative models were estimated, as follows:

$$\text{Risk}_{\text{add}}(D, s, e, a) = \text{Base}(s, e, a) + \beta_{s,\text{add}} D \exp(\gamma e^*) (a/60)^\eta \quad (\text{C.7})$$

$$\text{Risk}_{\text{mult}}(D, s, e, a) = \text{Base}(s, e, a) [1 + \beta_{s,\text{mult}} D \exp(\gamma e^*) (a/60)^\eta] \quad (\text{C.8})$$

The above representation is adapted from BEIR VII table 12–2 [N19] to represent total, rather than excess risk as in the original table. The uncertain, sex-specific parameters $\beta_{s,\text{add}}$ and $\beta_{s,\text{mult}}$ are specified in the BEIR VII report [N19] as log-normal random variables with tabulated medians and 95% confidence intervals, pertaining to exposure age e and attained age a . The symbol e^* represents $(e - 30)/10$ for $e \leq 30$ and zero for $e > 30$ for all cancer sites represented by the BEIR VII committee.⁵ Both the original and the adapted formulae are complex, requiring eight footnotes in the original publication to record details.

C19. For present purposes, which are concerned with lifetime risk projection, it is sufficient to consider two examples: female breast cancer, and stomach cancer among males. The BEIR VII committee's preferred model [N19] for female breast cancer was that of additive risk which, as estimated from a pooled analysis by Preston et al. [P11], was consistent across four exposed population data sets including the Japanese atomic bombing survivors and three populations of American women exposed for reasons unrelated to breast disease, two of which received multiple chest fluoroscopy examinations during lung collapse therapy for tuberculosis and one which received radiation therapy during infancy for a condition that was at one time considered to be a dangerously enlarged thymus gland. The preferred linear model risk estimate, that for excess absolute risk per 10^4 person–years per gray at age a following exposure at age e , is

$$\text{EAR}(D, e, a) = \beta D \exp(-0.51 \max(0, e-30)/10) (a/60)^\eta \quad (\text{C.9})$$

where β is distributed as log-normal with median 9.4 and 95% confidence intervals (6.7, 13.3), and the value of η is 3.5 for $a \leq 60$ and 1.1 for $a > 60$, and where a 5-year minimum lag period was assumed between radiation exposure and cancer diagnosis.

C20. An interactive computer program under development at the United States National Cancer Institute and called RadRAT for “Radiation Risk Assessment Tool,” calculates estimated lifetime, site-specific excess cancer risks associated with user-provided data on organ-specific radiation dose, age at exposure, sex, and other factors of interest [B8]. The concept is straightforward: age-specific excess risk at age a following a single exposure at age e is modelled as an uncertain function of a , e , and dose D as in the BEIR VII-based risk model formula given in the previous paragraph. For a single exposure, age-specific risk estimates are calculated for each attained age a following the stipulated exposure age e , and summarized as a life table-weighted sum over all ages a greater than e , conditional on survival until age e . For several exposures at different ages, separate calculations could be performed for each exposure and summed, conditional on survival until the oldest exposure age.

C21. For gastric cancer among males, the additive BEIR VII model [N19] for excess absolute risk at age a per 10^4 person-years per gray following exposure at age e is

$$\text{EAR}_{\text{add}}(D, e, a) = \beta D \exp(-0.41 \max(0, e-30)/10) (a/60)^{2.8} \quad (\text{C.10})$$

where β is log-normal 4.9 (95% CI: 2.7, 8.9).

⁵ There is a possible exception for breast and thyroid, because the text on BEIR VII pages 272-273 [N19] is contradictory.

C22. The BEIR VII report [N19] allows for the possibility that radiation-related gastric cancer risk is multiplicative as well as additive with respect to baseline risk. The corresponding absolute risk value for a multiplicative risk model is

$$\text{EAR}_{\text{mult}}(D, e, a) = \text{Base}(s, a) \text{ERR}(D, e, a) \quad (\text{C.11})$$

where $\text{Base}(s, a)$ is the baseline risk for sex s and attained age a at dose zero assuming survival until age a .

$$\text{ERR}(D, e, a) = \beta D \exp(-0.30 \times \max(0, e-30)/10) (a/60)^{-1.4} \quad (\text{C.12})$$

again assuming survival to age a , and where β is log-normal 0.21 (95% CI: 0.11, 0.40).

C23. The BEIR VII report recommended that the multiplicative and additive model estimates should be combined in the form of a weighted geometric mean of $\text{EAR}_{\text{add}}(D, e, a)$ and $\text{EAR}_{\text{mult}}(D, e, a)$ ([N19], table 12–5B). As discussed above in section A of this appendix, there are some arguments against the use of geometric as opposed to arithmetic means.

III. TRANSFER TO LOW-DOSE AND LOW-DOSE-RATE EXPOSURE WITH LOW-LET RADIATION

C24. The estimates of excess cancer risks among the atomic bombing survivors relate to acute exposure with mainly moderate to high doses of low-LET radiation. Most radiation exposures in occupational or medical diagnostic settings, however, occur at low doses or low dose rates and over longer times. For radiation protection purposes, an extrapolation of risk coefficients obtained from the LSS for the atomic bombing survivors has been used in conjunction with a “dose and dose-rate effectiveness factor (DDREF)” [I14]. This specific interpretation of DDREF has to be differentiated from the results of biological experiments, in which some biological end points are studied for animals or cell cultures with different radiation exposures but otherwise similar conditions. To be more specific, it is not straightforward to apply radiobiological results of the DDREF derived from biological experiments directly to transfer risk values from the LSS to occupational or medical exposures in populations that have a lifestyle and genetic background different from the atomic bombing survivors. However, such an application of radiobiological results is justified as an approximate approach so long as no sufficient epidemiological data are available. In this context it is important to note that epidemiological studies of cancer risks after low-dose or low-dose-rate exposures are becoming increasingly relevant because of the longer follow-up of the historical cohorts of exposed persons, and because of improvements in dosimetry, health data and statistical methods. The present section reviews the emergence of the concept of DDREF and relevant new radiobiological and epidemiological evidence; and provides an evaluation of the uncertainty related to extrapolating risk coefficients from the LSS to low-dose and low-dose-rate exposures of other populations.

A. Statements of various bodies up to the UNSCEAR 2006 Report

1. UNSCEAR

C25. In the UNSCEAR 1977 Report, the Committee based the derivation of dose–response relationships for radiation-induced cancer on experimental work on animals, because “the human epidemiological evidence is (in general) too limited, either in the range of radiation exposures or in the precision of estimated cancer induction at each dose, to establish clearly the mathematical form of this dose–effect relationship” [U6]. The Committee concluded that the excess cancer risk per unit dose at low doses might be substantially lower than the values derived from the atomic bombing survivors with exposures to gamma rays with doses of the order of 1 Gy. According to annex G, “Radiation carcinogenesis in man”, of the UNSCEAR 1977 Report, the Committee concluded on the basis of observations of genetic effects of low-LET radiation that excess risks per unit dose at low doses could be lower by a factor of 2 to 4 than those for doses of the order of 1 Gy. The Committee emphasized that dose–response curves varied among cancer locations, with cancer in the female breast possibly not showing any dose or dose-rate effect.

C26. In annex B, “Dose–response relationships for radiation-induced cancer”, of the UNSCEAR 1986 Report, the Committee used a linear–quadratic dose–response model for analysing experimental data on chromosomal exchanges, mutations and induction of some malignancies [U7]. It was estimated that incidence of radiation-induced health effects per unit dose at about 10 mGy are lower than at about 1 Gy by a factor of about 1.5 to 3.0. Based on animal data, the Committee concluded that a linear extrapolation of risk coefficients obtained at acute exposures with doses of the order of 1 Gy to low dose or low dose rates “would very likely overestimate the real risk, possibly by a factor of up to 5”. The Committee defined low dose as being less than 0.2 Gy and low dose rate independent of the dose as being less than 0.05 mGy/min.

C27. In its 1988 Report, the Committee concluded that the risk at low doses might be lower than the estimated values by a factor in the range of 2 to 10, depending on the dose, dose rate and exposed organ [U8].

C28. Based on fractionation effects observed for the induction of cancer in animal studies, the Committee defined in its 1993 Report [U9] low dose rates as those less than 0.1 mGy/min of low-LET radiation averaged over an hour. The Committee recommended the application of a DDREF for the assessment of cancer risks from low-dose or low-dose-rate exposures. Annex F of the 1993 Report concluded that DDREF values obtained from animal experiments ranged up to 10. However, the Committee pointed out that there was little evidence in epidemiological studies of a lower effectiveness for solid cancer induction after low-dose exposures, with the exception of breast and thyroid cancer. For cancer in these two tissues, the Committee judged the DDREF to be of the order of 3. The Committee recommended the adoption of a value for the DDREF not larger than 3.

C29. In its 2006 Report, the Committee notes that a value of DDREF much larger than 2 would not be consistent with the data for the atomic bombing survivors ([U12] annex A). In contrast to its earlier reports, the Committee explicitly calculated lifetime cancer risks using a linear–quadratic and a linear–quadratic–exponential dose–response model. In a related publication, the linear–quadratic model was favoured [L19]. According to this model, the lifetime risks per unit dose at doses of 0.01 Sv and 0.1 Sv were lower than that at a dose of 1.0 Sv by about 20%. In the linear–quadratic–exponential model, the risks per unit dose at 0.01 and 0.1 Sv were lower than that at a dose of 1.0 Sv by a factor of 2 and 3, respectively. Both models implicitly adjust for extrapolation to low doses. The Committee added that no extra adjustment for chronic exposure (i.e. the application of a DDREF) was needed. Because of the

large uncertainties involved, the calculations are consistent with an assumed value of 2 for the DDREF at low-dose and low-dose-rate exposures. Based on these considerations, the Committee defined a value of 0.1 Gy as an upper value of the low dose range ([U12] annex A, table 6).

C30. Non-targeted and delayed cellular effects of radiation (including genomic instability), i.e. bystander effects* that manifest in neighbours or descendants of cells directly hit by radiation, have been reported for exposures with low and moderate dose. These effects raised concerns about the linear no-threshold dose–effect model. Annex C of the 2006 Report of the Committee surveyed these new developments in radiation biology [U13], but concluded at that time that the data currently available did not require changes in risk coefficients for cancer and hereditary effects in humans of radiation exposure. Nevertheless the Committee continues to follow developments in this area.

2. Other bodies

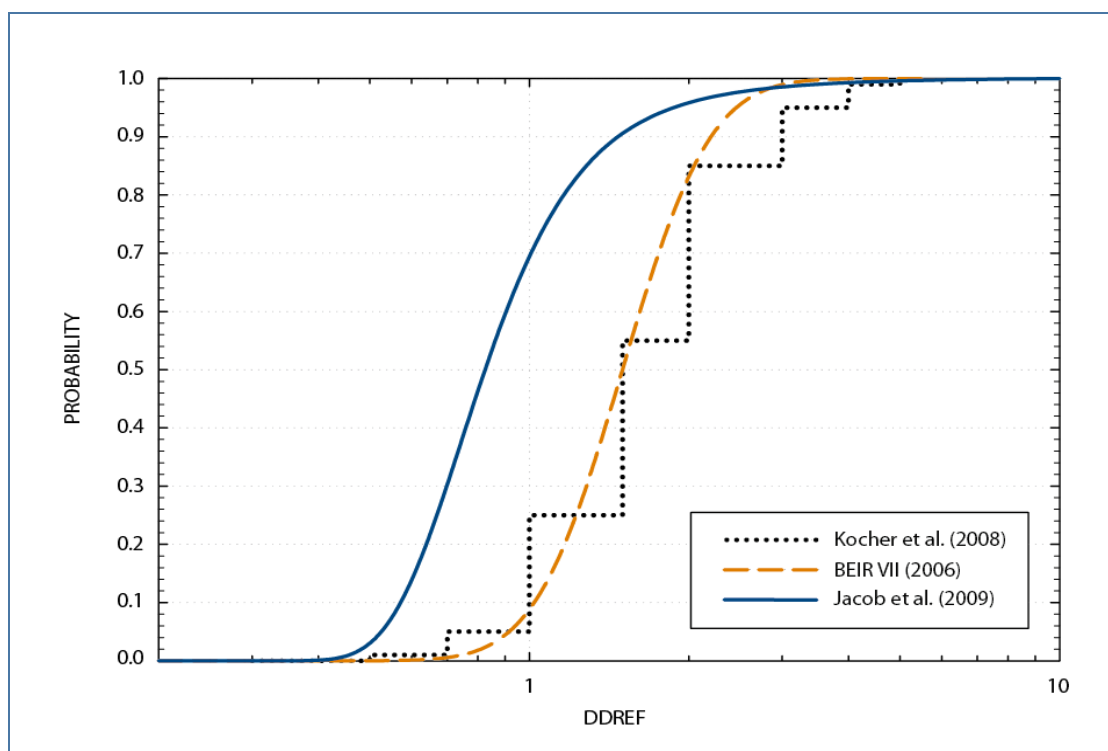
C31. In its 1990 Recommendations of the International Commission on Radiological Protection, ICRP included a DDREF in the calculation of nominal risk coefficients for exposures with absorbed doses below 200 mGy and for exposures with higher absorbed doses when the dose rate is less than 100 mGy per hour [I26]. These values are broadly consistent with the definition of low dose and low dose rate adopted by the Scientific Committee in its 1988 Report [U8]. ICRP noted that “the full range of DDREF values obtained from studies in animals, namely 2–10, may extend over a broader dose range than human data and therefore include higher values than are relevant,... some human experience shows little evidence of fractionation effects while others indicate possible effects of up to 3 or 4 at most” and “direct statistical assessment of the A-bomb survivor data does not seem to allow for much more than a factor of 2 for the DDREF”. Based on these observations, ICRP adopted a value of 2 for the DDREF and considered this as conservative. In the 2007 Recommendations of the International Commission on Radiological Protection ICRP continued to use a value of 2 for the DDREF in calculations of nominal risk coefficients for exposure with doses below about 100 mSv and emphasized that “different dose and dose-rate effects may well apply to different organs/tissues” [I14].

C32. The BEIR VII committee of the United States National Research Council derived a probability density function for the DDREF for an analysis of cancer risks at low doses or low dose rates of ionizing radiation and its uncertainties [N19]. Low doses were defined by the range of doses below 100 mGy of low-LET radiation, low dose rates by the range below 0.1 mGy per minute. Medium doses are defined as doses in excess of 100 mGy up to 1 Gy. BEIR VII analysed mouse data to motivate the assumption that the reduction in risk for low doses is equal to the reduction in risk for dose protraction. Based on a Bayesian analysis of animal data on cancer risk and life shortening, a probability density function of the DDREF with a mode of 1.5 and a 95% credible interval from 1.0 to 4.4 was obtained. An analysis of the atomic bombing survivors resulted in a probability density function for the DDREF with a mode of 1.3 and a 95% credible interval from 0.8 to 2.6. Combining both distributions, BEIR VII obtained a probability density function for the DDREF with a mode of 1.5 and a 95% credible interval from 1.1 to 2.3. Having performed this analysis, BEIR VII considered the resulting uncertainty distribution as misleadingly narrow and increased the variance of the logarithm of the DDREF to a subjectively chosen value of 0.09. Assuming a log-normal distribution this corresponds to a geometric standard deviation of 1.35, which leads to a 95% adjusted credible interval of 0.82 to 2.73.

C33. In the Interactive RadioEpidemiological Program (IREP), Kocher et al. use a discrete probability density function for the DDREF [K7]. The distribution has a mean of 1.8, the lowest value assumed is 0.5, the highest value is 4.0 (see figure C-II).

Figure C-II. Cumulative probability density functions for the DDREF

The smooth solid line corresponds to the inverse of a combined estimator of the ratio of the excess relative risks for solid cancer in low-dose-rate, moderate-dose studies and the excess relative risk among atomic bombing survivors for the same group of cancer types, organ dose, gender distribution and corresponding age at exposure and age attained [J5]. The smooth broken line gives the distribution as derived by BEIR VII [N19]. Note that BEIR VII used in its risk calculations an uncertainty distribution with a width larger than that given in the figure. The dotted line gives the discrete distribution used in IREP [K7]



B. New radiobiological information

C34. The Committee summarized biological effects at low radiation doses in annex G of its 2000 Report [U11] and updated the statement by information on non-targeted and delayed biological effects of exposure to ionizing radiation in the 2006 Report [U12]. This present section summarizes shortly new information in the field of radiobiological research potentially relevant to an evaluation of the uncertainty in the DDREF for solid cancer after exposure to low-LET radiation with low doses, or with moderate doses with low dose rates.

C35. Recent research supports the thesis that radiation causes damage to DNA in linear proportion to dose over a wide range of doses down to very low doses [L20]. Also, the reduction rate of the number of phosphorylated ataxia telangiectasia mutated (ATM) foci with time after exposure did not depend on dose in a range of 10 mGy to 1,000 mGy [S34]. However, a number of observations show that the DNA damage response to that damage might well be non-linear [G24, N13, O2]. A DNA damage threshold level seems to be required, for example, for the activation of the early G2/M cell cycle checkpoint resulting in low-dose hypersensitivity in the survival of many—but not all—cell types [D7, L21, W12]. In summary, it is unclear whether double-strand-break (DSB) repair is equally efficient after exposures with low and moderate/high doses.

C36. Bystander effects, such as mutations, chromosomal aberrations or apoptosis, are induced at low doses and saturate at moderate doses [N1, P7]. It is presently unclear whether such bystander effects influence carcinogenesis after radiation exposure, and, if yes, whether they are protective or detrimental.

C37. Gene expression and phosphoproteomics profiling suggest differences in processes induced by low and moderate doses of low-LET radiation. A number of studies identified genes that were modulated by low doses but not by high doses [F6, J14, K18, L24, S13]. In another study, the number of genes with changed expression was found to increase with dose rate, indicating that higher dose rates influence more cellular processes than low dose rates [U4]. Analyses of the proteome indicated overlapping and unique biological processes after exposures with 20 mGy and with 500 mGy [Y2]. Overall, the state of knowledge on gene expression and proteome abundance after exposure to ionizing radiation and its relevance to carcinogenesis is still very limited.

C38. In its 2006 Report [U12], the Committee stated that the implications of non-linear dose responses of cellular effects for the form of the dose response of carcinogenesis in humans are unclear. The statement remains valid for the new finding described above. In summary, cellular radiation biology contributes in only a limited manner to an extrapolation of observable cancer risks at high/moderate doses to low doses, and thus to quantifying the DDREF.

C39. Recent experiments on solid cancer in irradiated mice resulted in values of the excess relative risk per unit dose at about 0.1 Gy comparable or even larger than those at about 1.0 Gy [C19, S3, S4]. There is thus little evidence in recent animal experiments that the ERR per unit dose for solid cancer is lower for low doses than for dose values that were relevant for determining risk values in the LSS (0.2 to 2 Gy).

C40. It has been argued in the literature that the response of cells, tissues, organs or the whole body to damage caused by ionizing radiation may involve deterministic mechanisms that may lead to practical thresholds in the dose response [F3, T9]. Such mechanisms include: scavenging of toxins; molecular repair of DNA; removal of damaged cells by apoptosis, necrosis, phagocytosis, cell senescence or immune responses; or loss of the potential for self-renewal of preneoplastic cells by differentiation. A prolongation of life span of mice exposed at low dose rates has been found and associated with immunological modifications [I20]. The Committee acknowledges that developments in studies on these kinds of mechanisms need to be followed to gain better insight for the evaluation of health risks from low-dose or low-dose-rate exposures.

C. New epidemiological information

C41. Muirhead et al. analysed an update and extension of mortality and cancer incidence data for the United Kingdom National Registry for Radiation Workers [M21]. This study is a large study of cancer after occupational exposures. It includes 114,541 workers with exposures mostly to X-rays and gamma-rays. The mean badge dose was 24.9 mSv. In total, 68% of the workers had doses below 10 mSv, 26% in the range of 10–100 mSv, and 6% of the doses exceeded 100 mSv. The data on workers demonstrated a strong healthy worker effect: the standardized mortality ratio for malignant neoplasms was 0.84 with a 95% confidence interval from 0.82 to 0.86. As in most epidemiological studies, the confidence interval is just based on statistical fluctuations and does not take into account other sources of uncertainty, such as uncertainties of the dose estimates. In analyses with a linear dose–response model, all four estimates of excess relative risks per unit dose for mortality from and

incidence of leukaemia and of malignant neoplasms excluding leukaemia were found to be significant (table C2) and to be consistent with corresponding values among the atomic bombing survivors.

Table C2. Best estimates and 90% confidence intervals of excess relative risks per unit dose (Sv^{-1}) in the third analysis of the United Kingdom National Registry for Radiation Workers [M21]

Outcome	Leukaemia excluding CLL	Malignant neoplasms excluding leukaemia
Mortality	1.7 (0.06, 4.3)	0.28 (0.02, 0.56)
Incidence	1.8 (0.17, 4.4)	0.27 (0.04, 0.51)

C42. A larger number of epidemiological studies on solid cancer risks after low-dose-rate, moderate-dose exposures has been published recently and is summarized in appendix D.

C43. Jacob et al. evaluated 12 recent studies of solid cancer mortality and incidence after protracted exposure with moderate cumulative doses [J5]. For each of the low-dose-rate, medium-dose studies, they calculated the risk for the same types of cancer among the atomic bombing survivors with the same gender proportion and matched quantities for dose, mean age attained and mean age at exposure. The main analysis included seven independent mortality studies: five on radiation workers, one on emergency and clean-up workers after the Chernobyl accident, and one on the residents of villages located along the banks of the Techa River in the Southern Urals. Analyses of the remaining mortality studies and of the incidence studies were consistent with the main analysis. In the main analysis, the combined estimator of the ratio of the excess relative risk per unit dose from the low-dose-rate, medium-dose study to the corresponding value for the atomic bombing survivors was found to be 1.21 (90% CI: 0.51, 1.90). Omitting one of the studies changes the best estimate of the ratio at most by 26%. The lowest risk ratio with a value of 0.96 (90% CI: 0.12, 1.80) was obtained when the study of the Techa River residents was excluded. The highest risk ratio with a value of 1.44 (90% CI: 0.48, 2.41) was obtained when the study of the United Kingdom radiation workers was excluded. It is noted that none of the low-dose-rate, moderate-dose studies took dose uncertainties into account. It can be expected that the uncertainty ranges of the risk estimates become larger, if such uncertainties are taken into account.

D. Evaluation of the uncertainty of the DDREF

C44. This section summarizes results on the distribution of the DDREF specifically for the transfer of excess risks as observed among the atomic bombing survivors to low-dose or low-dose-rate exposures. Figure C-II illustrates distributions obtained by:

- (a) BEIR VII from a Bayesian analysis of cancer and life shortening data in mouse experiments, and of solid cancer incidence among the atomic bombing survivors [N19];
- (b) Kocher et al. by evaluating radiobiological and epidemiological data for an application in the Interactive RadioEpidemiological Program [K7];
- (c) Jacob et al. by a comparative analysis of recent low-dose-rate, medium-dose epidemiological studies and data for the atomic bombing survivors [J5].

The ratio of the upper and lower bounds of the 95% confidence intervals for the DDREF were 3.2 in the risk calculations of BEIR VII [N19] and 5.7 in the distribution assumed in [K7]. In the analysis of

recent epidemiological data the ratio of the bounds of the 90% confidence interval was 3.7 [J5]. Based on these results, the Committee considers that the present knowledge or degree of belief of the value of the DDREF may be expressed by an uncertainty range with a ratio of the upper and lower bounds of the 90% confidence interval in the order of four but not smaller.

C45. The Committee acknowledges that recent epidemiological studies do now allow for a direct assessment of the uncertainty distribution for the ratio of relative cancer risks in low-dose-rate, medium-dose exposure scenarios and among atomic bombing survivors. Such exposure scenarios are typical for workers with higher occupational exposures. Recent epidemiological work indicates risk per unit dose values for such exposures similar to those observed in the LSS for the atomic bombing survivors. The geometric standard deviation of the probability density function for the DDREF is estimated to be about 1.5 (see figure C-II). For higher dose rates/doses the uncertainty of the DDREF is assumed to be less, for lower dose rates/doses to be larger.

E. Uncertainty associated with the projection of risk to the region of low and very low doses

C46. Sometimes situations arise where a projection of risk is required for exposed or potentially exposed individuals or populations in which cumulative doses are substantially below levels for which there is direct epidemiological evidence of a statistically significant increase in health effects. In these situations, the uncertainty in risk projection should include uncertainty in the dose–response models used to extrapolate risk beyond the domain of direct epidemiological evidence. Model uncertainty (see appendix B) ought to be addressed through consideration of alternative dose–response functions each of which represents a plausible biological explanation for the extrapolation of risk to low and very low cumulative doses (cumulative doses substantially less than 100 mGy in addition to the 1 mGy to 10 mGy contributed annually by background from natural sources of radiation).

C47. Alternative risk projection models used to extrapolate risk to the region of low and very low cumulative dose may include dose–response functions that are non-linear with respect to the incremental cumulative dose above background. Such dose–response functions may include a threshold dose, below which the incremental increase in risk with increasing dose is zero, or negative. The degree of plausibility attributed to a given dose–response model is represented by an assigned fraction or weight. This weight would be determined by (a) the extent to which the model adequately explains the dose–response function in epidemiological studies for which there is direct evidence of a statistically significant relationship between an increase in cumulative dose and an increase in disease and (b) the extent to which there is evidence for biological mechanisms that support the extension of the model to estimate risk in the region of low and very low cumulative dose.

C48. Information about biological mechanisms that could be used to support a risk projection model applied at low cumulative doses may come from in vivo experiments in animals or in vitro cultures of human or animal tissues and cells. Models of carcinogenesis are particularly suited to integrate knowledge about biological mechanisms in the risk projection. In the case of maximum uncertainty, all risk projection models that are considered reasonably plausible are assigned equal weight (the weight would be $1/N$, where N is the number of plausible alternative risk projection models under consideration).

C49. When risk estimation involves risk projection to the region of low and very low cumulative dose, the overall uncertainty in the risk ought to be larger than the uncertainty in risk at dose levels for which there is direct epidemiological evidence.

C50. At low to very low dose, the lower bound of the uncertainty interval may overlap zero additional risk. The final result will depend on the dose–response functions employed by the models used for low-dose risk projection and the plausibility weights assigned to each of the alternative risk projection approaches. It is likely, however, that the upper limit of uncertainty on the estimated risk will not be substantially affected by uncertainty in dose–response models used for risk projection, unless the weight of evidence supporting risk thresholds at low and very low dose is strong [I12, L4].

IV. TRANSFER FOR EXPOSURES TO OTHER TYPES OF RADIATION

A. Modifying factors to estimate risks of cancer for different radiation types

C51. Estimates of cancer risks from exposure to ionizing radiation are based primarily on analyses of data on dose response for members of the LSS cohort, who mainly received acute exposures to high-energy photons. When those data are used to estimate cancer risks from exposure to other types of radiation (for example, neutrons, alpha particles, and lower-energy photons and electrons), estimated risks for the LSS cohort should be modified to account for the possible dependence of risks at a given absorbed dose in radiation type. In radiation protection, this dependence is represented by the quality factor (Q) and radiation weighting factor (w_R) [I14]. However, those quantities are defined point values with no uncertainty that are used to calculate the protection quantities dose equivalent, equivalent dose, and effective dose; they are not intended for use in estimating risks of cancer from actual exposures of identified individuals or groups [I7, I14].

C52. This section discusses a modifying factor to represent the effectiveness of different radiation types, compared with high-energy photons, in inducing cancer in humans. It also discusses uncertainty distributions for that factor that were developed for use in estimating risks from actual exposures. For a given radiation type, this factor is a quantity analogous to Q and w_R that modifies an estimate of absorbed dose in an organ or tissue of concern to obtain a biologically significant dose on which the risk of cancer in that organ or tissue is assumed to depend. Modifying factors for different radiation types and their uncertainties are estimated mainly on the basis of data on relative biological effectiveness (RBE) obtained from radiobiological studies. Modifying factors for some radiation types can also be estimated on the basis of epidemiological data.

C53. The modifying factor to represent the effectiveness of a given radiation type in inducing cancer in humans for the purpose of estimating risks from actual exposures was called a “radiation effectiveness factor” by Kocher et al. [K6]. Use of a term other than RBE to denote this modifying factor was based on two considerations: (a) an RBE, as strictly defined [N4], represents the results of radiobiological studies under controlled conditions; and (b) whereas an RBE is a ratio of absorbed doses of different radiation types that give the same biological response [N4] the quantity of interest in estimating cancer risks is a ratio of risks at the same absorbed dose, in a manner analogous to the use of

Q and w_R in radiation protection. The two ratios generally are not the same. Other investigators have incorrectly referred to this modifying factor as an RBE.

C54. Specification of a reference radiation, with a defined biological effectiveness of one, is important in estimating modifying factors to represent the effectiveness of different radiation types in inducing cancer in humans. In radiobiological studies to estimate RBEs, the reference radiation often is high-energy gamma rays from decay of ^{60}Co or, less commonly, ^{137}Cs or orthovoltage (180–250 kVp) X-rays. However, many radiobiological studies have shown a significant difference in the effectiveness of high-energy gamma rays and X-rays in inducing stochastic effects.* High-energy photons, such as ^{60}Co gamma rays, are the more appropriate reference radiation when it is considered that their energies are closer to the mean energy of photons in exposures of the LSS cohort [I11, K6].

B. Quantification of modifying factors up to UNSCEAR 2006 Report

C55. In past UNSCEAR reports, including its 2006 Report [U12], the Committee did not evaluate radiobiological and epidemiological data for the purpose of estimating modifying factors to represent the effectiveness of different radiation types in inducing cancer in humans. Although ICRP [I11] evaluated data on RBE, the purpose was to inform judgements about values of Q and w_R for use in radiation protection. ICRP's evaluation was not aimed at developing estimates of modifying factors for specific radiation types and their uncertainties for use in cancer risk assessments.

C56. Prior to the UNSCEAR 2006 Report [U12], Kocher et al. [K6] presented the first effort to estimate modifying factors and their uncertainties for all the radiation types of primary concern in exposures of workers and the public, including lower-energy low-LET radiations as well as neutrons and alpha particles. Subjective probability density functions of modifying factors to represent their uncertainty were developed on the basis of an evaluation of radiobiological and epidemiological data. Those probability density functions are incorporated in models to estimate cancer risks and their uncertainty in the Interactive RadioEpidemiological Program (IREP) [K7, L5].

C57. Since the analysis by Kocher et al. [K6] was first presented, other investigators have developed estimates of modifying factors and their uncertainties for alpha particles and tritium beta particles.

C58. The following sections discuss values for modifying factors and their uncertainties for neutrons, alpha particles, lower-energy photons, and low-energy electrons that were developed for use in cancer risk assessments. Modifying factors for other radiation types that are of concern only in certain medical procedures, unusual occupational exposures, or travel in space (i.e. protons, fission fragments, and heavy ions) are not considered. A recent NCRP report [N12] includes a detailed review of modifying factors and their uncertainties for all radiation types of potential concern, including radiation types not considered in this report.

C. Modifying factors for neutrons

C59. An analysis by Kocher et al. [K6] is the only effort to date to develop subjective probability density functions of modifying factors for neutrons. Modifying factors were developed that applied over the ranges of energies defined by the step-function representation of w_R recommended in ICRP Publication 60 [I7]. Separate modifying factors for induction of solid cancers and leukaemias were

developed on the basis of estimates of RBE for cancer induction or life shortening due primarily to cancer in laboratory animals, which indicated that the effectiveness of neutrons in inducing leukaemias is substantially lower. Ratios of the upper bound to the lower bound of the 95% CI of subjective probability density functions ranged from 10 to 30, depending on the cancer type (solid cancers or leukaemias) and neutron energy.

C60. Several issues arise in estimating modifying factors for neutrons and their uncertainties [K6, N12]. In addition to accounting for a difference in the effectiveness of neutrons in inducing solid cancers and leukaemias, challenges include (a) the paucity of relevant data on RBE at energies outside the energy range of most fission neutrons, (b) the likelihood that RBEs for induction of cancers and life shortening due primarily to cancers in laboratory animals overestimate the effectiveness of neutrons in inducing cancer in humans [I11], and (c) the observed increases in RBEs with decreasing dose. In addressing the last issue, Kocher et al. [K6] adopted an approach of developing modifying factors for induction of solid cancers that applied at any dose and dose rate on the basis of estimates of RBE at high acute doses, RBE_H [C9, E1, E2]. The advantage of that approach, which can be used when a linear dose response in humans is assumed, is that it reduces uncertainty in modifying factors. That approach could not be used in developing modifying factors for induction of leukaemias, given the assumption of a linear–quadratic dose response in humans. Those modifying factors were based on estimates of RBE at low doses and low dose rates, RBE_M .

C61. Kocher et al. [K6] applied a small correction to the assumed probability density functions of modifying factors for neutrons to account for a possible inverse dose-rate effect in cases of chronic exposure. That correction, which was assumed to be uncertain, takes into account that the effectiveness in inducing cancer may increase when a given dose of neutrons is delivered at lower dose rates [C9, I7, I11, N4].

D. Modifying factors for alpha particles

C62. Several issues arise in developing modifying factors for alpha particles and their uncertainties [K6, N12]. Perhaps the most important issue is a consequence of the short ranges of alpha particles in tissue [I19]. When the location of critical target cells relative to the location of internally deposited alpha-emitting radionuclides is not known precisely, estimates of absorbed dose in the critical cells may be highly uncertain, and estimates of RBE for alpha particles and inferences about modifying factors may be erroneous. This issue may be especially important when alpha emitters are incorporated in the skeleton and bone cancer or leukaemia is the disease of concern.

C63. Other challenges in developing modifying factors for alpha particles include (a) the pronounced increases in values of RBE with decreasing dose in radiobiological studies [N4], (b) the possible dependence of modifying factors on cancer type, including differences in modifying factors for induction of specific solid cancers as well as a difference in modifying factors for induction of solid cancers and leukaemias, and (c) the use of low-LET reference radiations other than high-energy gamma rays in radiobiological studies to estimate RBEs, especially the use of beta-emitting radionuclides in studies of bone or lung cancer in animals. Given that most estimates of RBE for alpha particles were obtained under conditions of chronic exposure, risks of solid cancers, as well as leukaemias, must be estimated using modifying factors at low doses and low dose rates that are based on estimates of RBE_M .

C64. Estimates of modifying factors for alpha particles and their uncertainties developed by various investigators are summarized in table C3 and described below.

Table C3. Summary of subjective probability density functions of values of modifying factors for exposures to alpha particles developed by various investigators for use in cancer risk assessments^a

Reference	Cancer type	Modifying factor		
		95% subjective confidence interval	Median	Mean
Kocher et al. [K6]	All solid cancers	(3.0, 80) ^b	15.5	22
Grogan et al. [G20, G21, G22]	Lung	(9.3, 96) ^b	30	36
	Liver	(8.0, 50) ^b	20	22
	Bone	(10, 156) ^b	40	51
EPA [U3]	All solid cancers except bone ^c	(4.1, 49) ^b	14	17
Gilbert et al. [G9]	Lung	(14, 98)	33 ^d	
Jacob et al. [J3]	Lung	(6, 112)	15 ^d	
ICRP [I11]	Bone	(6.7, 380) ^b	50	85
Kocher et al. [K6]	Leukaemias	(1.0, 33) ^e	3.6	6.7
Grogan et al. [G20, G21]	Leukaemias	(0.95, 9.5) ^b	3.0	3.6
EPA [U3]	Leukaemias	(1.0, 3.9) ^b	2.0	2.1

^a Modifying factors are intended to represent the effectiveness of alpha particles in inducing cancer in humans, compared with high-energy photons; they apply at low doses and low dose rates.

^b Assumed probability density function is log-normal.

^c Modifying factor of 10 for bone cancer is assumed; uncertainty was not assessed.

^d Value was "central estimate" and was not identified as median or mean.

^e Assumed probability density function is three-component hybrid distribution.

1. Modifying factors for alpha particles and solid cancers

C65. Kocher et al. [K6] developed a subjective probability density function of a modifying factor for induction of all solid cancers on the basis of estimates of RBE_M for induction of bone or lung cancer in laboratory animals [I6, M20, N4]. This distribution was supported by estimates of RBE_M for various stochastic effects in cell systems.

C66. Grogan et al. [G20, G21, G22] developed separate subjective probability density functions of modifying factors for induction of lung, liver, or bone cancer. These distributions were based in part on estimates of RBE_M for induction of cancers in laboratory animals [I6, M20, N4]. The probability density functions for liver and bone cancer also were based on comparisons of estimated risks in medical patients who were administered Thorotrast with estimated risks for the LSS cohort. The probability density function for bone cancer also took into account an estimate of the relative toxicities of ²³⁹Pu and ⁹⁰Sr in inducing bone tumours in beagles.

C67. The United States Environmental Protection Agency (EPA) used an analysis of selected data (including a comparison of estimated risks of lung cancer for underground miners from exposure to radon decay products with estimated risks for the LSS cohort) to develop a subjective probability density function of a modifying factor for induction of all solid cancers [U2]. That distribution was retained in EPA's recent revision of its cancer risk models [U3], except a modifying factor of 10 for

bone cancer, with no uncertainty, was adopted on the basis of a comparison of data on induction of bone cancer in beagles injected with ^{226}Ra or ^{90}Sr . EPA [U3] also discussed (a) recent estimates of RBE_M for induction of lung cancer in beagles, which range from about 1.5 (95% CI: 0.7, 9) to about 20, and (b) comparisons of risks of lung cancer for underground miners and for the LSS cohort based on recent data, which suggest that the modifying factor for lung cancer could be in the range of about 2–11.

C68. Gilbert et al. [G9] and Jacob et al. [J3] developed subjective probability density functions of a modifying factor for induction of lung cancer on the basis of comparisons of estimated risks for Mayak workers exposed to plutonium with estimated risks for the LSS cohort. The modifying factor developed by Gilbert et al. [G9] applies to male and female workers, whereas the modifying factor developed by Jacob et al. [J3] applies to males only. By using an alternative risk model for Mayak workers, Jacob et al. [J3] also obtained a modifying factor with a 95% CI of (9, 81).

C69. ICRP [I11] reviewed estimates of RBE for alpha particles and derived a subjective probability density function of a modifying factor for induction of bone cancer. ICRP [I11] also discussed estimates of RBE obtained in studies of stochastic effects in cells.

2. Modifying factors for alpha particles and leukaemias

C70. Kocher et al. [K6] developed a subjective probability density function of the modifying factor for induction of leukaemias on the basis of three lines of evidence: (a) a comparison of estimated risks for medical patients who were administered Thorotrast with an estimated risk at low doses and low dose rates of high-energy photons derived by EPA [U3] from data for the LSS cohort and an assumed DDREF; (b) an evaluation by EPA [U2] of risks of leukaemias for radium dial painters who ingested ^{226}Ra and for medical patients who were administered ^{224}Ra compared with risks for Thorotrast patients; and (c) estimates of RBE for induction of leukaemias in mice by fission neutrons and an assumption that RBEs for alpha particles and fission neutrons should be similar [I18, S21]. Subjective weights were assigned to probability density functions that were assumed to represent each of those data sets.

