

SOURCES, EFFECTS AND RISKS OF IONIZING RADIATION

UNSCEAR **2019 Report**

Report to the General Assembly

SCIENTIFIC ANNEXES A and B



UNITED NATIONS

SOURCES, EFFECTS AND RISKS OF IONIZING RADIATION

United Nations Scientific Committee on the
Effects of Atomic Radiation

UNSCEAR 2019
Report to the General Assembly,
with Scientific Annexes



UNITED NATIONS
New York, 2020

NOTE

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

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Chapter I

Introduction

1. Since the establishment of the United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) 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 Scientific Committee thoroughly reviews and evaluates global and regional exposures to radiation. The Committee also evaluates evidence of radiation-induced health effects in exposed groups and 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, workers and patients against ionizing radiation;² those standards, in turn, are linked to important legal and regulatory instruments.

2. Exposure to ionizing radiation arises from naturally occurring sources (such as radiation from outer space and radon gas emanating from rocks in the Earth) and from sources with an artificial origin (such as medical diagnostic and therapeutic procedures; radioactive material resulting from nuclear weapons testing; energy generation, including by means of nuclear power; unplanned events such as the nuclear power plant accidents at Chernobyl in April 1986 and that following the great east-Japan earthquake and tsunami of March 2011; and workplaces where there may be increased exposure to artificial or naturally occurring 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. The terms of reference of the Committee are set out in resolution 913 (X). The Scientific 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 Scientific 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 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 radiation protection and safety of radiation sources, currently co-sponsored by the European Commission, the Food and Agriculture Organization of the United Nations (FAO), the International Atomic Energy Agency (IAEA), the International Labour Organization (ILO), the Nuclear Energy Agency of the Organization for Economic Cooperation and Development (OECD), the Pan American Health Organization, the United Nations Environment Programme (UNEP) and the World Health Organization (WHO).

Chapter II

Deliberations of the United Nations Scientific Committee on the Effects of Atomic Radiation at its sixty-sixth session

3. The Scientific Committee held its sixty-sixth session in Vienna from 10 to 14 June 2019.³ The Committee elected as officers of the Committee for its sixty-sixth and sixty-seventh sessions: Gillian Hirth (Australia) as Chair; Jing Chen (Canada), Anna Friedl (Germany) and Jin Kyung Lee (Republic of Korea) as Vice-Chairs; and Ingemar Lund (Sweden) as Rapporteur.

4. The Scientific Committee took note of and discussed General Assembly resolution [73/261](#) on the effects of atomic radiation, in which the Assembly, inter alia: (a) noted with concern the developments which resulted in the request by the Scientific Committee at its sixty-fifth session to the Office of Internal Oversight Services to conduct (i) an investigation or inspection into the process to recruit the Scientific Secretary to ensure that the successful candidate is selected on the basis of scientific qualifications and credibility and that the process is aligned with Article 101, paragraph 3, of the Charter of the United Nations; and (ii) an internal audit or evaluation to clarify whether the United Nations Environment Programme (UNEP) is the most appropriate body to serve the Committee in the future; (b) requested UNEP to continue, within existing resources, to service the Committee and to disseminate its findings to Member States, the scientific community and the public and to ensure that the administrative measures in place are appropriate, including clear roles to efficiently service the Committee in a predictable and sustainable manner and effectively facilitate the use of the invaluable expertise offered to the Committee by its members in order that the Committee may discharge the responsibilities and mandate entrusted to it by the General Assembly; (c) regretted that the UNEP secretariat had not appointed a new Secretary of the Committee in a timely manner, thereby jeopardizing continuity in the Committee secretariat, and insisted that all steps be taken to ensure such continuity and that any ongoing selection process is expedited and managed in a transparent manner; (d) requested the Secretary-General to strengthen support for the Committee within existing resources, particularly with regard to the deputization of the Secretary of the Committee, the avoidance of disruptions in staffing and the increase to operational costs in the case of a further increase in membership, and to report to the General Assembly at its seventy-fourth session on those issues; and (e) adopted a procedure for possible further increases in the membership of the Committee.

5. In regard to point (c), the Scientific Committee welcomed the new Secretary, Borislava Batandjjeva-Metcalf, who was appointed by UNEP at the end of 2018 and commenced work in the role of Secretary on 16 April 2019. In regard to point (e), the Committee also welcomed the new and transparent procedure for the possible future increase in membership of the Committee.