C71. Grogan et al. [G20, G21] developed a subjective probability density function of a modifying factor for induction of leukaemias on the basis of (a) a comparison of estimated risks of leukaemia for Thorotrast patients and the LSS cohort and (b) estimates of RBE for induction of leukaemias in mice by fission neutrons. A single probability density function was assumed to represent both data sets.

C72. As noted above, EPA [U2] initially derived a modifying factor for induction of leukaemias on the basis of estimated risks in radium dial painters and two groups of medical patients. That modifying factor was in the range 0–1. In the recent revision of its cancer risk models, EPA [U3] took into account (a) estimated risks for Thorotrast patients; (b) recent estimates of risks for the LSS cohort; and (c) a recent analysis of risks for ankylosing spondylitis patients who were injected with ^{224}Ra . The higher modifying factor now assumed by EPA was supported by an RBE for induction of leukaemias in mice by fission neutrons [U3].

C73. ICRP [I11] discusses data for Thorotrast patients and the LSS cohort, which indicated that the modifying factor for induction of leukaemias is much less than the w_R of 20, and notes a conclusion by the International Agency for Research on Cancer [I4] that the modifying factor is in the range of 1–2. ICRP [I11] also discusses a study in haematopoietic stem cells in mice, which indicated an RBE relative to X-rays of about 11 for a chromosome aberration associated with leukaemia. The RBE relative to high-energy gamma rays could be higher.

C74. Assessments of risks of leukaemias due to intakes of alpha-emitting radionuclides depend on an assumption that ICRP's dosimetric models for alpha emitters deposited in the skeleton are accurate. However, this assumption can be questioned when the location of alpha emitters relative to critical stem cells in bone marrow is not known precisely [K6, U3]. Possible errors in dosimetric modelling could result in an underestimation of the uncertainty in the modifying factor for induction of leukaemias. Possible errors in dosimetric modelling can be taken into account, at least to some extent, by incorporating estimates of RBE for induction of leukaemias in mice by fission neutrons into the probability density function for the modifying factor for alpha particles [G20, G21, K6]. Kocher et al. [K6] also emphasized the desirability of separating the problem of dosimetric modelling for internal alpha emitters from the problem of estimating the effectiveness of alpha particles in inducing cancer.

3. Correction for inverse dose-rate effect

C75. Kocher et al. [K6] applied a small correction to their assumed probability density functions of modifying factors for alpha particles to account for the possibility of an inverse dose-rate effect at low doses. The uncertain correction was assumed to be smaller for alpha particles than for neutrons.

C76. It can be argued that an inverse dose-rate effect should not be taken into account explicitly in estimating cancer risks in humans from intakes of alpha-emitting radionuclides [K6]. For example, this effect has not been seen in studies of underground miners at the lowest levels of exposure to radon decay products [L25], and estimates of RBE_M obtained in radiobiological studies under conditions of chronic exposure may account for any such effect in humans. However, an assumption of a small inverse dose-rate effect at low doses may be supported by an analysis of risks of lung cancer from exposure to radon decay products in homes [F4], which suggests that the risk per unit exposure is somewhat larger in residential settings than at higher levels of exposure in underground mines.

4. Discussion of modifying factors for alpha particles

C77. The subjective probability density functions of modifying factors for alpha particles summarized in table C3 illustrate a number of important points. Uncertainties in the modifying factors are large, ranging from about 6 to nearly 60. Central estimates and their uncertainties can depend on cancer type, even for different solid cancers. Some differences in modifying factors are a consequence of differences in assumptions about radiobiological and epidemiological data to be used in an analysis. Finally, all the analyses illustrate the importance of subjective scientific judgement in estimating modifying factors and their uncertainties.

E. Modifying factors for lower-energy photons

C78. Many radiobiological studies and microdosimetric calculations have indicated that the effectiveness of X-rays at about 250 kVp or less in inducing stochastic effects at low doses and low dose rates is a factor of about 2–3 higher than the effectiveness of high-energy gamma rays [B18, I18]. The BEIR VII Committee [N19] and ICRP [I11, I14] acknowledged that the greater effectiveness of X-rays is potentially important in cancer risk assessments.

1. Modifying factors as a function of photon energy

C79. An analysis by Kocher et al. [K6] is the only effort to date to develop subjective probability density functions of modifying factors for lower-energy photons. One modifying factor was assumed to apply at energies of 30–250 keV, and a higher modifying factor was assumed to apply at energies less than 30 keV. The uncertainty in the assumed modifying factors was a factor of about 5 at 30–250 keV and about 6 at the lowest energies. Photons of energy greater than 250 keV were assumed to have a modifying factor of 1.0, with no uncertainty.

C80. The subjective probability density function of the modifying factor at photon energies of 30–250 keV [K6] was based in large part on estimates of RBE_M for induction of dicentric chromosome aberrations in human blood lymphocytes by 220–250 kVp X-rays [N4]. That distribution also took into account (a) indirect estimates of RBE for X-rays obtained by comparing estimates of RBE for radiations other than photons relative to X-rays with estimates for the same end point in the same biological system relative to high-energy gamma rays; (b) comparisons of risks of specific cancers for the LSS cohort (for example, thyroid and breast cancer) with risks for medical patients exposed to X-rays; and (c) a comparison of incidences of thyroid tumours in rats exposed to ^{131}I beta particles or X-rays. Comparisons of cancer risks for the LSS cohort and medical patients and the study in rats were inconclusive owing to large uncertainties in the data. For example, the 95% CI of the RBE for X-rays inferred from the data on risks of thyroid cancer for the LSS cohort and medical patients was 0.2–4.0 [K6].

C81. The subjective probability density function of the modifying factor at photon energies less than 30 keV [K6] was based on the probability density function at 30–250 keV and an increase in the effective quality factor for photons at energies less than 30 keV ([I18] Fig. 3).

2. Recent estimates of RBE for lower-energy photons

C82. A variety of radiobiological data more recent than data reviewed by NCRP [N4] could be used to develop subjective probability density functions of modifying factors for lower-energy photons. Examples include an extensive set of estimates of RBE_M and their uncertainties for induction of dicentric and acentric chromosome aberrations in human blood lymphocytes [B24, K16, S7, S8]. ICRP [I11] concluded that the data for dicentric provide the most reliable information on RBE_M for conventional (orthovoltage) and lower-energy (for example, mammography) X-rays. RBE and their uncertainties also have been obtained in studies of chromosome aberrations in human mammary gland epithelial cells [B10], micronucleus formation in various human and mouse cells [H20, L11, S22, V2], and neoplastic transformations in CGL1 human hybrid cells [F7, G13, H12]. However, several of these studies used orthovoltage X-rays as the reference radiation, and not all estimates are for an RBE_M .

C83. Estimates of RBE for induction of various aberrations in human blood lymphocytes by low-energy photons also have been obtained in recent studies using multi-fluor fluorescence in situ hybridization (mFISH) or FISH [M11, M12]. Data on dose response for induction of dicentric chromosome aberrations or apparently simple translocations obtained in one study [M11] gave estimates of RBE_M for 30 kVp X-rays relative to ^{60}Co gamma rays substantially lower than the RBE_M for induction of dicentric by 29 kVp X-rays reported by Schmid et al. [S7]. Other estimates of RBE for low-energy photons obtained in studies using FISH or mFISH are relative to 120 or 180 kVp X-rays.

3. Validity of estimates of RBE_M for induction of dicentric chromosome aberrations

C84. Studies of induction of dicentric chromosome aberrations in human blood lymphocytes provide the most extensive set of data on RBE_M over a wide range of photon energies. Recent estimates of RBE_M for dicentrics [B24, K16, S7, S8] and the earlier estimates used by Kocher et al. [K6] were obtained in studies in which aberrations were scored by conventional Giemsa staining [I2]. However, recent studies using mFISH have raised doubts about the validity of using such estimates of RBE_M to estimate modifying factors for lower-energy photons. Studies using mFISH revealed two concerns about the data for dicentrics and the conventional use of a linear–quadratic model to represent the dose responses for lower-energy photons and the reference radiation and to derive estimates of RBE_M [N12, T7].

C85. A study of induction of chromosome aberrations in human lymphocytes following acute exposure to high doses of high-energy gamma rays using mFISH [L22] showed that the upward curvature in the dose response that is commonly observed when those aberrations are scored by conventional Giemsa staining is due mainly to the competing influences of simple chromosome exchanges (which are important at any dose) and complex exchanges (which are important only at high doses), rather than a curvature in the dose response for a single end point (simple exchanges). Furthermore, the dose response for simple exchanges was nearly linear at all doses, with only a slight upward curvature. When a linear–quadratic model is used to represent a dose response for multiple end points, none of which is linear–quadratic in form, derivation of an RBE_M from the initial slopes of the modelled dose responses for the lower- and higher-energy photons may produce misleading estimates [L23]. In such an analysis, the curvilinear dose responses for complex exchanges, which are important only at higher doses, distort (mask) the initial linear slopes in the dose responses for simple exchanges only.

C86. The second important observation resulted from a study of induction of chromosome aberrations in human fibroblasts by high-energy gamma rays using mFISH [L23]. Data for simple aberrations were obtained under conditions of acute exposure or chronic exposure at low dose rates. As in the study discussed above [L22], the dose response for simple aberrations following acute exposure was nearly linear at all doses. The dose response for chronic exposure at low dose rates also was linear, but the slope was a factor of 5–6 less than the slope of the dose response at high dose rates. This large difference was contrary to an expectation based on an assumption of a linear–quadratic model that the slope of the linear dose response for simple chromosome exchanges ought to be independent of dose rate.

C87. Studies using mFISH described above indicate that data on dose response for dicentric chromosome aberrations in human lymphocytes that are scored by conventional Giemsa staining probably cannot be used to estimate modifying factors for lower-energy photons and their uncertainty. The same concern arises in using data on acentric aberrations.

4. Adequacy of data to estimate modifying factors for lower-energy photons

C88. Given the problem with conventional studies of dicentric chromosome aberrations in human lymphocytes noted above, which probably invalidates the use of the most extensive data on RBE_M to estimate modifying factors for lower-energy photons, other radiobiological data appear to be inadequate to characterize the energy dependence of the modifying factor for photons. This limitation is an important concern when X-rays over a broad range of energies are commonly used in medicine. Although radiobiological data for other end points and recent data on chromosome aberrations using

mFISH could be analysed, those data are not extensive, and their applicability to cancer induction in humans can be questioned.

C89. Ideally, modifying factors for lower-energy photons would be estimated on the basis of epidemiological data. However, definitive analyses of cancer risks for populations exposed to lower-energy photons, such as medical X-rays of various energies, compared with risks for the LSS cohort have not been performed. Such comparisons are difficult for several reasons. The statistical power of studies must be high, given that cancer risks for populations exposed to lower-energy photons may be no more than a factor of 2–3 higher than comparable risks for the LSS cohort. It is apparent, for example, that the sizes of populations exposed to medical X-rays that were used in the analysis by Kocher et al. [K6] were too small to detect a difference in the effectiveness of those radiations and high-energy photons in inducing cancer. Other sources of uncertainty not considered in that analysis include (a) the possible importance of a DDREF in dose responses for lower-energy photons in medical patients who received highly fractionated exposures and (b) an assumption about the transfer of risks for the LSS cohort to medical patients of other nationalities with different baseline cancer rates.

C90. The biological effectiveness of lower-energy photons relative to high-energy photons also can be investigated using microdosimetric calculations, as described in a recent review [N16]. Analyses of track structure and biophysical models of radiation action suggest that the primary determinant of biological effects of low-LET radiation is damage to DNA produced by secondary electrons with energies of about 0.1–5 keV at the ends of radiation tracks. On the basis of such analyses, an RBE for lower-energy photons relative to ^{60}Co gamma rays can be estimated from calculated fractions of the absorbed dose from each radiation type delivered by low-energy secondary electrons. Calculations suggest that the RBE for orthovoltage X-rays should be about 1.5 and the highest RBE at lower photon energies should be about 3 [N15]. Nikjoo and Lindborg [N16] also caution, however, that it probably is naive to assume that there are such simple relationships between microdosimetric calculations, which are based on physics only, and biological effects including cancer.

C91. Estimation of modifying factors to represent the effectiveness of lower-energy photons in inducing cancer in humans and their uncertainty over a wide range of energies of interest is difficult at the present time. Nevertheless, cancer risk assessments that attempt to account for uncertainty in risks from exposure to lower-energy photons should include an estimate of this modifying factor and its uncertainty. Given the current state of knowledge, it might be said that the modifying factor for orthovoltage X-rays and other photons of similar energies could be in the range of about 1–4, and that the modifying factor for lower-energy photons could be somewhat higher. An assumption that the modifying factor for photons of all energies is 1.0 with no uncertainty would not be consistent with the current state of knowledge.

F. Modifying factors for low-energy electrons

1. Beta particles from tritium decay

C92. Many radiobiological studies, including studies of induction of cancer in animals, have indicated that low-energy electrons from beta decay of tritium are more effective in inducing stochastic effects than high-energy gamma rays or orthovoltage X-rays [A2, C12, N4, S33]. However, several issues arise in estimating a modifying factor for tritium beta particles on the basis of estimates of RBE from those studies [K6]. Some studies used orthovoltage X-rays, rather than high-energy gamma rays,

as the reference radiation. The reference radiation dose was delivered as an acute exposure in some studies, rather than as a chronic exposure to match typical exposures from tritium. In studies in which tritium was administered as tritiated water (HTO), which is the usual practice, the uncertainty in the absorbed dose due to uncertainty in the water content of an organism or cell type can be substantial. Finally, RBEs for organically-bound tritium (OBT) are substantially higher than RBEs for HTO or tritium incorporated in amino acids [S33].

C93. In estimating cancer risks for humans, the quantity of interest is the modifying factor at low doses and low dose rates. Probability density functions of modifying factors for tritium beta particles developed by various investigators are summarized in table C4 and described below.

Table C4. Summary of probability density functions of modifying factors for tritium beta particles developed by various investigators for use in cancer risk assessments^a

Reference	Reference radiation	Modifying factor		
		95% credible interval	Median	Mean
Kocher et al. [K6]	>250 keV photons	(1.2, 5.0) ^b	2.4	2.6
Hamby [H2]	High-energy gamma rays	(1.0, 3.5) ^c	2.3	2.3
Harrison et al. [H6]	High-energy gamma rays	(1.0, 2.5) ^d	1.8	1.8
Little and Lambert [L18]	High-energy gamma rays	(2.04, 2.33) ^e	2.19	2.19
	Orthovoltage X-rays	(0.96, 1.39) ^e	1.17	1.17

^a Modifying factors are intended to represent the effectiveness of beta particles from tritium decay in inducing cancer in humans, compared with indicated reference radiation; they apply at low doses and low dose rates.

^b Assumed probability density function is log-normal. Probability density function is assumed to apply at energies of discrete electrons, including internal conversion and Auger electrons, and at average energies in continuous spectra of beta particles less than 15 keV, except when Auger-emitting radionuclide is incorporated in DNA.

^c Assumed probability density function is normal.

^d Assumed probability density function is uniform with lower and upper bounds of 1.0 and 2.5.

^e Form of assumed probability density function is not specified.

C94. Kocher et al. [K6] developed a subjective probability density function of the modifying factor on the basis of estimates of RBE for various stochastic end points, including induction of solid tumours or leukaemias in animals, obtained in studies reviewed by Straume and Carsten [S33]. Estimates of RBE obtained in studies using X-rays as the reference radiation were taken into account by assuming a nominal modifying factor for X-rays relative to high-energy photons of 2. Those data and data indicating higher RBEs for OBT compared with RBEs for HTO influenced the upper bound of the assumed probability density function.

C95. The modifying factor developed by Kocher et al. [K6] was assumed to apply to electrons of energy less than 15 keV, including low-energy internal conversion electrons and certain Auger electrons emitted in radioactive decay. In cases of exposure to beta-emitting radionuclides, the modifying factor was assumed to apply when the average energy of the continuous spectrum of electrons is less than 15 keV.

C96. Hamby [H2] used estimates of RBE for HTO in studies of stochastic end points reviewed by Straume and Carsten [S33] to develop a subjective probability density function of the modifying factor that represents estimates of RBE in studies that used high-energy gamma rays as the reference radiation. Estimates of RBE relative to X-rays and estimates for OBT were not taken into account.

Harrison et al. [H6] used estimates of RBE for HTO and OBT relative to high-energy gamma rays obtained from the same review [S33] to develop a subjective probability density function of the modifying factor. Upper bounds of the probability density functions developed by Hamby [H2] and Harrison et al. [H6] are substantially lower than the upper bound of the probability density function developed by Kocher et al. [K6].

C97. Little and Lambert [L18] used estimates of RBE for several stochastic end points obtained in studies reviewed by the United Kingdom's Advisory Group on Ionising Radiation (AGIR) [A2] to develop probability density functions of the modifying factor. Studies that used high-energy gamma rays or orthovoltage X-rays delivered chronically as the reference radiation were considered separately. By applying strict selection criteria, only six studies using high-energy gamma rays as the reference radiation and three studies using X-rays were judged to provide reliable estimates of RBE. The small uncertainties in the modifying factors estimated by Little and Lambert [L18] were a consequence of combining estimated uncertainties in RBE from each study by assuming statistical independence. Such small uncertainties based on radiobiological data may not represent the current state of knowledge of the effectiveness of tritium beta particles in inducing cancer in humans.

C98. Similar to the analyses for alpha particles discussed above, differences in the modifying factors for tritium beta particles and their uncertainties developed by different investigators are a consequence of different assumptions about relevant radiobiological and epidemiological data and the importance of subjective scientific judgement.

C99. Epidemiological data that could be used to estimate the effectiveness of low-energy tritium beta particles in inducing cancer compared with high-energy photons have not been reported [A2, C12]. The lack of epidemiological evidence to support estimation of a modifying factor for tritium beta particles is a potentially important shortcoming.

2. Biological effectiveness of Auger electrons

C100. The biological effectiveness of Auger electrons requires special consideration as a consequence of their very low energies (often a few kiloelectronvolts or less [I15]), their high intensities (often exceeding one per disintegration of a radionuclide [I15]), their short range in tissue (usually less than 1 μm [S14], and the tendency of some Auger-emitting radionuclides to be incorporated in DNA [I7, I11].

C101. Limited data on RBE are summarized by ICRP [I7, I11]. When an Auger-emitting radionuclide penetrates a cell but is not incorporated in DNA, estimates of RBE for a number of end points are similar to RBEs for low-energy tritium beta particles. However, when Auger emitters are incorporated in DNA, much higher RBEs have been reported (for example, for cell transformation). Such high RBEs are supported by calculated patterns of energy deposition.

C102. On the basis of these considerations, Kocher et al. [K6] assumed that the modifying factor for tritium beta particles applies to Auger electrons of energy less than 15 keV unless an Auger-emitting radionuclide is known to be incorporated in DNA. Those investigators concurred with a recommendation by ICRP [I7] and NCRP [N5] that the biological effectiveness of Auger emitters incorporated in DNA should be evaluated as special cases using techniques of microdosimetry (see also [I14]).

G. Summary of modifying factors

C103. Assessments of uncertainties in estimated risks of cancer from exposure to ionizing radiation should take into account modifying factors to represent the effectiveness of radiation types other than high-energy photons in inducing cancer and their uncertainties. The quantities Q and w_R developed for use in radiation protection generally are inappropriate for use in estimating risks of cancer from actual exposures of identified individuals or groups. However, neither the Committee nor other authoritative national or international organizations (such as ICRP, NCRP, or the BEIR committee) have developed recommendations on these modifying factors and their uncertainties for use in cancer risk assessments.

C104. Various investigators have used radiobiological and epidemiological data to develop subjective probability density functions to represent uncertainty in modifying factors for different radiation types including neutrons, alpha particles, lower-energy photons (such as orthovoltage or mammography X-rays), and low-energy electrons (especially beta particles from decay of tritium). Those probability density functions indicate that uncertainties in the modifying factors based on the current state of knowledge are substantial. If the ratio of the upper bound to the lower bound of a 95% credible interval is used to represent uncertainty, the uncertainty may range from about 10 to 30 or more for neutrons and alpha particles, and may be a factor of about 4 for lower-energy photons and low-energy electrons.

C105. Many of the probability density functions of the modifying factors developed by various investigators may not properly represent the effectiveness of particular radiation types in inducing cancer in humans. Estimates of modifying factors and their uncertainties may be particularly problematic (a) for neutrons at energies lower or higher than the predominant energies of fission neutrons, owing to the scarcity of radiobiological data, and (b) for lower-energy photons, for which there are concerns about the validity of radiobiological data on induction of dicentric chromosome aberrations in human lymphocytes. For all radiation types, there are concerns about the applicability of radiobiological data in cells or laboratory animals to cancer induction in humans, and relevant epidemiological data are limited. Estimation of modifying factors for lower-energy photons on the basis of epidemiological data is especially desirable, given the widespread use of X-rays of various energies in medicine. Obtaining reliable estimates of modifying factor for various radiation types of concern in exposure of workers and the public is an important area of future research.

V. INTEGRATIVE APPROACHES FOR QUANTIFYING THE OVERALL UNCERTAINTY IN RISK ESTIMATES

C106. Once uncertainties and their dependencies have been identified and quantified for each term in a risk assessment algorithm, they must be properly combined in order to produce an estimate of the uncertainty in risk. This procedure would include uncertainties in exposure for specific age groups of the exposed population and for each sex. When the risk assessment algorithm is simplified to a series of uncertain multiplicative terms, estimation of the uncertainty in risk can proceed using algebraic closed-form solutions to the propagation of the variances of logarithms of all terms used to estimate risk (see appendix A). This simplified approach was used to quantify uncertainty in risk coefficients by BEIR VII [N19]. Propagation of the variances of logarithms through a multiplicative series of uncertain terms was also employed to estimate uncertainty in thyroid dose for the dose reconstructions performed for public exposures to Nevada Test Site fallout [N3, S20].

C107. In most cases, however, risk assessment algorithms cannot be simplified to a multiplicative series of terms and these algorithms are sufficiently complex that there are no closed form solutions to the propagation of uncertainty. In these cases, Monte Carlo simulation is applied to propagate uncertainty in risk (see appendix A). Monte Carlo uncertainty propagation was the method used to quantify uncertainty in risks from CT scan exposures [B7], from exposures to fallout from atmospheric testing of nuclear weapons in the Marshall Islands [L6], and for estimation of uncertainty in radiogenic cancer risk coefficients for absorbed doses received by specific organs and tissues [B8, K7, N7, U3]. It is also the most common form of uncertainty propagation used in dose reconstructions to support risk assessments or epidemiological studies [N10].

C108. The terms in the risk assessment algorithm that contribute most to the overall uncertainty in risk will vary according to the specific question being addressed. For the estimate of the risk to all organs combined resulting from low-dose-rate uniform whole-body exposure from external radiation, uncertainty in the dose and dose-rate effectiveness factor (DDREF) and uncertainty in the form of the dose–response model will dominate over statistical uncertainties and uncertainty of risk transfer between populations [K7, U3]. For the estimate of the risk to specific organs from internal emitters affecting only a few organ sites (i.e. thyroid gland), uncertainty in the estimate of the absorbed organ dose, and statistical uncertainty in the risk coefficient for that organ site will tend to dominate over other sources as long as the cumulative dose received is above levels at which there are substantial questions about the correct form of the dose–response model. For specific organ sites in which there are substantial differences in the baseline rates of disease between the exposed population of interest and epidemiological cohorts from which risk coefficients have been obtained, the transfer of risk between populations can be an important source of uncertainty [K7, U3]. The use of the excess relative risk to calculate the assigned share for a given diagnosed case of disease includes (a) all of the uncertainties involved with the estimation of the uncertain dose received and the relevant age and sex-specific excess relative risk per unit dose, as well as (b) uncertainties associated with the extrapolation of a cohort-based risk estimate to infer the chance that radiation caused or contributed to a specific case of disease in a specific person [K7, R4].

APPENDIX D. UNCERTAINTIES IN SELECTED RISK EVALUATIONS

I. INTRODUCTION	241
II. SOLID CANCER RISKS AFTER EXTERNAL EXPOSURE TO RADIATION WITH CUMULATIVE DOSES OF THE ORDER OF 100 MILLIGRAYS	242
A. Summary of the UNSCEAR 2006 Report	242
B. Epidemiological studies	244
C. Studies with focus on uncertainty analysis	250
D. Selected risk evaluations.....	251
E. Summary.....	258
III. THYROID CANCER AFTER RADIATION EXPOSURE DURING CHILDHOOD	259
A. Summary from previous UNSCEAR reports.....	259
B. New evidence, not accounting for the impact of dose and model uncertainties.....	260
C. Impact of dose and model uncertainties	261
D. Selected risk evaluation.....	262
IV. LUNG CANCER AFTER RESIDENTIAL EXPOSURE TO RADON DECAY PRODUCTS.....	267
A. Uncertainties in radon exposure assessment.....	268
B. Implications of exposure uncertainties on risk estimates.....	271
C. Use of glass objects for radon dosimetry.....	279
D. Evaluation of the risk and its uncertainty.....	280

I. INTRODUCTION

D1. This appendix contains examples of risk evaluations that (a) summarize the present relevant knowledge; (b) provide estimations of risk quantities and their uncertainty; and (c) indicate the impact of different sources of uncertainty on the estimation of the risk and its uncertainty. Criteria for selecting the examples of risk evaluations were: (i) importance for decisions involving the safe use of ionizing radiation or addressing public controversy; (ii) availability of a sufficient amount of information allowing a meaningful assessment of uncertainties; (iii) existence of publications also addressing sources of uncertainty other than simple statistical uncertainty (for example, exposure or dose

uncertainties, or model uncertainties); and (iv) existence of a recent epidemiological study related to the issue of the risk evaluation. Based on these criteria, the following risk issues were evaluated:

- (a) Solid cancer after external exposure to radiation with cumulative doses in the order of 100 mGy above normal background radiation;
- (b) Thyroid cancer after childhood exposure to radioiodine;
- (c) Lung cancer after exposure to residential radon.

D2. For each of the first two risk evaluations, two calculations are performed in this appendix: one is based on studies excluding the recent study of the issue of interest, and one takes the recent study into account. The purpose of this approach is to elucidate how the recent studies have actually improved knowledge on the specific risk issue that they had addressed.

II. SOLID CANCER RISKS AFTER EXTERNAL EXPOSURE TO RADIATION WITH CUMULATIVE DOSES OF THE ORDER OF 100 MILLIGRAYS

D3. In the past, risk estimates for solid cancer after protracted exposures with cumulative doses of the order of 100 mGy have mainly been derived from data on survivors of the atomic bombings. Owing to the nature of the event, atomic bombing survivors were acutely exposed to a wide range of doses. More recently, observational studies focussing on populations with protracted exposures leading to cumulative doses of the order of 100 mGy have become available. In some of these studies sources of uncertainty beyond statistical random variation were taken into account in estimating solid cancer risks. These studies, together with recent data published by the Committee and other material, are summarized and discussed. The focus in terms of risk coefficients is on the excess relative risk per unit dose, one of the core statistical risk measures estimated in many radiation epidemiology studies.

A. Summary of the UNSCEAR 2006 Report

D4. The impact of dose levels on the precision of risk estimates was discussed in the UNSCEAR 2006 Report, annex A [U12]. It was concluded that very large studies are needed to provide bounds on the risk estimate at low doses that will be informative and useful. It was also noted that the influence of confounding factors becomes increasingly important at low doses. The risk of solid cancer after external irradiation with cumulative doses of the order of 100 mGy has been investigated in large studies, and increases in rates of solid cancer are judged to be the main contributor to excess mortality after such exposures.

D5. The UNSCEAR 2006 Report also summarized the impact of dose measurement errors and other uncertainties on study associations and risk estimates, pointing out recent developments in methods for evaluating such uncertainties. The core concepts outlined in that report included systematic and random error; the topics of differential and non-differential errors, as well as different error models, are developed in more detail in this report. It was also noted that new epidemiological studies had begun to provide estimates of risk from radiation exposure corrected for dose uncertainties. Newly developed statistical approaches to deal with other uncertainties including those arising from

methodological biases such as misclassification, non-response and confounding [G16] were still under scientific debate.

D6. The UNSCEAR 2006 Report noted that a complete model to correct for uncertainties would need to take into account all the sources of uncertainty in a given study. However, as frequently only limited information is available in this regard, researchers have to use whatever information is available to make judgements about the distributions of these uncertainties. It was also noted that some systematic biases in studies may be difficult or impossible to account for properly in analyses.

D7. In terms of total solid cancers in the LSS cohort, the report included mortality data with follow-up until the end of the year 2000, using the most recent dosimetry system DS02 [P12]. Risk estimates were found to be somewhat lower than in previous follow-ups. Other features such as the linearity in dose of the excess solid cancer risk and the modification of ERR per unit dose by age at exposure and attained age as well as previously noted sex differences in risk were similar to those from earlier evaluations.

D8. For solid cancer mortality in the LSS, the average ERR at 1 Sv was given as 0.48 (90% CI: 0.40, 0.57) for the total cohort excluding survivors with weighted colon dose below 0.005 Sv, over the full range of doses. When restricting the analysis to specific dose ranges, a statistically significant positive trend first occurred over the 0–0.2 Sv dose range, with an ERR per unit dose estimate of 0.53 (95% CI: 0.02, 1.07) Sv^{-1} . For lower dose ranges, the risk coefficient was not statistically significant. The corresponding values for solid cancer incidence were given as 0.62 (90% CI: 0.55, 0.69) Sv^{-1} , with a statistically significant positive trend, 0.58 (95% CI: 0.20, 0.98) Sv^{-1} in the dose range 0–0.25 Sv. Some reasons for the discrepancy of these findings to previous evaluations, mainly related to the methodological approach, were discussed in the report.

D9. The report also included risk estimates for solid cancer derived from other cohort studies, mainly among workers in the nuclear industry, for comparison. For mortality from solid cancer, the average ERR per unit dose in these studies ranged from -0.07 to 0.97 Sv^{-1} , and for solid cancer incidence from -0.67 to 2.3 Sv^{-1} . In general, workers in these studies received low radiation doses at low dose rates. Some of these studies included explicit approaches for dealing with uncertainties, and have been reviewed in more detail here.

D10. The UNSCEAR 2006 Report also presented a series of estimates for lifetime cancer risk based on mortality [P12] and incidence [K13] data from the LSS cohort of atomic bombing survivors. Projected lifetime cancer risks were calculated at three test doses: 0.01 Sv, 0.1 Sv and 1 Sv. The report discussed several important factors on which the results depended, notably:

- (a) The exposed population for which risk estimates were developed;
- (b) The models used to describe risk at low doses;
- (c) The methods used to extend the excess risk models beyond the period of observation of the population used to develop those models;
- (d) The cause-specific incidence and mortality rates and the age structure of the populations to which rates were applied;
- (e) The methods used to transfer estimates of excess cancer risk based on models for one population to another population;
- (f) The method used to allow for dose fractionation or dose-rate effects.

D11. Annex A, chapter IV of the UNSCEAR 2006 Report [U12] adjusted the risk estimates for dosimetric errors using a regression calibration approach. Following work of Jablon [J1], the Committee assumed dose uncertainties to be log-normally distributed, and used a central estimate of 35% for the general dose uncertainty.

D12. The Committee's report used several linear and linear–quadratic models specifically developed for the lifetime risk estimations; these included models employing Bayesian MCMC methods to account for uncertainty in dose estimates. The results illustrated the sensitivity of lifetime risk estimates to variations in underlying rates. Differences in risk estimates were of a similar magnitude to those due to different transfer or risk projection methods. It was also noted that uncertainties in estimates of risk for specific types of cancers were generally greater than for all cancers combined.

D13. Applying the linear models to five specific populations, the report estimated the mean lifetime risk of exposure-induced death due to solid cancer after an acute exposure to a dose of 100 mSv (equivalent to about 100 mGy) to be about 3.6%–7.7% Sv^{-1} . Bayesian models yielded slightly lower risk estimates, ranging from 2.3%–5.4% Sv^{-1} . These estimates were noted to be somewhat lower than those previously estimated by the Committee, owing mainly to the use of different risk projection and transfer models. A smaller contribution of the revised dosimetry—in the order of 8%—was also noted. The statistical uncertainty of the estimates was assumed to be in the order of a factor of 2, and lower bounds of the confidence interval included zero.

B. Epidemiological studies

1. Worker studies

D14. The UNSCEAR 2006 Report reviewed the international worker study of Cardis et al. [C4]. In short, the authors had studied mortality in a large cohort of workforces from 15 countries and 154 nuclear facilities, including 407,391 workers monitored for external photon (X and gamma) radiation with personal dosimeters. The average individual effective dose was 19.4 mGy, and 90% of the workers received doses less than 50 mGy. Thus, this study is regarded as potentially highly informative for the dose range of interest in this report, also owing to the fact that specific attempts were made to study errors in recorded doses across facilities and time [T2], as well as conducting sensitivity and confounding factor analyses.

D15. The surprisingly large influence of the data from Canada and potential reasons for this were discussed in the UNSCEAR 2006 Report. Major differences between an earlier analysis of Canadian nuclear workers and the Canadian cohort included in the international worker study were apparently related to the exclusion of a particular group of workers, namely Ontario Hydro employees, from the pooled study. Thus the Canadian cohort results were largely driven by the cohort of workers from Atomic Energy of Canada Limited (AECL) sites. In the framework of a sensitivity (or influence) analysis of the international worker study, the removal of the Canadian cohort resulted in a markedly diminished ERR per unit dose for all cancer other than leukaemia, 0.58 (95% CI: –0.22, 1.55) Gy^{-1} , compared with the statistically significant value of 0.97 (95% CI: 0.14, 1.97) Gy^{-1} for all cohorts combined. Problems associated with the Canadian data were assessed in detail by Ashmore et al. [A13]. From their analysis it could be concluded that the handling of records for the AECL cohort contributed importantly to the observed upward shift in risk found in the international analysis. In particular there was a failure to include records of workers with zero recorded doses during the period 1956–1970 in

the data set used for the international workers study. The Canadian Nuclear Safety Commission has recently published a preliminary summary of their re-analysis of the Canadian nuclear worker data [C13], which also indicates that there were problems with the reporting of dose for the early AECL workers. In general terms, this example shows how influential systematic errors in a subset of data for a large pooled study can be with regard to the overall study results.

D16. In terms of measures of uncertainties of effect, vital status in the international worker study was ascertained through linkage with national or regional death registries, or in some cases through compiling death records individually from relevant authorities. Follow-up completeness ranged from 87% to 100%, and for over 90% of deaths the cause was known. No systematic missing value mechanism seems to have been assumed in the study.

D17. The separate study of errors in dosimetry had the objectives: (a) to evaluate the comparability across facilities and time of currently available dose estimates; and (b) to identify and quantify bias and uncertainties in available dose estimates [T2]. Dosimetry technology, workplace exposure conditions, and calibration practices were identified as major sources of dosimetric errors for doses from high-energy photons, with administrative practices contributing little to errors. Through detailed sub-studies, errors were quantified and bias factors specific to the doses to each organ of interest calculated for each dosimeter model and by facility type (nuclear power plants and mixed activities facilities), with associated uncertainties. Finally, “corrected” organ doses were calculated by dividing recorded doses by the appropriate organ dose bias factor.

D18. The study of dosimetry errors did not reveal major biases as the result of using any specific dosimeter or calibration technique. Therefore, bias correction factors were generally close to one, with varying magnitude of the uncertainties. It was noted that biases were time-dependent, with larger bias in earlier study periods, where also the doses received by the workers tended to be larger. Since also the information on technology, exposures and practices were less detailed for these periods, this study confirms the challenges inherent in attempts to quantify errors and uncertainties. Even if reasonable assumptions about the magnitude of errors and the distribution of uncertainties can be made in situations of scarce information, a considerable risk of bias remains.

D19. Confounding in the international worker study was assessed through various statistical approaches. However, the quality and extent of information on potential confounding factors varied between cohorts. For smoking, only indirect approaches (via the exclusion of lung and pleural cancers strongly associated with smoking) could be implemented [C3, C4]. Excluding these cancers from the category of “all cancers except leukaemia” markedly reduced the power and thus increased the statistical uncertainty of risk estimates. Duration of employment as a known confounding factor was included in the main analyses.

D20. Risks of solid cancer were also estimated by Atkinson et al. [A15] from the workforce cohort of the United Kingdom Atomic Energy Authority (UKAEA). This cohort includes 51,367 workers, of whom 51% were classified radiation workers. The mean cumulative dose was given as 18.8 mSv. Adjustments to recorded doses were made to account for doses below the detection limit, non-returned dosimeters and unit changes. The standardized mortality ratio (SMR) for all cancer in the total workforce was 0.80 (95% CI: 0.77, 0.83) and 0.76 (95% CI: 0.72, 0.79) for radiation workers. In trend analyses, no association with dose was found, and no estimates for ERR per unit dose were given. Issues of uncertainty beyond statistical variability were not addressed.

D21. Muirhead et al. [M21] studied cancer incidence and mortality among 174,541 workers in the most recent analysis of the United Kingdom’s National Registry of Radiation Workers, with follow-up to the end of 2001. The mean lifetime dose was just below 25 mGy, but varied markedly between

facilities. Values of ERR per unit dose were calculated with a linear model, using maximum likelihood methods. Age, sex, calendar period, industrial classification and first employer were included as risk factors in the analyses. For all cancers excluding leukaemia, an ERR per unit dose of 0.275 (90% CI: 0.02, 0.56) Gy⁻¹ for mortality and of 0.266 (90% CI: 0.04, 0.51) Gy⁻¹ for incidence were calculated. Very similar ERR values were found when the strongly smoking and asbestos-related lung and pleural cancers were excluded, which indicates that smoking and asbestos were probably not confounding the ERR estimates to a large extent. The study is notable for its size, completeness of follow-up (only 0.6% not traced) and length of follow-up. Uncertainties in dose estimates or from other sources were not modelled.

D22. Wing and Richardson [W10] estimated cancer risks for workers at the Hanford facility who were exposed both to internal and external radiation. Missing values in the dosimetry records were primarily confined to the early time periods after 1944 and missing doses from external exposure were imputed through a stepwise algorithm. The mean (median) dose for all ages was 27.9 (4.3) mGy. Risk factors included in the analyses were age-at-risk, birth cohort, sex, race, socio-economic status, employment status, in vivo monitoring, and plutonium exposure potential. Risk analyses focused on age at exposure, and statistical models linear and exponential in dose were used. The ERR per unit dose for all cancers (assuming a minimal lag time of 10 years) was 0.28 (90% CI: -0.30, 1.00) Gy⁻¹. For all cancers combined, no differences between workers potentially exposed to plutonium and other workers were noted. Also, only marginal differences between the models (linear versus exponential) were found. However, a strong potential for confounding due to smoking was noted, but no direct information on smoking was available. Furthermore, the analyses indicated that the confounding effect of smoking varies strongly with age, as high lung cancer risk coefficients were seen particularly for cohort members aged 55 and above.