6. In regard to points (a), (b), (c) and (d), the representative of Belgium made a statement about the negative impact of the delay in the appointment of a new Secretary, noting that there were a number of lessons to be learned to ensure that history did not repeat itself. The statement was supported by the representatives of Argentina, Germany and Poland. The representative of UNEP responded to the statement. Lessons learned, issues raised and the response by UNEP are reported in chapter II, section E, “Administrative issues”.

³ The sixty-sixth session of the Scientific Committee was attended by observers from Algeria, Iran (Islamic Republic of), Norway and the United Arab Emirates, in accordance with General Assembly, resolution [73/261](#), para. 20, and observers for the UNEP, the International Agency for Research on Cancer, IAEA, ILO, WHO, the European Union, the International Commission on Radiation Units and Measurements and FAO.

A. Completed evaluations

7. The Scientific Committee discussed two substantive evaluations in detail, adopted the scientific reports on the basis of the findings of those evaluations (see chapter III) and requested that the scientific annexes be published in the usual manner, subject to the agreed modifications.

8. The Scientific Committee decided at its sixty-third session that it was essential to have an expert estimation of the knowledge of risk based on published studies for five combinations of health effects and conditions of exposures to ionizing radiation: (a) leukaemia incidence after computed tomography (CT) scans in childhood; (b) leukaemia mortality after occupational exposure; (c) mortality from all solid cancers after occupational exposure; (d) thyroid cancer incidence after ^{131}I intake during childhood; and (e) cardiovascular disease mortality after exposure to external radiation. The objective was to perform quantitative risk evaluations of health effects in specific exposure situations with low-to-moderate doses for cancer and in situations with higher doses for circulatory diseases, taking into account various sources of uncertainty of risk estimation. At its sixty-sixth session, the Committee discussed and approved for publication the scientific annex on the evaluation of selected health effects and inference of risk due to radiation exposure.

9. At its sixty-third session, during deliberations on its future programme of work, the Scientific Committee recalled that it had previously assessed the effects of exposure to radon in homes and workplaces in annex E to the UNSCEAR 2006 report,⁴ in which it reiterated its assessment that inhalation of radon and its decay products was carcinogenic for the lungs. The Committee also noted that since that last comprehensive evaluation, there had been many new scientific publications concerning the issue and agreed to thoroughly re-assess the literature with a view to clarifying and assessing recent developments in risk estimates for lung cancer from exposure to radon.

10. The Scientific Committee agreed to conduct an evaluation on lung cancer from exposure to radon with the objective of addressing the following questions: (a) What is the current status of evidence and confidence regarding increased frequency of lung cancer for smokers and non-smokers, and for subgroups differentiated by age and sex, due to exposure to radon and thoron? (b) What are the associated uncertainties by assigning a dose to a given incorporation of radioactivity of radon (^{222}Rn) and thoron (^{220}Rn) in order to estimate health effects and risks or by estimating possible health effects attributable to radon and thoron exposure directly from epidemiological evidence? and (c) What dose conversion factors are to be used by the Committee in its future assessments of global exposure to radon (^{222}Rn) and thoron (^{220}Rn) in workplaces and homes? At its sixty-sixth session, the Committee discussed and approved for publication the scientific annex on lung cancer from exposure to radon.

B. Present programme of work

1. Biological mechanisms relevant for the inference of cancer risks from low-dose radiation

11. At its sixty-third session, the Scientific Committee decided to compile an up-to-date overview of current knowledge about the biological mechanisms by which radiation influences the development of disease, in particular at low incremental doses and dose rates; the implications for the dose-response relationships for health effects at low doses; and thus the relevance for estimating associated risks to health as well as the relevance for the inference of cancer risks. An expert group was established

⁴ *Effects of Ionizing Radiation: United Nations Scientific Committee on the Effects of Atomic Radiation 2006 Report to the General Assembly*, vol. II (United Nations publication, Sales No. E.09.IX.5), annex E (“Sources-to-effects assessment for radon in homes and workplaces”).

that submitted progress reports to the Committee for consideration at its sixty-fourth, sixty-fifth and sixty-sixth sessions.

12. At its sixty-sixth session, the Scientific Committee discussed the draft manuscript prepared by the expert group, which had conducted substantial scientific literature searches and assessed the literature against an evaluation system based on annex A to the UNSCEAR 2017 report.⁵ The Committee considered the preparation of similar quality guidelines for the review of publications on biological mechanisms related to addressing the mechanisms of radiation effects.

13. The Scientific Committee's report will address mechanisms of radiation actions and biological reactions relevant for the inference of cancer risk after low-dose exposure. Given the well-advanced status of the draft report, the Committee expects to be able to consider a mature draft with a view to approval at its sixty-seventh session.

2. Assessments of human exposure to ionizing radiation

14. The Scientific Committee took note of the progress report by the secretariat on the collection, analysis and dissemination of data on radiation exposures of the public, patients and workers, obtained from reviews of the scientific literature and the data submissions by Member States. The Committee recognized the efforts of the secretariat in: (a) conducting outreach about the global surveys, which has contributed to an increased number of nominations of national contact persons; and (b) fostering the production of a simplified questionnaire to assist in the preparation of data submissions, which has had a positive impact on the number of submissions. As at 30 April 2019, 87 countries had nominated national contact persons (compared with 74 in 2018). Although this is a significant increase in participation, more contributions would be useful in view of the fact that there are 193 States Members of the United Nations. The Committee has therefore extended its deadline for data submission until 30 September 2019.

15. The Scientific Committee expressed its continued support for the creation of a network of national contact persons, using the UNSCEAR online platform as a tool for communication among them for exchanging experiences on the process of data collection. It also encouraged States Members of the United Nations to provide data on medical, occupational and public exposure and encouraged continued future cooperation of the Committee's secretariat with States Members of the United Nations and relevant international organizations.

(a) Medical exposure to ionizing radiation

16. Given that radiation exposures of patients worldwide are the main artificial source of human exposure to ionizing radiation, that there has been a continuing upward trend in collective doses to populations, and that the pace of technological development in this field continues to accelerate, the Scientific Committee's regular evaluations of collective doses to populations and trends continue to be an important priority.

17. As at 30 April 2019, 53 countries had submitted data on medical exposures, and the Scientific Committee recognized the efforts of the expert group in carefully and systematically reviewing the submitted data and working with national contact persons to clarify any ambiguities. As a number of Member States notified the Committee that they had additional or updated data, the Committee decided to extend the deadline for data collection until 30 September 2019 to accommodate them. The Committee also asked the secretariat to continue its outreach to national contact persons, especially in low- and middle-income countries, during this period to encourage further submissions.

⁵ *Sources, Effects and Risks of Ionizing Radiation: United Nations Scientific Committee on the Effects of Atomic Radiation 2017 Report to the General Assembly* (United Nations publication, Sales No. E.18.IX.1), annex A ("Principles and criteria for ensuring the quality of the Committee's reviews of epidemiological studies of radiation exposure").

18. The Scientific Committee provided guidance to the expert group on a number of technical and editorial issues and noted the importance of completing the analysis of the data in order to have the technical document submitted for approval at its sixty-seventh session.

(b) Occupational exposure to ionizing radiation

19. The Scientific Committee's evaluations of worldwide occupational exposure to ionizing radiation provide information relevant for policy and decision-making regarding the use and management of radiation. The resulting dose distributions and trends give insight into the main sources and situations of exposure and provide information about the main factors influencing exposures. The evaluations assist in identifying emerging issues and may indicate situations that should be subjected to more attention and scrutiny.

20. The Scientific Committee has conducted evaluations of worldwide occupational exposure and trends on the basis of two sources: (a) data from the UNSCEAR Global Survey of Occupational Radiation Exposures; and (b) reviews of analyses conducted and published by others. With respect to the first source, by 30 April 2019, 50 countries (compared with 39 in 2018) had submitted data for occupational exposures. With respect to the second source, a systematic review of more than 700 articles identified about 300 as applicable to the evaluation. Because a number of Member States notified the Committee that they had additional or updated data, the Committee decided to extend the deadline for data collection until 30 September 2019 to accommodate them.

21. The Scientific Committee acknowledged the efforts of the expert group in conducting its systematic review of the literature and provided guidance to the group on a number of technical and editorial issues. The Committee noted the importance of completing the analysis of the data in order to have the technical document submitted for approval at its sixty-seventh session.

(c) Public exposure to ionizing radiation

22. The Scientific Committee recalled the sixty-fourth session, at which the proposal to evaluate public exposure to ionizing radiation had been discussed. The Committee decided at that time to postpone project initiation until its evaluation on lung cancer from exposure to radon had been completed. At its sixty-sixth session, the Committee decided to commence its evaluation of public exposure to ionizing radiation.