D23. Telle-Lamberton et al. [T1] estimated the risk of all cancers for a French cohort of 29,204 nuclear workers that were partially included in the international worker study [C4]. A substantial number of workers in this cohort analysis were also exposed to internal radiation contamination. The mean cumulative external radiation dose was 8.3 mGy, and recorded doses were categorized in 11 groups for dose-response analyses. Relative risks for a dose of 100 mGy were calculated, adjusted according to the protocol of the international worker study. For all cancers the RR estimate was non-significantly elevated, $RR_{\text{linear}} = 1.2$ (90% CI: 0.99, 1.45) for 100 mGy. Confounding due to smoking and other factors could not be assessed.

D24. Cancer mortality of about 21,500 workers at the Mayak complex was reported by Shilnikova et al. [S12]. Individual uncorrected gamma dose estimates were used in the analyses, and dose-response analyses were adjusted for internal exposures via a surrogate index of plutonium exposure. Average worker doses were 0.8 Gy. Cohort follow-up was 90%, and information on cause of death was rather complete for workers at the main plants, but somewhat less so for workers at auxiliary plants. A high percentage of autopsies for deaths of cohort members residing in Ozyorsk, a town close to the Mayak complex, was noted. Linear ERR models involving doses from both internal and external exposure were employed. The ERR per unit dose for solid cancers excluding lung, liver and skeletal cancer was estimated as 0.08 (90% CI: 0.03, 0.14) Gy⁻¹ from a linear model. Adding a quadratic dose term indicated non-linearity of the dose-response, and led to a more than doubled risk coefficient for doses below 3 Gy; the ERR per unit dose was 0.21 (90% CI: 0.06, 0.37) Gy⁻¹. No sex differences were seen, but there was a decreasing risk with increasing age at hire. Several sensitivity analyses were conducted, including separate analyses for migrated and non-migrated cohort members, which showed no significant differences. With regard to uncertainties, issues related to the precision and possible errors of external and internal exposure estimates, as well as confounding due to smoking and other occupational exposures, are limitations of the study.

D25. Silver et al. [S19] examined cancer mortality in an updated cohort of Portsmouth Naval Shipyard (PNS) workers in the United Kingdom, who were employed at PNS between 1952 and 1992, and followed until 1996. The total cohort comprises 37,853 workers, including a subcohort of 13,468 workers with monitoring records for external radiation exposure. The mean doses from shipyard exposures were 19.95 mSv, and the mean total exposures were 20.59 mSv when off-site doses were included. Further non-radiological exposures to potential carcinogens (asbestos, silica, welding fumes, and organic solvents) were considered. Cancer mortality varied substantially among subcohorts. Cancer cases were slightly increased in the total cohort, SMR = 1.06 (95% CI: 1.02, 1.10), while cancer deaths in the unexposed group were close to unity, SMR = 1.01 (95% CI: 0.87, 1.18). Strong dose–response relationships were found for leukaemia (with a 2-year lag), and lung cancer (a 15-year lag). Both exposure groups presented very different occupational exposure histories, which might have led to a differential distribution of risk factors such as smoking/health lifestyle within the subcohorts. These differences might partially explain the observed variations in cancer mortality within the different exposure groups. Asbestos exposure as a confounding factor is likely to explain a proportion of the elevated lung cancer risk observed in the cohort. Further limitations may be due to unknown/missing information on vital status, under-ascertainment of the cause of death, and misclassification of exposure status, as well as missing information on prior exposures. Owing to the absence of quantifiable information, risk estimates did not take these sources of uncertainty into account.

D26. Boice et al. [B15] analysed mortality among nuclear technology development workers at Rocketdyne facilities in California, United States who were employed between 1948 and 1999. Vital status was obtained from various mortality databases, while cumulative doses were collected from company records in addition to record linkage with national dosimetric registers. The 5,801 workers, of whom 2,232 were monitored for radionuclide intake, had a mean radiation dose of 13.5 mSv. The SMR analysis (compared with the general population of California) found no significant elevation of the risk of all cancers combined, with an SMR of 0.93 (95% CI: 0.84, 1.02). The RR at 100 mSv for all cancers, excluding leukaemia, was 1.00 (95% CI: 0.81, 1.24). When considering radiation exposure due to Rocketdyne activities only, there was an increase in the RR to 1.11 (95% CI: 0.81, 1.52). However, no significant dose–response trends were observed for any cancer. Overall, the results in this study are based on small numbers of deaths and low occupational doses.

D27. Ivanov et al. [I24, I26] assessed the mortality among Chernobyl emergency workers in a cohort of 65,905 persons with registered low to moderate doses from external exposure between 1991 and 1998. The cumulative doses ranged between 5 mGy and 300 mGy with a mean dose of 116 mGy. Relative to the Russian population as a whole, the risk for cancer (malignant neoplasms) was slightly reduced: the SMR was 0.87 (95% CI: 0.80, 0.95). Circulatory disease mortality however showed an increased risk: SMR was 1.07 (95% CI: 1.03, 1.13). Furthermore, statistically significant dose–response analyses presented elevated excess risks for cancer with ERR per unit dose of 2.11 (95% CI: 1.31, 2.92) Gy⁻¹ (with an external control: Russian population) and 2.04 (95% CI: 0.45, 4.31) Gy⁻¹ (internal control), respectively. These risk estimates are in accordance with those derived from the LSS cohort. Uncertainties were acknowledged by Ivanov et al. with regard to the potential impact on risk estimates of the administrative control of recording maximum permissible doses, in particular due to varying values of maximum permissible doses at different times after the accident. When a worker exceeded the maximum permissible dose, the worker was simply ordered to leave the radiation area. Thus, the documented doses may be equal or even less than the maximum permissible dose, even though the worker in fact exceeded the dose limit. This may have led to overestimates for the mortality risk. These uncertainties were not accounted for in risk estimates. A further important source of uncertainties in the risk estimates is the adopted value for the time of the latent period in the development of radiation-induced cancers. Both the latent period and the ERR for solid cancer incidence were assessed by Ivanov et al. [I25] in a cohort of 59,770 Chernobyl emergency workers for the follow-up period 1986 to 2005.

Using maximum likelihood methods, the minimal latent period was estimated to be 4 years (95% CI: 3.3, 4.9), with the corresponding ERR per unit dose of 0.96 (95% CI: 0.28, 1.72) Gy⁻¹. The maximum estimated latent period of 10 years corresponded to an estimate for the ERR per unit dose of 0.20 (95% CI: -0.04, 0.80) Gy⁻¹.

D28. Risk estimates for the solid cancer incidence during the period 1991–2001 in this cohort (based on 55,718 emergency workers) resulted in an ERR per unit dose of 0.33 (95% CI: -0.39, 1.22) Gy⁻¹ for the period 1991–2001, and a slightly lower value of 0.19 (95% CI: -0.66, 1.27) Gy⁻¹ for the truncated period 1996–2001. As is known for this cohort, some 15% of dose estimates are not based on individual measurements but on group measurements or imputations. Large uncertainties may thus be associated with the dose estimates, but for the majority of doses the uncertainties are not likely to exceed 50%.

D29. Sigurdson et al. [S18] analysed the cancer incidence among 90,305 United States radiologic technologists between 1983 and 1998 including a large proportion of women (77%). Cancer incidence was collected from mailed questionnaires and from death records. Individual dose information was not available, and exposure time windows were used as surrogates. Female technologists showed an increased risk for all solid cancers combined; the standardized incidence ratio, SIR, was 1.06 (95% CI: 1.02, 1.10). For breast cancer the SIR was 1.16 (95% CI: 1.09, 1.23). Since no individual doses were estimated for this analysis, risk coefficients could not be calculated. No relevant uncertainties were mentioned apart from minor limitations related to design of the study (such as non-responses). Cohort workers may not be representative of the general population (a possible healthy worker effect), but as indicated the study contributes little to improving risk estimates for solid cancer associated with specific radiation dose levels.

2. Environmental exposures

D30. Residents along the Techa River have been exposed to ionizing radiation due to releases from the Mayak complex. Cancer mortality for the extended Techa river cohort of 29,873 residents (of whom 60% are women) was reported by Krestinina et al. [K12]. The follow-up included the period 1950 to 1999. There was considerable loss to the cohort owing to migration out of the catchment area. Residence and vital status and causes of death were registered through collaboration with local address bureaux and local statistical offices, as well as through interviews. Dosimetry was provided through a specific dose reconstruction system, including internal and external exposure, with individual doses based on local measurements and individual-specific modifications such as detailed residence histories. Dose to the stomach was used for the analysis. For solid cancers excluding bone cancers (owing to potential effects of ⁹⁰Sr exposure), the ERR per unit dose was estimated as 0.92 (95% CI: 0.2, 1.7) Gy⁻¹; the risk coefficient is 70% higher for women than for men, but the difference is not significant. Risk estimates increase with increasing age at exposure and attained age, contradicting findings from Mayak studies or the LSS. Limitations of this study include the loss to follow-up and a high percentage of missing information on cause of death, as well as uncertainties in individual dose estimates. Data on potential confounding factors are generally not available. Preliminary assessments of the potential impact of medical exposures suggested no serious biases in the health effect estimates. Improvements to the dosimetry system are ongoing.

D31. Cancer incidence in the extended Techa River cohort for the period 1956 to 2002 was also studied by Krestinina et al. [K13]. Some 60% of the original cohort could be included. Cancer incidence data were obtained through various sources, and with different quality and completeness for the different time periods. The mean and median stomach doses for cohort members were 40 and 8 mGy, respectively. Using a linear model, the estimated ERR per unit dose was 1.0 (95% CI: 0.3, 1.9) Gy⁻¹. In a model with a

quadratic dose–response term, markedly higher ERR per unit dose estimates were computed for high doses, but for low doses the risks were lower than in the linear dose–response model. Women had slightly lower risks than men in the analyses. Limitations are similar to the mortality analyses, but the cohort is even smaller and therefore estimates somewhat less precise. No systematic approach is provided to include uncertainties related to dose or to confounding factors in developing the risk estimates and their confidence intervals.

D32. Background ionizing radiation in relation to cancer incidence was studied by Nair et al. [N2] in Kerala, India. A cohort of 69,958 men and women (ages 30–84) from areas of high background radiation was studied. Information on age and sex as well as other risk factors that could act as confounding factors, such as smoking bidis, education and occupation, was available from a baseline survey. Cancer diagnoses were based on histopathology and death certificate information, but a non-negligible proportion (about 20%) came from clinical observations or tests. Individual gamma doses were estimated from measurements conducted in households and outdoors, and occupancy as well as migration were taken into account. Cosmic ray components were subtracted from the measured dose to obtain estimates of terrestrial background radiation. The average individual cumulative (terrestrial) dose at the end of follow-up was estimated as 161 mGy. No associations between all cancer excluding leukaemia and annual or cumulative radiation dose were found. The ERR per unit dose was -0.13 (95% CI: $-0.58, 0.46$) Gy^{-1} , calculated using a linear model. The study includes information on some important potential confounding factors; however, limitations related to the dose estimation, to the accuracy of the data on potential confounding factors, and to the end point verification are noteworthy.

D33. In Taiwan, residents were exposed to high levels of external radiation in buildings where steel contaminated with ^{60}Co was used for construction [H22]. A cohort of 7,271 people was assembled and followed-up from 1983 to 2002. Doses were reconstructed through a specific dosimetry system based on environmental measurements and taking occupancy and other factors into account. The 6,246 persons for whom doses could be reconstructed received mean cumulative doses of 47.8 mGy (excluding background), ranging from less than 1 to about 2,360 mGy. Cancers were ascertained through the National Cancer Registry. Relative risks for different dose categories were calculated, and for all solid cancers a RR of 1.2 (95% CI: 0.5, 2.9) for those receiving doses greater than 50 mGy compared to those receiving less than 1 mGy was estimated. Higher relative risk estimates were found for women compared to men. The most recent follow-up of this cohort includes three more years of follow-up (1983 to 2005); hazard ratios (HR) for an increase of 100 mGy in dose were estimated. For leukaemia (excluding chronic lymphatic leukaemia, CLL) an increased HR at 100 mGy of 1.19 (90% CI: 1.01, 1.31) was reported, and slightly lower hazard ratios for breast cancer (HR at 100 mGy of 1.12, 90% CI: 0.99, 1.21) [H23]. The risk estimates in both reports were adjusted for attained age, but no other confounding factors such as smoking and socio-economic status were included. Thus the confidence intervals for the risk estimates do not reflect any uncertainties beyond statistical variability.

D34. Bauer et al. [B2] analysed radiation exposure due to local fallout from atmospheric nuclear weapons testing and reported results from a study on a historical cohort exposed in the vicinity of the Semipalatinsk nuclear test site in Kazakhstan. The cohort of 19,545 inhabitants included residents from exposed villages with a mean cumulative dose estimate of 634 mSv and residents of comparison villages who were each assigned a common effective dose estimate of 20 mSv. The follow-up time ranged from 1960 to 1999. The study found a significant dose trend for solid cancers with an ERR per unit dose of 1.77 (95% CI: 1.35, 2.27) Gy^{-1} for the total cohort, and 0.81 (95% CI: 0.46, 1.33) Gy^{-1} when considering the exposed group separately. Uncertainties in this study were related to follow-up loss (that is unclear information of vital status) due to emigration in the 1990s particularly in the exposed group. However, sensitivity analyses restricted to 30-year follow-up showed fairly consistent results compared to the 40-year follow-up. As additional selection bias in the comparison group could not be ruled out, results from the exposed group were assumed to be more reliable than those for the

total cohort. The exposure data used in this study did not allow for specific lag and age–time windows. In addition, a risk assessment for low dose ranges could not be made as no individual exposure information in the comparison group was available.

3. A joint analysis of low-dose-rate studies

D35. A joint analysis of epidemiological studies of populations with low-dose-rate exposures of the order of several hundred milligrays included most of the studies mentioned previously [J5]. Both solid cancer incidence and mortality were investigated, and risk estimates from these studies of chronic exposures were individually compared to ERR estimates derived from appropriately selected subsets of data from the LSS of acutely exposed atomic bombing survivors. A joint estimate of the ratio of the risk estimates from these studies and the LSS was then derived. Individual estimates of the ERR per unit dose ranged from 0 Gy^{-1} to 4.8 Gy^{-1} for mortality studies and from 0.3 Gy^{-1} to 1 Gy^{-1} for incidence studies, whereas the comparison risk estimates from the LSS showed much smaller variation. In six of twelve studies, the best estimate of the ERR per unit dose was larger than in the LSS, and in five studies the estimates were of comparable magnitude to the LSS estimate. The overall study results as well as sensitivity analyses indicated that the ERR per unit dose values from the studies of chronic exposure were similar to those calculated from the LSS. Limitations of individual studies with regard to dosimetry and to absence of information of potential confounding factors impair the ability to interpret the result, but there was consistency between results of different analyses using varying study subsets. Uncertainty beyond statistical variability could not be incorporated in the study.

C. Studies with focus on uncertainty analysis

D36. Using data from the study of workers at Oak Ridge National Laboratory, Stayner et al. [S25] presented a method to estimate uncertainties from shared errors in exposure assessment. More specifically, they used Monte Carlo methods to estimate confidence intervals that specifically reflect statistical sampling errors and errors from uncertainties in exposure estimates. Shared errors in exposure estimates arise from the use of group means to assign individual doses, as commonly is the case when job–exposure matrices are used. Similarly, shared errors occur when individual dose estimates are available and corrections are applied that are the same across specific jobs or facilities, which is the situation in the international worker study and the data used by Stayner et al. [S25].

D37. Starting from a model with measurement errors of the assignment type, including both shared and unshared errors between subjects, the authors propose a Bayesian approach, using Monte Carlo simulations techniques to randomly select realizations from the distribution of true dose given the measured dose. Central estimates and confidence intervals are then computed using maximum likelihood approaches. No additional covariates such as age or sex are included as potential effect modifiers, and the authors note that this is a simplification.

D38. Analyses of the risk of all cancers excluding leukaemia in the ORNL dataset were then carried out, using the bias factors derived with the methods of the dosimetry errors sub-study for the international worker study [S25]. The ORNL workers study had previously shown a positive dose–response relationship between all cancers and radiation dose, but these analyses had not included any specific approach to deal with exposure or other uncertainties [W10]. Whereas the earlier, non-simulated analysis led to a value for ERR per unit dose of 5.38 (90% CI: $0.54, 12.58$) Gy^{-1} (originally Sv^{-1}), the Monte Carlo

maximum likelihood method yielded an ERR per unit dose of 4.82 (90% CI: 0.41, 13.31) Gy⁻¹. The two risk coefficient estimates were statistically not distinguishable.

D39. As expected, the simulation approach yielded broader confidence intervals than the conventional analysis, but in the case of ORNL data the differences seemed rather marginal; the lower confidence bound decreased by about 24%, the upper increased by about 6%. This may be due to the comparatively good quality of exposure information in this and comparable studies of radiation workers with individual measurements. Overall, the authors point out that the Monte Carlo maximum likelihood estimates appear to be indicated only for a situation where shared errors are of concern, while for situations where unshared errors predominate, less complex approaches are recommended by the authors.

D40. Little et al. [L17] expanded on the analyses in the UNSCEAR 2006 Report [U12] that explicitly take account of dosimetric and other uncertainties. The general approach is very similar to the UNSCEAR 2006 Report, fitting generalized linear, linear–quadratic and linear–quadratic–exponential models to the most recent data on survivors of the atomic bombings. Lifetime risk projections for 5 contemporary populations are provided for test doses of 0.01 Sv, 0.1 Sv and 1 Sv, based on both Bayesian and classical regression calibration approaches. In terms of model choice, simple models linear in dose fitted the data about as well as the more complex models, but statistical and other arguments were put forward to motivate the preferential choice of linear–quadratic models. Through the Bayesian modelling, random dose errors as well as uncertainties in the model parameters describing the shape of the dose–response curve are taken into account. In addition, variations of risk with time since exposure and age at exposure are considered. The estimated solid cancer risks did not differ markedly between the different modelling approaches and test doses applied, however, central risk estimates were somewhat lower than those calculated in earlier UNSCEAR reports. Uncertainties reflected in the Bayesian credible intervals were slightly larger than those from regression calibration approaches without adjustment for dosimetric errors.

D41. A different approach to risk estimation is mechanistic modelling of the carcinogenic process. A study by Jacob et al. [J4] focused on the inclusion of non-linear dose effects at low doses. Different forms of the two-stage clonal expansion (TSCE) model of carcinogenesis were applied to data from the atomic bombing survivors, and the biologically motivated models were compared to empirical risk models conventionally used in the LSS analyses. Including low-dose hypersensitivity in radiation-induced cell inactivation did not materially improve model fit, but differences in estimates of ERR per unit dose between models with and without low-dose hypersensitivity were noted when doses below 1 Gy were studied. For young age at exposure, TSCE models yielded lower excess relative risks than conventional models. As a way to take this model uncertainty into account, Jacob et al. proposed to use the upper and lower limits of the uncertainty range for estimates derived from mechanistic and empirical models with comparably good fit as guidance. With such an approach, the uncertainty range of the empirical ERR estimate for the LSS data on solid cancer (age at exposure 10 years, attained age 70 years) would be inflated by some 30%, which is seen to reflect model uncertainty. The nominal value of the factor by which the width of the uncertainty range would be expanded depends on the specific exposure situation investigated as well as the choice of models that are being compared.

D. Selected risk evaluations

D42. For this scenario the Committee has considered a hypothetical population of workers who began work at age 30 and received occupational exposures to low-LET radiation from the ages of 30 to 44 with a total dose of 100 mGy. More specifically, annual doses of 8 mGy are assumed for the first five years, 7 mGy annually for the next 5 years and 5 mGy annually for the last five years. Follow-up is

presumed to start at age 45. The quantities of primary interest are the rate of radiation-associated cases, the attributable fraction (which is defined as the ratio of the number of excess cases to the total number of cases), the mean life lost per case and the mean life lost per person.

D43. The Committee has considered two approaches to the evaluation of radiation-related solid cancer risks and associated uncertainties are considered. The first approach relies on the NRRW for the risk levels for all organs combined and considers possible age-related changes in the magnitude of the healthy worker effect. This is feasible for this scenario since the NRRW is a large study with published risk estimates based on dose estimates of high quality and relatively lengthy follow-up. However, since the published analyses provide little information on possible temporal variation, the Life Span Study results were used to characterize potential temporal variation in the excess relative risks. Because risk estimates were defined directly in terms of the results of an analysis of the population of interest, DDREF was not considered in this uncertainty assessment. For the second approach, the nature of the radiation effect on solid cancer rates was characterized using site-specific BEIR VII risk models derived primarily from LSS cancer incidence data without any consideration of the actual NRRW results and with no allowance for healthy worker effects.

1. NRRW-based risk and uncertainty assessment

D44. Using information on the risk estimates from the third analysis of data from the United Kingdom's National Registry for Radiation Workers (NRRW) [M21] an estimate was made of the expected rate of (occupational) radiation-associated non-leukaemia deaths in a population of male workers who receive a total dose of 100 mGy as a result of long-term low-dose-rate occupational exposures. The focus here is on allowing for the effect of uncertainty in risk parameter estimates, in the form of the risk model and, to some extent, in the differences in solid cancer and all-cause mortality rates between the NRRW workers and the general population of the United Kingdom. In this scenario there is no attempt to deal with the effect of dose uncertainty since the published data do not include enough information to address this issue. However since the doses were based on badge dose readings, it is likely that classical measurement error is the primary source of dose uncertainty, but that the magnitude of this uncertainty is such that it should have little impact on the risk estimates. It is also assumed that age-specific rates for all-cause and mortality and cancer incidence are fixed at the 2009 United Kingdom population values.

D45. The fitted risk models in [M21] are limited to simple time-constant ERR models. The estimate for the ERR per unit dose for solid cancer (excluding non-melanoma skin cancer) is given as 0.275 (90% CI: 0.02, 0.56) Gy⁻¹. The reported confidence interval for the time constant estimate is almost symmetric, therefore the Committee considers it reasonable to approximate the (asymptotic) standard error of the reported ERR per unit dose as 0.13 and describe the uncertainty in the parameter for this model as having a normal distribution N(0.28, 0.13).

D46. Although [M21] notes that there was no evidence of significant temporal variation in the ERR, the Committee considers it reasonable to assume that such variation is possible, and even quite likely. It has allowed for this possibility by considering both time-constant and age-varying ERR models to be equally plausible. For this exercise the Committee developed uncertainty distributions for the parameters in the age-varying ERR model using expert judgement as follows. First, it assumed that the time-constant ERR is a reasonable estimate of the ERR at age 60 with a standard error similar to that for the time-constant model and with an "estimated" attained age effect in which the ERR varies in proportion to a power of age. Based loosely on the atomic bombing survivor data the Committee assumed that the ERR would tend to decrease in proportion to the inverse of age, i.e. attained age to the

power -1 but that this value is uncertain and could even be positive. Uncertainty in this parameter was assumed to correspond to a standard error of about 0.75 (which, in terms of frequentist hypothesis testing based on asymptotic normality implies a two-sided P value of about 0.2). Further the correlation between estimates of the two parameters in the age-varying ERR model (ERR at age 60 and the power of age) was assumed to be 0.5 (which is similar to the correlation between similar parameter estimates in models fitted to the atomic bombing survivor cancer incidence data).

D47. As for many occupational cohorts, the rate of deaths from all causes and from cancer for male workers in the NRRW are less than predicted on the basis of national rates. Such differences are often said to reflect a “healthy worker effect”, in which people who are working or who had long working careers tend to be somewhat healthier than the general population. The Committee decided to allow for the healthy worker effect in these risk projections but to assume that there is some uncertainty in how the ratio of rates in a (retired) worker cohort to that of the general population varies with age. In particular, it assumed that rates in NRRW cohort members were less than the national rates throughout the 40s but that this difference gradually attenuates as the population ages. The analysis in [M21] found standardized mortality (SMR) ratios of about 0.8 for both all causes and for cancer. The Committee has applied an SMR of 0.8 from the start of follow-up (at age 45) to age 50 but that from age 51 to 90 it allowed the SMR to increase linearly to a random value between 0.8 and 1 (SMR_{90}) and then remain at this level for the remainder of life. The value of SMR_{90} for a specific trial was sampled from a beta density function with parameters 1.5 and 0.5 that was scaled to the range of 0.8 to 1 with a mean of 0.95.

D48. The computations made use of a United Kingdom life-table for 2009 obtained from [U5] and national death and cancer incidence rates for the same year [O1]. These rates were given for the first year of life, for ages 1 to 4 years, then in five-year intervals to age 84 with rates for category of people aged 85 and over. The life-table included ages up to 110 years. For ages up to 90, non-leukaemia cancer incidence and mortality rates were defined for each year of age using linear interpolation between the available rates assuming that the reported values were a good approximation to the rates at the midpoints of the age intervals. From age 91 onwards the age-specific rates were set equal to the estimated rate for age 90.

D49. Computations of radiation-associated cases were based on the “risk of exposure-induced deaths/cases” (REID/C) method described in [T3] and used in [U12]. The REID/C method computes the exposure-associated “excess” in a given year as the product of probability of survival (cancer-free survival in the case of incidence data) to that year given the exposure and the difference between the disease rates for exposed and unexposed populations for the outcome of interest in that year. (Equations for the REID/C and some alternative measures of lifetime risks are given in the glossary.) The total expected number of exposure-associated cases is then the sum of the expected excess cases over the years of interest. Since the number of excess cases does not provide a complete summary of the impact of the exposure, it is useful to augment this value with some estimates of when the exposure-associated cases are expected to occur. There are several possible summaries. One summary that has been used by UNSCEAR [U10] and the ICRP [I14] and in various other reports (for example in [P12]) is the expected years of (cancer-free) life lost per excess case. However the interpretation of this statistic is not consistent with people’s intuitive sense, meaning it is not directly related to changes in life expectancy or the time to cancer diagnosis among exposed individuals. One reason for this is that it is probably more realistic to think of radiation exposure as resulting in a dose-dependent acceleration of the cancer development process in exposed individuals than as affecting only those who develop a radiation-induced excess case. Therefore this report also considers two other, more intuitive summaries of the temporal impact of exposure. These are (a) the expected cancer-free life lost per person (i.e. change in life expectancy) and (b) the expected cancer-free life lost per cancer case (changes in expected age at cancer diagnosis/death). Because of the magnitude of these two summary statistics, the values are expressed in units of days of life lost per person or per cancer case.

D50. Monte Carlo methods were used to generate samples from the probability densities for the model, parameter estimates, and limiting SMR described above. For each of these samples the total risk in the exposed population, and the life expectancy of this population and an analogous unexposed population, were estimated. Table D1 presents estimates and 95% credible intervals for these values drawn from the empirical distribution of the statistics over 5,000 samples.

Table D1. NRRW-3 based estimates of lifetime exposure-associated non-leukaemia cancer cases^a and related quantities for United Kingdom nuclear workers who received an absorbed dose of 100 mGy between the ages of 30 and 44 with no additional occupational exposure

Statistic	Mean	95% credible interval	
		Lower	Upper
Cancer cases (baseline)	40.3	38.9	41.4
Excess cases (radiation-associated)	0.96	0.07	1.97
Attributable fraction (%)	2.4	0.2	4.8
Life lost ^b per person (days)	45	3	89
Life lost ^b per cancer case (days)	111	9	217
Life lost ^b per excess case (years)	12.8	12.1	14.4
Life expectancy, unexposed	77.7	77.3	78.5
Life expectancy, exposed	77.5	77.2	78.3

^a Cancer cases and excess cases are for an assumed population of 100 workers with follow-up from age 45 through to the end of life. Risk estimates are based on risk models from the NRRW cohort studies.

^b Since these values are for incident cancer cases, life lost is actually cancer-free life lost and life expectancy is cancer-free life expectancy.

D51. The results indicate that for this scenario the lifetime risk of developing a non-leukaemia cancer (other than non-melanoma skin cancer) is expected to be about 40 per 100 exposed workers while the expected risk of an exposure-associated cancer is slightly less than 1 case per 100 exposed workers. This indicates that about 2.4% of the cancers are expected to be associated with the exposure. Exposure has only a small effect on life expectancy in the population as a whole, and cancers in the exposed population are predicted to be diagnosed about 4 months earlier on average than in an unexposed population.

D52. Table D2 provides information on the expected age distribution of the risk of exposure-associated cancer death and the estimated proportion of the risk of death for each age group due to the exposure. The results indicate that for each age-group considered, between 2.2% and 2.6% of the relevant cancer risks are expected to be associated with the exposure. However, because the Committee has given some consideration to models for which the ERR is allowed to vary with age at diagnosis, assuming a decrease more likely than an increase, there is a slight decrease in the expected attributable fraction for the older age groups.

Table D2. NRRW-3 based estimates of exposure-associated non-leukaemia cancer risk and attributable fractions by age at diagnosis for United Kingdom nuclear workers who received an absorbed dose of 100 mGy between the ages of 30 and 44 with no additional occupational exposure

<i>Age at diagnosis</i>	<i>Mean</i>	<i>95% credible interval</i>	
		<i>Lower</i>	<i>Upper</i>
EXCESS RISK (PER 100 WORKERS)			
45–59	0.128	0.010	0.242
60–64	0.109	0.008	0.215
65–69	0.149	0.011	0.300
70–74	0.166	0.012	0.343
75–79	0.161	0.011	0.338
80–84	0.128	0.008	0.272
85–89	0.077	0.004	0.166
90+	0.047	0.003	0.104
ATTRIBUTABLE FRACTION (%)			
45–59	2.4	0.2	4.5
60–64	2.6	0.2	4.9
65–69	2.5	0.2	4.9
70–74	2.4	0.2	4.9
75–79	2.3	0.2	4.9
80–84	2.3	0.1	4.8
85–89	2.3	0.1	4.8
90+	2.2	0.1	4.8

2. BEIR VII/NCI-based risk and uncertainty assessment

D53. The risk models from the third analysis of the NRRW cohort applied above to estimate risk for the case of United Kingdom male workers exposed to 100 mGy do not have well-defined age-varying terms and they are based on a population with a relatively short follow-up. It is of interest to estimate risk for the same example case using risk models developed from longer follow-up of the Japanese atomic bombing survivors (LSS cohort). The most recent, well-established risk assessment methodology based on the LSS data has been developed by the United States National Research Council/National Academy of Science (NRC/NAS) BEIR VII committee [N19]. The BEIR VII methodology includes risk models for 11 site-specific cancers: stomach, colon, liver, lung, breast, uterus, ovary, prostate, bladder, thyroid and leukaemia, plus a risk model for all remaining solid tumours (excluding non-melanoma skin cancer). This methodology has been further expanded by the United States National Cancer Institute [B7] to include risk models for seven additional cancer sites: oral cavity and pharynx, oesophagus, gall bladder, pancreas, rectum, kidney, and brain/central nervous system (CNS), plus a modified risk model for the new remaining solid tumours (still excluding non-melanoma skin cancer). This section describes how the BEIR VII/NCI risk assessment methodology

has been applied to assess the risk of cancer incidence for the example case of United Kingdom workers exposed to 100 mGy.

D54. The standard BEIR VII/NCI models for both the ERR and EAR of solid cancers other than of the breast and thyroid have the form $\beta_s D \exp[\gamma e^*] (a^*)^\eta$ where β_s is the site-specific risk coefficient (for males or females), D is the dose in gray, γ is the age at exposure parameter, e^* is $(e - 30)/10$ for e less than 30 and zero for e greater than or equal to 30, where e is age at exposure in years, η is the attained age parameter and $a^*=(a/60)$ where a is the attained age in years. The parameters were estimated using the 1958–1998 cancer incidence data from the LSS and DS02 dosimetry [N17]. For most cancer sites this dataset offers many advantages including its large size, high quality cancer incidence data, wide range of doses and inclusion of all ages and both sexes. For breast and thyroid cancer, detailed pooled analyses are available based on data from the LSS and medically exposed populations. The risk of thyroid cancer is based on the ERR model derived from the pooled data of seven studies described by Ron et al. [R3], as analysed by Land et al. [L5] and modified for sex-dependency by the BEIR VII committee [N19]. The ERR thyroid model is similar in form to the standard model for solid cancers, but depends only on age at exposure and not on attained age (i.e. η is equal to zero). The preferred model for breast cancer is the EAR model from the pooled analysis of four cohorts by Preston et al. [P11]. That model has the same form as the standard model for solid cancers, but e^* is $(e - 25)/10$ for all ages e at exposures, and a^* is $(a/50)$. For leukaemia, models are based on the LSS data for the period 1950–2000 and exclude chronic lymphocytic leukaemia (CLL). The ERR or EAR BEIR VII models for leukaemia are linear–quadratic in dose and depend on sex, age at exposure (e) and time since exposure (t). The linear–quadratic model is applied for acute exposures, but only the linear term can be applied for chronic exposure (meaning that the quadratic term can be dropped). To account for the lower risk during the latency* period of cancers, S-shaped adjustment factors that vary from 0 to 1 were applied for all risk models, for the first few years after exposure, as described by Kocher et al. [K7]. The uncertain latency adjustment is phased in between 4 and 11 years after exposure for solid cancers, 0.4 and 4.1 years for leukaemia and 2.5 and 7.6 years for thyroid cancer.

D55. The exposure was assumed to be chronic starting at age 30 and ending at age 44 and a total dose of 100 mGy was assigned to each of the seventeen cancer sites and to the remainder cancer grouping. The excess risk of cancer incidence was calculated for each cancer site separately and a total risk was estimated by summing across cancer sites. Leukaemia was not included in this summation, so that the resulting risk is comparable to the estimates based on the NRRW cohort. Since the LSS cohort was exposed acutely to (relatively) high doses of radiation, the risk for the assumed chronic exposure of United Kingdom workers was adjusted by a dose and dose-rate effectiveness factor (DDREF) described by a log-normal distribution with a geometric mean of 1.5 and a geometric standard deviation of 1.35 [N19]. The risk from radiation exposure for the United Kingdom worker population was projected using a risk transport model that linearly combines the ERR and EAR risk projections with 70% weight for the ERR model and 30% weight to the EAR model (except for lung cancer for which the weights are reversed, thyroid cancer for which only an ERR model was used, and breast cancer for which only an EAR model was used).

D56. The United Kingdom baseline cancer incidence rates [O1] and life-tables [U5] for the year 2009 used in this calculation are the same as those used in the computation based on the NRRW cohort. The baseline rates were adjusted to account for the “healthy worker effect” in the same way as in the NRRW calculation; that is, a standardized mortality ratio (SMR) of 0.8 has been applied from up to age 50, after which the SMR was allowed to increase linearly from 0.8 at age 51 to $SMR_{90}=1.0$ at age 90 and stay constant for the remainder of life. The SMR_{90} was considered to be uncertain and described by a beta probability density function with parameters 1.5 and 0.5, scaled to range from 0.8 to 1.0.

D57. The estimated risk of cancer incidence was expressed as the rate of radiation-related cases, and it is based on the “risk of exposure-induced death/cases” (REID/C) method [T3]. The uncertainty in the risk estimates was obtained using Monte Carlo methods (sample size of 500 with Latin Hypercube Sampling) to propagate uncertainties in the risk model parameters, latency adjustment, transport between population, DDREF, and healthy worker effect. Uncertainties associated with the assumed dose of 100 mGy and with selection of competing dose–response models were not considered.

D58. The BEIR VII/NCI [N19] methodology predicts a radiation-related risk from age 45 until the end of the remaining life of 0.81 (95% CI: 0.32, 1.6) cases per 100 exposed workers (table D3) and a total expected rate of cases of 41.8 cases (95% CI: 38, 44) per 100, leading to a predicted attributable fraction of 1.9 (95% CI: 0.8, 3.7) per cent. The uncertainty in these estimates for all cancers combined is dominated by the uncertainty in the DDREF. Age groups 70–74 and 75–79 seem to account for the largest excess risk, each with about 16% of the total excess risk of 0.81 cases per 100. However, the attributable fraction is largest for age group 45–59 and it decreases with increasing age group up to age 70 after which it remains relatively constant. The cancer-free life lost per person was estimated at about 53 days, while the cancer-free life lost per cancer case is 129 days and the cancer-free life loss per excess case is 16 years.

Table D3. Estimates of exposure-related risk of cancer incidence, based on the BEIR VII/NCI risk assessment methodology, for United Kingdom nuclear workers who received an absorbed dose of 100 mGy between the ages of 30 and 44 with no additional occupational exposure

Statistic	Mean	95% credible interval	
		Lower	Upper
Total cancer cases ^a	41.8	38.6	43.5
Excess cases ^a	0.81	0.32	1.6
Attributable fraction (%)	1.9	0.8	3.7
NOTIONAL EXCESS CASES BY AGE AT DIAGNOSIS			
Age at diagnosis	Mean	Lower	Upper
45–49	0.024	0.011	0.044
50–54	0.043	0.019	0.079
55–59	0.064	0.026	0.127
60–64	0.087	0.032	0.184
65–69	0.111	0.037	0.243
70–74	0.122	0.041	0.259
75–79	0.125	0.048	0.256
80–84	0.108	0.047	0.206
85–89	0.072	0.031	0.130
90+	0.050	0.019	0.101

Statistic	Mean	95% credible interval	
		Lower	Upper
ATTRIBUTABLE FRACTION (%) BY AGE AT DIAGNOSIS			
Age at diagnosis	Mean	Lower	Upper
45–49	3.6	1.6	6.4
50–54	3.3	1.5	6.1
55–59	2.6	1.1	5.1
60–64	2.2	0.80	4.5
65–69	1.8	0.61	3.9
70–74	1.7	0.58	3.5
75–79	1.7	0.64	3.3
80–84	1.7	0.74	3.2
85–89	1.8	0.76	3.3
90+	2.0	0.76	3.9

^a Total cancer cases and excess cases are expected values for an assumed population of 100 workers with follow-up from age 45 through to the end of life. The number of cases includes all solid tumours, except non-melanoma skin cancer.

E. Summary

D59. As detailed above, risk estimates for solid cancer after exposures in the order of 100 mGy can be derived from a number of studies of diverse populations and exposure conditions. The group of solid cancers is made up of a large number of subgroups of individual cancer sites. In terms of statistical power, risk estimates for the combined group of solid cancers are usually based on comparatively large numbers whereby the statistical uncertainty is reduced. However, in biological terms the group is made up of rather diverse entities. Carcinogenic processes and causal associations with radiation as with other important risk factors vary substantially between individual solid cancer sites. Thus, risk estimates for the overall group need to be interpreted with caution even if detailed exposure, outcome, confounding factor and other information are available.