23. The exposure of the public to artificial sources in the environment (including potential accidents) are of considerable interest to Governments and civil society. The most significant database in this regard is the database on Discharges of Radionuclides to the Atmosphere and the Aquatic Environment (DIRATA), developed by the International Atomic Energy Agency (IAEA).⁶ With regard to any future assessment of public exposure from discharges, the Scientific Committee noted that the secretariat held preliminary discussions with IAEA to explore methods of updating and using the datasets for its evaluation of public exposure to ionizing radiation.

(d) Levels and effects of radiation exposure due to the accident at the Fukushima Daiichi nuclear power station: implications of information published since the UNSCEAR 2013 report

24. At its sixty-fifth session, the Scientific Committee considered the project plan to produce an update to annex A to the UNSCEAR 2013 report.⁷ The aim was to

⁶ See <https://dirata.iaea.org>. The database includes information on atmospheric and aquatic discharges of radionuclides from nuclear and non-nuclear facilities, where available, and has interfaces for the entry, editing, interrogation and reporting of data.

⁷ *Sources, Effects and Risks of Ionizing Radiation: United Nations Scientific Committee on the Effects of Atomic Radiation 2013 Report to the General Assembly*, vol. I (United Nations publication, Sales No. E.14.IX.1), annex A ("Levels and effects of radiation exposure due to the nuclear accident after the 2011 Great East Japan Earthquake and tsunami").

produce a report setting out a summary of all information available, up to the end of 2019, on levels and effects of radiation exposure due to the accident at the Fukushima Daiichi nuclear power station, and the implications of the new information for the UNSCEAR 2013 Fukushima report.

25. At its sixty-sixth session, the Scientific Committee discussed the draft document prepared by the expert group. The Committee endorsed the more focused scope of the detailed analyses of doses to the public and concurred that the outreach material on issues of considerable media or public interest should be dealt with separately, as part of the secretariat's outreach plan. The Committee expected that the technical document would be submitted to the Committee at its sixty-seventh session with a view to its approval.

3. Second primary cancer after radiotherapy

26. At its sixty-third session, the Scientific Committee considered the issue of second primary cancer after radiotherapy and discussed preliminary plans to launch a project based on a proposal by the French delegation. After further discussions at the sixty-fourth session, the Committee reached agreement at its sixty-fifth session on a project plan to evaluate second primary cancer after radiotherapy, emphasizing that while the project was a priority, the work could not be started until after the appointment of the new Secretary.

27. At its sixty-sixth session, the Scientific Committee took note of a progress report on the project. That report included an update on the actions taken by the secretariat to establish an expert group that will commence work in the third quarter of 2019. The evaluation will summarize the current state of knowledge regarding second primary cancer frequency and risk, considering out-of-field dosimetry and epidemiological findings, as well as genomic and molecular sciences. The final report will also include a summary written in language that should be understood by members of the public. In the first year, the group will begin to review the literature, applying the principles and quality criteria for epidemiological studies as published in annex A to the UNSCEAR 2017 report and the literature review process established by the secretariat. The expert group will provide a progress report, including a first selection of literature evaluated on second primary cancer after radiotherapy, an updated timetable and an advanced table of contents, for discussion by the Committee at its sixty-seventh session.

4. Epidemiological studies of radiation and cancer

28. At its sixty-third session, the Scientific Committee discussed a preliminary plan to provide a comprehensive scientific review of epidemiological studies of radiation and cancer to update annex A to the UNSCEAR 2006 report.⁸ The Committee agreed at its sixty-fifth session to initiate the comprehensive scientific review after both the appointment of the new Secretary and the initiation of the project on second primary cancer after radiotherapy.

29. At its sixty-sixth session, the Scientific Committee approved the project, the results of which will provide experts, decision makers, the scientific community, civil society and national and international organizations with up-to-date scientific information on cancer risk following exposure to ionizing radiation. It will also provide a sound basis for informed decision-making on radiation-related issues. The final report will also include a summary written in language that should be understood by members of the public.

30. The expert group will commence work in the third quarter of 2019. The group will begin to review the literature, applying the principles and quality criteria for epidemiological studies as published in annex A to the UNSCEAR 2017 report and

⁸ *Effects of Ionizing Radiation: United Nations Scientific Committee on the Effects of Atomic Radiation 2006 Report to the General Assembly*, vol. I (United Nations publication, Sales No. E.08.IX.6), annex A ("Epidemiological studies of radiation and cancer").

the literature review process established by the secretariat. The expert group will provide a progress report, including a first selection of literature evaluated on epidemiological studies on radiation and cancer, an updated timetable and an advanced table of contents, for discussion by the Scientific Committee at its sixty-seventh session.