D60. Overall the body of evidence on solid cancer risks after external irradiation with cumulative doses in the order of 100 mGy is established by highly sophisticated analyses of data from the atomic bombing survivors on the one hand and a growing number of studies of persons externally irradiated through their occupation or environment on the other hand.

D61. In terms of sources of uncertainty beyond statistical sampling error, most work has focussed on dosimetric errors, notably in the LSS but also in other studies, for example, the international workers study. Uncertainty from other sources, be it from procedural aspects of conducting the study to absence of or lack of precision of information on potential confounding factors, are frequently noted in terms of a qualitative assessment, but usually not formally incorporated into risk estimation. Methods for multiple bias modelling are under development, but since basic information is not available at times, there will be limits to statistical treatment of biases also in the future.

D62. Crude risk estimates for solid cancer that do not take into account any uncertainty considerations are presented in numerous studies. The statistical precision of such estimates is greatest when estimated from LSS data, simply owing to the comparatively large power of the study and the wealth of information. On the other hand, the exposure situation and many other aspects limit the usefulness of LSS-based risks for describing the risks of solid cancers after protracted exposure at low cumulative doses. Thus, direct risk estimates from studies of populations with low-dose-rate exposures, even if less powerful and more prone to bias, need to be considered.

D63. There is evidence of a positive dose response from these studies involving low-dose or low-dose-rate exposures (e.g. [K12, S12]), and the observed ERR per unit dose values are generally consistent with those estimated from the LSS. An expected result of including additional uncertainties into the risk estimation is the widening of the uncertainty range around the ERR central estimate.

D64. The best estimates of the two approaches agree very well on a lifetime excess risk for cancer incidence of 1% among United Kingdom radiation workers with a total dose of 100 mGy. Thus the new study of cancer cases among members of the United Kingdom NRRW increases the confidence in the transfer of all estimates of cancer risk from the Japanese survivors of the atomic bombings to other populations. Although this approach took into account uncertainties due to the risk transfer from Japanese to United Kingdom populations, and from exposures ranging from acute to protracted, the calculated 95% credible interval (0.32% to 1.6%) is considerably smaller than the one derived from the NRRW study (0.07% to 1.97%). The large uncertainty in the latter approach is due to the limited statistical power which the NRRW study had in spite of its large size (177,000 workers). Whether or not the uncertainty range based on the risk transfer is too narrow cannot be answered at the present stage.

III. THYROID CANCER AFTER RADIATION EXPOSURE DURING CHILDHOOD

D65. Thyroid cancer after radiation exposure during childhood is a major concern after accidental releases of radioactive isotopes of iodine from nuclear installations. A number of studies documented that children are substantially more sensitive to radiation exposure than adults. Before the Chernobyl accident, most of the knowledge on thyroid cancer risk in humans related to external exposures [R3]. A major question was then how to transfer the risk from external exposures to that from internal exposures to radioactive iodine. After the Chernobyl accident, direct knowledge on the effects of exposure to ¹³¹I were gained by epidemiological studies of thyroid cancer among those in Belarus and Ukraine, who were exposed during childhood or adolescence. The present section summarizes the knowledge on thyroid cancer after childhood exposures to ionizing radiation, and discusses uncertainties for the hypothetical example of an ¹³¹I-exposure at age of 10 years with a thyroid dose of 200 mGy.

A. Summary from previous UNSCEAR reports

D66. Annex A of the UNSCEAR 2006 Report summarized epidemiological studies of radiation and cancer [U12]. It concluded that the thyroid is highly susceptible to the carcinogenic effects of external irradiation during childhood. A pooled analysis of thyroid cancer risk after external exposure during

childhood resulted in an estimate of the ERR per unit dose of 7.7 (95% CI: 2.1, 28.7) Gy⁻¹ and of the EAR per unit dose of 4.4 (95% CI: 1.9, 10.1) cases per 10⁴ PY Gy. Thyroid cancer risks remain elevated after such exposures for long times with some indication that the ERR begins to decline at about 20 years after exposure. The dependence of the excess risk on sex was considered to be unclear. The excess risk decreases strongly with increasing age at exposure.

D67. Annex D of the UNSCEAR 2008 Report [U14] discussed health effects due to radiation from the Chernobyl accident. It concluded that the substantial increase in thyroid cancer incidence seen among those exposed as children or adolescents in Belarus, the Russian Federation and Ukraine showed no signs of diminishing up to 20 years after exposure. The ingestion and inhalation of radioiodine contributed substantially to the thyroid dose. A number of epidemiological studies had been performed and resulted in consistent estimates of the ERR for thyroid cancer after an exposure during childhood or adolescence with a thyroid dose of 1 Gy. There was, however, conflicting evidence as to whether or not iodine deficiency increased the risk from radiation exposure. It was emphasized that medical surveillance of thyroid diseases increased in the affected countries after the accident leading to an increase of the thyroid cancer cases reported in the registries. This factor has to be taken into account in making any kind of risk projection.

B. New evidence, not accounting for the impact of dose and model uncertainties

D68. Gilbert et al. [G11] updated the analyses of thyroid cancer rates in the aftermath of the Nevada atmospheric nuclear bomb tests. Data on thyroid cancer incidence from eight “Surveillance, Epidemiology, and End Results” tumour registries were analysed for the period 1973–2004. The calculation was based on the assumption that persons remained in the same county from 1951 to 2004. Mean thyroid doses were estimated for each county, sex, and age in the calendar years 1951, 1952, 1953, 1955, 1957, 1958 and 1962 (representing 1961 and subsequent years). An increased thyroid cancer risk was observed for mean thyroid doses in the range of 60 to 120 mGy received before one year of age. The ERR per unit dose estimated for this age-at-exposure group was 1.8 (95% CI: 0.5, 3.2) Gy⁻¹. There was no evidence that this estimate declined with follow-up time. Furthermore there was no evidence that the thyroid cancer risk increased after exposures at ages above 1 year. The authors admit that the study results need to be interpreted in light of limitations and biases inherent in geographical correlation studies, including large uncertainty in individual dose estimates and case ascertainment resulting from migration.

D69. Bhatti et al. [B11] updated a study of second primary thyroid cancer among childhood cancer survivors. Data were analysed for 12,547 of 5-year survivors of radiation therapy for childhood leukaemia, Hodgkin lymphoma, non-Hodgkin lymphoma, central nervous system cancer, soft tissue sarcoma, kidney cancer, bone cancer and neuroblastoma diagnosed between 1970 and 1986. In total, there were 119 subsequent pathologically confirmed thyroid cancer cases. A maximum of the relative risk for thyroid cancer of 14.6 (95% CI: 6.8, 31.5) was found for a thyroid dose of 20 Gy. For lower doses, the risk increased linearly with increasing doses, and the ERR decreased with age at exposure. The EAR was higher for females and increased with time after exposure.

D70. Adams et al. [A1] analysed data on thyroid cancer among about 1,300 individuals, who had radiation treatment of an enlarged thymus between 1926 and 1957, and among about 1,770 siblings. Almost all of the exposed (96%) were treated at 1 year of age with a mean thyroid dose of 1.29 Gy. Thyroid cancer occurred in 50 irradiated subjects, and in 13 non-irradiated siblings. Including the

lowest dose group receiving 0.01–0.24 Gy, thyroid cancer risk was increased in all dose groups except one. Only the group receiving 0.25–0.49 Gy had low statistical power and no case occurred in this group. The ERR per unit dose was 3.2 (95% CI: 1.5, 6.6) Gy⁻¹, the EAR per unit dose was 2.2 (95% CI: 1.4, 3.2) per 10,000 person-year Gy. Thyroid cancer incidence appeared to decrease 40 years after exposure and remained elevated up to 70 years after exposure.

D71. Brenner et al. [B20] analysed thyroid cancer in a cohort of about 12,500 Ukrainians who were under 18 years of age when the Chernobyl accident occurred and had individual radioactivity measurements taken within the following two months. The arithmetic mean of the thyroid doses was 0.64 Gy, and the geometric mean was 0.20 Gy. Cohort members underwent up to four thyroid screening examinations. While the first examination reflected cancer prevalence [T8], results of the last three screenings between 2001 and 2007 could be used to calculate incidence risk [B20]. The ERR per unit dose was 1.9 (95% CI: 0.4, 6.3) Gy⁻¹, the EAR per unit dose was 2.2 (95% CI: 0.04, 5.8) per 10,000 person-year Gy. The ERR per unit dose varied significantly by oblast (region) of residence, but not by time since exposure, use of iodine prophylaxis, iodine status, sex, age, or tumour size.

D72. In summary, the two new analytical studies on external exposures confirmed earlier analyses by deriving risk estimates either similar [B11] to the previous study of the same cohort, or a lower estimate of the ERR per unit dose [A1]. The latter can probably be attributed to a decrease of risk with very long follow-up times that had a median of 57.5 years in that cohort. The new study of thyroid cancer after the Chernobyl accident was conducted over a longer time period after exposure than earlier studies and tended to have a lower estimate of the ERR per unit dose.

C. Impact of dose and model uncertainties

D73. Mallick et al. [M6] constructed Bayesian methods for modelling a monotonic regression function when the dose estimates are subject to classical measurement errors, assignment errors, or a mixture of the two (see also appendix B). They applied their method to the study of thyroid neoplasms in relation to radioactive fallout from the Nevada Test Site (NTS). They showed that as the ratio of classical to assignment errors increases the estimated ERR per unit dose increases, as do the length and upper end of the corresponding 95% credible interval. Neglecting all errors, that is, working with the geometric mean of the dose distribution for each of the individuals, resulted in an ERR per unit dose of 13 (95% CI: 1.5, 18) at 1 Gy. If, however, all errors were assumed to be random variability of true dose about an assigned value, that is, to be assignment errors, then the result was 9.0 (95% CI: 2.1, 12). On the other hand, if dose uncertainties were 100% classical measurement errors, then the ERR would be 18 (95% CI: 7.0, 32). Thus, in this case, neglecting the uncertainties in dose estimates would only be misleading (a too low estimate, and a too narrow credible interval), if most of the uncertainty would be due to classical measurement error.

D74. Li et al. [L14] refined methodologies to deal with the complex error structure in the dosimetry for the NTS Thyroid Disease Study. Their methods take account of the fact that assignment errors could be shared within subgroups of the cohort. They assume further that the errors are a mixture of classical measurement errors and assignment errors. They compare the results with an analysis, in which it is assumed that all errors are 100% due to unshared assignment errors and regression calibration is used with the expectation value of the individual dose. The point estimate and the upper limit of the 95% credible interval of the ERR for thyroid neoplasms are found to increase by about a factor of 2–4 depending on assumptions made about the overall uncertainty in dose estimation. The authors conclude that using regression calibration and expectation values for individual doses can lead to a substantial

underestimation of risk-per-unit-dose values, when sources of uncertainty include mixtures of classical measurement error and shared sources of assignment error.

D75. Kopecky et al. [K10] analysed data on thyroid cancer in the Bryansk oblast, Russia, among individuals, who were 0–19 years old at the time of the Chernobyl accident. The population-based case–control study included 66 primary thyroid cancer cases diagnosed after the accident up to September 1998. Thyroid dose estimates were based on a model for environmental concentrations and had uncertainties assumed to be log-normally distributed (median geometric standard deviation of 2.2). The authors assumed that all of the error in the doses was due to classical measurement error. No consideration was made for shared sources of uncertainty. Correcting for such a kind of error resulted in an increase of the estimated ERR per unit dose by a factor of three. However, the adjusted estimate is likely to be too large, since not all of the random dose uncertainty arose from classical measurement error. On the other hand, the effect of shared sources of dose uncertainty remains to be evaluated.

D76. Walsh et al. [W3] analysed the impact of using different models for the estimate of the thyroid cancer risk after exposure to ionizing radiation during childhood. They identified the modelling of the baseline risk as the reason for contradictions in results that had been obtained previously by two different papers [J2, L15] in analysing thyroid cancer incidence in Ukraine after the Chernobyl accident. Different quality-of-fit criteria favoured parametric modelling of the baseline to various stratified models of the baseline. Differences in ERR estimates amounted to more than a factor of 3 for ages below 4 years old at exposure. EAR estimates are predicted to be very similar using the different models. For thyroid cancer incidence at 12 years after exposure of the atomic bomb survivors, ERR values predicted by a model with a parametric baseline risk were higher than a model with a stratified baseline risk by more than a factor of 3 for ages below 7 years at exposure.

D77. In summary, methods to correct thyroid neoplasm risk estimates for random dose errors have been implemented in two studies, both of which are characterized by large dose errors. In these cases, corrected estimates of the ERR per unit dose are larger by a factor of about three than those in a regression calibration with mean values used for individual dose. The impact of shared sources of uncertainty can influence the dose response further, but these shared errors remain to be evaluated explicitly. The Committee emphasizes that reliable risk estimates are normally derived from studies with more certain dose estimates, and are thus less affected by dose uncertainties. The impact of the choice of the model on estimates of thyroid cancer risk from exposure to radiation has been analysed for two studies with more reliable dose estimates. For a time since exposure of 12 years, ERR estimates for young ages of exposure were strongly influenced by modelling of the baseline rates. EAR estimates were more stable.

D. Selected risk evaluation

D78. For this scenario the Committee considered a hypothetical group of Ukrainians aged 10 years at the time of the Chernobyl accident. Their cumulative thyroid dose was 200 mGy. The dose was nearly exclusively due to incorporation of ¹³¹I, so that short-lived radioiodines and external radiation do not need to be considered. Surveillance of thyroid diseases in this hypothetical group should reflect the situation in the higher contaminated parts of Ukraine about one to two decades after the accident. The quantities of primary interest are the expected total rate of baseline and radiation-associated cases (per 10,000 people) up to the end of April 2004 and up to the end of life of the group members.

1. Risk estimation taking account of studies after the Chernobyl accident

D79. In the recent analysis of the UkrAm cohort, excess risks for thyroid cancer incidence in the period 2001 to 2007 were estimated for Ukrainians, who have been exposed during childhood or adolescence in 1986 to radioiodine released from the Chernobyl nuclear power plant [B20]. Two post-accident case–control studies in Belarus and Russia made estimates of the ERR at about 8 years after exposure [C2, K10]. The time dependence of the ERR and of the EAR over a period of 4 to 15 years after exposure has been assessed in a population study in Belarus and Ukraine [J2]. The results of these four studies agree within their ranges of uncertainty (figure D-I). They indicate a decreasing ERR during the first 20 years of exposure whereas the EAR varied less with time after exposure.

D80. The post-accident studies cover a period from 4 to 21 years after exposure. In order to make lifetime predictions, results from other studies are needed. The recent analysis of cancer incidence in the LSS covers a period from 13 to 53 years after exposure [P14]. Figure D-I shows two kinds of transfer of the LSS data (transfer of the ERR and transfer of the EAR) to the population of Ukraine including an extrapolation to times after exposure shorter than the period for which incidence data are available for the LSS. The extrapolation of the ERR in the LSS agrees within the uncertainty ranges for each of the ERR results of the post-accident studies [B20, C2, J2, K10] (upper panel of figure D-I). On the other hand, the post-accident studies indicate a time-since-exposure (TSE) effect (according to Jacob et al. [J2]: the ratio of the ERR at TSE = 5 years to that at TSE = 15 years is 4) that is captured better by the transfer of the extrapolated EAR than by the transfer of the extrapolated ERR (TSE effect of about 2). Also, the post-accident EAR results agree better with the transfer of the extrapolated EAR than with the transfer of the extrapolated ERR (lower panel of figure D-I).

D81. For the transfer of risk quantities for thyroid cancer from one population to another, generally the ERR is used [N19, U12]. This is motivated by the pattern of thyroid cancer rates observed during thyroid screening and surveillance, and the assumption that ERR estimates are less influenced by these conditions. It is, however, noted that the estimates of the ERR per unit dose differed in four cohorts of a pooled study by a factor of 13, whereas the estimates of EAR per unit dose differed only by a factor of 3 [R3]. A better agreement of EAR estimates was also found between the LSS data and results for thyroid cancer in Ukraine after the Chernobyl accident (figure D-I). In the present exercise, the ERR is transferred according to a generally adopted procedure, and results in:

$$ERR_{\text{Ukraine}} = ERR_{\text{LSS}}; \quad EAR_{\text{Ukraine}} = ERR_{\text{LSS}} \times \text{baseline}_{\text{Ukraine}} \quad (\text{D.1})$$

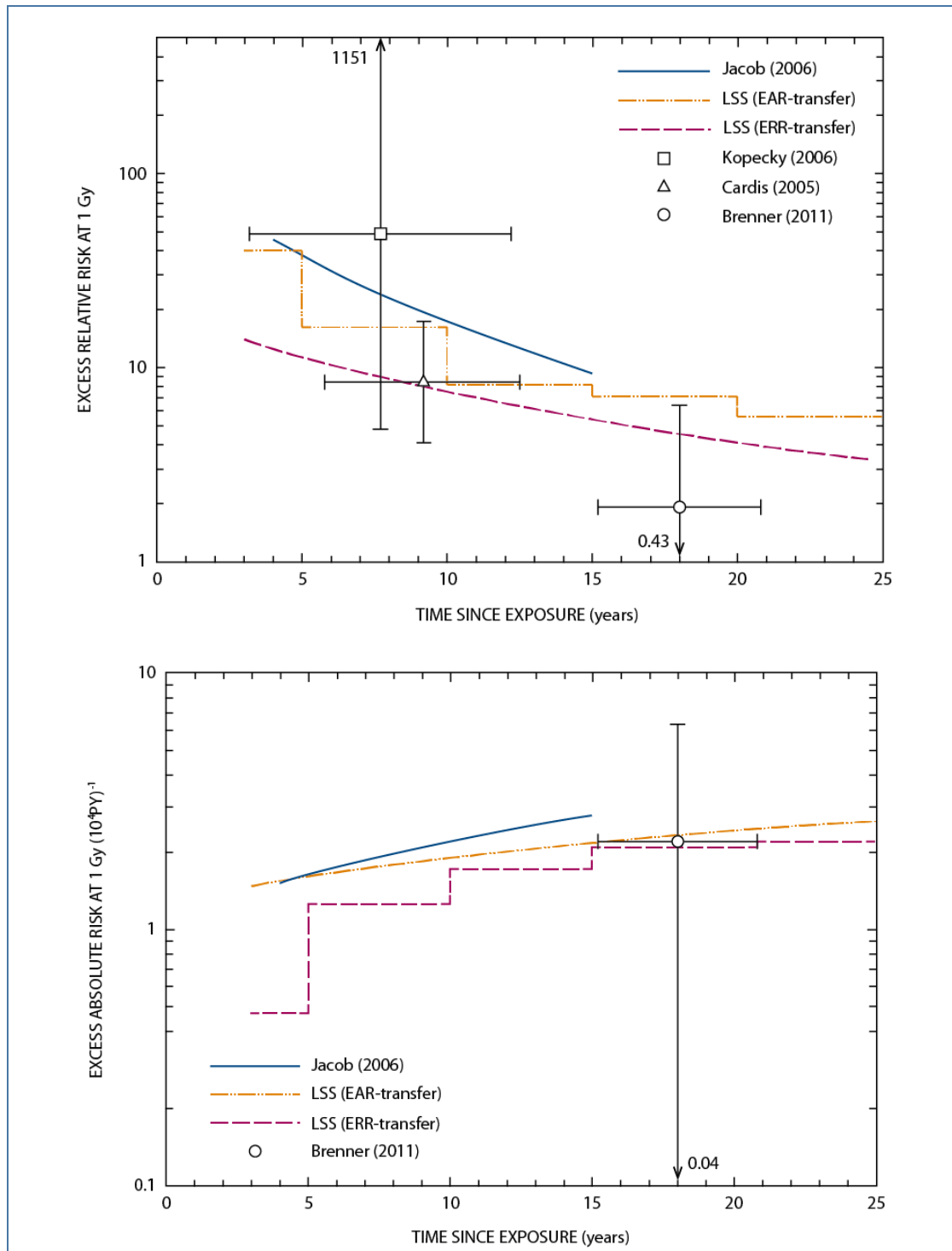
and as an alternative, the EAR is transferred according to the relatively good agreement of EAR estimates obtained in different studies, and results in:

$$ERR_{\text{Ukraine}} = EAR_{\text{LSS}}/\text{baseline}_{\text{Ukraine}}; \quad EAR_{\text{Ukraine}} = EAR_{\text{LSS}} \quad (\text{D.2})$$

D82. The upper parts of tables D4 and D5 summarize results of the calculations for the period 1986 to 2004. According to the thyroid cancer incidence in 2009 for the whole of Ukraine, which is not expected to be significantly affected by the radiation exposure from the Chernobyl accident, about six baseline thyroid cancer cases are expected among 10,000 females who were of age 10 at the time of the accident. Independent of whether the ERR or the EAR are transferred from the LSS to this Ukrainian population group, about nine additional thyroid cancer cases are expected to be induced by an ¹³¹I exposure with a thyroid dose of 200 mGy. The baseline incidence among males who were of age 10 at the time of the accident is more than a factor of four lower than among females. For males, the transfer of the EAR model results in nearly twice as many predicted excess thyroid cancer cases than the ERR model transfer.

Figure D-I. Estimates of excess risk of thyroid cancer after the exposure to ¹³¹I of Ukrainians at age 10 with a thyroid dose of 1 Gy

The upper panel gives results on the ERR, the lower panel results on EAR. The triangle with 95% confidence intervals gives results for the UkrAm cohort [B20]; the circle and square results for two case-control studies [C2, K10]; the solid line results for the Ukrainian population [J2]; the dashed line results for the transfer of the (extrapolated) EAR for the LSS [P14]; and the dashed-dotted line results for the transfer of the (extrapolated) ERR for the LSS [P14]



D83. The lower parts of tables D4 and D5 summarize results of the calculations for lifetime risks. According to the thyroid cancer incidence in 2009 for the whole of Ukraine, about sixty baseline thyroid cancer cases are expected among 10,000 females who were of age 10 at the time of the accident. According to the transfer of the EAR model, this number is doubled by an ^{131}I exposure with a thyroid dose of 200 mGy. A transfer of the ERR model results in a considerably lower number of excess cases. The baseline incidence during lifetime for males who were of age 10 at the time of the accident is lower than for females by more than a factor of four. For males, the transfer of the EAR results in more than twice as many predicted excess thyroid cancer cases than the ERR transfer. It may be noted that the difference is here because of an uncertainty in the risk model, and not because of an uncertainty in the transfer model. If the EAR model estimate for the EAR is replaced by the product of the ERR and the baseline in the LSS, then the difference of the lifetime risks of the two transfer models is relatively small.

Table D4. Estimates of hypothetical number of thyroid cancer cases among 10,000 Ukrainians, who were of age 10 years at the time of the Chernobyl accident and received a thyroid dose of 200 mGy from incorporation of ^{131}I , using the ERR model for the transfer of the risk

Calculations took into account post-accident studies, and were based on LSS data

<i>Period and sex</i>	<i>Baseline</i>	<i>Excess</i>	<i>Total</i>
1986–2004			
Males	1.3	1.4	2.7
Females	5.7	8.3	14
Lifetime			
Males	13	5.6	3.9
Females	61	34	96

Table D5. Estimates of hypothetical number of thyroid cancer cases among 10,000 Ukrainians, who were of age 10 years at the time of the Chernobyl accident and received a thyroid dose of 200 mGy from incorporation of ^{131}I , using the EAR model for the transfer of the risk

Calculations took into account post-accident studies, and were based on LSS data

<i>Period and sex</i>	<i>Baseline</i>	<i>Excess</i>	<i>Total</i>
1986–2004			
Males	1.3	2.6	3.9
Females	5.7	9.6	15
Lifetime			
Males	13	13	26
Females	61	60	121

2. Risk estimation not taking account of studies after the Chernobyl accident

D84. The radiation-related excess risk was calculated using a risk model derived from the pooled data of seven studies described by Ron et al. [R3], as analysed by Land et al. [L5] and modified for sex-dependency by the BEIR VII committee [N19]. The pooled analysis included the LSS cohort of Japanese survivors externally exposed to radiation from the atomic bomb detonations in Hiroshima and Nagasaki, and cohorts of patients externally exposed to medical X-rays mostly in childhood.

D85. The risk model is linear in dose, accounts for a decrease of risk with increasing age at exposure, and does not depend on attained age. The mathematical form of the ERR model is $\beta_S D \exp[\gamma e^*]$ where β_S is the ERR per unit dose, D is the dose in grays, γ is the age at exposure parameter, e^* is $(e-30)/10$ for e less than 30 and zero for e greater than or equal to 30, where e is age at exposure in years. Parameter β_S has a value of 0.53 for males and of 1.03 for females and its uncertainty is described by a log-normal probability density function with a GSD of 1.96 for both males and females. The age-dependent parameter γ has the same value of -0.83 for both males and females.

D86. The risk of thyroid cancer incidence was estimated by applying the risk model to the 2009 baseline thyroid cancer incidence rates for Ukraine [N5] weighted by the survival function for Ukraine determined from 2009 life-tables [U5]. The exposure scenario assumes males and females who were 10 years of age at the time of Chernobyl accident in 1986 received thyroid doses from intake of ^{131}I equal to 200 mGy. Doses from ^{131}I are delivered as a chronic exposure, and thus the BEIR VII DDREF (log-normal distribution, GM = 1.5, GSD = 1.35) was applied. Given that only individuals of age 10 are assumed to have been exposed and that, for thyroid cancer, mortality is very low compared to incidence, the survival function of the exposed population is virtually identical to the survival function in the absence of exposure. Thus, for this exposure scenario, the lifetime attributable risk (LAR) is a very good approximation for the risk of exposure-induced deaths/cases (REID/C).

D87. Uncertainties in all risk estimates were calculated using Monte Carlo uncertainty propagation (sample size of 500 with Latin Hypercube Sampling) and are presented as an arithmetic mean and a 95% credible interval. Uncertainties in the results include uncertainties in model parameters and in DDREF. Uncertainty associated with the assumed dose of 200 mGy and with the selection of competing dose-response models for estimating the excess risk per unit dose were not considered.

D88. The upper part of table D6 summarizes results of the calculations for the period 1986 to 2004. Of the total expected number of about 2 cases among 10,000 males, the mean value of the predicted excess cases constitutes about 30%; and of the total number of 11 cases among 10,000 females, the mean value of predicted excess cases constitutes about 50%. Baseline and relative risks from radiation exposure are assumed to be larger for females than for males. Upper and lower bounds of the 95% credible intervals for the radiation-associated cases differ by a factor of about 16. The uncertainty is dominated by the statistical uncertainty in the BEIR VII estimate of the ERR per unit dose (GSD = 1.96), followed by the BEIR VII uncertainty in the DDREF (GM = 1.5, GSD = 1.35).

D89. The lower part of table D6 summarizes results of the calculations for lifetime risks. Of the total number of 20 cases among 10,000 males, the mean value of the predicted cases constitutes about 30%; and of the total number of about 120 cases among 10,000 females, the mean value of the predicted cases constitutes about 50%. Baseline and relative risks from radiation exposure are assumed to be larger for females than for males. Upper and lower bounds of the 95% credible intervals for the radiation-associated cases differ by a factor of 18. Again, the uncertainty is dominated by the uncertainty in the ERR per unit dose and DDREF estimates.

Table D6. Estimates of hypothetical number of thyroid cancer cases (best estimates and 95% credible intervals) per 10,000 Ukrainians, who were of age 10 years at the time of the Chernobyl accident and received a thyroid dose of 200 mGy from incorporation of ^{131}I , using the BEIR VII models [N19]

Calculations did not take into account post-accident studies

<i>Period and sex</i>	<i>Baseline</i>	<i>Excess</i>	<i>Total</i>
1986–2004			
Males	1.3 (–)	0.56 (0.11, 1.8)	1.9 (1.4, 3.1)
Females	5.8 (–)	5.2 (0.94, 15)	11 (6.7, 20)
Lifetime			
Males	14 (–)	6.6 (1.2, 21)	20 (15, 35)
Females	62 (–)	59 (11, 210)	121 (73, 272)

3. Summary from the two risk estimations

D90. The two calculations agree quite well on the estimates of the radiation-related thyroid cancer risk during their lifetime of a hypothetical group of Ukrainians exposed after the Chernobyl accident to ^{131}I . In the BEIR VII model, it is assumed that the ERR can be directly applied to the Ukrainian population after the Chernobyl accident. A comparison with the results after the Chernobyl accident, however, shows a better consistency with a transfer of the EAR from the LSS to the Ukrainian population. The EAR transfer results in a predicted number of radiation-related thyroid cancer cases during their lifetime that is higher than that derived using an ERR transfer by a factor of 3 for males and by a factor of 2 for females. The transfer of risk introduces an uncertainty additional to those discussed in the last subsection.

D91. The BEIR VII model assumes an ERR that is independent of time after exposure. Post-accident experiences, however, demonstrated higher ERR values for a few years after exposure than at times after more than a decade. As a consequence, the predictions that take into account the experiences of the Chernobyl accident result in higher risk estimates for the first two decades after the exposure than the BEIR VII model. The difference is most expressed for males, for whom the EAR (ERR) transfer results in a number of predicted excess cases larger than those in the BEIR VII approach by a factor of about 5 (2.5).

IV. LUNG CANCER AFTER RESIDENTIAL EXPOSURE TO RADON DECAY PRODUCTS

D92. Inhalation of radon gas and its progeny represents one of the main sources of radiation exposure of the general population. The annual per caput dose resulting from this type of exposure typically represents about half of the effective dose received by members of the public from all natural sources of radiation exposure [U12].

D93. The principal health effect from exposure to radon decay products is an increased risk of lung cancer. Review of available epidemiological data shows no consistent evidence for an association between radon concentration and any cancer other than lung cancer [I17]. Prior to the past decade, estimates of this risk were based on studies of miners. Meanwhile, however, there is direct evidence from studies of residential radon exposure for a causal relationship between indoor radon exposure and the risk of lung cancer in the general population [U13, W8]. More than 20 analytical studies (mostly case–control studies) of residential radon exposure and lung cancer have been published and reviewed by the Committee [U13]. Most of the studies showed a positive association between radon exposure and risk of lung cancer; however, the estimated risk coefficients varied substantially between studies and often did not reach statistical significance. For this reason, pooled analyses of the individual data of 13 European [D2, D3], 7 North American [K14, K15] and 2 Chinese studies [L30], respectively, were performed by the three respective research groups. These pooled studies consistently showed an approximately linear increase in the risk of lung cancer with increasing long-term radon exposure.

A. Uncertainties in radon exposure assessment

D94. The greatest challenge in epidemiological studies of residential radon exposure is to assess accurately the radon concentrations for the relevant period of interest, i.e. 3–5 years (represent a minimum latency period for lung cancer) to about 35 years before diagnosis of lung cancer or date of interview for the controls [L26]. Usually one-year radon measurements in one or two rooms of the current home and all other dwellings inhabited by the cases and controls during the period of interest were performed. Indoor radon concentrations in the population are considered to be log-normally distributed. They vary considerably with time (day, season, year) and location. Sources of uncertainty in the assessment of retrospective exposure to radon have been extensively discussed [B14, H10, L26, S27, U13].

D95. Uncertainty in the assessment of residential radon exposure arises from detector measurement error, the use of current measurements of radon concentrations in air to reflect past levels of up to 30 or more years ago, spatial variations within a home, gaps from missing radon concentration measurements, failure to link radon concentrations with subjects' mobility, and measuring radon gas concentration as a surrogate for dose from radon progeny [B14, L26, W8]. The impact of formally adjusting for uncertainties in the assessment of radon exposure has been investigated in a few studies of residential radon exposure [D1, D2, D3, L1, U13]. In the European pooled analysis of 13 studies of residential exposure to radon the adjusted linear excess relative risk for an increased concentration of 100 Bq/m³ was estimated to be 0.16 (95% CI: 0.05, 0.31) [D1]. In paragraph 4 of annex E of the UNSCEAR 2006 Report the Committee considered this estimate as an appropriate, if possibly conservative, estimate of the risk from residential exposure to radon [U13].

D96. Heid et al. [H10] provided a comprehensive list of the sources of errors in the assessment of radon exposure and classified them by type of error (classical or assignment) (see table D7). The authors defined classical error as either repeated observations with values varying about the true value (such as detector measurement error), or if one measurement is used as proxy for the average, and if repeated measurements would vary about the average (such as room-to-room or year-to-year variation). In most studies of residential exposure to radon, one-year measurements of the radon concentration were made by means of alpha-track detectors. The average radon concentration is estimated by counting the number of etched tracks made on a plastic film by alpha particles. This process is subject to error, which has been estimated to be about 15%–25% [L26]. Next to that, radon concentrations vary with placement of the detector in a specific room or between rooms. In most studies one measurement

was conducted in each of the main living room and the bedroom, while in the other occupied rooms no measurements were performed; the values for these rooms were assumed to be equal to those rooms with measurements. Seasonal variation is another source of error, if radon concentrations measured over a period of less than one year are used to estimate the annual average. Thus most residential radon studies perform one measurement over a year or two consecutive 6-month measurements to avoid this type of error.

D97. The major source of classical error in exposure assessment, however, is the use of current measurements in order to reflect the conditions of previous years. Even if a person has lived only in one home over the whole exposure period of interest, there are major year-on-year variations owing to structural changes (such as insulation of windows), changes in living habits (more or less ventilation) and climate changes. Even more uncertainty may arise if the current home owner differs from the study participant. The potential size of this type of error was investigated in a range of studies by conducting measurements in the same dwelling in different years [D2, H21, L31, Z2]. Overall, considerable variability was found, exhibiting a coefficient of variation on a linear scale of 40%–50% on average.

D98. Based on measurement data of the West and East German residential studies, Gerken et al. [G5] identified factors that determine the radon concentration in homes. These included fixed factors such as type of house, and changeable factors (variates) such as the heating system (single oven versus central heating), windows insulation (for example, single glazing versus double glazing) and ventilation habits. Correction factors were developed by means of variance analyses in order to take into account differences for current residents and former residents. Correction factors for single variates ranged between 1.05 and 1.2. A maximum correction factor of 1.4 was reached in the rare case of changes in more than variate. Applying such correction factors for structural and ventilation changes, but also for seasonal variation in the case of short-term measurements, results in assignment error [H10]. This type of error occurs if a groups' observation is assigned to each individual of the group, but the value for individuals would differ within each group [H10].

D99. Uncertainty also arises from gaps in the exposure history owing to demolished homes, homes that cannot be located or were occupied briefly and not measured, or the current occupant refuses measurements or died within the measurement period. Weinberg et al. [W7] compared several methods for dealing with missing exposure values by imputation and evaluated the corresponding bias in risk estimates. These methods included: (a) to substitute each missing value with the mean across all measured values in the study; (b) to substitute each missing value with the mean across all measured exposure values of the controls; (c) to substitute each missing value of a case with the mean across the measured values of all cases, and each missing value of a control with the mean across the measured values of all controls; (d) to substitute the missing value with a concentration of zero; and (e) to substitute the missing value of a specific individual with the time-weighted average across all measured periods for that individual. Assuming no other source of error, the method of assigning the arithmetic mean across all measured control residences turned out to be the best method, inducing no bias in risk estimate and no distortion in the confidence interval coverage. This method can even be improved by imputation within strata of predictive information on the missing home (such as knowledge of the storey).

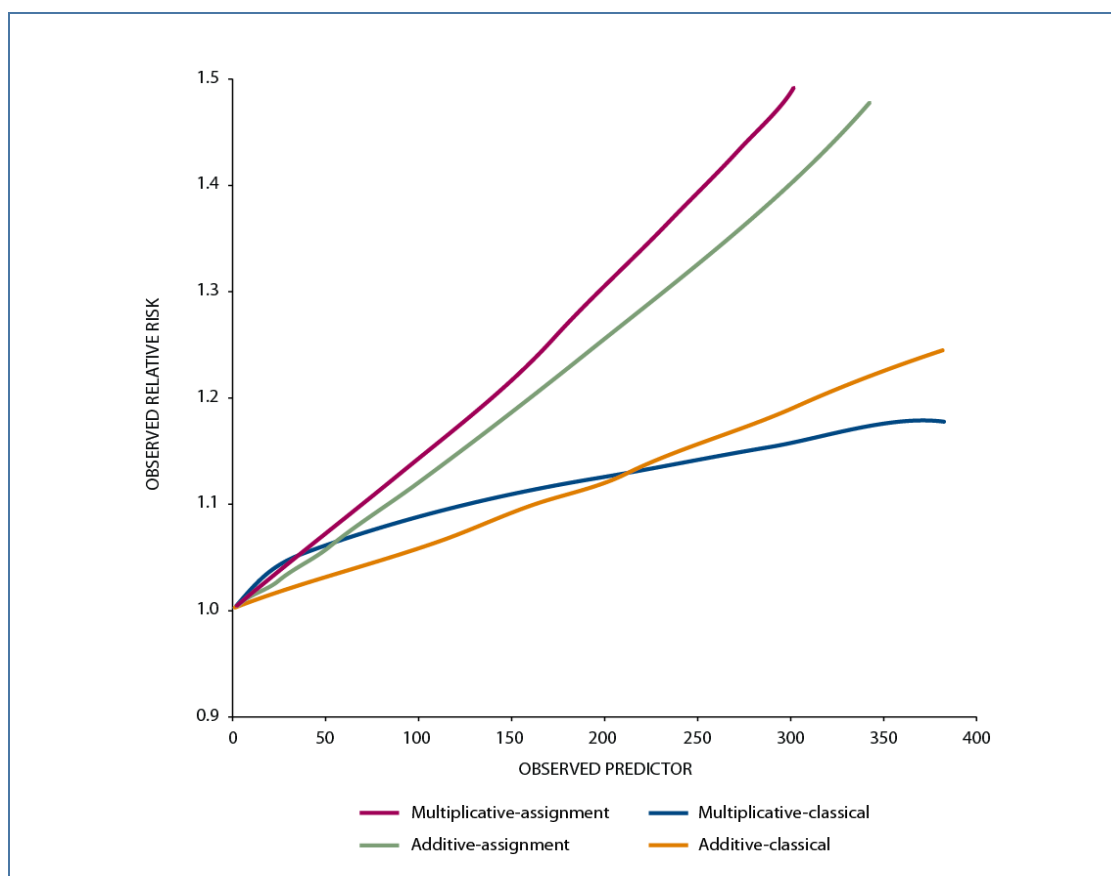
Table D7. Sources and type of error in assessing residential radon exposure (adapted from [H10])

<i>Type of error</i>	<i>Source of error</i>	<i>Comments</i>
Classical error	Variability between measurements	Deviation between measurements obtained repeatedly at the same time and place; detector measurement error
	Variability between placements	Variation depending on the placement of the detector in a room
	Variability between rooms	Radon concentrations in the rooms without measurements differ from radon concentrations measured, e.g. in the living room as proxy for the concentrations in other rooms
	Variability between seasons	There is strong seasonal variation in radon concentrations, with nearly twice as high radon concentration in the winter compared to the summer. Error occurs if short-term measurements were used to estimate the average one-year radon concentration
	Variability between years	Variations over the years due to differences in the weather, structural changes and the habits of the occupants in a home
	Variability between owners	Different ventilation habits and structural changes of the former and current inhabitant of a home, which leads to conditions in the home during measurement different from the conditions during residency of the study subject
	Differences in ventilation habits by room and time of day	The detector measures average radon concentration for the full day, but the bedroom is occupied during the night and the other rooms during the day. For example, if the bedroom is ventilated more during the day than at night, the measured bedroom concentration underestimates the concentration during the bedroom's occupancy
	Variability between environments	Radon concentrations in residential environments other than the principal home are not measured and assumed to be as high, on average, as the principal home
	False recall of occupancy or residency	False recall of occupancy times for rooms and residency times for homes
Assignment error	Imputation of missing values	Gaps in the exposure history arise from demolished homes, not traceable, homes outside the study area, and refusal to respond by or death of the current occupant. Missing measurement values were imputed, e.g. by assigning the arithmetic mean of measured homes of the controls to the missing values
	Applying correction factors for seasonal variation or previous owners	A certain factor is assigned to all individuals with (1) the same seasonal pattern, (2) the same house-alterations, or (3) the same changes in ventilation habits between current house owner and study participant
	Using exposure data as surrogate for the lung dose	Error in the equilibrium factor and from variability between persons. Lung doses of persons with the same radon and radon progeny exposure vary owing to respiratory differences

B. Implications of exposure uncertainties on risk estimates

D100. Based on theoretical considerations Heid et al. [H10] investigated the effect of additive and multiplicative classical and assignment error on the risk estimate derived from studies of residential exposure to radon and described intuitive measures of the size of error. A non-differential random homoscedastic error model was assumed. The authors noted that the impact of both types of error on the risk estimate differs substantially. The classical error could induce severe bias. It attenuated the dose–response curve and in the case of multiplicative error it could even distort the dose–response curve. In contrast to this, no notable bias on the risk estimates was induced by assignment error. If at all, multiplicative assignment error may lead to slightly increased risk estimates, while additive assignment error induces no bias. However, assignment error weakened the precision of the risk estimates. The resulting effects of multiplicative and additive classical and assignment error are illustrated in figure D-II [H10]. The figure shows the theoretically observed dose–response curve when the dose is measured with additive (standard deviation, SD = 50) or multiplicative error (GSD = $e^{0.4}$) of the classical or assignment type and a true relative risk of 1.12. The authors recommended conducting repeated measurements (for example, more detectors in one room, or several measurements over many years) in future epidemiological studies, in order to gain insight into the size of errors. Analyses of German data on repeated measurements of radon, for example, provided evidence for a multiplicative error owing to variabilities between measurements and between years in the West German study [H10].