5. Public information and outreach strategy (2020–2024)

31. At its sixty-sixth session, the Scientific Committee took note of a progress report of the secretariat on the implementation of outreach activities in the 2014–2019 period and endorsed the secretariat's proposal for a new strategy on outreach activities for the 2020–2024 period. The latter complements the secretariat's planned outreach activities on the update of annex A to UNSCEAR 2013 report on the levels and effects of radiation exposure due to the accident at the Fukushima Daiichi nuclear power station.

32. The Scientific Committee welcomed the online publication of the updated UNEP booklet *Radiation: Effects and Sources* (which is intended as information for the public) in all the official languages of the United Nations, and in five other languages as well. It encouraged the secretariat to further translate and promote the publication.

33. The Scientific Committee noted that the General Assembly encouraged the secretariat to continue to disseminate its findings and reports to the public. The Committee suggested that future work should be focused on the development of information material based on published UNSCEAR reports and should address specific topics, such as exposure due to radon or the follow-up of the radiological consequences of the Chernobyl accident. The Committee encouraged the secretariat to further enhance the UNSCEAR website. The Committee noted that the dissemination of the Committee's findings and further enhancements to the UNSCEAR website would depend on the financial and human resources made available to the secretariat.

C. Update on the Committee's long-term strategic directions

34. The Scientific Committee recalled that at its sixty-third session, it had considered its long-term strategic directions beyond the period covered by its present strategic plan (2014–2019) and had envisaged directing its future work in specific scientific areas. It also recalled the possible need to implement a range of strategies that would support its efforts to serve the scientific community as well as wider audiences. Those strategies were foreseen to include:

(a) Establishing working groups focused on sources and exposure, or effects and mechanisms;

(b) Increasing the Scientific Committee's efforts to present its evaluations, and summaries thereof, in a manner that attracts readers without compromising scientific rigour and integrity;

(c) Liaising closely with other relevant international bodies to avoid duplication of efforts to the extent possible, while maintaining its lead in providing authoritative scientific evaluations to the General Assembly.

35. At its sixty-sixth session, the Scientific Committee reviewed and updated the terms of reference of its Bureau and its long-term strategic directions to reflect (a) the establishment of the ad hoc working group on sources and exposure and (b) the prolongation of the activities of the ad hoc working group on effects and mechanisms until its sixty-seventh session in 2020.

(a) Establishing working groups focused on areas of sources and exposure, and effects and mechanisms

36. At its sixty-fifth session, the Scientific Committee endorsed the establishment of an ad hoc working group on effects and mechanisms as a trial to assist the Bureau in developing a future programme of work on mechanisms and effects of radiation exposure for 2020–2024 by providing recommendations based on their scientific insights in the Committee’s priority areas. The working group successfully prepared the proposal for the future programme of work of the Committee (2020–2024), which was discussed by the Committee at its sixty-sixth session. The Committee also decided to extend the mandate of the working group for another year to support the Bureau in following up developments in science and new information relevant to the implementation of the Committee’s programme of work.

37. At its sixty-sixth session, the Scientific Committee also endorsed the establishment of a second ad hoc working group on sources and exposure following the experience of the ad hoc working group on effects and mechanisms. The working group will consist of individual expert scientists selected for their competence, commitment and objectivity.

38. The Scientific Committee emphasized that, except for the administrative support from the secretariat, the establishment of the ad hoc working groups and their methods of work will be provided cost-free to the United Nations.

(b) Inviting, on an ad hoc basis, scientists from other States Members of the United Nations to participate in evaluations regarding the above areas

39. The Scientific Committee noted that the secretariat and the Bureau had taken steps to involve scientists from other States Members of the United Nations in supporting the secretariat in conducting ongoing evaluations. The Committee noted the support of Norway in the preparation of the report entitled “Lung cancer from exposure to radon”, approved by the Committee at its sixty-sixth session.