Figure D-II. Theoretical observed dose–response curves when the dose is measured with additive (standard deviation = 50) or multiplicative (standard deviation on log-scale = 0.4) error of the classical or assignment type and a true relative risk of 1.12 (see the line “none = add Berk”) (adapted from [H10])



D101. Investigators have addressed uncertainties in exposure assessment by formally adjusting risk estimates using various models [D1, D2, D3, H11, L1, L31, R1], using glass-based measurements instead of measurements in air [A5, L2], limiting participants to long-term residents by study design [F4], conducting sensitivity analyses limited to subjects with more accurate information [D3, K14, K15, L30] or improving the exposure assessment through linkage with spatial and temporal mobility [F5]. Applying these methods, an increase in the order of 50% to 100% in the estimate of excess relative risk of lung cancer per unit dose was observed [B14]. The different methods of accounting for uncertainty will be discussed in detail in the following paragraphs. Table D8 provides an overview of the results of studies of residential exposure to radon with formal adjustment for error in the exposure estimate.

D102. The Swedish radon study [L1] adjusted risk estimates for multiplicative classical error arising from uncertainty in radon exposure assessment. The study included 1,360 lung cancer cases and 2,847 controls. Radon was measured in 8,996 dwellings that had been occupied at some time since 1947. Overall, 27.4% of dwellings could not be measured. Empirical data from Sweden had been used to estimate uncertainty in the assessment of radon exposure using a Monte Carlo modelling technique. Simulations included sources of errors related to the detector, extrapolation of three-month measurements to one-year measurements, year-on-year variation due to structural and ventilation changes, gaps in exposure history, and spatial and temporal (age-dependent) variation in occupancy patterns. Adjusted risk estimates were obtained from regression analyses based on expected values for true time-weighted average of the radon concentration (TWA), conditional on the observed TWA. A linear exposure–response, a log-normal distribution for the true TWA, and a log-normal distribution for a relative error with constant coefficient of variation were assumed. The estimated ERR per unit TWA of radon concentration was 0.10 (95% CI: 0.01, 0.22) per 100 Bq/m³ without adjustment for error. It increased to about 0.15 to 0.20 Bq/m³ after adjustment. Assuming a best coefficient of variance of about 50%, the estimate for the ERR per unit TWA of radon concentration was 0.17 (95% CI: 0.03, 0.37) per 100 Bq/m³.

D103. Uncertainties in the assessment of radon exposure have also been formally taken into account in the south-west England study [D1]. The study included 982 lung cancer cases and 3,185 controls. Radon concentrations had been measured in homes occupied during the 30-year period ending 5 years before interview. Two consecutive 6-monthly measurements had been performed in the living room and bedroom. The average annual radon concentration was estimated assuming an occupancy time of 45% in the living area and 55% in the bedroom. The time-weighted average radon concentration over the 30-year period of interest was calculated. Missing radon concentrations were imputed by the arithmetic mean in each geographical group of controls according to Weinberg et al. [W7]. The estimated ERR per unit TWA of radon concentration without adjustment for uncertainties in exposure was 0.08 (95% CI: -0.03, 0.20) per 100 Bq/m³; this value became 0.14 (95% CI: 0.01, 0.29) per 100 Bq/m³, after excluding subjects with incomplete coverage of measurements over the 30-year period. Uncertainties were taken into account according the methodology of Reeves et al. [R1] for logistic regression. A coefficient of variance on the original scale of 51% was assumed based on external data from a study on repeated radon measurements. After accounting for error the estimated ERR per unit TWA of radon concentration increased to 0.12 (95% CI: -0.05, 0.33) per 100 Bq/m³ for the full data set and to 0.24 (95% CI: -0.01, 0.56) per 100 Bq/m³ in the restricted group.

Table D8. Studies of residential exposure to radon that estimate risk before and after accounting formally for uncertainty in the assessment of radon exposure or compare air-based with glass-based detectors (adapted from [B14])

Study location, author	Number of cases	Number of controls	ERR per 100 Bq/m ³ (95% CI)		Comments
FORMAL ADJUSTMENT FOR MEASUREMENT ERROR					
Sweden [L1]	1 281	2 576	0.10 0.17	(0.01, 0.22) (0.03, 0.37)	No adjustment for uncertainty in radon exposure Adjustment for uncertainty in radon exposure (CV of 50%)
South-west England, United Kingdom [D1]	982	3 185	0.08 0.12	(-0.03, 0.20) (-0.05, 0.33)	All subjects, no adjustment for error Adjustment for error in exposure according Reeves et al. [R1] (CV of 51%)
	484	1 637	0.14 0.24	(0.01, 0.29) (-0.01, 0.56)	Complete coverage of 30 years with measurements, no adjustment for error Adjusted for error in exposure according Reeves et al. [R1] (CV of 51%)
Gansu, China [W5]	768	1 659	0.16 0.29	(0.03, 0.40) (0.03, 1.04)	All subjects Adjusted for error in exposure (CV of 43%)
Gansu, China [L31]	463	1 143	0.23 0.65	(0.06, 0.57) (0.16, 3.04)	≥70% coverage of exposure time window with measurements Adjusted for error in exposure (CV of 43%)
East Germany [H11]	1 053	1 667	0.04 0.11 0.16	(-0.04, 0.12) (-0.12, 0.42) (-0.04, 0.48)	No adjustment for uncertainty in radon exposure Adjustment for error in radon exposure (size 0.4) Adjustment for error in radon exposure (size 0.4) and smoking (error 0.5)
West Germany [H11]	1 449	2 297	-0.03 0.02 0.12	(-0.19, 0.15) (-0.38, 0.68) (-0.32, 0.83)	No adjustment for uncertainty in radon exposure Adjustment for error in radon exposure (size 0.4) Adjustment for error in radon exposure (size 0.4) and smoking (error 0.5)
Europe [D2, D3]	7 148	14 208	0.08 0.16	(0.03, 0.16) (0.05, 0.31)	No adjustment for uncertainty in radon exposure Adjustment for measurement error using regression calibration methods
Europe [F2]			0.16	(0.05, 0.31)	Adjustment for measurement error using integrated likelihood methods
COMPARISON OF AIR-BASED WITH SURFACE-BASED RADON DETECTORS					
Missouri [A5]	247 372	299 471	0.04 0.63	(-0.13, 0.57) (0.07, 1.93)	Air-based measurements with alpha-track detectors Glass-based detectors with surface monitors
Sweden II [L2]	109	229	0.33 0.75	(-0.12, 2.00) (-0.04, 4.30)	Air-based measurements with alpha-track detectors Glass-based detectors with surface monitors

CV: Coefficient of variation on the original scale.

D104. Lubin et al. [L31] investigated sources of uncertainties in radon exposure assessment in a sub-study of the residential exposure study in Gansu Province in China [W5]. Within this sub-study, 1,654 detectors were placed in between one and five rooms in 55 houses over three consecutive years. The variations of radon concentrations within rooms, between rooms within a dwelling, between dwellings, and over time were evaluated. Temporal variation turned out to be the single largest source of uncertainty; however, substantial residual variation remained unexplained. The maximum likelihood estimate of the total variation from sources other than the type of dwelling was 0.17 with a standard deviation of 0.011, resulting in a geometric standard deviation for uncertainties from these factors of 1.50 (95% CI: 1.47, 1.55) or a coefficient of variance of 0.43 (95% CI: 0.40, 0.46). A modified regression calibration approach was used to adjust risk estimates in the full study for uncertainty of exposure. To exclude as far as possible additional assignment bias, through imputation of missing radon values using radon concentrations of the controls, risk analyses were performed using the full data set and the data set restricted to subjects with 70% coverage of measurements in the 5–30 year period of interest. The unadjusted odds ratios at 100 Bq/m³ were 0.16 (95% CI: 0.02, 0.44) for the full data set and 0.24 (95% CI: 0.06, 0.62) for the restricted data. After taking uncertainties into account, the odds ratios increased to 0.29 (95% CI: 0.03, 1.04) and 0.65 (95% CI: 0.16, 3.04).

D105. Uncertainty may not only be present in the assessment of radon exposure, but also in the assessment of potential confounding factors. Heid et al. [H11] investigated the impact of measurement error in radon exposure and of smoking on the risk estimate. She applied the regression calibration method adopting a bivariate multiplicative error model of the classical type. By means of sensitivity analyses the effects of various errors in exposure on the odds ratios were explored within the West and East German residential radon study. Both variables were assumed to be log-normally distributed and the error to be non-differential random and homoscedastic. A small negative correlation between radon and smoking was observed (−0.06). The original uncorrected odds ratios per average radon concentration in air had been 0.97 (95% CI: 0.81, 1.15) per 100 Bq/m³ in the West study and 1.04 (95% CI: 0.96, 1.12) per 100 Bq/m³ in the East study, respectively. The odds ratios increased after correction for errors in radon exposure, for example to 1.02 and 1.11 respectively, assuming a measurement error of 0.4 (explaining 40% of the variance of the log of radon exposures among controls) in radon exposure and accounting for the correlation between radon and smoking. Additionally accounting for an error of, for example, 0.5 in the smoking variable even increased the odds ratios to 1.12 (95% CI: 0.68, 1.83) and 1.16 (95% CI: 0.91, 1.48) respectively, again after accounting for correlation of both variables. Generally, adjustment for measurement error led to wider confidence intervals. The authors noted that the correlation between radon exposure and the smoking variable affects the correction even if the smoking variable is error-free.

D106. So far the largest and most informative study on lung cancer and indoor radon is the pooled analysis of 13 European case-control studies published by Darby et al. [D2, D3]. It included 7,148 cases and 14,208 controls, all with detailed information on smoking histories and radon measurements in homes that the individual had occupied during the past 15 years or more. The available radon measurements covered a mean of 23 years in the relevant radon exposure period 5–34 years prior to interview. Individual exposure to radon (called “measured” radon concentration) was calculated as the time-weighted average of the radon concentrations in all the homes occupied over the past 5–34 years. Missing radon values were substituted by the mean concentration of the controls in the specific study or specific area strata [D3]. A linear regression model was used, with stratification for study, age, sex, region or residence within each study, and detailed smoking history.

D107. Formal adjustment of the risk estimates for classical (year-on-year variability of measurements) and assignment (imputation of missing values) measurement errors was performed. In order to account for classical measurement errors, a log-normal distribution of the “true” (or long-term average) radon

concentration within each geographical district was assumed. Next to that, it was assumed that, on a logarithmic scale, the variability associated with repeated measurements of radon concentrations in the same dwelling was normally distributed about the true concentration for that dwelling [D3]. For those countries where repeated radon measurements had been made, these data were used to estimate a country-specific coefficient of variation for the classical measurement errors. For all countries with no data available the median of the estimated values for the other countries was used (CV = 40%). Two different methods for correcting estimates of risk from residential radon exposure for errors were used [D2, D3, F2]: the regression calibration method, and the method of integrated likelihood.

D108. Regression calibration was used to replace the measured radon concentrations by their expected values. After correction, the mean of the TWA of radon concentration among cases and controls decreased: for cases from 104 Bq/m³ (observed) to 90 Bq/m³ (corrected); and for controls from 97 Bq/m³ (observed) to 86 Bq/m³ (corrected). The main effect of regression calibration is that the values for people exposed to high observed radon concentrations tended to be substantially lower after correction, while for those exposed to low observed radon concentrations, the corrected values tended to be somewhat increased. This can be seen in table D9, where for example, in the group of 181 persons (66 cases and 115 controls) with a measured concentration of more than 800 Bq/m³, the mean measured value was 1,204 Bq/m³, whereas the mean corrected value was 678 Bq/m³. Similarly, among those persons (566 cases and 1,474 controls combined) with a measured concentration of less than 25 Bq/m³, the mean measured value was 17 Bq/m³, whereas the mean corrected value was 21 Bq/m³.

Table D9. Mean observed and corrected radon concentrations by categories of observed radon concentration for the cases and controls [D3]

Observed radon concentrations (Bq/m ³)	Number of cases	Number of controls	Mean observed radon concentration ^a (Bq/m ³)	Mean corrected radon concentration ^b (Bq/m ³)
<25	566	1 474	17	21
25–49	1 999	3 904	39	42
50–99	2 618	5 033	71	69
100–199	1 296	2 247	136	119
200–399	434	936	273	236
400–799	169	498	542	433
≥800	66	115	1 204	678

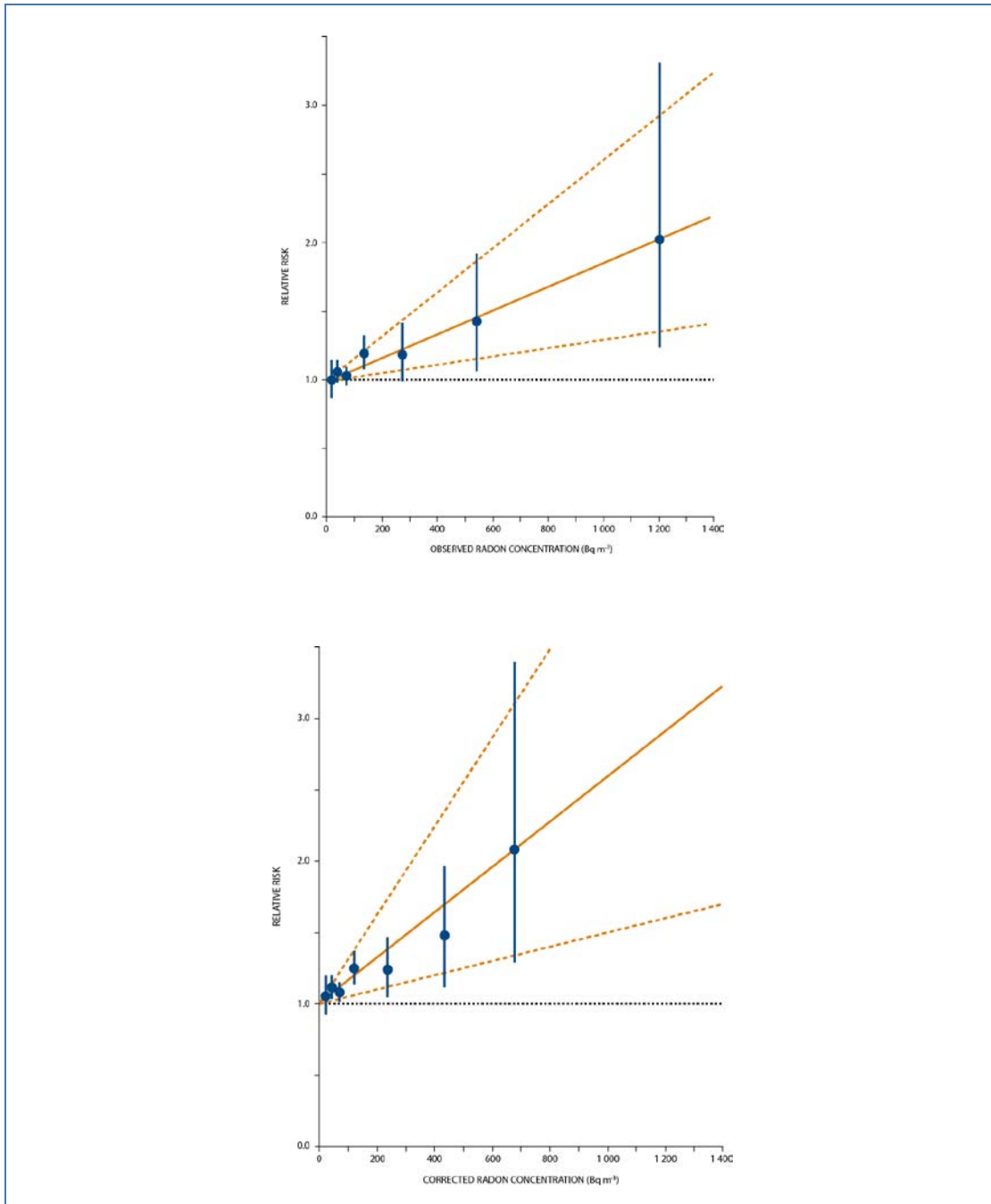
^a Observed radon concentration for each address in the 30-year period ending 5 years prior to the index date, weighted according to the length of time that the person lived there.

^b Corrected radon concentration, after uncertainties in the assessment of the radon concentrations were taken into account.

D109. In the European pooled study the estimate for the ERR per unit TWA of radon concentration was 0.084 (95% CI: 0.03, 0.16) per 100 Bq/m³ without adjustment for measurement error. After adjustment for uncertainty in the assessment of radon exposure the estimate increased to 0.16 (95% CI: 0.05, 0.30) per 100 Bq/m³ using regression calibration [D3]. A similar result was obtained when the method of Monte Carlo integration of the likelihood was used (estimated ERR per unit TWA of radon concentration was 0.16 (95% CI: 0.05, 0.31) per 100 Bq/m³). Figure D-III shows on the right the linear relationship between the relative risk of lung cancer and TWA-corrected radon concentration. Also shown on the right are relative risk estimates plotted against the mean corrected radon concentration for persons in categories. Owing to the fact that the corrected mean in the highly exposed group is only about half the mean observed value, the slope of the relationship is steeper after accounting for errors.

Figure D-III. Relative risk of lung cancer according to the TWA of observed radon concentration (on the left) and the TWA-corrected radon concentration (on the right)

The relative risks and 95% CI are shown for the analyses by category, as are the estimated linear relationships (solid lines) with 95% CI (dashed lines). The risks were calculated after stratification by study, age, sex, region of residence, and smoking history. On the right, the estimated linear relationship was calculated using the method of integrated likelihood, and the relative risks from the analysis based on categories of observed radon concentration were plotted against the mean corrected radon concentration for each of these categories [D3]



D110. Analyses of effect modification by sex, age, smoking status and histological type of lung cancer gave similar results with and without correction for measurement errors, although the correction had a proportionately greater impact on the ERR estimate for ex-smokers and lifelong non-smokers than on the corresponding estimate for current smokers. Nevertheless, there was no statistically significant heterogeneity in the ERR estimates between smoking categories, either with or without adjustment for measurement errors. Furthermore, the ERR estimates and confidence intervals from the analyses of effect modification were similar using the regression calibration and integrated likelihood approaches. Fearn et al. [F2] suggested that regression calibration should perform very well in adjusting for measurement errors in studies of residential exposure to radon and lung cancer and that more sophisticated approaches are not required.

D111. Table D10 summarizes the estimated ERR per unit measured radon concentration for the three pooled analyses in Europe [D2, D3], North America [K14, K15] and China [L30]. While the European study was formally adjusted for uncertainties in radon exposure, no such adjustments have been made so far in the pooled North American and Chinese studies. However, sensitivity analyses have been performed by restricting subjects to those assumed to have more accurate exposure estimates, that is, complete or higher coverage of the period of interest with radon measurements or lower mobility (living in only 1 or 2 homes). Risk estimates increased with increasing assumed accuracy of dosimetry, leading to nearly doubling of the estimate.

Table D10. Estimates and 95% confidence intervals of excess relative risk per unit radon concentration from pooled residential studies with and without restriction to more accurate exposure

<i>Study, restrictions</i>	<i>Number of cases</i>	<i>Number of controls</i>	<i>ERR per unit radon concentration (per 100 Bq/m³)</i>	<i>95% CI</i>
EUROPE [D2, D3]				
All subjects	7 148	14 208	0.08	(0.03, 0.16)
<3 residences, ≥20 years measured	4 221	8 371	0.09	(0.03, 0.18)
NORTH AMERICA [K14, K15]				
All subjects, no restriction to mobility	3 662	4 966	0.11	(0.00, 0.28)
≥15 years measured	2 764	3 857	0.13	(0.00, 0.31)
≥20 years measured	2 263	3 172	0.14	(0.01, 0.35)
25 years measured	1 621	2 323	0.21	(0.03, 0.50)
Subjects residing in 1 or 2 houses only				
≥15 years measured	2 171	3 009	0.17	(0.01, 0.41)
≥20 years measured	1 910	2 651	0.18	(0.02, 0.43)
25 years measured	1 552	2 170	0.21	(0.03, 0.52)
CHINA [L30]				
All subjects	1 050	1 995	0.13	(0.01, 0.36)
complete coverage of exposure period	n.a.	n.a.	0.32	(0.09, 0.88)
subjects residing in one home	n.a.	n.a.	0.33	(0.08, 0.96)

D112. The pooled North American residential radon study [K14, K15] included a total of 3,662 cases and 4,966 controls. Residential radon levels were measured for one year by alpha-track detectors. For each individual the time-weighted average of the radon concentrations in the homes was calculated for the period 5–30 years prior to the date of interview. The ERR per unit average radon concentration was 0.11 (95% CI: 0.00, 0.28) per 100 Bq/m³. Analyses restricted to individuals with presumed “more accurate dosimetry” resulted in increased risk estimates. For example, for individuals who lived in only one or two homes in the 5–30 year period and for which alpha-track measurements covered 25 years of this period, the ERR per unit average radon concentration was 0.21 (95% CI: 0.03, 0.52) per 100 Bq/m³. The Chinese pooled study [L30] included 1,050 cases and 1,996 controls. Similarly to the North-American pooled study, the time-weighted average of the radon concentration in the homes within the exposure period 5–30 years was calculated. The ERR per unit increase in measured radon concentration was 0.13 (95% CI: 0.01, 0.36) per 100 Bq/m³. When analyses were restricted to individuals resident in only one home and with complete measurement coverage in the relevant period the estimate of ERR per unit average radon concentration increased to 0.33 (95% CI: 0.08, 0.96) per 100 Bq/m³.

D113. Field et al. [F5] reported on the variation in risk estimates related to different exposure scenarios within the Iowa Radon Lung Cancer Study [F4]. The study was restricted to individuals who lived in their current home for at least 20 years. It included a total of 413 cases and 614 controls. Information on the temporal and spatial occupancy pattern in the home, outside and in other buildings was obtained via mailed questionnaire and face-to-face interviews. One-year radon measurements were conducted in various areas in the home. In addition, data from regional outdoor radon measurements were used and the subject’s exposure when in other buildings was assessed. Several methods were used to calculate the cumulative radon exposure in the period 5 years to 20 years prior to interview. The preferred model was based on radon measurements in the home, outdoors, and in another building with linkage of these values to the individual’s spatial and temporal occupancy patterns. Other models used radon measurements in either solely the basement, the living and/or bedroom, assuming a 70% standard occupancy time for all subjects. Overall, the preferred radon-exposure model exhibited slightly higher risk estimates and the lowest measurement error as compared with the other models that ignored the individual mobility pattern. The findings were similar when the analyses were restricted to the subjects still alive (283 cases and 614 controls) with presumably more accurate information on mobility and more representative radon measurements. The lowest risk estimate and the highest measurement error were found for the model using solely basement radon measurements. Here, misclassification of exposure was expected to be high, because radon concentrations in the basement were particularly high, while occupancy was low. The authors argued that the improved dosimetry model reduced exposure misclassification, and thus was likely to contribute to increased risk estimates.

D114. Heid et al. [H9] investigated how bias in risk estimates from additive and multiplicative measurement error differs between groups with different parameter values of exposure. For example, in the West German residential radon study [K11] higher risk estimates have been observed when data were restricted to individuals living in radon-prone matching areas (365 cases and 565 controls) as compared to the entire study (1,449 cases and 2,297 controls). The subgroup was characterized by a larger mean and standard deviation of observed radon exposure (59 Bq/m³ and 66 Bq/m³) compared to the entire group (49 Bq/m³ and 47 Bq/m³), respectively. The effect of varying exposure parameters on the bias from measurement error was investigated by means of theoretical considerations and simulations, assuming a non-differential homoscedastic random error. Results showed that bias from both additive and multiplicative assignment error was independent of exposure distribution parameters. In contrast to this, bias from additive classical error decreased with increasing exposure variance, but was independent of the exposure mean. Bias from multiplicative classical error decreased with increasing geometric standard deviation or increasing coefficient of variation of exposure, but was independent of the geometric mean of exposure. The results indicate that the bias possibly differs

between groups where these parameters differ. Therefore, if groups with for example varying exposure variance are compared, the bias on the estimates of the risk coefficient possibly differs between groups even if the true underlying risk coefficient and the size of measurement error is assumed to be the same across groups and for all individuals.

C. Use of glass objects for radon dosimetry

D115. An innovative method to potentially improve retrospective assessment of radon exposure are dosimetry techniques based on the ^{210}Po surface activity on glass objects that have been in a subject's home through the whole or the major part of the exposure period of interest [B13, M5, S26, W6]. CR-39 alpha-particle detectors, so-called surface monitors, are made from an alpha-sensitive material, allyl diglycol carbonate. They directly assess long-term (20-year or more) cumulative exposure by analysing glass objects in the home. The surface monitors take advantage of the fact that the first long-lived radon progeny, ^{210}Pb (half-life 22 years), becomes embedded in glass surfaces in homes. The alpha-activity of ^{210}Po , a decay product of ^{210}Pb , is measured in glass objects.

D116. A critical point in using glass-based monitors are factors affecting the deposition of radon daughters on the surface of the object, such as the aerosol concentration, the relative extent of surface areas compared to the volume of the room, the air-exchange rate and air motion in the room or the position of the object [W1]. It was argued that tobacco smoke reduces the plate-out of radon progeny on surfaces and that this could introduce bias [W6]. Bochicchio et al. [B13] compared air-based and glass-based measurements in a sample of 26 dwellings. The correlation between both methods was relatively high (0.83) for objects exposed in non-smoky dwellings, while it vanished (-0.01) when the objects were exposed in smoky dwellings. Other critical issues concern accuracy of estimates of the age of the glass objects, history of the glass before it was used in the homes, and in large-scale epidemiological studies the existence of suitable glass objects to cover the exposure period.

D117. It has been discussed whether glass-based measurements can provide a better representation of the cumulative radon exposure in the exposure period of interest than air-based measurements in the current dwellings. Two residential radon studies used both methods of measurements [A5, L28]. In both studies substantially higher risk estimates based on measurements on glass compared to measurements in air were observed (see table D8). Results indicate a presumably greater precision in the estimation of past exposure when using surface monitors compared to air-based monitors. However, some unexplained bias that affects cases and controls differently cannot be ruled out completely.

D118. The Missouri residential radon study [A5] was the first epidemiological study that provided risk estimates based on both types of dosimetry: air radon detectors and CR-39 surface monitors. The study included 512 lung cancer cases and 553 controls. Indoor air dosimeters had been placed in the current dwellings for one year, and the annual time-weighted average radon concentrations for the 5–25 years exposure period were calculated. Two glass objects for cumulative radon measurement by surface monitors were identified by questionnaire and interview. The detectors were affixed for 4 weeks to the glass objects after being cleaned. The cumulative radon values from surface detectors were converted into annual TWA of radon concentration by dividing the cumulative readings by the number of years the subject owned the glass object. Correction factors were empirically derived [M5] to adjust for differential deposition rates among smokers and non-smokers and for window-glass or not. A statistically significant excess odds ratio at 150 Bq/m^3 of 0.95 (95% CI: 0.1, 2.9) for TWA of the radon concentrations measured by surface monitors was found, while no elevated ERR was present when measurements were based on indoor air detectors. Alavanja et al. [A5] argued that a possible explanation for this result would be that surface monitors are less prone to random error than air-based

monitors. He demonstrated using a Monte Carlo simulation study that a year-on-year variability in the range, as estimated by Steck et al. [S26], could completely dilute a risk of the magnitude observed using surface monitors when current measurements using air-based monitors are employed to reflect the exposure period.

D119. Both glass-based and air-based measurements had also been performed in a Swedish case-control study on lung cancer among never-smokers [L2]. The study included 110 lung cancer cases and 231 controls. Two air measurements were performed for 3 months in the heating period in all dwellings occupied by the individual for at least 2 years in the 32-year period ending 3 years before interview, and the annual TWA of the radon concentration was calculated. Two surface-based measurements were performed using glass objects that were preferably at least 20 years old, and new when present for the first time in the subject's home. Calibration factors were applied to translate surface activity into average radon concentration for the exposure period of interest. The ERR per unit average radon concentration was estimated to be 0.33 (95% CI: -0.12, 2.0) per 100 Bq/m³ for air-based radon measurements and 0.75 (95% CI: -0.04, 4.30) per 100 Bq/m³ for surface-based radon measurements. Exposure to environmental tobacco smoke did not modify the relation between surface-based and air-based radon concentration estimates.

D. Evaluation of the risk and its uncertainty

D120. Overall the three major pooled analyses of residential radon exposure and lung cancer provide consistent risk estimates (see table D11). Without adjustment for uncertainty in the assessment of radon exposure, the estimate of ERR per unit TWA of radon concentration is 0.08 (95% CI: 0.03, 0.16) per 100 Bq/m³ in the European study [D2, D3], 0.11 (95% CI: 0.00, 0.28) per 100 Bq/m³ in the North American study [K14, K15] and 0.13 (95% CI: 0.01, 0.36) per 100 Bq/m³ in the Chinese study [L30]. Risk estimates based on measured radon concentrations without accounting for error are likely to underestimate the true risk. In the European pooled study, so far the largest study, the ERR per unit TWA of radon concentration increased from 0.08 per 100 Bq/m³ to 0.16 per 100 Bq/m³ after taking into account year-on-year variation. The joint risk estimate from the three pooled studies, when assuming a similar effect of adjusting for year-on-year variation in the Chinese and North American studies as in the European study, would be around 0.20 per 100 Bq/m³ [W8].

Table D11. Summary of risk estimates derived from pooled residential studies (adapted from [W8])

Study	Number of cases	Number of controls	ERR per unit radon concentration (per 100 Bq/m ³) (95% CI)	Adjusted ERR per unit radon concentration (per 100 Bq/m ³) (95% CI) ^a
Europe [D2, D3]	7 148	14 208	0.08 (0.03, 0.16)	0.16 (0.05, 0.31)
North America [K14, K15]	3 662	4 966	0.11 (0.00, 0.28)	-
China [L30]	1 050	1 995	0.13 (0.01, 0.36)	-
Weighted average of above results of pooling studies			0.10	0.20 ^b

^a Adjusted for year-on-year random variability in indoor radon concentrations.

^b Informal estimate, indicating the likely effect of removing the bias induced by random year-on-year variation in radon concentration.

D121. Sources of uncertainty in the assessment of past radon exposure include year-on-year variation, detector measurement error, failure to link spatial and temporal mobility, gaps in exposure history, and use of radon exposure as a proxy for radon progeny dose. Several methods have been applied to

account for these uncertainties in exposure assessment, such as using glass-based measurements instead of air measurements [A5, L2], limiting participants to long-term residents by study design [F2], conducting sensitivity analyses with restriction to subjects with more accurate information [D3, K14, K15, L30] or improving the exposure assessment through linkage, with spatial and temporal mobility [F5]. Applying these methods consistently led to an increase of the excess relative risk of lung cancer in the order of 50% to 100%. In addition, uncertainty in the assessment of major confounding factors such as smoking may be present, possibly leading to bias in the estimated risk [H11]. This indicates that the true ERR per unit TWA of radon concentration could be somewhat higher, even after correction for year-on-year variation in measured radon concentrations [W8].

D122. The excess risk of lung cancer associated with indoor radon concentration is small, therefore confounding is of particular concern. Most of the individual studies were matched by age and sex, ensuring little confounding by these factors. The three pooled analyses were additionally stratified by age, sex and study. There was substantial negative confounding by smoking. In the European pooled study much effort was spent to control adequately for smoking in the risk analyses [D2]. Detailed sensitivity analyses suggested that it is appropriate to control for smoking by stratification into 20 groups: never-smokers, current cigarette smokers in 12 groups (subdivided by age at starting smoking and cigarettes per day smoked), ex-smokers in six groups (subdivided by time since stopping smoking and cigarettes smoked per day), and smokers of pipe, cigars, and cigarillos. The ERR per unit TWA of radon concentration stratified by age, sex and study without stratification for smoking increased from 0.023 to 0.084 after additional stratification for smoking. Also restricting the risk analyses to lifelong non-smokers led to a comparable statistically significant risk of 0.11 (95% CI: 0.003, 0.28) per 100 Bq/m³; for current cigarette smokers, a value of 0.07 (95% CI: -0.01, 0.22) per 100 Bq/m³ was obtained [D3]. It is interesting to note, that a similar result was obtained in a joint analysis of three European case-control studies among uranium miners: The ERR per unit exposure was 0.012 (95% CI: 0.005, 0.026) per WLM among never smokers and long-term ex-smokers, while a value of 0.007 (95% CI: 0.003, 0.013) per WLM was found for short-term ex-smokers and current smokers. Other potential confounding factors such as social status or employment in an occupation with an established lung cancer risk have been investigated in the European radon indoor study as well [D3]. Inclusion of these risk factors in the model, however, did not change the risk estimate.

D123. Misclassification of disease could be another issue of bias in the risk estimates. In most studies lung cancer cases were collected from study clinics. Inclusion criteria for a case were a histological or cytological confirmation of a primary lung cancer. In the pooled European analyses, fewer than 10% of the cases and controls were based on death certificates only. The ERR per unit TWA of radon concentration did not differ between studies with ascertainment of the cases based on clinical information or death certificates only. Another issue is selection bias through the use of population-based or hospital-based controls. Again, there were no significant differences in the estimated effect of radon exposure. Similarly, there was no difference according to whether or not surrogate interviews were accepted.

D124. There was little evidence of effect modification by age in the pooled European [D2] and North American study [K14, K15]. In the European pooled study [D2], the ERR per unit observed TWA of radon concentration were 0.11, -0.02, 0.14, 0.8 and 0.00 per 100 Bq/m³ for the age categories: younger than 45, 45-54, 55-64, 65-74, older than 75 years, respectively (*P* value for trend test: 0.98). The same held true for the risk estimates related to the corrected radon concentrations (*P* value for trend test: 0.28). Here the corresponding risk estimates were -0.12, 0.13, 0.16, 0.16 and 0.57 per 100 Bq/m³, respectively.

D125. In the European pooled study, the effect of different measures of the radon concentration and of different models for the relationship between radon concentration and lung cancer were investigated [D2]. The published results are based on the time-weighted average of radon concentration in the

30-year period of interest (5–35 years prior to interview). Using the time-weighted average of the 5–14 years, 15–24 years or 25–35 years in the past only, or the time-period weighting factors of the BEIR VI model led to nearly similar results. When instead of linear relative risk model ($RR = 1 + \beta x$), a linear–quadratic relationship ($RR = 1 + \beta_1 x + \beta_2 x^2$) or a log-linear relationship ($RR = \exp(\beta x)$) was applied, there was no statistically significant improvement in the fit.

D126. The cumulative risk of death from lung cancer by age 75, 80 and 85 years for lifelong non-smokers and continuing smokers of 15 to 24 cigarettes per day at various levels of observed radon concentration and corrected radon concentrations was evaluated in the pooled European case–control study [D2]. The authors assumed that the relative risk of lung cancer increases by 0.08 (95% CI: 0.03, 0.16) per increase of 100 Bq/m³ in the observed radon concentration regardless of smoking status. This overall risk estimate was taken, because there was no heterogeneity between the estimated relative risks for the three different smoking categories. The corresponding risk estimates had been 0.11 (95% CI: 0.003, 0.28) per 100 Bq/m³ for lifelong non-smokers, 0.08 (95% CI: 0.003, 0.21) per 100 Bq/m³ for ex-smokers and 0.07 (95% CI: –0.01, 0.22) per 100 Bq/m³ for current smokers, respectively. The cumulative risk was additionally calculated after adjustment for the effect of random uncertainties in the assessment of radon concentration according the regression calibration method. It was assumed that the relative risk of lung cancer increases by 0.16 (95% CI: 0.05, 0.31) per increase of 100 Bq/m³ corrected radon concentration again regardless of smoking status. The corresponding risk estimates for lifelong non-smokers, ex-smokers and current smokers had been 0.20 (95% CI: 0.02, 0.53), 0.18 (95% CI: 0.02, 0.47) and 0.09 (95% CI: <0.08, 0.37) per 100 Bq/m³. Again there was no evidence of heterogeneity between these risk estimates. The authors assumed a relative risk of lung cancer for continuing smokers compared to lifelong non-smokers of 25, which refers to the overall estimate in the study. The absolute risk of lung cancer for the lifelong non-smokers was taken from a prospective study of the American Cancer Society [P3], because no comparable data had been available for Europe. A comparable relative risk per unit TWA of radon concentration for smokers and non-smokers means that the excess absolute risk (number of cases per person years of risk) is considerably higher for smokers than for non-smokers.