(c) Increasing the Committee’s efforts to present its evaluations, and summaries thereof, in a manner that attracts readers without compromising scientific rigour and integrity

40. The Scientific Committee referred to the outreach activities reported under section B.5 above.

(d) While maintaining its lead in providing authoritative scientific evaluations to the General Assembly, liaising closely with other relevant international bodies to avoid duplication of efforts

41. The importance of the Scientific Committee’s findings in providing the scientific evidence upon which decisions are made by the international community and safety standards developed was also demonstrated in the period since the sixty-fifth session. For example, the UNSCEAR 2012 report was considered by the IAEA Commission on Safety Standards to determine its possible impact on radiation protection standards. In addition, the preparation of the upcoming report of the Secretary-General highlighted the importance of the Committee’s scientific evaluation for the Inter-Agency Task Force on Chernobyl.⁹

42. The Scientific Committee welcomed and supported the continued future cooperation of the secretariat with United Nations and other international organizations¹⁰ with a view to promoting the Committee’s work and exploring

⁹ See <http://chernobyl.undp.org/english/partners.shtml>.

¹⁰ For example, UNEP, IAEA, the Nuclear Energy Agency of OECD, the Inter-Agency Committee on Radiation Safety, the International Radiation Protection Association, the International Commission on Radiological Protection and International Commission on Radiation Units and Measurements.

synergies and joint activities that will contribute to that work and support the collection and analysis of scientific data.

D. Future programme of work

43. At its sixty-fifth session, the Scientific Committee established the ad hoc working group on effects and mechanisms. Since the sixty-fifth session, the ad hoc working group has collected and analysed the experience of and lessons learned by the Committee in recent years and developed a draft programme of work for the 2020–2024 period that was presented to the Committee at its sixty-sixth session. The ad hoc working group also supported the Bureau in further developing the project proposals on (a) second primary cancer after radiotherapy and (b) epidemiological studies of radiation and cancer.

44. During its sixty-sixth session, the Scientific Committee considered a draft programme of work for the 2020–2024 period and agreed that very high priority should be given to starting a study on diseases of the circulatory system. The Committee discussed several other high-priority topics, and reached agreement on priorities to be considered in the future, subject to the completion of ongoing projects and further literature reviews. With regard to the topic of acute radiation sickness directly attributable to high radiation exposure and the possible long-term consequences, the Committee requested that the scope of the topic be reviewed and expanded. Further updates by the ad hoc working group on those topics will be considered during the sixty-seventh session.

45. The Scientific Committee also acknowledged the proposals for development of an UNSCEAR glossary in the future. It emphasized that the programme implementation depended on available resources in the secretariat and asked the Secretary to consider how the secretariat would implement the future programme of work.

E. Administrative issues

46. The Scientific Committee took note of General Assembly resolution [73/261](#) on the effects of atomic radiation, in which the Assembly:

(a) Noted with concern the developments which resulted in the request by the Scientific Committee at its sixty-fifth session to the Office of Internal Oversight Services to conduct: (i) an investigation or inspection into the process to recruit the Scientific Secretary to ensure that the successful candidate is selected on the basis of scientific qualifications and credibility and that the process is aligned with Article 101, paragraph 3, of the Charter of the United Nations; and (ii) an internal audit or evaluation to clarify whether UNEP is the most appropriate body to serve the Committee in the future;

(b) Requested UNEP to continue, within existing resources, to service the Committee and to disseminate its findings to Member States, the scientific community and the public and to ensure that the administrative measures in place are appropriate, including clear roles to efficiently service the Committee in a predictable and sustainable manner and effectively facilitate the use of the invaluable expertise offered to the Committee by its members in order that the Committee may discharge the responsibilities and mandate entrusted to it by the General Assembly;

(c) Regretted that the UNEP secretariat had not appointed a new Secretary of the Committee in a timely manner, thereby jeopardizing continuity in the Committee secretariat, and insists that all steps to be taken to ensure such continuity and that any ongoing selection process is expedited and managed in a transparent manner;

(d) Requested the Secretary-General to strengthen support for the Committee within existing resources, particularly with regard to the deputization of the Secretary of the Committee, the avoidance of disruptions in staffing and the increase to

operational costs in the case of a further increase in membership, and to report to the General Assembly at its seventy-fourth session on these issues.

47. In considering the requests of the General Assembly, the Scientific Committee recalled the negative impact that the delay in the Secretary's recruitment had had on the Committee's work and recalled that the Committee had requested the United Nations Office of Internal Oversight Services in New York to investigate the recruitment procedure and whether UNEP was the most appropriate body to serve the Committee in the future. The Committee noted that the investigation of the recruitment was in the past and that, with the appointment of the new Secretary, it had an opportunity to make a fresh start. The Committee welcomed the upgrading of the post of Scientific Officer to Deputy Secretary.

48. The Scientific Committee noted that it was important to learn from the lessons of the previous few years and to make every effort not to repeat such situations in future. In particular, the Committee must be more involved in the appointment of a new Secretary and should be fully involved in the evaluation of the written assessments in order to be sure that the candidate has the scientific expertise required of the role of Secretary. The Committee also noted that there should be a timely closure of the process. In this context, it was noted that the Committee had been without a Secretary for more than one year, which had caused serious problems, and that better administrative support should be provided by UNEP to cover management agreements, administrative procedures and channels of communication. If these had been in place, the previous problems would have been less serious.

49. The Scientific Committee noted the statement by the representative of UNEP, who recalled the substance of resolution [73/261](#) as set out in paragraph 46 (b)–(d) above, noting that UNEP had engaged with the Chair of the Committee through the three rounds of recruitment and that the United Nations rules and procedures had been followed, with a focus on gender balance. The Committee welcomed the assurance of UNEP that the new post of Deputy Secretary would soon be announced and that the Programme was ready to support the Committee and the secretariat with a number of activities, such as the collection of data by taking over the DIRATA database from IAEA in the coming months and outreach activities.

50. The Scientific Committee agreed to hold its sixty-seventh session in Vienna from 13 to 17 July 2020.

Chapter III

Scientific reports

51. Two scientific annexes, on the evaluation of selected health effects and inference of risk due to radiation exposure and on lung cancer from exposure to radon, provide the rationale for the findings expressed below. The Scientific Committee discussed the use of “effective dose” for the purpose of its scientific evaluations.

52. The Scientific Committee noted that in 1982 it had informed the General Assembly that its reporting would differ from previous reports in one important aspect: instead of estimating the absorbed doses to only a limited number of important tissues, the Committee would combine the doses in all organs and tissues in an expression of dose called the “effective dose equivalent”, which the Committee believed to better represent the whole risk incurred by the exposed populations.¹¹ The effective dose equivalent (now known as “effective dose”) is a quantity that was introduced by the International Commission on Radiological Protection for radiation protection purposes and is used worldwide in radiation protection standards. The Committee intends to reconsider the appropriateness of continuing employing this quantity for discharging its own functions while it also uses the concept of “absorbed dose”.

A. Evaluation of selected health effects and inference of risk due to radiation exposure

53. Following on from the UNSCEAR 2012 report, annex B,¹² the Scientific Committee more thoroughly addressed the various sources of uncertainty involved in risk estimation for specific scenarios with exposure to ionizing radiation. The scenarios were chosen to be relevant for present-day exposure situations of different exposed groups and ages, and to represent, as far as possible, the conditions of recent large epidemiological studies. The estimation of risk was based on rates of disease that have been observed in the past.

54. The Scientific Committee decided at its sixty-third session that it would be essential to have an expert estimation of the knowledge of risk based on published studies for five combinations of health effects and conditions of exposures to ionizing radiation: (a) leukaemia incidence after CT scans in childhood; (b) leukaemia mortality after occupational exposure; (c) mortality from all solid cancers after occupational exposure; (d) thyroid cancer incidence after ¹³¹I intake during childhood; and (e) cardiovascular disease mortality after exposure to external radiation. The objective was to perform quantitative risk evaluations of health effects in specific exposure situations with low-to-moderate doses for cancer and in situations with higher doses for circulatory diseases.

55. At its sixty-sixth session, the Scientific Committee reviewed and approved the annex on evaluation of selected health effects and inference of risk due to radiation exposure. The Committee concluded the following:

(a) In annex B to the UNSCEAR 2012 report, the Committee addressed more thoroughly the various sources of uncertainty involved in the estimation of risk for specific scenarios with exposure to ionizing radiation. The scenarios were chosen to be relevant for present-day exposure situations of different exposed groups and ages, and to correspond as far as possible to the conditions of recent large epidemiological studies. The estimation of risk was based on rates of disease that have been observed

¹¹ See *Official Records of the General Assembly, Thirty-seventh Session. Supplement No. 45* (A/37/45).