D127. Table D12 shows the results of the estimated cumulative risk of death from lung cancer by age 75 and 85 years in relation to observed and corrected radon concentrations for lifelong non-smokers and current smokers. For lifelong non-smokers with no exposure to radon, the cumulative risk of death from lung cancer was estimated to be 0.42% or 0.81% by the age of 75 or 85 years, respectively [D2]. For lifelong non-smokers with finite exposure to radon, the cumulative risks of death from lung cancer were somewhat greater, for example, with values of 0.71% or 1.35% at 800 Bq/m³ by the age of 75 or 85 years, respectively. For continuing smokers of 15–24 cigarettes per day, not only was the cumulative risk of death from lung cancer with no exposure to radon much higher (10.4% or 19.1% at age 75 or 85 years, respectively), but the increase in the cumulative risk with an increasing observed radon concentration was also substantially higher. For example, with an observed radon concentration of 800 Bq/m³ the cumulative risks associated were evaluated as 16.8% or 29.8% by age 75 or 85 years, respectively. It is important to note that the cumulative risks for ex-smokers who had quit smoking less than 10 years previously would be about 80% of those of continuing smokers. For those who quit smoking more than 10 years previously the risks would be lower [D2].

D128. When instead of observed radon concentrations, the corrected radon concentrations were considered, a similar pattern of risk was observed, however, with consistently higher risk estimates (see table D12). The cumulative risk of death from lung cancer for lifelong non-smokers with no radon exposure was estimated to be 0.41% or 0.78% by the age of 75 or 85 years, respectively. For lifelong non-smokers with finite exposure to radon, the cumulative risks were estimated to be somewhat higher, for example, with a value of 0.91% or 1.78% by age 75 or 85 years for 800 Bq/m³, respectively. For continuing smokers of 15–24 cigarettes per day, the cumulative risk of death from lung cancer

increased from 10.11% with no radon exposure to 21.6% at 800 Bq/m³ by age 75, and from 18.5% with no radon exposure to 37.3% at 800 Bq/m³ by age 85, respectively. As for the results on observed radon concentrations, the cumulative risks for ex-smokers who gave up smoking less than 10 years previously would be about 80% of the risk for continuing smokers.

Table D12. Cumulative risk of death from lung cancer by age 75 and 85 years for lifelong non-smokers and continuing smokers of 15–24 cigarettes per day at various levels of observed and corrected radon-concentration

From source ([D2], tables 29 and 38)

By age	Radon concentration (Bq/m ³)	Lifelong non-smokers		Continuing smokers of 15–24 cigarettes per day	
		Cumulative risk (%)	95% CI	Cumulative risk (%)	95% CI
75 years	TIME-WEIGHTED AVERAGE OF OBSERVED RADON CONCENTRATION				
	0	0.42	-	10.43	-
	100	0.46	0.42, 0.49	11.25	10.45, 11.97
	200	0.49	0.43, 0.56	12.07	10.48, 13.49
	400	0.56	0.43, 0.69	13.68	10.54, 16.45
	800	0.71	0.43, 0.95	16.81	10.66, 22.06
	TIME-WEIGHTED AVERAGE OF CORRECTED RADON CONCENTRATION				
	0	0.41	-	10.11	-
	100	0.47	0.43, 0.54	11.63	10.59, 13.03
	200	0.54	0.45, 0.66	13.12	11.06, 15.85
	400	0.67	0.49, 0.91	16.03	12.00, 21.23
	800	0.93	0.57, 1.42	21.57	13.86, 30.98
85 years	TIME-WEIGHTED AVERAGE OF OBSERVED RADON CONCENTRATION				
	0	0.81	-	19.06	-
	100	0.88	0.81, 0.94	20.48	19.11, 21.72
	200	0.95	0.81, 1.06	21.88	19.16, 24.29
	400	1.08	0.82, 1.32	24.61	19.26, 29.18
	800	1.35	0.83, 1.82	29.78	19.47, 38.04
	TIME-WEIGHTED AVERAGE OF CORRECTED RADON CONCENTRATION				
	0	0.78	-	18.51	-
	100	0.91	0.82, 1.03	21.13	19.34, 23.52
	200	1.03	0.86, 1.27	23.67	20.16, 28.22
	400	1.28	0.94, 1.75	28.51	21.77, 36.77
	800	1.78	1.10, 2.70	37.29	24.91, 50.94

- Absolute risk of lung cancer for the lifelong non-smokers taken from a prospective study of the American Cancer Society [P3].

- The relative risk of lung cancer for continuing smokers of 15–24 cigarettes per day was assumed to be equal to the overall estimates in the study.

- The relative risk of lung cancer was assumed to increase by 0.08 (95% CI: 0.033, 0.158) per 100 Bq/m³ increase in the time-weighted-average (TWA) of observed radon concentrations and to increase by 0.16 (95% CI: 0.05, 0.31) per 100 Bq/m³ increase in the TWA of corrected radon concentrations regardless of smoking status.

REFERENCES

- A1 Adams, M.J., R.E. Shore, A. Dozier et al. Thyroid cancer risk 40+ years after irradiation for an enlarged thymus: an update of the Hempelmann cohort. *Radiat Res* 174(6): 753-762 (2010).
- A2 AGIR. Review of risks from tritium. Advisory Group on Ionising Radiation. RCE-4. Health Protection Agency, Chilton, 2007.
- A3 Akaike, H. Information theory and an extension of the maximum likelihood principle. pp.267-288 in: *Proceedings of the 2nd International Symposium on Information Theory* (B.N. Petrov and F. Caski, eds.). Akademiai Kiado, Budapest, 1973.
- A4 Akaike, H. A New Look at the Statistical Model Identification. *IEEE Trans Autom Control* 19(6): 716-723 (1974).
- A5 Alavanja, M.C., J.H. Lubin, J.A. Mahaffey et al. Residential radon exposure and risk of lung cancer in Missouri. *Am J Public Health* 89(7): 1042-1048 (1999).
- A6 Allodji, R.S., K. Leuraud, S. Bernhard et al. Assessment of uncertainty associated with measuring exposure to radon and decay products in the French uranium miners cohort. *J Radiol Prot* 32(1): 85-100 (2012).
- A7 Anderson, D.R. *Model Based Inference in the Life Sciences: A Primer on Evidence*. Springer, New York, 2008.
- A8 Annest, A., R.E. Bumgarner, A.E. Raftery et al. Iterative Bayesian Model Averaging: a method for the application of survival analysis to high-dimensional microarray data. *BMC Bioinformatics* 10: 72 (2009).
- A9 Apostoaei, A.I., R.E. Burns, F.O. Hoffman et al. Iodine-131 releases from radioactive lanthanum processing at the X-10 site in Oak Ridge, Tennessee (1944-1956) -- An assessment of quantities released, off-site radiation doses, and potential excess risks of thyroid cancer. *Reports of the Oak Ridge Dose Reconstruction*. Vols. 1 and 1A: Tennessee Department of Health 1999.
- A10 Apostoaei, A.I. and L.F. Miller. Uncertainties in dose coefficients from ingestion of ^{131}I , ^{137}Cs , and ^{90}Sr . *Health Phys* 86(5): 460-482 (2004).
- A11 Apostoaei, A.I., B.A. Thomas, D.C. Kocher et al. Doses to the public from atmospheric releases of radionuclides from the Idaho Chemical Processing Plant at the Idaho National Engineering Laboratory (1957-1959). Final Report. Centers for Disease Control and Prevention, I. SENES Oak Ridge, Tennessee, 2005.
- A12 Armitage, P. and R. Doll. The age distribution of cancer and a multi-stage theory of carcinogenesis. *Br J Cancer* 8(1): 1-12 (1954).
- A13 Ashmore, J.P., N.E. Gentner and R.V. Osborne. Incomplete data on the Canadian cohort may have affected the results of the study by the International Agency for Research on Cancer on the radiogenic cancer risk among nuclear industry workers in 15 countries. *J Radiol Prot* 30(2): 121-129 (2010).

- A14 Astakhova, L.N., L.R. Anspaugh, G.W. Beebe et al. Chernobyl-related thyroid cancer in children of Belarus: a case-control study. *Radiat Res* 150(3): 349-356 (1998).
- A15 Atkinson, W.D., D.V. Law, K.J. Bromley et al. Mortality of employees of the United Kingdom Atomic Energy Authority, 1946-97. *Occup Environ Med* 61(7): 577-585 (2004).
- B1 Barndorff-Nielsen, O.E. and D.R. Cox. *Asymptotic Techniques for Use in Statistics*. Chapman and Hall, London, 1989.
- B2 Bauer, S., B.I. Gusev, L.M. Pivina et al. Radiation exposure due to local fallout from Soviet atmospheric nuclear weapons testing in Kazakhstan: solid cancer mortality in the Semipalatinsk historical cohort, 1960-1999. *Radiat Res* 164(4 Pt 1): 409-419 (2005).
- B3 Båverfält, U. and G.A. Swedjemark. Where are the errors when we estimate radon exposure in retrospect? *Radiat Prot Dosim* 36(2/4): 107-112 (1991).
- B4 Beebe, G.W. and M. Usagawa. *The major ABCC samples*. RERF TR/12-68 Radiation Effects Research Foundation, 1968.
- B5 Berhane, K., M. Hauptmann and B. Langholz. Using tensor product splines in modeling exposure-time-response relationships: application to the Colorado Plateau Uranium Miners cohort. *Stat Med* 27(26): 5484-5496 (2008).
- B6 Bernardo, J.M. and A.F.M. Smith. *Bayesian Theory*. Wiley, New York, 2007.
- B7 Berrington de Gonzalez, A., M. Mahesh, K.P. Kim et al. Projected cancer risks from computed tomographic scans performed in the United States in 2007. *Arch Intern Med* 169(22): 2071-2077 (2009).
- B8 Berrington de Gonzalez, A., A. Iulian Apostoaei, L.H. Veiga et al. RadRAT: a radiation risk assessment tool for lifetime cancer risk projection. *J Radiol Prot* 32(3): 205-222 (2012).
- B9 Berry, D., J.K. Wathen and M. Newell. Bayesian model averaging in meta-analysis: vitamin E supplementation and mortality. *Clin Trials* 6(1): 28-41 (2009).
- B10 Beyreuther, E., W. Dorr, A. Lehnert et al. Relative biological effectiveness of 25 and 10 kV X-rays for the induction of chromosomal aberrations in two human mammary epithelial cell lines. *Radiat Environ Biophys* 48(3): 333-340 (2009).
- B11 Bhatti, P., L.H. Veiga, C.M. Ronckers et al. Risk of second primary thyroid cancer after radiotherapy for a childhood cancer in a large cohort study: an update from the childhood cancer survivor study. *Radiat Res* 174(6): 741-752 (2010).
- B12 Birchall, A., M. Puncher, J. Harrison et al. Plutonium worker dosimetry. *Radiat Environ Biophys* 49(2): 203-212 (2010).
- B13 Bochicchio, F., J.P. McLaughlin and C. Walsh. Comparison of radon exposure assessment results: ²¹⁰Po surface activity on glass objects vs. contemporary air radon concentration. *Radiat Meas* 36(1): 211-215 (2003).
- B14 Bochicchio, F. Radon epidemiology and nuclear track detectors: Methods, results and perspectives. *Radiat Meas* 40(2-6): 177-190 (2005).
- B15 Boice, J.D., S.S. Cohen, M.T. Mumma et al. Mortality among radiation workers at Rocketdyne (Atomics International), 1948-1999. *Radiat Res* 166(1 Pt 1): 98-115 (2006).

- B16 Boice, J.D., Jr., G. Engholm, R.A. Kleinerman et al. Radiation dose and second cancer risk in patients treated for cancer of the cervix. *Radiat Res* 116(1): 3-55 (1988).
- B17 Bolch, W.E., A.P. Shah, C.J. Watchman et al. Skeletal absorbed fractions for electrons in the adult male: considerations of a revised 50-microm definition of the bone endosteum. *Radiat Prot Dosim* 127(1-4): 169-173 (2007).
- B18 Bond, V.P., C.B. Meinhold and H.H. Rossi. Low-dose RBE and Q for x-ray compared to gamma-ray radiations. *Health Phys* 34(5): 433-438 (1978).
- B19 Box, G.E.P. Science and statistics. *J Am Stat Assoc* 71(356): 791-799 (1976).
- B20 Brenner, A.V., M.D. Tronko, M. Hatch et al. I-131 dose response for incident thyroid cancers in Ukraine related to the Chernobyl accident. *Environ Health Perspect* 119(7): 933-939 (2011).
- B21 Breslow, N.E. Statistics in epidemiology: the case-control study. *J Am Stat Assoc* 91(433): 14-28 (1996).
- B22 Breslow, N.E., T. Lumley, C.M. Ballantyne et al. Using the whole cohort in the analysis of case-cohort data. *Am J Epidemiol* 169(11): 1398-1405 (2009).
- B23 Brugmans, M.J., S.M. Rispens, H. Bijwaard et al. Radon-induced lung cancer in French and Czech miner cohorts described with a two-mutation cancer model. *Radiat Environ Biophys* 43(3): 153-163 (2004).
- B24 Buermann, L., M. Krumrey, M. Haney et al. Is there reliable experimental evidence for different dicentric yields in human lymphocytes produced by mammography X-rays free-in-air and within a phantom? *Radiat Environ Biophys* 44(1): 17-22 (2005).
- B25 Burnham, K.P. and D.R. Anderson. Multimodel inference: Understanding AIC and BIC in model selection. *Sociol Methods Res* 33(2): 261-304 (2004).
- C1 Cardis, E. and J. Estève. International Collaborative Study of Cancer Risk Among Nuclear Industry Workers, II—Protocol. International agency for research on cancer, Lyon, 1992.
- C2 Cardis, E., A. Kesminiene, V. Ivanov et al. Risk of thyroid cancer after exposure to ¹³¹I in childhood. *J Natl Cancer Inst* 97(10): 724-732 (2005).
- C3 Cardis, E., M. Vrijheid, M. Blettner et al. Risk of cancer after low doses of ionising radiation: retrospective cohort study in 15 countries. *Br Med J* 331(7508): 77 (2005).
- C4 Cardis, E., M. Vrijheid, M. Blettner et al. The 15-Country Collaborative Study of Cancer Risk among Radiation Workers in the Nuclear Industry: estimates of radiation-related cancer risks. *Radiat Res* 167(4): 396-416 (2007).
- C5 Carpenter, L., V. Beral, P. Fraser et al. Health related selection and death rates in the United Kingdom Atomic Energy Authority workforce. *Br J Ind Med* 47(4): 248-258 (1990).
- C6 Carr, Z.A., R.A. Kleinerman, M. Stovall et al. Malignant neoplasms after radiation therapy for peptic ulcer. *Radiat Res* 157(6): 668-677 (2002).
- C7 Carroll, R.J., D. Ruppert, L.A. Stefanski et al. Measurement Error in Nonlinear Models: A Modern Perspective. Second Edition. Chapman & Hall/CRC, Boca Raton, 2006.
- C8 Chib, S. and E. Greenberg. Understanding the Metropolis–Hastings algorithm. *Am Stat* 49(4): 327-335 (1995).

- C9 CIRRPC. Neutron quality factor. ORAU 95/F-29. Committee on Interagency Radiation Research and Policy Coordination, Washington D.C., 1995.
- C10 Claeskens, G. and N.L. Hjort. Model Selection and Model Averaging. Cambridge University Press, Cambridge, 2008.
- C11 Clayton, D. and M. Hills. Statistical Models in Epidemiology. Oxford University Press, Oxford, 1993.
- C12 CNSC. Health Effects, Dosimetry and Radiological Protection of Tritium. INFO-0799. Canadian Nuclear Safety Commission, Ottawa, 2010.
- C13 CNSC. Verifying Canadian Nuclear Energy Worker Radiation Risk: A Reanalysis of Cancer Mortality in Canadian Nuclear Energy Workers (1957-1994) Summary Report. INFO-0811. Canadian Nuclear Safety Commission, Ottawa, 2011.
- C14 Cohen, B.L. Test of the linear-no threshold theory of radiation carcinogenesis for inhaled radon decay products. *Health Phys* 68(2): 157-174 (1995).
- C15 Cook, J.R. and L.A. Stefanski. Simulation-extrapolation estimation in parametric measurement error models. *J Am Stat Assoc* 89(428): 1314-1328 (1994).
- C16 Cox, D.R. Regression models and life-tables. *J R Stat Soc* 34(2): 187-220 (1972).
- C17 Cox, D.R. and D.V. Hinkley. Theoretical Statistics. Chapman and Hall, London, 1974.
- C18 Cristy, M. and K.F. Eckerman. Specific absorbed fractions of energy at various ages from internal photon sources. ORNL/TM-8381/VI. Oak Ridge National Laboratory, USA, 1987.
- C19 Crump, K.S., P. Duport, H. Jiang et al. A meta-analysis of evidence for hormesis in animal radiation carcinogenesis, including a discussion of potential pitfalls in statistical analyses to detect hormesis. *J Toxicol Environ Health B Crit Rev* 15(3): 210-231 (2012).
- D1 Darby, S., E. Whitley, P. Silcocks et al. Risk of lung cancer associated with residential radon exposure in south-west England: a case-control study. *Br J Cancer* 78(3): 394-408 (1998).
- D2 Darby, S., D. Hill, A. Auvinen et al. Radon in homes and risk of lung cancer: collaborative analysis of individual data from 13 European case-control studies. *BMJ* 330(7485): 223 (2005).
- D3 Darby, S., D. Hill, H. Deo et al. Residential radon and lung cancer--detailed results of a collaborative analysis of individual data on 7148 persons with lung cancer and 14,208 persons without lung cancer from 13 epidemiologic studies in Europe. *Scand J Work Environ Health* 32(Suppl 1): 1-83 (2006).
- D4 Davesne, E., P. Casanova, E. Chojnacki et al. Integration of uncertainties into internal contamination monitoring. *Health Phys* 99(4): 517-522 (2010).
- D5 Davesne, E., F. Paquet, E. Ansoborlo et al. Absorption of plutonium compounds in the respiratory tract. *J Radiol Prot* 30(1): 5-21 (2010).
- D6 Davis, S., K.J. Kopecky, T.E. Hamilton et al. Thyroid neoplasia, autoimmune thyroiditis, and hypothyroidism in persons exposed to iodine 131 from the hanford nuclear site. *J Am Med Assoc* 292(21): 2600-2613 (2004).
- D7 Deckbar, D., J. Birraux, A. Krempler et al. Chromosome breakage after G2 checkpoint release. *J Cell Biol* 176(6): 749-755 (2007).

- D8 Drozdovitch, V., E. Maceika, V. Khrouch et al. Uncertainties in individual doses in a case-control study of thyroid cancer after the Chernobyl accident. *Radiat Prot Dosim* 127(1-4): 540-543 (2007).
- D9 Drozdovitch, V., V. Khrouch, E. Maceika et al. Reconstruction of radiation doses in a case-control study of thyroid cancer following the Chernobyl accident. *Health Phys* 99(1): 1-16 (2010).
- D10 Dunning, D.E., Jr. and G. Schwarz. Variability of human thyroid characteristics and estimates of dose from ingested ¹³¹I. *Health Phys* 40(5): 661-675 (1981).
- E1 Edwards, A.A. Relative biological effectiveness of neutrons for stochastic effects. *Doc. NRPB* 8(2) (1997).
- E2 Edwards, A.A. Neutron RBE values and their relationship to judgements in radiological protection. *J Radiol Prot* 19(2): 93-105 (1999).
- E3 Eidemuller, M., E. Holmberg, P. Jacob et al. Breast cancer risk among Swedish hemangioma patients and possible consequences of radiation-induced genomic instability. *Mutat Res* 669(1-2): 48-55 (2009).
- F1 Farris, W.T., B.A. Napier, T.A. Ikenberry et al. Atmospheric pathway dosimetry report, 1944-1992. PNWD-2228 HEDR. Battelle Pacific Northwest Laboratories, Richland, 1994.
- F2 Fearn, T., D.C. Hill and S.C. Darby. Measurement error in the explanatory variable of a binary regression: regression calibration and integrated conditional likelihood in studies of residential radon and lung cancer. *Stat Med* 27(12): 2159-2176 (2008).
- F3 Feinendegen, L.E., M. Pollycove and R.D. Neumann. Low-dose cancer risk modeling must recognize up-regulation of protection. *Dose Response* 8(2): 227-252 (2010).
- F4 Field, R.W., D.J. Steck, B.J. Smith et al. Residential radon gas exposure and lung cancer: the Iowa Radon Lung Cancer Study. *Am J Epidemiol* 151(11): 1091-1102 (2000).
- F5 Field, R.W., B.J. Smith, D.J. Steck et al. Residential radon exposure and lung cancer: variation in risk estimates using alternative exposure scenarios. *J Expo Anal Environ Epidemiol* 12(3): 197-203 (2002).
- F6 Franco, N., J. Lamartine, V. Frouin et al. Low-dose exposure to gamma rays induces specific gene regulations in normal human keratinocytes. *Radiat Res* 163(6): 623-635 (2005).
- F7 Frankenberg, D., K. Kelnhofer, K. Bar et al. Enhanced neoplastic transformation by mammography X rays relative to 200 kVp X rays: indication for a strong dependence on photon energy of the RBE(M) for various end points. *Radiat Res* 157(1): 99-105 (2002).
- F8 Fritsch, P. Uncertainties in committed equivalent doses to the thyroid after ingestion or inhalation of different chemical forms of 125-129-131I. *Radiat Prot Dosim* 127(1-4): 548-552 (2007).
- F9 Frome, E.L. and H. Checkoway. Epidemiologic programs for computers and calculators. Use of Poisson regression models in estimating incidence rates and ratios. *Am J Epidemiol* 121(2): 309-323 (1985).
- F10 Fung, K.Y. and D. Krewski. On measurement error adjustment methods in Poisson regression. *Environmetrics* 10(2): 213-224 (1999).

- F11 Furukawa, K., D.L. Preston, S. Lonn et al. Radiation and smoking effects on lung cancer incidence among atomic bomb survivors. *Radiat Res* 174(1): 72-82 (2010).
- G1 Gavrilin, Y., V. Khrouch, S. Shinkarev et al. Individual thyroid dose estimation for a case-control study of Chernobyl-related thyroid cancer among children of Belarus-part I: ¹³¹I, short-lived radioiodines (¹³²I, ¹³³I, ¹³⁵I), and short-lived radiotelluriums (¹³¹MTe and ¹³²Te). *Health Phys* 86(6): 565-585 (2004).
- G2 Gavrilin, Y.I., V.T. Khrouch, S.M. Shinkarev et al. Chernobyl accident: reconstruction of thyroid dose for inhabitants of the Republic of Belarus. *Health Phys* 76(2): 105-119 (1999).
- G3 Gelman, A., J.B. Carlin, H.S. Stern et al. *Bayesian Data Analysis*. Chapman & Hall/CRC, London, 2004.
- G4 Geman, S. and D. Geman. Stochastic relaxation, gibbs distributions, and the bayesian restoration of images. *IEEE Trans Pattern Anal Mach Intell* 6(6): 721-741 (1984).
- G5 Gerken, M., L. Kreienbrock, J. Wellmann et al. Models for retrospective quantification of indoor radon exposure in case-control studies. *Health Phys* 78(3): 268-278 (2000).
- G6 Gilbert, E.S. Some confounding factors in the study of mortality and occupational exposures. *Am J Epidemiol* 116(1): 177-188 (1982).
- G7 Gilbert, E.S., J.J. Fix and W.V. Baumgartner. An approach to evaluating bias and uncertainty in estimates of external dose obtained from personal dosimeters. *Health Phys* 70(3): 336-345 (1996).
- G8 Gilbert, E.S. Accounting for errors in dose estimates used in studies of workers exposed to external radiation. *Health Phys* 74(1): 22-29 (1998).
- G9 Gilbert, E.S., N.A. Koshurnikova, M.E. Sokolnikov et al. Lung cancer in Mayak workers. *Radiat Res* 162(5): 505-516 (2004).
- G10 Gilbert, E.S., I. Thierry-Chef, E. Cardis et al. External dose estimation for nuclear worker studies. *Radiat Res* 166(1 Pt 2): 168-173 (2006).
- G11 Gilbert, E.S., L. Huang, A. Bouville et al. Thyroid cancer rates and ¹³¹I doses from Nevada atmospheric nuclear bomb tests: an update. *Radiat Res* 173(5): 659-664 (2010).
- G12 Gilks, W.R., S. Richardson and D.J. Spiegelhalter. *Markov Chain Monte Carlo in Practice*. Chapman & Hall/CRC, London, 1996.
- G13 Goggelmann, W., C. Jacobsen, W. Panzer et al. Re-evaluation of the RBE of 29 kV x-rays (mammography x-rays) relative to 220 kV x-rays using neoplastic transformation of human CGL1-hybrid cells. *Radiat Environ Biophys* 42(3): 175-182 (2003).
- G14 Gossner, W. Target cells in internal dosimetry. *Radiat Prot Dosim* 105(1-4): 39-42 (2003).
- G15 Gössner, W., R. Masse and J.W. Stather. Cells at risk for dosimetric modelling relevant to bone tumour induction. *Radiat Prot Dosim* 92(1-3): 209-213 (2000).
- G16 Greenland, S. Multiple-bias modelling for analysis of observational data (with discussion). *J R Stat Soc Ser A* 168(2): 267-305 (2005).
- G17 Greenland, S. Introduction to Bayesian statistics. pp.328-344 in: *Modern Epidemiology* (K.J. Rothman et al., eds.). Lippincott Williams & Wilkins, Philadelphia, 2008.

- G18 Greenland, S. and T.L. Lash. Bias analysis. pp.345-380 in: *Modern Epidemiology* (K.J. Rothman et al., eds.). Lippincott Williams & Wilkins, Philadelphia, 2008.
- G19 Griem, M.L., R.A. Kleinerman, J.D. Boice, Jr. et al. Cancer following radiotherapy for peptic ulcer. *J Natl Cancer Inst* 86(11): 842-849 (1994).
- G20 Grogan, H.A., W.K. Sinclair and P.G. Voillequé. Assessing risks of exposure to plutonium. Part of Task 3: Independent analysis of exposure, dose and health risk to offsite individuals. RAC Report No. 5-CDPHE-RFP-1998-FINAL. Radiological Assessment Corporation, Neeses, 2000.
- G21 Grogan, H.A., W.K. Sinclair and P.G. Voilleque. Risks of fatal cancer from inhalation of 239,240plutonium by humans: a combined four-method approach with uncertainty evaluation. *Health Phys* 80(5): 447-461 (2001).
- G22 Grogan, H.A., W.K. Sinclair and P.G. Voillequé. Risks of fatal cancer from inhalation of 239,240Pu by humans: a combined four-method approach with uncertainty evaluation; Erratum. *Health Phys*. 82(3): 404 (2002).
- G23 Group, T.J.U.-J.W. Reassessment of the Atomic Bomb Radiation Dosimetry for Hiroshima and Nagasaki: Dosimetry System 2002. (R.W. Young and G.D. Kerr, eds.). Radiation Effects Research Foundation, Japan, 2005.
- G24 Grudzenski, S., A. Raths, S. Conrad et al. Inducible response required for repair of low-dose radiation damage in human fibroblasts. *Proc Natl Acad Sci U S A* 107(32): 14205-14210 (2010).
- H1 Hall, P., A. Mattsson and J.D. Boice, Jr. Thyroid cancer after diagnostic administration of iodine-131. *Radiat Res* 145(1): 86-92 (1996).
- H2 Hamby, D.M. Uncertainty of the tritium dose conversion factor. *Health Phys* 77(3): 291-297 (1999).
- H3 Hamby, D.M. and R.R. Benke. Uncertainty of the iodine-131 ingestion dose conversion factor. *Radiat Prot Dosim* 82(4): 245-256 (1999).
- H4 Harrell, F.E.J. *Regression Modelling Strategies: With Applications to Linear Models, Logistic Regression, and Survival Analysis*. Springer-Verlag, New York, 2001.
- H5 Harrison, J. Biokinetic and dosimetric modelling in the estimation of radiation risks from internal emitters. *J Radiol Prot* 29(2A): A81-A105 (2009).
- H6 Harrison, J.D., A. Khursheed and B.E. Lambert. Uncertainties in dose coefficients for intakes of tritiated water and organically bound forms of tritium by members of the public. *Radiat Prot Dosim* 98(3): 299-311 (2002).
- H7 Hartge, P. and J. Cahill. Field methods in epidemiology. pp.492-510 in: *Modern Epidemiology* (K.J. Rothman et al., eds.). Lippincott Williams & Wilkins, Philadelphia, 2008.
- H8 Harvey, R.P., D.M. Hamby and T.S. Palmer. Uncertainty of the thyroid dose conversion factor for inhalation intakes of 131I and its parametric uncertainty. *Radiat Prot Dosim* 118(3): 296-306 (2006).
- H9 Heid, I.M., H. Kuchenhoff, J. Wellmann et al. On the potential of measurement error to induce differential bias on odds ratio estimates: an example from radon epidemiology. *Stat Med* 21(21): 3261-3278 (2002).

- H10 Heid, I.M., H. Kuchenhoff, J. Miles et al. Two dimensions of measurement error: classical and Berkson error in residential radon exposure assessment. *J Expo Anal Environ Epidemiol* 14(5): 365-377 (2004).
- H11 Heid, I.M., H. Kuchenhoff, A.S. Rosario et al. Impact of measurement error in exposures in german radon studies. *J Toxicol Environ Health A* 69(7): 701-721 (2006).
- H12 Heyes, G.J. and A.J. Mill. The neoplastic transformation potential of mammography X rays and atomic bomb spectrum radiation. *Radiat Res* 162(2): 120-127 (2004).
- H13 Hildreth, N.G., R.E. Shore and P.M. Dvoretzky. The risk of breast cancer after irradiation of the thymus in infancy. *N Engl J Med* 321(19): 1281-1284 (1989).
- H14 Hill, A.B. The environment and disease: association or causation? *Proc R Soc Med* 58: 295-300 (1965).
- H15 Hoeting, J.A., D. Madigan and A.E. Raftery. Bayesian model averaging: a tutorial. *Stat Sci* 14(4): 382-417 (1999).
- H16 Hofer, E. Hypothesis testing, statistical power, and confidence limits in the presence of epistemic uncertainty. *Health Phys* 92(3): 226-235 (2007).
- H17 Hofer, E. Correspondence: Response to Stram et al. *Health Phys*. 93(4): 327-328 (2007).
- H18 Hofer, E. How to account for uncertainty due to measurement errors in an uncertainty analysis using Monte Carlo simulation. *Health Phys* 95(3): 277-290 (2008).
- H19 Hoffman, F.O., A.J. Ruttenger, A.I. Apostoaei et al. The Hanford Thyroid Disease Study: an alternative view of the findings. *Health Phys* 92(2): 99-111 (2007).
- H20 Huber, R., H. Schraube, U. Nahrstedt et al. Dose-response relationships of micronuclei in human lymphocytes induced by fission neutrons and by low LET radiations. *Mutat Res* 306(2): 135-141 (1994).
- H21 Hunter, N., C.B. Howarth and J.C.H. Miles. Year-to-year variations in radon levels in a sample of UK houses with the same occupants. pp.438-447 in: *The Natural Radiation Environment VII* (J.P. McLaughlin et al., eds.). Elsevier Ltd., Oxford, 2005.
- H22 Hwang, S.L., H.R. Guo, W.A. Hsieh et al. Cancer risks in a population with prolonged low dose-rate gamma-radiation exposure in radiocontaminated buildings, 1983-2002. *Int J Radiat Biol* 82(12): 849-858 (2006).
- H23 Hwang, S.L., J.S. Hwang, Y.T. Yang et al. Estimates of relative risks for cancers in a population after prolonged low-dose-rate radiation exposure: a follow-up assessment from 1983 to 2005. *Radiat Res* 170(2): 143-148 (2008).
- I1 IAEA. Evaluating the reliability of predictions made using environmental transfer models. Safety Series No. 100. International Atomic Energy Agency, Vienna, 1989.
- I2 IAEA. Cytogenetic analysis for radiation dose assessment: A manual. Technical Reports 405. International Atomic Energy Agency, Vienna, 2001.
- I3 IARC. IARC Monographs on the evaluation of carcinogenic risks to humans. Ionizing radiation, Part 1: X- and gamma (γ)-radiation, and neutrons. IARC Monograph 75. International Agency for Research on Cancer, Lyon, 2000.

- 14 IARC. IARC Monographs on the evaluation of carcinogenic risks to humans. Ionizing radiation, Part 2: Some internally deposited radionuclides. IARC Monograph 78. International Agency for Research on Cancer, Lyon, 2001.
- 15 IARC. Cancer Incidence in Five Continents. IARC Publication No. 160, Volume IX (M.P. Curado et al., eds.). International Agency for Research on Cancer, Lyon, 2009.
- 16 ICRP. Biological effects of inhaled radionuclides. ICRP Publication 31. Annals of the ICRP 4(1-2). International Commission on Radiological Protection, Pergamon Press, Oxford, 1980.
- 17 ICRP. 1990 Recommendations of the International Commission on Radiological Protection. ICRP Publication 60. Annals of the ICRP 21(1-3). International Commission on Radiological Protection, Pergamon Press, Oxford, 1991.
- 18 ICRP. Age-dependent doses to members of the public from intake of radionuclides: Part 2. Ingestion dose coefficients. ICRP Publication 67. Annals of the ICRP 23(3-4). International Commission on Radiological Protection, Pergamon Press, Oxford, 1993.
- 19 ICRP. Human respiratory tract model for radiological protection. ICRP Publication 66. Annals of the ICRP 24(1-3). International Commission on Radiological Protection, Pergamon Press, Oxford, 1994.
- I10 ICRP. Basic anatomical and physiological data for use in radiological protection: the skeleton. ICRP Publication 70. Annals of the ICRP 25(2). International Commission on Radiological Protection, Pergamon Press, Oxford, 1995.
- I11 ICRP. Relative biological effectiveness (RBE), quality factor (Q), and radiation weighting factor (w_R). ICRP Publication 92. Annals of the ICRP 33(4). International Commission on Radiological Protection, Pergamon Press, 2003.
- I12 ICRP. Low-dose extrapolation of radiation-related cancer risk. ICRP Publication 99. Annals of the ICRP 35(4). International Commission on Radiological Protection, Elsevier Ltd., 2005.
- I13 ICRP. Human alimentary tract model for radiological protection. ICRP Publication 100. Annals of the ICRP 36(1-2). International Commission on Radiological Protection, Elsevier Ltd., 2006.
- I14 ICRP. The 2007 Recommendations of the International Commission on Radiological Protection. ICRP Publication 103. Annals of the ICRP 37(2-4). International Commission on Radiological Protection, Elsevier Ltd., 2007.
- I15 ICRP. Nuclear decay data for dosimetric calculations. ICRP Publication 107. Annals of the ICRP 38(3). International Commission on Radiological Protection, Elsevier Ltd., 2008.
- I16 ICRP. Adult reference computational phantoms. ICRP Publication 110. Annals of the ICRP 39(2). International Commission on Radiological Protection, Elsevier Ltd., 2009.
- I17 ICRP. Lung cancer risk from radon and progeny and statement on radon. ICRP Publication 115. Annals of the ICRP 40(1). International Commission on Radiological Protection, Elsevier Ltd., 2010.
- I18 ICRU. The quality factor in radiation protection. ICRU Report 40. International Commission on Radiation Units and Measurements, 1986.
- I19 ICRU. Stopping powers and ranges for protons and alpha particles. ICRU Report 49. International Commission on Radiation Units and Measurements, 1993.

- I20 Ina, Y. and K. Sakai. Further study of prolongation of life span associated with immunological modification by chronic low-dose-rate irradiation in MRL-lpr/lpr mice: effects of whole-life irradiation. *Radiat Res* 163(4): 418-423 (2005).
- I21 Inskip, P.D., R.R. Monson, J.K. Wagoner et al. Cancer mortality following radium treatment for uterine bleeding. *Radiat Res* 123(3): 331-344 (1990).
- I22 Ivanov, V.K., A.F. Tsyb, A.I. Gorsky et al. Leukaemia and thyroid cancer in emergency workers of the Chernobyl accident: estimation of radiation risks (1986-1995). *Radiat Environ Biophys* 36(1): 9-16 (1997).
- I23 Ivanov, V.K., A.F. Tsyb and A.P. Konogorov. Case-control analysis of leukaemia among Chernobyl accident emergency workers residing in the Russian Federation 1986-1993. *J Radiol Prot* 17(3): 137-157 (1997).
- I24 Ivanov, V.K., A.I. Gorski, M.A. Maksoutov et al. Mortality among the Chernobyl emergency workers: estimation of radiation risks (preliminary analysis). *Health Phys* 81(5): 514-521 (2001).
- I25 Ivanov, V.K., A.I. Gorski, A.F. Tsyb et al. Solid cancer incidence among the Chernobyl emergency workers residing in Russia: estimation of radiation risks. *Radiat Environ Biophys* 43(1): 35-42 (2004).
- I26 Ivanov, V.K., K.A. Tumanov and V.V. Kashcheev. Mortality in Chernobyl clean-up workers: analysis of dose-effect relationship. *Radiation and Risk* 15: 11-22 (2006). (Russian).
- J1 Jablon, S. Atomic bomb radiation dose estimation at ABCC. ABCC-Technical Report 23: ABCC, 1971.
- J2 Jacob, P., T.I. Bogdanova, E. Buglova et al. Thyroid cancer risk in areas of Ukraine and Belarus affected by the Chernobyl accident. *Radiat Res* 165(1): 1-8 (2006).
- J3 Jacob, P., R. Meckbach, M. Sokolnikov et al. Lung cancer risk of Mayak workers: modelling of carcinogenesis and bystander effect. *Radiat Environ Biophys* 46(4): 383-394 (2007).
- J4 Jacob, P., L. Walsh and M. Eidemuller. Modeling of cell inactivation and carcinogenesis in the atomic bomb survivors with applications to the mortality from all solid, stomach and liver cancer. *Radiat Environ Biophys* 47(3): 375-388 (2008).
- J5 Jacob, P., W. Ruhm, L. Walsh et al. Is cancer risk of radiation workers larger than expected? *Occup Environ Med* 66(12): 789-796 (2009).
- J6 Jacob, P., R. Meckbach, J.C. Kaiser et al. Possible expressions of radiation-induced genomic instability, bystander effects or low-dose hypersensitivity in cancer epidemiology. *Mutat Res* 687(1-2): 34-39 (2010).
- J7 Jaynes, E.T. *Probability Theory: The Logic of Science*. Cambridge University Press, Cambridge 2003.
- J8 JCGM. Evaluation of measurement data – Guide to the expression of uncertainty in measurement. JCGM 100:2008 GUM 1995 with minor corrections. Joint Committee for Guides in Metrology, 2008.
- J9 JCGM. Evaluation of measurement data – Supplement 1 to the “Guide to the expression of uncertainty in measurement” – Propagation of distributions using a Monte Carlo method. JCGM 101:2008. Joint Committee for Guides in Metrology, 2008.

- J10 JCGM. Evaluation of measurement data – An introduction to the “Guide to the expression of uncertainty in measurement” and related documents. JCGM 104:2009. Joint Committee for Guides in Metrology, 2009.
- J11 JCGM. International vocabulary of metrology – Basic and general concepts and associated terms (VIM). JCGM 200:2012. Joint Committee for Guides in Metrology, 2012.
- J12 Jeffreys, H. An invariant form for the prior probability in estimation problems. *Proc R Soc Lond A Math Phys Sci* 186(1007): 453-461 (1946).
- J13 Jewell, N.P. *Statistics for Epidemiology*. CRC Press, Florida, 2004.
- J14 Jin, Y.W., Y.J. Na, Y.J. Lee et al. Comprehensive analysis of time- and dose-dependent patterns of gene expression in a human mesenchymal stem cell line exposed to low-dose ionizing radiation. *Oncol Rep* 19(1): 135-144 (2008).
- J15 Johnson, C.J. Cancer incidence in an area of radioactive fallout downwind from the Nevada Test Site. *JAMA* 251(2): 230-236 (1984).
- K1 Kaiser, J.C. and W.F. Heidenreich. Comparing regression methods for the two-stage clonal expansion model of carcinogenesis. *Stat Med* 23(21): 3333-3350 (2004).
- K2 Kaiser, J.C., P. Jacob, R. Meckbach et al. Breast cancer risk in atomic bomb survivors from multi-model inference with incidence data 1958-1998. *Radiat Environ Biophys* 51(1): 1-14 (2012).
- K3 Kapur, J.N. and H.K. Kesavan. *Entropy Optimization Principles with Applications*. Academies Press, Boston, 1992.
- K4 Kaul, D.C., S.D. Egbert and W.A. Woolson. DS02 uncertainty analysis. pp.921-944 in: *Reassessment of the Atomic Bomb Radiation Dosimetry for Hiroshima and Nagasaki: Dosimetry System 2002*. Report of the Joint US-Japan Working Group. Radiation Effects Research Foundation, Japan, 2005.
- K5 Kerber, R.A., J.E. Till, S.L. Simon et al. A cohort study of thyroid disease in relation to fallout from nuclear weapons testing. *J Am Med Assoc* 270(17): 2076-2082 (1993).
- K6 Kocher, D.C., A.I. Apostoaei and F.O. Hoffman. Radiation effectiveness factors for use in calculating probability of causation of radiogenic cancers. *Health Phys* 89(1): 3-32 (2005).
- K7 Kocher, D.C., A.I. Apostoaei, R.W. Henshaw et al. Interactive RadioEpidemiological Program (IREP): a web-based tool for estimating probability of causation/assigned share of radiogenic cancers. *Health Phys* 95(1): 119-147 (2008).
- K8 Kopecky, K.J., S. Davis, T.E. Hamilton et al. Estimation of thyroid radiation doses for the hanford thyroid disease study: results and implications for statistical power of the epidemiological analyses. *Health Phys* 87(1): 15-32 (2004).
- K9 Kopecky, K.J., L. Onstad, T.E. Hamilton et al. Thyroid ultrasound abnormalities in persons exposed during childhood to ¹³¹I from the Hanford nuclear site. *Thyroid* 15(6): 604-613 (2005).
- K10 Kopecky, K.J., V. Stepanenko, N. Rivkind et al. Childhood thyroid cancer, radiation dose from Chernobyl, and dose uncertainties in Bryansk Oblast, Russia: a population-based case-control study. *Radiat Res* 166(2): 367-374 (2006).

- K11 Kreienbrock, L., M. Kreuzer, M. Gerken et al. Case-control study on lung cancer and residential radon in western Germany. *Am J Epidemiol* 153(1): 42-52 (2001).
- K12 Krestinina, L.Y., D.L. Preston, E.V. Ostroumova et al. Protracted radiation exposure and cancer mortality in the Techa River Cohort. *Radiat Res* 164(5): 602-611 (2005).
- K13 Krestinina, L.Y., F. Davis, E. Ostroumova et al. Solid cancer incidence and low-dose-rate radiation exposures in the Techa River cohort: 1956-2002. *Int J Epidemiol* 36(5): 1038-1046 (2007).
- K14 Krewski, D., J.H. Lubin, J.M. Zielinski et al. Residential radon and risk of lung cancer: a combined analysis of 7 North American case-control studies. *Epidemiology* 16(2): 137-145 (2005).
- K15 Krewski, D., J.H. Lubin, J.M. Zielinski et al. A combined analysis of North American case-control studies of residential radon and lung cancer. *J Toxicol Environ Health A* 69(7): 533-597 (2006).
- K16 Krumrey, M., G. Ulm and E. Schmid. Dicentric chromosomes in monolayers of human lymphocytes produced by monochromatized synchrotron radiation with photon energies from 1.83 keV to 17.4 keV. *Radiat Environ Biophys* 43(1): 1-6 (2004).
- K17 Kukush, A., S. Shklyar, S. Masiuk et al. Methods for estimation of radiation risk in epidemiological studies accounting for classical and Berkson errors in doses. *Int J Biostat* 7(1): 15 (2011).
- K18 Kurpinski, K., D.J. Jang, S. Bhattacharya et al. Differential effects of x-rays and high-energy ^{56}Fe ions on human mesenchymal stem cells. *Int J Radiat Oncol Biol Phys* 73(3): 869-877 (2009).
- L1 Lagarde, F., G. Pershagen, G. Akerblom et al. Residential radon and lung cancer in Sweden: risk analysis accounting for random error in the exposure assessment. *Health Phys* 72(2): 269-276 (1997).
- L2 Lagarde, F., R. Falk, K. Almren et al. Glass-based radon-exposure assessment and lung cancer risk. *J Expo Anal Environ Epidemiol* 12(5): 344-354 (2002).
- L3 Land, C.E. Estimating cancer risks from low doses of ionizing radiation. *Science* 209(4462): 1197-1203 (1980).
- L4 Land, C.E. Uncertainty, low-dose extrapolation and the threshold hypothesis. *J Radiol Prot* 22(3A): A129-135 (2002).
- L5 Land, C.E., E. Gilbert, J.M. Smith et al. Report of the NCI-CDC Working Group to Revise the 1985 NIH Radioepidemiological Tables. NIH Publication 03-5387. National Cancer Institute, Bethesda, MD, 2003.
- L6 Land, C.E., A. Bouville, I. Apostoaei et al. Projected lifetime cancer risks from exposure to regional radioactive fallout in the Marshall Islands. *Health Phys* 99(2): 201-215 (2010).
- L7 Langholz, B. and J. Jiao. Computational methods for case-cohort studies. *Comput Stat Data Anal* 51(8): 3737-3748 (2007).
- L8 Leggett, R.W. Reliability of the ICRP's dose coefficients for members of the public. 1. Sources of uncertainty in the biokinetic models. *Radiat Prot Dosim* 95(3): 199-213 (2001).

- L9 Leggett, R.W., L.R. Williams, D.R. Melo et al. A physiologically based biokinetic model for cesium in the human body. *Sci Total Environ* 317(1-3): 235-255 (2003).
- L10 Leggett, R.W., K.F. Eckerman, V.F. Khokhryakov et al. Mayak worker study: an improved biokinetic model for reconstructing doses from internally deposited plutonium. *Radiat Res* 164(2): 111-122 (2005).
- L11 Lehnert, A., W. Dorr, E. Lessmann et al. RBE of 10 kV X rays determined for the human mammary epithelial cell line MCF-12A. *Radiat Res* 169(3): 330-336 (2008).
- L12 Leuraud, K., M. Schnelzer, L. Tomasek et al. Radon, smoking and lung cancer risk: results of a joint analysis of three European case-control studies among uranium miners. *Radiat Res* 176(3): 375-387 (2011).
- L13 Li, W.B., M. Zankl, H. Schlattl et al. Impact on ¹⁴¹Ce, ¹⁴⁴Ce, ⁹⁵Zr, and ⁹⁰Sr beta emitter dose coefficients of photon and electron SAFs calculated with ICRP/ICRU reference adult voxel computational phantoms. *Health Phys* 99(4): 503-510 (2010).
- L14 Li, Y., A. Guolo, F.O. Hoffman et al. Shared uncertainty in measurement error problems, with application to Nevada Test Site fallout data. *Biometrics* 63(4): 1226-1236 (2007).
- L15 Likhtarev, I., A. Bouville, L. Kovgan et al. Questionnaire- and measurement-based individual thyroid doses in Ukraine resulting from the Chernobyl nuclear reactor accident. *Radiat Res* 166(1 Pt 2): 271-286 (2006).
- L16 Lindberg, S., P. Karlsson, B. Arvidsson et al. Cancer incidence after radiotherapy for skin haemangioma during infancy. *Acta Oncol* 34(6): 735-740 (1995).
- L17 Little, M.P., D.G. Hoel, J. Molitor et al. New models for evaluation of radiation-induced lifetime cancer risk and its uncertainty employed in the UNSCEAR 2006 report. *Radiat Res* 169(6): 660-676 (2008).
- L18 Little, M.P. and B.E. Lambert. Systematic review of experimental studies on the relative biological effectiveness of tritium. *Radiat Environ Biophys* 47(1): 71-93 (2008).
- L19 Little, M.P., P. Vineis and G. Li. A stochastic carcinogenesis model incorporating multiple types of genomic instability fitted to colon cancer data. *J Theor Biol* 254(2): 229-238 (2008).
- L20 Lobrich, M., N. Rief, M. Kuhne et al. In vivo formation and repair of DNA double-strand breaks after computed tomography examinations. *Proc Natl Acad Sci U S A* 102(25): 8984-8989 (2005).
- L21 Lobrich, M. and P.A. Jeggo. The impact of a negligent G2/M checkpoint on genomic instability and cancer induction. *Nat Rev Cancer* 7(11): 861-869 (2007).
- L22 Loucas, B.D. and M.N. Cornforth. Complex chromosome exchanges induced by gamma rays in human lymphocytes: an mFISH study. *Radiat Res* 155(5): 660-671 (2001).
- L23 Loucas, B.D., R. Eberle, S.M. Bailey et al. Influence of dose rate on the induction of simple and complex chromosome exchanges by gamma rays. *Radiat Res* 162(4): 339-349 (2004).
- L24 Lowe, X.R., S. Bhattacharya, F. Marchetti et al. Early brain response to low-dose radiation exposure involves molecular networks and pathways associated with cognitive functions, advanced aging and Alzheimer's disease. *Radiat Res* 171(1): 53-65 (2009).
- L25 Lubin, J.H., J.D. Boice, Jr., C. Edling et al. Radon-exposed underground miners and inverse dose-rate (protraction enhancement) effects. *Health Phys* 69(4): 494-500 (1995).

- L26 Lubin, J.H., J.D. Boice, Jr. and J.M. Samet. Errors in exposure assessment, statistical power and the interpretation of residential radon studies. *Radiat Res* 144(3): 329-341 (1995).
- L27 Lubin, J.H. and J.D. Boice, Jr. Lung cancer risk from residential radon: meta-analysis of eight epidemiologic studies. *J Natl Cancer Inst* 89(1): 49-57 (1997).
- L28 Lubin, J.H. The potential for bias in Cohen's ecological analysis of lung cancer and residential radon. *J Radiol Prot* 22(2): 141-148 (2002).
- L29 Lubin, J.H., D.W. Schafer, E. Ron et al. A reanalysis of thyroid neoplasms in the Israeli tinea capitis study accounting for dose uncertainties. *Radiat Res* 161(3): 359-368 (2004).
- L30 Lubin, J.H., Z.Y. Wang, J.D. Boice, Jr. et al. Risk of lung cancer and residential radon in China: pooled results of two studies. *Int J Cancer* 109(1): 132-137 (2004).
- L31 Lubin, J.H., Z.Y. Wang, L.D. Wang et al. Adjusting lung cancer risks for temporal and spatial variations in radon concentration in dwellings in Gansu Province, China. *Radiat Res* 163(5): 571-579 (2005).
- L32 Lundell, M., A. Mattsson, T. Hakulinen et al. Breast cancer after radiotherapy for skin hemangioma in infancy. *Radiat Res* 145(2): 225-230 (1996).
- L33 Lunn, D.J., N. Thomas, A. Best et al. WinBUGS - A Bayesian modelling framework: concepts, structure, and extensibility. *Stat Comput* 10(4): 325-337 (2000).
- L34 Lyon, J.L., S.C. Alder, M.B. Stone et al. Thyroid disease associated with exposure to the Nevada nuclear weapons test site radiation: a reevaluation based on corrected dosimetry and examination data. *Epidemiology* 17(6): 604-614 (2006).
- M1 Machado, S.G., C.E. Land and F.W. McKay. Cancer mortality and radioactive fallout in southwestern Utah. *Am J Epidemiol* 125(1): 44-61 (1987).
- M2 MacMahon, B., P. Cole and J. Brown. Etiology of human breast cancer: a review. *J Natl Cancer Inst* 50(1): 21-42 (1973).
- M3 Madigan, D. and A.E. Raftery. Model selection and accounting for model uncertainty in graphical models using Occam's window. *J Am Stat Assoc* 89(428): 1535-1546 (1994).
- M4 Madigan, D. and J. York. Bayesian graphical models for discrete data. *Int Stat Rev* 63(2): 215-232 (1995).
- M5 Mahaffey, J.A., M.A. Parkhurst, T.E. Hui et al. Factors affecting use of CR-39 surface monitor technology to estimate past exposure to indoor radon. *J Expo Anal Environ Epidemiol* 6(4): 425-437 (1996).
- M6 Mallick, B., F.O. Hoffman and R.J. Carrol. Semiparametric regression modeling with mixtures of Berkson and classical error, with application to fallout from the Nevada test site. *Biometrics* 58(1): 13-20 (2002).
- M7 Marsh, J.W. and A. Birchall. Sensitivity analysis of the weighted equivalent lung dose per unit exposure from radon progeny. *Radiat Prot Dosim* 87(3): 167-178 (2000).
- M8 Mattsson, A., B.I. Ruden, P. Hall et al. Radiation-induced breast cancer: long-term follow-up of radiation therapy for benign breast disease. *J Natl Cancer Inst* 85(20): 1679-1685 (1993).
- M9 McCulloch, C.E. Maximum likelihood algorithms for generalized linear mixed models. *J Am Stat Assoc* 92(437): 162-170 (1997).

- M10 Melintescu, A., D. Galeriu and H. Takeda. Reassessment of tritium dose coefficients for the general public. *Radiat Prot Dosim* 127(1-4): 153-157 (2007).
- M11 Mestres, M., M.R. Caballin, L. Barrios et al. RBE of X rays of different energies: a cytogenetic evaluation by FISH. *Radiat Res* 170(1): 93-100 (2008).
- M12 Mestres, M., L. Benkhalel, M.R. Caballin et al. Induction of incomplete and complex chromosome aberrations by 30 kVp X rays. *Radiat Res* 175(2): 201-207 (2011).
- M13 Mikhalskii, A.I., V.K. Ivanov and S.Y. Chekin. Accounting of heterogeneity in the estimation of radiation risks. *Autom Remote Control* 69(6): 1045-1050 (2008).
- M14 Miller, G., H.F. Martz and T.T. Little. Bayesian graphical models for discrete data. *Radiat Prot Dosim* 98(2): 191-198 (2002).
- M15 Miller, G. Variability and uncertainty of biokinetic model parameters: the discrete empirical Bayes approximation. *Radiat Prot Dosim* 131(3): 394-398 (2008).
- M16 Miller, G., R. Guilmette, L. Bertelli et al. Uncertainties in internal doses calculated for Mayak workers--a study of 63 cases. *Radiat Prot Dosim* 131(3): 316-330 (2008).
- M17 Modan, B., E. Ron and A. Werner. Thyroid cancer following scalp irradiation. *Radiology* 123(3): 741-744 (1977).
- M18 Moolgavkar, S.H. and D.J. Venzon. Two-event models for carcinogenesis: incidence curves for childhood and adult tumors. *Math Biosci* 47(1-2): 55-77 (1979).
- M19 Moolgavkar, S.H. and A.G. Knudson, Jr. Mutation and cancer: a model for human carcinogenesis. *J Natl Cancer Inst* 66(6): 1037-1052 (1981).
- M20 Muirhead, C.R., R. Cox and J.W. Stather. Estimates of late radiation risks to the UK population. *NRPB* 4: 15-157 (1993).
- M21 Muirhead, C.R., J.A. O'Hagan, R.G. Haylock et al. Mortality and cancer incidence following occupational radiation exposure: third analysis of the National Registry for Radiation Workers. *Br J Cancer* 100(1): 206-212 (2009).
- M22 Muirhead, C.R., O'Hagan, J.A. and R.G.E. Haylock. Third analysis of the National Registry for Radiation Workers: occupational exposure to ionising radiation in relation to mortality and cancer incidence. *HPA-RPD-062* (2009).
- N1 Nagasawa, H. and J.B. Little. Induction of sister chromatid exchanges by extremely low doses of alpha-particles. *Cancer Res* 52(22): 6394-6396 (1992).
- N2 Nair, R.R., B. Rajan, S. Akiba et al. Background radiation and cancer incidence in Kerala, India-Karanagappally cohort study. *Health Phys* 96(1): 55-66 (2009).
- N3 NCI. Estimated exposures and thyroid doses received by the American people from iodine-131 in fallout following the Nevada atmospheric nuclear bomb tests. *DHHS/NIH/NCI, NIH Publication No. 97-4264*, National Cancer Institute, 1997.
- N4 NCRP. The relative biological effectiveness of radiations of different quality. *NCRP Report No. 104*. National Council on Radiation Protection and Measurements, 1990.
- N5 NCRP. Limitation of exposure to ionizing radiation. *NCRP Report No. 116*. National Council on Radiation Protection and Measurements, 1993.

- N6 NCRP. A guide for uncertainty analysis in dose and risk assessments related to environmental contamination. NCRP Commentary No. 14. National Council on Radiation Protection and Measurements, Bethesda, 1996.
- N7 NCRP. Uncertainties in fatal cancer risk estimates used in radiation protection. NCRP Report No. 126. National Council on Radiation Protection and Measurements, Bethesda, 1997.
- N8 NCRP. Development of a biokinetic model for radionuclide-contaminated wounds and procedures for their assessment, dosimetry and treatment. NCRP Report No. 156. National Council on Radiation Protection and Measurements, 2006.
- N9 NCRP. Uncertainties in the measurement and dosimetry of external radiation. NCRP Report No. 158. National Council on Radiation Protection and Measurements, Bethesda, 2008.
- N10 NCRP. Radiation dose reconstruction: Principles and practices. NCRP Report No. 163. National Council on Radiation Protection and Measurements, 2010.
- N11 NCRP. Uncertainties in internal radiation dose assessment. NCRP Report No. 164. National Council on Radiation Protection and Measurements, Bethesda, 2010.
- N12 NCRP. Uncertainties in the estimation of radiation risks and probability of disease causation. NCRP Report No. 171. National Council on Radiation Protection and Measurements, Bethesda, 2012.
- N13 Neumaier, T., J. Swenson, C. Pham et al. Evidence for formation of DNA repair centers and dose-response nonlinearity in human cells. *Proc Natl Acad Sci U S A* 109(2): 443-448 (2012).
- N14 Neyman, J. and E.S. Pearson. On the use and interpretation of certain test criteria for purposes of statistical inference, part II. *Biometrika* 20A(3-4): 263-294 (1928).
- N15 Nikjoo, H. and D.T. Goodhead. Track structure analysis illustrating the prominent role of low-energy electrons in radiobiological effects of low-LET radiations. *Phys Med Biol* 36(2): 229-238 (1991).
- N16 Nikjoo, H. and L. Lindborg. RBE of low energy electrons and photons. *Phys Med Biol* 55(10): R65-109 (2010).
- N17 Nishizawa, S., S. Kojima, S. Teramukai et al. Prospective evaluation of whole-body cancer screening with multiple modalities including [18F]fluorodeoxyglucose positron emission tomography in a healthy population: a preliminary report. *J Clin Oncol* 27(11): 1767-1773 (2009).
- N18 NRC. Health effects of exposure to radon. Committee on Health Risks of Exposure to Radon, BEIR VI. National Research Council, National Academy Press, Washington, D.C., 1999.
- N19 NRC. Health risks from exposure to low levels of ionizing radiation. Committee to Assess Health Risks from Exposure to Low Levels of Ionizing Radiation, BEIR VII - Phase 2. National Research Council, The National Academies Press, Washington D.C., 2006.
- O1 Office for National Statistics. Cancer statistics registrations. Registrations of cancer diagnosed in 2009, England. MB1 40. London, UK, 2011.
- O2 Ojima, M., N. Ban and M. Kai. DNA double-strand breaks induced by very low X-ray doses are largely due to bystander effects. *Radiat Res* 170(3): 365-371 (2008).

- O3 Omar, R.Z., J.A. Barber and P.G. Smith. Cancer mortality and morbidity among plutonium workers at the Sellafield plant of British Nuclear Fuels. *Br J Cancer* 79(7-8): 1288-1301 (1999).
- P1 Pawel, D.J., R.W. Leggett and K.F. Eckerman. Uncertainties in cancer risk coefficients for environmental exposure to radionuclides. An uncertainty analysis for risk coefficients reported in Federal Guidance 13. ORNL/TM-2006/583. Oak Ridge National Laboratory, USA, 2007.
- P2 Pershagen, G., G. Akerblom, O. Axelson et al. Residential radon exposure and lung cancer in Sweden. *N Engl J Med* 330(3): 159-164 (1994).
- P3 Peto, R., A.D. Lopez, J. Boreham et al. Mortality from tobacco in developed countries: indirect estimation from national vital statistics. *Lancet* 339(8804): 1268-1278 (1992).
- P4 Pierce, D.A., D.O. Stram and M. Vaeth. Allowing for random errors in radiation dose estimates for the atomic bomb survivor data. *Radiat Res* 123(3): 275-284 (1990).
- P5 Pierce, D.A. and A.M. Kellerer. Adjusting for covariate errors with nonparametric assessment of the true covariate distribution. *Biometrika* 91(4): 863-876 (2004).
- P6 Pierce, D.A., M. Vaeth and J.B. Cologne. Allowance for random dose estimation errors in atomic bomb survivor studies: a revision. *Radiat Res* 170(1): 118-126 (2008).
- P7 Portess, D.I., G. Bauer, M.A. Hill et al. Low-dose irradiation of nontransformed cells stimulates the selective removal of precancerous cells via intercellular induction of apoptosis. *Cancer Res* 67(3): 1246-1253 (2007).
- P8 Posada, D. and T.R. Buckley. Model selection and model averaging in phylogenetics: advantages of akaike information criterion and bayesian approaches over likelihood ratio tests. *Syst Biol* 53(5): 793-808 (2004).
- P9 Preston, D.L., H. Kato, K. Kopecky et al. Studies of the mortality of A-bomb survivors. 8. Cancer mortality, 1950-1982. *Radiat Res* 111(1): 151-178 (1987).
- P10 Preston, D.L., J.H. Lubin and D.A. Pierce. *Epicure User's Guide*. Hirosoft International Corporation, Seattle, Washington, 1993.
- P11 Preston, D.L., A. Mattsson, E. Holmberg et al. Radiation effects on breast cancer risk: a pooled analysis of eight cohorts. *Radiat Res* 158(2): 220-235 (2002).
- P12 Preston, D.L., Y. Shimizu, D.A. Pierce et al. Studies of mortality of atomic bomb survivors. Report 13: Solid cancer and noncancer disease mortality: 1950-1997. *Radiat Res* 160(4): 381-407 (2003).
- P13 Preston, D.L., D.A. Pierce, Y. Shimizu et al. Effect of recent changes in atomic bomb survivor dosimetry on cancer mortality risk estimates. *Radiat Res* 162(4): 377-389 (2004).
- P14 Preston, D.L., E. Ron, S. Tokuoka et al. Solid cancer incidence in atomic bomb survivors: 1958-1998. *Radiat Res* 168(1): 1-64 (2007).
- P15 Preston, D.L., L.Y. Krestinina, M.E. Sokolnikov et al. How much can we say about site-specific cancer radiation risks? *Radiat Res* 174(6): 816-824 (2010).
- P16 Puncher, M. and A. Birchall. A Monte Carlo method for calculating Bayesian uncertainties in internal dosimetry. *Radiat Prot Dosim* 132(1): 1-12 (2008).

- P17 Puncher, M., A. Birchall and R.K. Bull. Uncertainties on lung doses from inhaled plutonium. *Radiat Res* 176(4): 494-507 (2011).
- P18 Puncher, M. and J.D. Harrison. Uncertainty analysis of doses from ingestion of plutonium and americium. *Radiat Prot Dosim* 148(3): 284-296 (2012).
- P19 Puskin, J.S. Smoking as a confounder in ecologic correlations of cancer mortality rates with average county radon levels. *Health Phys* 84(4): 526-532 (2003).
- R1 Reeves, G.K., D.R. Cox, S.C. Darby et al. Some aspects of measurement error in explanatory variables for continuous and binary regression models. *Stat Med* 17(19): 2157-2177 (1998).
- R2 Richardson, D., H. Sugiyama, N. Nishi et al. Ionizing radiation and leukemia mortality among Japanese Atomic Bomb Survivors, 1950-2000. *Radiat Res* 172(3): 368-382 (2009).
- R3 Ron, E., J.H. Lubin, R.E. Shore et al. Thyroid cancer after exposure to external radiation: a pooled analysis of seven studies. *Radiat Res* 141(3): 259-277 (1995).
- R4 Rothman, K.J. and S. Greenland. Causation and causal inference in epidemiology. *Am J Public Health* 95 (Suppl 1): S144-150 (2005).
- R5 Rothman, K.J., S. Greenland and T.L. Lash. Case-control studies. pp.111-127 in: *Modern Epidemiology* (K.J. Rothman et al., eds.). Lippincott Williams & Wilkins, Philadelphia, 2008.
- R6 Rothman, K.J., S. Greenland and T.L. Lash. Validity in epidemiologic studies. pp.128-147 in: *Modern Epidemiology* (K.J. Rothman et al., eds.). Lippincott Williams & Wilkins, Philadelphia, 2008.
- R7 Rothman, K.J., S. Greenland and T.L. Lash. *Modern Epidemiology*. Third edition. Lippincott Williams & Wilkins, Philadelphia, 2008.
- S1 Saccomanno, G., O. Auerbach, M. Kuschner et al. A comparison between the localization of lung tumors in uranium miners and in nonminers from 1947 to 1991. *Cancer* 77(7): 1278-1283 (1996).
- S2 Samet, J.M., J. Stolwijk and S.L. Rose. Summary: International workshop on residential Rn epidemiology. *Health Phys* 60(2): 223-227 (1991).
- S3 Sasaki, S. and N. Fukuda. Dose-response relationship for life-shortening and carcinogenesis in mice irradiated at day 7 postnatal age with dose range below 1 Gy of gamma rays. *J Radiat Res* 47(2): 135-145 (2006).
- S4 Sasaki, S. and N. Fukuda. Dose-response relationship for induction of ovarian tumors in mice irradiated during prenatal, early postnatal and elder periods. *J Radiat Res* 49(6): 623-633 (2008).
- S5 Schafer, D.W., J.H. Lubin, E. Ron et al. Thyroid cancer following scalp irradiation: a reanalysis accounting for uncertainty in dosimetry. *Biometrics* 57(3): 689-697 (2001).
- S6 Schafer, D.W. and E.S. Gilbert. Some statistical implications of dose uncertainty in radiation dose-response analyses. *Radiat Res* 166(1 Pt 2): 303-312 (2006).
- S7 Schmid, E., D. Regulla, H.M. Kramer et al. The effect of 29 kV X rays on the dose response of chromosome aberrations in human lymphocytes. *Radiat Res* 158(6): 771-777 (2002).

- S8 Schmid, E., M. Krumrey, G. Ulm et al. The maximum low-dose RBE of 17.4 and 40 keV monochromatic X rays for the induction of dicentric chromosomes in human peripheral lymphocytes. *Radiat Res* 160(5): 499-504 (2003).
- S9 Schneider, U. and L. Walsh. Cancer risk above 1 Gy and the impact for space radiation protection. *Adv Space Res* 44(2): 202-209 (2009).
- S10 Schwarz, G. Estimating the dimension of a model. *Ann Stat* 6(2): 461-464 (1978).
- S11 Shagina, N.B., E.I. Tolstykh, T.P. Fell et al. In utero and postnatal haemopoietic tissue doses resulting from maternal ingestion of strontium isotopes from the Techa River. *Radiat Prot Dosim* 127(1-4): 497-501 (2007).
- S12 Shilnikova, N.S., D.L. Preston, E. Ron et al. Cancer mortality risk among workers at the Mayak nuclear complex. *Radiat Res* 159(6): 787-798 (2003).
- S13 Shin, S.C., Y.M. Kang and H.S. Kim. Life span and thymic lymphoma incidence in high- and low-dose-rate irradiated AKR/J mice and commonly expressed genes. *Radiat Res* 174(3): 341-346 (2010).
- S14 Shleien, B., L.A.J. Slaback and B.K. Birky. *Handbook of Health Physics and Radiological Health*. Lippincott Williams & Wilkins, Baltimore, Maryland, 1998.
- S15 Shore, R.E., N. Hildreth, E. Woodard et al. Breast cancer among women given X-ray therapy for acute postpartum mastitis. *J Natl Cancer Inst* 77(3): 689-696 (1986).
- S16 Shuryak, I., P. Hahnfeldt, L. Hlatky et al. A new view of radiation-induced cancer: integrating short- and long-term processes. Part I: approach. *Radiat Environ Biophys* 48(3): 263-274 (2009).
- S17 Siegfried, T. Odds are, it's wrong: Science fails to face the shortcomings of statistics. *Sci News* 177(7): 26-29 (2010).
- S18 Sigurdson, A.J., M.M. Doody, R.S. Rao et al. Cancer incidence in the US radiologic technologists health study, 1983-1998. *Cancer* 97(12): 3080-3089 (2003).
- S19 Silver, S.R., R.D. Daniels, T.D. Taulbee et al. Differences in mortality by radiation monitoring status in an expanded cohort of Portsmouth Naval Shipyard workers. *J Occup Environ Med* 46(7): 677-690 (2004).
- S20 Simon, S.L., L.R. Anspaugh, F.O. Hoffman et al. 2004 update of dosimetry for the Utah Thyroid Cohort Study. *Radiat Res* 165(2): 208-222 (2006).
- S21 Sinclair, W.K. Experimental RBE values of high LET radiations at low doses and the implications for quality factor assignment. *Radiat Prot Dosim* 13(1-4): 319-326 (1985).
- S22 Slonina, D., K. Spekl, A. Panteleeva et al. Induction of micronuclei in human fibroblasts and keratinocytes by 25 kV x-rays. *Radiat Environ Biophys* 42(1): 55-61 (2003).
- S23 Sokolnikov, M.E., E.S. Gilbert, D.L. Preston et al. Lung, liver and bone cancer mortality in Mayak workers. *Int J Cancer* 123(4): 905-911 (2008).
- S24 Spiegelhalter, D.J., N.G. Best and B.P. Carlin. Bayesian measures of model complexity and fit. *J R Stat Soc Ser B* 64(4): 583-639 (2002).

- S25 Stayner, L., M. Vrijheid, E. Cardis et al. A Monte Carlo maximum likelihood method for estimating uncertainty arising from shared errors in exposures in epidemiological studies of nuclear workers. *Radiat Res* 168(6): 757-763 (2007).
- S26 Steck, D.J., M.C. Alavanja, R.W. Field et al. ²¹⁰Po implanted in glass surfaces by long term exposure to indoor radon. *Health Phys* 83(2): 261-271 (2002).
- S27 Steck, D.J. and R.W. Field. Dosimetric challenges for residential radon epidemiology. *J Toxicol Environ Health A* 69(7): 655-664 (2006).
- S28 Stepanenko, V.F., P.G. Voilleque, Y.I. Gavrilin et al. Estimating individual thyroid doses for a case-control study of childhood thyroid cancer in Bryansk Oblast, Russia. *Radiat Prot Dosim* 108(2): 143-160 (2004).
- S29 Stevens, W., J.E. Till and D.C. Thomas. Assessment of leukemia and thyroid disease in relation to fallout in Utah: Report of a cohort study of thyroid disease and radioactive fallout from the Nevada test site. University of Utah, Salt Lake City, 1992.
- S30 Stram, D.O., B. Langholz and M. Huberman. Measurement error correction of lung cancer risk estimates in the Colorado Plateau cohort. Part I: Dosimetry analysis. Technical Report 126. University of Southern California School of Medicine, 1998.
- S31 Stram, D.O., B. Langholz, M. Huberman et al. Correcting for exposure measurement error in a reanalysis of lung cancer mortality for the Colorado Plateau Uranium Miners cohort. *Health Phys* 77(3): 265-275 (1999).
- S32 Stram, D.O. and K.J. Kopecky. Power and uncertainty analysis of epidemiological studies of radiation-related disease risk in which dose estimates are based on a complex dosimetry system: some observations. *Radiat Res* 160(4): 408-417 (2003).
- S33 Straume, T. and A.L. Carsten. Tritium radiobiology and relative biological effectiveness. *Health Phys* 65(6): 657-672 (1993).
- S34 Suzuki, K., H. Okada, M. Yamauchi et al. Qualitative and quantitative analysis of phosphorylated ATM foci induced by low-dose ionizing radiation. *Radiat Res* 165(5): 499-504 (2006).
- T1 Telle-Lamberton, M., E. Samson, S. Caer et al. External radiation exposure and mortality in a cohort of French nuclear workers. *Occup Environ Med* 64(10): 694-700 (2007).
- T2 Thierry-Chef, I., M. Marshall, J.J. Fix et al. The 15-Country Collaborative Study of Cancer Risk among Radiation Workers in the Nuclear Industry: study of errors in dosimetry. *Radiat Res* 167(4): 380-395 (2007).
- T3 Thomas, D., S. Darby, F. Fagnani et al. Definition and estimation of lifetime detriment from radiation exposures: principles and methods. *Health Phys* 63(3): 259-272 (1992).
- T4 Thompson, D.E., K. Mabuchi, E. Ron et al. Cancer incidence in atomic bomb survivors. Part II: Solid tumors, 1958-1987. *Radiat Res* 137(2 Suppl): S17-S67 (1994).
- T5 Tirmarche, M., D. Laurier and F. Bochicchio. Quantification of cancer and non-cancer risks associated with multiple chronic radiation exposures: Epidemiological studies, organ dose calculation and risk assessment. Final scientific report in the frame of the European project "Alpha Risk". EUR Report 24599, 2010.
- T6 Tosteson, T.D., L.A. Stefanski and D.W. Schafer. A measurement-error model for binary and ordinal regression. *Stat Med* 8(9): 1139-1147; discussion 1149 (1989).

- T7 Trabalka, J.R. and D.C. Kocher. Energy dependence of dose and dose-rate effectiveness factor for low-let radiations: potential importance to estimation of cancer risks and relationship to biological effectiveness. *Health Phys* 93(1): 17-27 (2007).
- T8 Tronko, M.D., G.R. Howe, T.I. Bogdanova et al. A cohort study of thyroid cancer and other thyroid diseases after the chornobyl accident: thyroid cancer in Ukraine detected during first screening. *J Natl Cancer Inst* 98(13): 897-903 (2006).
- T9 Tubiana, M., L.E. Feinendegen, C. Yang et al. The linear no-threshold relationship is inconsistent with radiation biologic and experimental data. *Radiology* 251(1): 13-22 (2009).
- T10 Turner, J.E., H.A. Wright and R.N. Hamm. A Monte Carlo primer for health physicists. *Health Phys* 48(6): 717-733 (1985).
- T11 Turner, M.C., D. Krewski, Y. Chen et al. Radon and lung cancer in the American Cancer Society cohort. *Cancer Epidemiol Biomarkers Prev* 20(3): 438-448 (2011).
- U1 U.S. EPA. Cancer risk coefficients for environmental exposure to radionuclides. EPA 402-R-99-001. U.S. Environmental Protection Agency, Washington D.C., 1999.
- U2 U.S. EPA. Estimating radiogenic cancer risks. Addendum: Uncertainty analysis. EPA Report 402-R-00-003. U.S. Environmental Protection Agency, 1999.
- U3 U.S. EPA. EPA radiogenic cancer risk models and projections for the U.S. population. U.S. Environmental Protection Agency, Washington, D.C., 2011.
- U4 Uehara, Y., Y. Ito, K. Taki et al. Gene expression profiles in mouse liver after long-term low-dose-rate irradiation with gamma rays. *Radiat Res* 174(5): 611-617 (2010).
- U5 University of California and Max Planck Institute for Demographic Research. The human mortality database. Berkeley, USA, 2011.
- U6 UNSCEAR. Sources and Effects of Ionizing Radiation. UNSCEAR 1977 Report. United Nations Scientific Committee on the Effects of Atomic Radiation, 1977 Report to the General Assembly, with annexes. United Nations sales publication E.77.IX.1. United Nations, New York, 1977.
- U7 UNSCEAR. Genetic and Somatic Effects of Ionizing Radiation. UNSCEAR 1986 Report. United Nations Scientific Committee on the Effects of Atomic Radiation, 1986 Report to the General Assembly, with annexes. United Nations sales publication E.86.IX.9. United Nations, New York, 1986.
- U8 UNSCEAR. Sources, Effects and Risks of Ionizing Radiation. UNSCEAR 1988 Report. United Nations Scientific Committee on the Effects of Atomic Radiation, 1988 Report to the General Assembly, with annexes. United Nations sales publication E.88.IX.7. United Nations, New York, 1988.
- U9 UNSCEAR. Sources and Effects of Ionizing Radiation. UNSCEAR 1993 Report. United Nations Scientific Committee on the Effects of Atomic Radiation, 1993 Report to the General Assembly, with scientific annexes. United Nations sales publication E.94.IX.2. United Nations, New York, 1993.
- U10 UNSCEAR. Sources and Effects of Ionizing Radiation. UNSCEAR 1994 Report. United Nations Scientific Committee on the Effects of Atomic Radiation, 1994 Report to the General Assembly, with scientific annexes. United Nations sales publication E.94.IX.11. United Nations, New York, 1994.

- U11 UNSCEAR. Sources and Effects of Ionizing Radiation. Volume II: Effects. UNSCEAR 2000 Report. United Nations Scientific Committee on the Effects of Atomic Radiation, 2000 Report to the General Assembly, with scientific annexes. United Nations sales publication E.00.IX.4. United Nations, New York, 2000.
- U12 UNSCEAR. Effects of Ionizing Radiation. Volume I: Report to the General Assembly, Scientific Annexes A and B. UNSCEAR 2006 Report. United Nations Scientific Committee on the Effects of Atomic Radiation. United Nations sales publication E.08.IX.6. United Nations, New York, 2008.
- U13 UNSCEAR. Effects of Ionizing Radiation. Volume II: Scientific Annexes C, D and E. UNSCEAR 2006 Report. United Nations Scientific Committee on the Effects of Atomic Radiation. United Nations sales publication E.09.IX.5. United Nations, New York, 2009.
- U14 UNSCEAR. Sources and Effects of Ionizing Radiation. Volume II: Effects. Scientific Annexes C, D and E. UNSCEAR 2008 Report. United Nations Scientific Committee on the Effects of Atomic Radiation. United Nations sales publication E.11.IX.3. United Nations, New York, 2011.
- V1 Vasilenko, E.K., V.F. Khokhryakov, S.C. Miller et al. Mayak worker dosimetry study: an overview. *Health Phys* 93(3): 190-206 (2007).
- V2 Verhaegen, F. and A. Vral. Sensitivity of micronucleus induction in human lymphocytes to low-LET radiation qualities: RBE and correlation of RBE and LET. *Radiat Res* 139(2): 208-213 (1994).
- V3 Vrijheid, M., E. Cardis, M. Blettner et al. The 15-Country Collaborative Study of Cancer Risk Among Radiation Workers in the Nuclear Industry: design, epidemiological methods and descriptive results. *Radiat Res* 167(4): 361-379 (2007).
- W1 Walsh, C. and J.P. McLaughlin. Correlation of ²¹⁰Po implanted in glass with radon gas exposure: sensitivity analysis of critical parameters using a Monte-Carlo approach. *Sci Total Environ* 272(1-3): 195-202 (2001).
- W2 Walsh, L. A short review of model selection techniques for radiation epidemiology. *Radiat Environ Biophys* 46(3): 205-213 (2007).
- W3 Walsh, L., P. Jacob and J.C. Kaiser. Radiation risk modeling of thyroid cancer with special emphasis on the Chernobyl epidemiological data. *Radiat Res* 172(4): 509-518 (2009).
- W4 Walsh, L. and J.C. Kaiser. Multi-model inference of adult and childhood leukaemia excess relative risks based on the Japanese A-bomb survivors mortality data (1950-2000). *Radiat Environ Biophys* 50(1): 21-35 (2011).
- W5 Wang, Z., J.H. Lubin, L. Wang et al. Residential radon and lung cancer risk in a high-exposure area of Gansu Province, China. *Am J Epidemiol* 155(6): 554-564 (2002).
- W6 Weinberg, C.R. Potential for bias in epidemiologic studies that rely on glass-based retrospective assessment of radon. *Environ Health Perspect* 103(11): 1042-1046 (1995).
- W7 Weinberg, C.R., E.S. Moledor, D.M. Umbach et al. Imputation for exposure histories with gaps, under an excess relative risk model. *Epidemiology* 7(5): 490-497 (1996).
- W8 WHO. WHO Handbook on indoor radon: A public health perspective (H. Zeeb and F. Shannoun, eds.). World Health Organization, Geneva, 2009.

- W9 Willett, W.C. Nutritional epidemiology. pp.580-597 in: *Modern Epidemiology* (K.J. Rothman et al., eds.). Lippincott Williams & Wilkins, Philadelphia, 2008.
- W10 Wing, S. and D.B. Richardson. Age at exposure to ionising radiation and cancer mortality among Hanford workers: follow up through 1994. *Occup Environ Med* 62(7): 465-472 (2005).
- W11 Wintle, B.A., M.A. McCarthy and C.T. Volinsky. The use of Bayesian model averaging to better represent uncertainty in ecological models. *Conserv Biol* 17(6): 1579-1590 (2003).
- W12 Wykes, S.M., E. Piasentin, M.C. Joiner et al. Low-dose hyper-radiosensitivity is not caused by a failure to recognize DNA double-strand breaks. *Radiat Res* 165(5): 516-524 (2006).
- Y1 Yamada, Y., S. Tokonami and W. Zhuo. Rn-Tn discriminative measurements and their dose estimates in Chinese loess plateau. *International Congress Series* 1276: 76-80 (2005).
- Y2 Yang, Y. Can the strengths of AIC and BIC be shared? A conflict between model identification and regression estimation. *Biometrika* 92(4): 937-950 (2005).
- Y3 Young, S.S. and A. Karr. Deming, data and observational studies. *Significance* 8(3): 116-120 (2011).
- Z1 Zankl, M., N. Petoussi-Hens, U. Fill et al. The application of voxel phantoms to the internal dosimetry of radionuclides. *Radiat Prot Dosim* 105(1-4): 539-548 (2003).
- Z2 Zhang, Z., B. Smith, D.J. Steck et al. Variation in yearly residential radon concentrations in the upper midwest. *Health Phys* 93(4): 288-297 (2007).

GLOSSARY

Abscopal effect: A biological consequence induced by radiation that is observed at a distance from the irradiated tissue (see annex C of [U2]).

Absorbed dose, D: The fundamental dose quantity given by

$$D = \frac{d\bar{\varepsilon}}{dm}$$

where $d\bar{\varepsilon}$ is the mean energy imparted to matter of mass dm by ionizing radiation. The SI unit for absorbed dose is joule per kilogram (J/kg) and its special name is gray (Gy).

Acute exposure: Exposure received within a short time period. (See also: Chronic exposure).

Adaptive response: Refers to the phenomenon by which cells irradiated with a sublethal dose of ionizing radiation (an “adaptive” dose of a few centigrays) become less susceptible to subsequent exposure to high doses of radiation (a “challenge” dose of several grays).

Akaike Information Criterion (AIC): The AIC is a relative measure of goodness of fit taking into account the “likelihood” of the data being observed given an assumed model and number of model parameters. It is a concept derived from information theory, and is defined as $AIC = -2 \ln(L) + 2p$, where $\ln(L)$ is the natural logarithm of the maximized “likelihood” for the model of interest and p is the number of free parameters in the model. For a given set of observed data and two models assumed to explain the observations, the model with the lower AIC is considered to have the higher probability of being correct. See “Bayesian Information Criterion” for an alternative approach to judge the probability of one model being correct over another.

Aleatory uncertainty (Type A uncertainty): Uncertainty due to stochastic variability in observations, measurements, or true values of the quantity of interest. For a cohort of individuals, some portion of the inter-individual variability of true values will be due to stochastic or aleatoric processes. Aleatory uncertainty (i.e. natural or random variability) can be characterized through research, if additional factors and conditions can be identified that explain the observed variability in the quantity of interest.

Assigned share: Assigned share is the probability that an observed health effect in an individual was caused by a specific radiation exposure. It is equal to the fraction of the total number of cases of a specific type of cancer diagnosed among individuals which is in excess to the baseline number of cases for persons who share the same attributes, such as absorbed organ dose, age, time since last exposure, sex, smoking history, etc. The assigned share (AS) is quantified as

$$AS = \frac{\text{excess relative risk}}{\text{relative risk}}$$

The AS is often referred to as the “attributable fraction” or “probability of causation” assuming that the calculated excess relative risk represents the net consequences of mechanisms of disease manifestation for a given individual diagnosed with disease.

Assignment error (“Berkson error”): Assignment error is relevant in situations where the difference (or ratio) of the assigned and true values of quantity of interest (e.g. a radiation dose) is independent of the assigned value. Such errors typically arise as the result of some sort of grouping in which all members of a defined subgroup are assigned a single representative value (e.g. an unbiased expected value of dose for each member of a subgroup, where the subgroup is identified by exposure characteristics, such as age, sex, location, diet, residence history and shielding). A fundamental characteristic of assignment error is that true values vary at random about the assigned value. Thus, the variance of true values will be larger than the variance of assigned values. Furthermore, the assigned value will equal (or closely approximate) the true mean value for the subgroup. In linear regression, the presence of additive assignment error in the independent variable does not lead to bias in the estimate of the regression slope. Assignment error can be contrasted with “measurement error” and “shared error”.

Attribution: The ascribing of an actual or manifest outcome to a cause. In the context of this report, attribution refers to the ascribing of an outcome—in particular a health effect—to radiation exposure.

- (a) An outcome may be an individual outcome (such as the occurrence of a health effect in an individual);
- (b) An outcome may also be a collective outcome (such as a change in the frequency of occurrence of health effects in a population or a group);
- (c) Attribution may require expert assessment (or the consensus of a number of expert assessments), which may be made on the basis of a combination of evidence (facts) and argument (explanation).

Attributability: The ability to attribute a cause to an outcome.

- (a) In the context of this report, attributability refers whether or not a manifest health effect in an individual or a manifest change in frequency of health effects in a population is capable of being ascribed as having being induced by radiation exposure;
- (b) Attributability can be expressed qualitatively as a level of confidence in attribution (such as unequivocally, confidently, reliably, and plausibly), based on evaluation of the type, amount, quality and consistency of evidence, and the degree of scientific consensus.

Attributable fraction (proportion): See “Assigned share”.

Baseline (hazard) rate (frequency): (Age-specific) disease rates for a population of interest in the absence of exposure or at some reference exposure level. See also “Hazard rate (function)” and “Excess (absolute) rate”.

Baseline risk: Baseline risk refers to the probability that an event of interest (e.g. diagnosis of cancer) will occur in an individual among an unexposed population over a given time period (e.g. lifetime following exposure). See “Risk”.

Bayesian inference: The method of inference that quantifies the degree of belief (or the analyst’s state of knowledge) of a true value or sets of values of a quantity of interest by combining their prior knowledge about these quantities with recent measurements, observations, or estimates. The degree of belief of the quantity of interest is often described by a subjective probability distribution representing possibly true values for that quantity. The distribution resulting from Bayesian inference is called a posterior distribution.

Bayesian Information Criterion (BIC): The BIC is a relative measure of goodness of fit taking into account the “deviance” of the observed data from the assumed model and the number of model parameters. The BIC is a measure derived from Bayesian statistics. For a given set of observed data and two assumed models, the model with the lower BIC is considered to have the higher probability of being correct. The BIC is given by the difference between (1) the product of the number of model parameters and the natural logarithm of the sample size, and (2) twice the natural logarithm of the “likelihood”. See “Akaike Information Criterion” for an alternative approach to judge the probability of one model being more correct over another.

Berkson error: See “Assignment error”.

Bias: A statistical estimation procedure is “biased” if the expected value of the estimate of the quantity of interest is not equal to the true value of the quantity. The “bias” of the procedure is the difference between the expected and true values.

Bystander effect: A non-targeted cellular action of radiation exposure meaning that not only the cell that was actually hit shows radiation consequences, but also neighbouring cells (see annex C of [U2]).

Causation: The relationship between cause (here, radiation exposure) and outcome (radiogenic health effect or associated risk). The term can also mean the action of causing something.

Chronic exposure: Exposure persisting in time. (See also: “Acute exposure” and “Protracted exposure”.)

Classical error: Classical error, or more precisely classical measurement error, applies in situations in which the difference between the measured or estimated value and the true value of a quantity of interest (e.g. a radiation dose) is independent of the true value. Classical measurement error is a type of random error; it arises when measured or estimated values of a quantity of interest are determined by imprecise measurements or by estimates of quantities used as independent variables in a regression analysis. A fundamental characteristic of classical measurement error is that the variance of measured or estimated values is larger than the variance of true values. The mean of the measured or estimated values is unbiased with respect to the true mean. In linear regression, the presence of classical measurement error in the independent variable biases the estimate of the regression slope toward zero. Classical measurement error can be contrasted with “assignment error” and with “shared error”.

Confidence interval: In “frequentist inference”, a confidence interval is an interval defined in terms of the sampling distribution of a statistic of interest (i.e. the distribution of estimates of the statistic that would arise from repeated—generally hypothetical—realizations of data generated from the same underlying distribution as the observed data) such that, for example, the probability that a 95% confidence interval for a given parameter contains the true value of that parameter is 0.95. (Compare this with “Credible intervals” used in “Bayesian inference”.)

Confounding factor or confounder: In statistics, a confounding factor is a variable that is correlated with both the dependent variable (e.g. radiation exposure or dose) and the independent (outcome) variable (e.g. risk of lung cancer) and, if not controlled for analytically may distort the conclusions. For example, occupation may be a confounding factor in a study of the relation between lung cancer incidence among non-smokers (dependent variable) and medical radiation exposure (independent variable). For instance, air crew are exposed to higher levels of radiation due to their employment (correlation with independent variable) while staff working in certain recreation industries are often occupationally exposed to cigarette smoke (correlation with dependent variable). This confounding might be controlled by introducing into the analysis an indicator for the occupational group. See also “Effect modification”. A variable may, but need not, be both a confounding factor and an effect

modifier in which case dose–response analyses need to allow for influence of the factor on the outcome of interest and for the interaction between dose and the factor.

Counterfactual analysis: Counterfactual analysis approaches causal hypotheses by considering a (counterfactual conditional) proposition of the form “If *A* had not occurred, would *B* not have occurred (at the same time and nature with which it was observed)?”

Credible interval: This term is used in *Bayesian inference* to refer to an interval defined from the distribution of the degree of belief of the value of the quantity of interest within which a certain probability is assigned (e.g. 90%) representing the assessor’s degree of belief that the true value of a quantity of interest falls within the interval. Credible intervals are sometimes called Bayesian credibility intervals or subjective confidence intervals. The interpretation of credible intervals is subtly different from that of frequentist confidence intervals (see “Confidence interval”).

Deterministic (health) effect: See “Health effects”.

(Radiation) Detriment: The total harm that would eventually be experienced by an exposed group and its descendants as a result of the group’s exposure to radiation from a source [I1].

Deviance: Deviance is a measure of the goodness of fit of a statistical model for a set of data. Deviance was originally defined for the class of generalized linear models (which includes ordinary linear regression, Poisson regression, logistic regression, and many other commonly used models) as a “likelihood ratio test”, which compares a specific fitted model (in which parameters were estimated using maximum likelihood methods) to a “saturated” model in which there is one parameter for each observation. If ℓ_M is the logarithm of the maximum likelihood for the model of interest with p parameters and ℓ_S is the logarithm of the likelihood for the saturated model with n parameters, the deviance is defined as $-2(\ell_M - \ell_S)$ and can, under certain conditions, be treated as the difference between the true value of a quantity of interest and a measurement of that value.

EAR: See “Excess absolute rate/risk”.

Effect modification: Effect modification (also called statistical “interaction”) occurs when the magnitude of the influence of the dependent variable of interest (e.g. radiation dose or exposure) on an independent (outcome) variable (e.g. lung cancer) depends upon the magnitude of some other factor (the effect modifier). For example, analyses of the atomic bombings survivors suggest that the magnitude of the outcome of ionizing radiation exposure on the excess relative risk of lung cancer depends on smoking intensity, with a larger outcome from unit dose among moderate smokers and much smaller outcome among heavy smokers. An effect modifier may or may not be a *confounding factor*, depending on whether or not there is a correlation between the dependent variable of interest and the effect modifying factor.

Epistemic uncertainty (Type B uncertainty): The subjective degree of belief about the true, fixed but unknown value for a given quantity of interest. Epistemic uncertainty for a fixed quantity can be contrasted with aleatory uncertainty (random variability of repeated measurements, observations, or of true values for the individuals within a population of interest). Epistemic uncertainty is often quantified using Bayesian inference. In principle, and in contrast to aleatory uncertainty, epistemic uncertainty can be reduced through research.

ERR: See “Excess relative risk/rate”.

Error: The difference between an observed or estimated value and the true (but unknown) value. Since the true value is unknowable, error cannot be quantified. Error can be contrasted with uncertainty, which can be estimated by repeated measurements or Bayesian inference.

Excess absolute risk/rate (EAR): The difference between the hazard rate in an exposed population and the “baseline rate” in that population. This is often a function of dose, age (or some other measure of time) and other factors (effect modifiers). Excess absolute rate is often called “excess absolute risk” or “excess rate”. Strictly risk would apply to a prospective estimate inferred from the data and reasoning, while rate would be the direct statistic calculated from the data.

Excess relative risk/rate (ERR): The “relative risk/rate” minus one. The excess relative rate is strictly a statistic calculated from observed frequencies/rates, while the excess relative risk is a prospective estimate inferred from the data and reasoning. The ERR is often considered as a function of dose and other factors.

Excess risk/rate: A measure of the statistical relationship between a given risk factor and a specific outcome. Depending on the context it can refer to some characterization of the influence on rates such as the “relative risk”, “excess relative risk”, or “excess (absolute) rate”, or, perhaps most appropriately, to estimates of the risk over some period of time (lifetime risk) associated with an exposure of interest. The excess rate is strictly a statistic calculated from observed frequencies/rates, while the excess risk is a prospective estimate inferred from the observations and reasoning.

Falsifiable: In the context of this annex, falsifiable means being able to be shown to be false (here it does not mean being able to alter information so as to mislead). According to critical rationalism as advanced by Popper and dominating the empirical sciences, only hypotheses that can be falsified with a severe empirical test belong to the field of science proper [P1]. The approach used for testing falsifiable hypotheses is in principle relatively straightforward. A question is formulated and a study is designed to provide an answer. The question is usually framed in the form of a hypothesis, such as “children exposed to low level radiation are more likely to develop cancer than children not exposed”. Most commonly the hypothesis is expressed in the negative (i.e. is falsifiable), such as “children exposed to low level radiation are no more likely to develop cancer than children not exposed”. This is termed the “null hypothesis” and research is conducted to prove that it is wrong (in epidemiological parlance, “to reject the null hypothesis of no effect”). After a hypothesis is developed and a study is designed, data are collected (something is measured or counted) and analysed, and then conclusions are drawn.

Frequency (of occurrence of disease): The number of new cases of the disease under study divided by the number of people in a population over a defined time period.

Frequentist inference: A method of inference in which parameter estimates, hypothesis tests, and confidence intervals for some quantities of interest are based on the chances of obtaining the observed data in repeated (hypothetical) realizations of the data given an assumed state of nature. The main alternative approach to frequentist inference is “Bayesian inference”.

Genomic instability: An all-embracing term to describe the increased rate of acquisition of alterations in the genome. As compared with the direct actions of radiation, i.e. those consequence directly induced by energy deposition, radiation-induced instability is observed in cells at delayed times after irradiation and manifests in the progeny of exposed cells multiple generations after the initial insult.

Hazard rate (function): A hazard rate refers to the limiting probability of occurrence of an event of interest in a short time interval ($t, t + \Delta t$) as the length of the interval approaches 0 given that the event can occur after time t . In radiation risk estimation, t generally refers to age or time since exposure.

Since hazard rates generally vary with time and other factors (e.g. sex or dose), the concept of a hazard function is often used.

Health effects (of radiation) (also radiogenic health effects):

Deterministic (health) effect: A health effect of radiation for which generally a threshold level of dose exists, which varies with person and circumstance, above which the severity of the health effect is greater for a higher dose. The ICRP has introduced a term “tissue reactions” to describe a group of health effects comprising deterministic effects and some health effects (such as cataracts and fibrosis) that are not determined solely at the time of irradiation but can be modified after radiation exposure [I1, I2].

Stochastic (health) effect: A radiation-related health effect, the probability of occurrence of which depends on radiation dose and the severity of which (if it occurs) is independent of dose. In radiation protection the so-called LNT-model is used (linear non-threshold) meaning that the assumption is made that one can linearly extrapolate from moderate/high doses to low and very low doses without a threshold. Note that this should not be confused with the stochastic actions or processes of radiation interaction at the molecular or cellular level.

Inference: The process of drawing conclusions from scientific observations, evidence and reasoning in the presence of uncertainty. While this report is focussed on prospectively inferring risk, note that estimating an assigned share (or probability of causation) is also inference, but retrospective.

Interaction: Refers to the situation in which the magnitude of the influence of one risk factor on disease rates depends upon the magnitude of one or more other risk factors (see “Joint effects”).

Joint effects: Refers to the combined influence of two or more risk factors (e.g. radiation exposure and smoking) on disease rates. Simple common types of joint effects include additive and multiplicative effects. If two risk factors, D and S , are additive, the excess rate $\rho(D)$ associated with factor D does not depend on the excess rate $\psi(S)$ for factor S , and the total rate is $\lambda_0 + \rho(D) + \psi(S)$, where λ_0 is the rate in the absence of exposure (baseline rate). This additive model can also be written in terms of “excess relative risks” as $\lambda_0(1 + \rho'(D) + \psi'(S))$, where $\rho'(D) = \rho(D) / \lambda_0$ and $\psi'(S) = \psi(S) / \lambda_0$ are excess relative risk functions. In the case of a (simple) multiplicative interaction, the magnitude of the excess rate associated with one risk factor depends on the level of the other risk factor; for example, risk is represented by $\lambda_0 + \rho(D) + \psi(S) + \rho(D)\psi(S)$ or, in terms of excess relative risk, risk = $\lambda_0(1 + \rho'(D))(1 + \psi'(S))$. A somewhat more general interaction model can be written (in terms of excess relative risks) as $\lambda_0(1 + \rho'(D) + \psi'(S) + \theta\rho'(D)\psi'(S))$, where θ is a parameter such that the joint effects are additive if $\theta=0$, multiplicative if $\theta=1$, sub-additive if $\theta<0$, sub-multiplicative if $0 < \theta < 1$ and super-multiplicative if $\theta > 1$. More general interactions can also be considered.

Latency (period): The period between exposure and manifestation of a health effect. This is also the period after which statistically significant increases in frequency of occurrence of the health effect in a population have been seen; theoretically, there might be an undetectable increased frequency of occurrence of the health effect in an exposed population during the presumed latency period, but this possibility becomes vanishingly small in the period shortly after exposure because there is a finite time required for damaged cells to replicate in an uncontrolled manner and manifest as a cancerous growth.

LET (linear energy transfer): The average linear rate of energy loss of charged particle radiation in a medium, i.e. the radiation energy lost per unit length of path through a material. That is, the quotient of dE by dl where dE is the mean energy lost by a charged particle owing to collisions with electrons in traversing a distance dl in matter.

$$L = \frac{dE}{dt}$$

The unit of L is J/m, often given in keV/ μ m.

Lifetime risk: An estimate of the risk associated with an exposure of interest over the (remaining) lifetime of an exposed population. Technically, the lifetime risk associated following an exposure to dose D is given by

$$\int_{t_0}^{\infty} h_c(u, D) S(u, D) du$$

where $h_c(u, D)$ is the assumed (hazard) rate for the cause of interest at time u given exposure to dose D and $S(u, D)$ is the probability of still being alive and at risk of having the event at time u given dose D . The excess lifetime risk is defined as

$$\int_{t_0}^{\infty} [h_c(u, D) - h_c(u, 0)] S(u, D) du$$

In the literature on radiogenic health effects and radiation protection, this quantity is often called the REID or REIC (risk of exposure-induced excess deaths or cases). It is sometimes approximated by the (LAR) (lifetime attributable risk), which is defined as

$$\int_{t_0}^{\infty} [h_c(u, D) - h_c(u, 0)] S(u, 0) du$$

or the ELR (excess lifetime risk) which is defined as

$$\int_{t_0}^{\infty} h_c(u, D) S(u, D) du - \int_{t_0}^{\infty} h_c(u, 0) S(u, 0) du$$

If $h_c(u, D) > h_c(u, 0)$, the ELR understates the impact of the exposure because it does not account for deaths (cases) that might occur earlier than they would have in the absence of exposure, while the LAR tends to overestimate the number of exposure-related events at higher doses. By limiting the range of integration in the above expressions, excess risks for periods of interest other than the full lifetime after exposure can be computed.

Likelihood: Generally, the state or fact of being likely or probable. The term may also be used to express a defined statistical concept. Specifically, given a set of data and a statistical model that describes the distribution of the data in terms of some parameters, the statistical concept of “likelihood” is a function of the model parameters that is proportional to the probability density function for the data (given the parameter values). For independent observations, the likelihood of the data is the product of the likelihood values for each observation. Likelihood functions play a central role in both “frequentist inference” and “Bayesian inference” (albeit with different interpretations). Frequentist inference often proceeds by finding parameters that maximize the likelihood given the data (maximum likelihood estimation) and using (asymptotic) properties of the maximized (log-) likelihood as the basis for inference.

Low dose rate: The Committee has defined “low dose rate” as 0.1 mGy per minute, averaged over one hour or less, for radiations such as external X-rays and gamma rays [U1, U3].

Measurement error: The difference between the true value of a quantity of interest and a measurement of that value. Measurement error can be random (see “Assignment error” and “Classical error”) or systematic (see “Shared error”).

Meta-analysis: In statistics, a meta-analysis combines the results of two or more studies that address a set of related research hypotheses, for example by estimating a certain unknown parameter or parametric function common to two or more data sets, while controlling or adjusting for differences in other parameters unrelated to those of immediate interest. The purpose is to obtain an estimate that is more informative than any obtainable from a single study, while ensuring that other data do not corrupt or bias the result. The term “meta-analysis” is also used for statistical pooling of results available in published form, in contrast with a *pooled analysis* of original data from two or more studies.

Model: An analytical or physical representation or quantification of a real system and the ways in which phenomena occur within that system, used to predict or assess the behaviour of the real system under specified (often hypothetical) conditions. This is in contrast to a relationship, which is simply the way two or more factors are connected or related (i.e. relationships include causal relationships, those based on models, and those that simply fit the observed data).

Model uncertainty: The value of a quantity of interest derived from a data set of observations depends in general on the model that has been assumed to analyse the data. The related uncertainty of that value (i.e. the range of values for a quantity of interest that is obtained from analysing the data with different assumed models) is called model uncertainty.

Molecular epidemiology: This epidemiological approach uses the currently available biomarkers (not radiation-specific) combined with classical epidemiological methods. Central to this are the –omics (genomics, transcriptomics, proteomics, metabolomics and others) which allow the detection of individual characteristics on various molecular levels (genes, transcripts, proteins, metabolism and others). The frequency of occurrence of these individual characteristics in exposed populations are then studied using classical epidemiological methods.

Monte Carlo uncertainty propagation: Computation of a probability distribution of an output of a model on the basis of repeated calculations using random sampling of values of uncertain input variables specified as probability distributions. The numerical sampling strategy used may be Simple Random Sampling, or a form of stratified sampling such as Latin Hypercube Sampling.

Multi-model inference: Multi-model inference derives the probability density function of a quantity of interest by accounting for results of more than one model applied to the same set of data.

Norms: A required or acceptable standard.

(a) Internal. Norms from within the scientific community (such as truthfulness, consistency, coherence, testability, reproducibility, validity, reliability, openness, impartiality and transparency).

(b) External. Norms from outside the scientific community that guide and justify scientific activities (such as social responsibility, ethics, utility, prudence, precaution and practicality of application).

Observed value: The often imprecisely determined and possibly biased value of a quantity of interest (e.g. a radiation dose). Observed values may include combinations of various types of classical measurement and assignment error. Errors may be shared between groups of individuals.

Plausible: This relates to an argument or statement that seems reasonable or probable, without it necessarily being so. For the purposes of this annex, the term is used to constrain the number of possibilities to those that currently appear to be supported by sound scientific reasoning, e.g. in the case of health effects and inferred risks, those that can be reasonably supported by arguments based on observed or known radiation action and response in biological systems. Other responses not supported by mechanistic reasoning or other observations may be possible, but without such reasoning are not considered plausible.

Pooled analysis: A combined analysis of original data from two or more data sets bearing on a common question of interest. The analysis may include parameters that distinguish between the different data sets. (Contrast with “*meta-analysis*”.)

Prediction – well-founded and conditional: The conventional meaning relates to foretelling that a specified outcome will occur in the future or will be a consequence of an action, event or set of conditions. In this report, a distinction is made between well-founded prediction and conditional prediction, both being included within the concept of science-based inference. A well-founded prediction is one that is based on a hypothesis that is deemed proven by the application of scientific method; a conditional prediction is one that is based on a hypothesis that is currently not deemed proven, but is based on scientific reasoning including the use of models and assumptions.

Probability density function (pdf): Function that describes the relative probability for a random variable to take on a given value. The probability of a random variable being in a specific range is equal to the integral of the pdf over that range. For discrete distributions the probability function (which gives the probability of the realization of specific values) is the analogue of the pdf.

Protracted exposure: Exposure received over a long time period (compare with “Acute exposure” and “Chronic exposure”).

Quantity of interest: The true but unknown value being estimated, measured, or observed (also known formally as the “measurand”). It can be a single value, such as the dose or risk to a specific individual, or a set of true values, such as the set of doses to each individual in a defined cohort.

Radiogenic health effects: See “Health effects (of radiation)”.

Random error: An error in which the difference between the true value and an estimated value occurs at random. Random error implies the absence of systematic bias in the central or mean value. Random error gives rise to classical measurement errors if each individual’s true dose is estimated using information obtained independently from each individual in a cohort. Random error gives rise to assignment errors when expected values of dose estimates are assigned to every individual having the same exposure characteristics, such as age, gender, occupation, residence history, and diet, and when the assigned dose to an individual is equal to the true mean dose for the exposure subgroup.

Rate: In general, the ratio of two quantities, where the denominator is usually a function of the period of time at risk. Rates of interest in epidemiology (and radiation risk estimation) are of the form $\frac{e}{PY}$, where e is the number of events over some time period of interest in a study population and PY (expressed as person-years) is the sum of time at risk during this time period for each person in the study population. Rates for an event of interest can vary with such factors as age, sex, and dose. Characterization of how rates depend on dose (or exposure) is central to radiation risk estimation. See also “Hazard function”, “Risk”, “Relative risk”, “Excess rate”, and “Relative risk”, and “Excess relative risk”.

RBE: See “Relative biological effectiveness”.

Regression calibration: Usually refers to a method used to adjust quantities measured with (classical) measurement error to reduce the bias in dose–response estimates derived from the estimated doses. More generally, regression calibration involves replacing the estimated dose by its expected value given the estimated dose, and using what is known about the magnitude of the measurement error and the distribution of true doses in the population of interest. As a further generalization, samples from the conditional distribution of dose given the estimated dose, and what is known about the measurement error and the distribution of true doses in the population could be used. In principle, complex (Monte Carlo) simulation systems are intended to provide such sets of dose realizations.

Relationship: The way two or more factors are connected or related (i.e. relationships include causal relationships, those based on models, and those that simply fit the observed data).

Relative biological effectiveness (RBE): For a specified radiation, RBE is the ratio of the (*a*) absorbed dose of a reference radiation required to produce a specific level of a response in a biological system to the (*b*) absorbed dose of the specified radiation required to produce an equal response, with all physical and biological variables, except radiation quality, being held as constant as possible. The reference radiation with a defined RBE of unity normally is gamma rays (often those from ⁶⁰Co) or X-rays (most commonly 180–250 kVp X-rays). RBE generally depends on dose, dose per fraction (if the dose is fractionated), dose rate, and biological end point. Note that RBE is an experimentally determined quantity and is not appropriate for the inference of risk and risk assessment, where a modifying factor that quantifies differences in risk for the same value of dose for a high-energy gamma ray compared with other types of radiation is more appropriate. (See also annex B, paragraphs C51–C58).

Relative risk/rate ratio: The ratio of disease rates in different groups (e.g. an exposed and unexposed group) or for different exposure conditions (e.g. people exposed at high dose rates and people exposed at low dose rates). It is often useful to view the relative risk as a function of variables, such as dose, sex, or age. Note that while this ratio is commonly called a relative risk, this is a misnomer; it is actually a ratio of rates, as are statistics derived from it (such as excess relative risk).

Risk: In the context of (radiation-related) health effects, risk refers to the probability that an event of interest (e.g. onset of cancer) will occur (i.e. it is prospective) during a given time period (e.g. the rest of life following an exposure). Risks can be estimated using evidence from epidemiological investigations of disease rates in previously exposed populations (i.e. based on past observations). The results from such retrospective analyses often are used, with appropriate modifying and adjustment factors, to make inferences about the risk for other exposure situations involving different populations for which direct epidemiological data on the dose–response relationship are not available.

Scientific method: A method of procedure that has characterized natural science since the 17th century, consisting in systematic observation, measurement, and experiment, and the formulation, testing, and modification of hypotheses.

Shared error: An error common to some or all members of a cohort or cohort subgroup. Shared error is a form of systematic error, which influences the direction and magnitude of the difference between the estimated value of the true value of a quantity of interest for individual members of a cohort or cohort subgroup. Uncertainty in the estimate of a true value for a model parameter used to quantify dose to a group of individuals is a common source of shared errors in dosimetry. Being a form of systematic error, shared errors should be distinguished from independent random errors such as “assignment errors” and “classical errors”. This distinction is especially important when estimates of the dose to an individual dose are used in an analysis of the dose–response relationship.

Stochastic (health) effect: See “Health effects”.

Systematic error: A systematic error affects bias in a group of measurements or in estimates of a quantity of interest. This bias will be in a given direction, but may apply to varying degrees for different cohort subgroups. As mentioned above, systematic error is related to “Shared error”.

Tissue reaction: See “Health effects”

True dose: The true but unknown value of dose for a specific individual. The state of knowledge about this unknown true value can be characterized by measurements and estimates that produce a distribution representing state of knowledge about possibly true values. In an epidemiological cohort, there will be a unique set of unknown true doses.

Type A uncertainty: Stochastic variability of true values of the quantity of interest (see aleatory uncertainty). Type A uncertainty as used in this report differs from “Type A evaluation of uncertainty” as defined in metrology. In metrology, “Type A evaluation of uncertainty” applies to situations in which statistical methods are used to address random variability of repeated measurements or observations to evaluate the uncertainty in a quantity of interest for which there is a single true but unknown value.

Type B uncertainty: Uncertainty about a true but unknown fixed value for a quantity of interest (see epistemic uncertainty). In the absence of data obtained from an appropriate experimental design, the estimation of Type B uncertainty relies on subjective approaches and Bayesian inference to characterize the state of knowledge about this true value. This state of knowledge or degree of belief is typically represented as a subjective probability distribution of possibly true values for the quantity of interest. Type B uncertainty in parameters of a model used to estimate dose to groups of individuals in a cohort is a source of shared errors. This shared error can result in systematic bias in the dose estimate because only one value for the parameter can be the true value and this true value could be substantially higher or lower than the central estimate of the unknown true value. Type B uncertainty as used in this report differs from “Type B evaluation of uncertainty” which, in metrology, applies to situations in which methods other than statistical are used to characterize uncertainty in a quantity of interest. In this report, both statistical and non-statistical methods can be used to characterize uncertainty about true fixed values for a quantity of interest.

Uncertainty: Expression of having doubt, or being unsure about study results, hypotheses, model-based estimations or results of measurements, and specifically the true value of a quantity of interest. This may be due to lack of complete knowledge about true values for an individual or to a lack of complete knowledge of factors explaining the inter-individual variability of true values in a defined subgroup or population. Unlike error, uncertainties can be quantified. Estimates of uncertainty represent the amount or percentage by which an observed or calculated value might differ from its true value. For a quantity of interest that has a true fixed value, uncertainty is defined here as a degree of belief probability distribution comprising many realizations of possibly true values. For a quantity of interest that is a group or population of true values, uncertainty can be characterized as many alternative realizations of sets of true values.

Uncertainty propagation: A method used to evaluate the uncertainty in the result of a calculation resulting from uncertainty in all inputs to the calculation. Uncertainty propagation can be carried out (a) using a closed-form algebraic solution if uncertainties are described as means, variances, or ranges in inputs to simple equations, or (b) by numerical methods with the aid of a computer. The most common method for evaluating the uncertainty in estimates made using complex models is Monte Carlo uncertainty propagation.

Unshared errors: Errors that are independent among individual members of a cohort. “Random aleatory uncertainty” is often considered a source of unshared error, when measurements are specific to an individual. “Classical errors” and “assignment errors” are considered sources of unshared errors.

Variability: Heterogeneity, diversity or a range which characterizes variation in estimated, measured, or true values of a quantity of interest. The term variability is often used to describe differences in measured or true values among individuals in a population or cohort. Examples include inter-individual differences in body weight and/or dose or inter-cohort differences in exposure–response due to differences in sensitivity to a hazardous agent. Further study cannot reduce variability, but may provide additional information to explain reasons why some of this variability occurs. This additional information can reduce the fraction of inter-individual variability initially treated as stochastic.

REFERENCES

- I1 ICRP. The 2007 Recommendations of the International Commission on Radiological Protection. ICRP Publication 103. Annals of the ICRP 37(2-4): International Commission on Radiological Protection, Elsevier Ltd., 2007.
- I2 ICRP. ICRP statement on tissue reactions / Early and late effects of radiation in normal tissues and organs – Threshold doses for tissue reactions in a radiation protection context. ICRP Publication 118. Annals of the ICRP 41(1-2): International Commission on Radiological Protection, Elsevier Ltd., 2012.
- P1 Popper, K.R. The Logic of Scientific Discovery. Basic Books, New York, 1959.
- U1 UNSCEAR. Sources and Effects of Ionizing Radiation. UNSCEAR 1993 Report. United Nations Scientific Committee on the Effects of Atomic Radiation, 1993 Report to the General Assembly, with scientific annexes. United Nations sales publication E.94.IX.2. United Nations, New York, 1993.
- U2 UNSCEAR. Effects of Ionizing Radiation. Volume II: Scientific Annexes C, D and E. UNSCEAR 2006 Report. United Nations Scientific Committee on the Effects of Atomic Radiation. United Nations sales publication E.09.IX.5. United Nations, New York, 2009.
- U3 UNSCEAR. Report of the United Nations Scientific Committee on the Effects of Atomic Radiation 2010. Fifty-seventh session, includes Scientific Report: Summary of low-dose radiation effects on health. UNSCEAR 2010 Report. United Nations Scientific Committee on the Effects of Atomic Radiation. United Nations sales publication M.II.IX.4. United Nations, New York, 2011.

This publication contains:

REPORT OF THE UNITED NATIONS SCIENTIFIC COMMITTEE ON THE EFFECTS
OF ATOMIC RADIATION TO THE GENERAL ASSEMBLY

Scientific Annexes

Annex A. Attributing health effects to ionizing radiation exposure and inferring risks

Annex B. Uncertainties in risk estimates for radiation-induced cancer



EVALUATING RADIATION SCIENCE FOR INFORMED DECISION-MAKING

In 1955 the United Nations General Assembly established the Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) in response to concerns about the effects of ionizing radiation on human health and the environment. At that time fallout from atmospheric nuclear weapons tests was reaching people through air, water and food. UNSCEAR was to collect and evaluate information on the levels and effects of ionizing radiation. Its first reports laid the scientific grounds on which the Partial Test Ban Treaty prohibiting atmospheric nuclear weapons testing was negotiated in 1963.

Over the decades, UNSCEAR has evolved to become the world authority on the global level and effects of atomic radiation. UNSCEAR's independent and objective evaluation of the science are to provide for—but not address—informed policymaking and decision-making related to radiation risks and protection.