¹² *Sources, Effects and Risks of Ionizing Radiation: United Nations Scientific Committee on the Effects of Atomic Radiation 2012 Report to the General Assembly* (United Nations publication, Sales No. E.16.IX.1), annex B (“Uncertainties in risk estimates for radiation-induced cancer”).

in the past. 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). As an example, for the leukaemia scenarios different ages were selected for exposure and follow-up. The scenario for children starts with exposure at age 1, and a 30-year follow-up selected, as that is the time span for which there is sufficient information to calculate credible intervals. In the scenario for adults, as a result of similar restrictions in available data, follow-up of the exposure starts at age 30 and ends at age 60;

(b) The Committee calculated risks with two approaches for the combinations of cancer risk. The first was based on the recent epidemiological study that was simulated by the scenario, the other on effects observed in the life span study of survivors of the atomic bombings of Hiroshima and Nagasaki. All known sources of uncertainties were discussed. Confidence intervals were calculated, disregarding those sources of uncertainties for which there was not sufficient information for a rigorous quantification. Conclusions were derived for two different conditions. First, for conditions for which there is a wealth of information, the results of the two approaches agree well, confirming that effects observed in the life span study may be transferred to other situations. However, for these specific conditions the recent epidemiological studies have a higher precision and reliability. Second, for other conditions the information content of the recent studies was limited. Dependencies of radiation-related effects on age at exposure, dose and period of follow-up could not be quantified. The life span study remains a main source of information. It has to be kept in mind, however, that the scientific basis for estimating uncertainties involved in the transfer of the effect observed in the study to other populations is limited;

(c) The Committee judged the size of all known sources of uncertainty in the estimation of health risks for conditions for which there is a wealth of information in recent studies. Some parameters, for example the development of disease rates in the future, are not known. In order to allow predictions to be made, assumptions were nevertheless made for those parameters. A Monte Carlo method to estimate the impact of the known uncertainties was used to establish a credible interval of the “preferred risk inference”,¹³

(d) For the assessment of radiation risk of leukaemia and myelodysplastic syndromes in children and young adults, baseline incidence rates were assumed to be the same as in the United Kingdom of Great Britain and Northern Ireland during the period 2011–2013. CT scans at age 1, with a total absorbed dose to the red bone marrow of 20 mGy, were estimated to increase the baseline of 9 cases among 10,000 persons up to age 30 by about 5 cases with a 95 per cent credible interval from 0 to 20 cases. Observations in the life span study indicate that the risk of radiation-induced cases is (a) small beyond the attained age of 30; and (b) for age at exposure of 10 smaller than for age at exposure of 1 by a factor of about 5;

(e) In the assessment of radiation-induced leukaemia mortality among occupationally exposed workers, survival functions (the probability that a person will be alive after any specified time t) were assumed to be the same as in the United States of America in 2000, and baseline rates of mortality from leukaemia as those in the data from the Surveillance, Epidemiology and End Results programme of the National Cancer Institute for the period 2000–2005. For occupational exposures to external radiation at age 30 to 45 with a total absorbed dose to the red bone marrow of 200 mGy, the increase of the baseline of about 10 mortalities from leukaemia excluding chronic lymphocytic leukaemia¹⁴ among 10,000 workers up to age 60 was estimated to be about 5 cases per 10,000 workers, with a 95 per cent credible interval from 1 to 10 mortalities. However, the baseline mortality from leukaemia increases

¹³ The preferred risk inference is the one that best fits the characteristics of the considered scenario, based on an expert judgement on the magnitude of all the uncertainties associated with it.

¹⁴ Chronic lymphocytic leukaemia is generally considered to be a non-radiogenic form of cancer.

steeply after the age of 60, and radiation-induced mortality is expected to increase, although the relative risk decreases with age;

(f) For the assessment of solid cancer, mortality data were taken from the same sources as for leukaemia. Occupational exposures to external radiation at age 30 to 45 with a total absorbed dose to the colon of 100 mGy were estimated to increase the baseline of about 230 mortalities from solid cancer among 10,000 workers up to age 60 by about 10 cases with a 95 per cent credible interval from 2 to 20 cases. The span of the credible interval by a factor of about 10 confirms an earlier estimation of the Committee in annex B to the UNSCEAR 2012 report. Confidence and trust in the range, however, had increased considerably by the time of the present study. As in the case of leukaemia, the baseline mortality from solid cancer increases steeply after the age of 60, and also radiation-induced mortality is expected to increase, although the relative risk decreases with age;

(g) Thyroid cancer after incorporation of ^{131}I may be influenced by factors like the amount of stable iodine present in drinking water. Nevertheless, in order to make an assessment of the risk, the Committee assumed those factors to be the same as in the Ukrainian-American study that was used to define the scenario. An intake of ^{131}I at age 10 with a total absorbed dose to the thyroid of 500 mGy was estimated to increase the baseline of about 3 cases per 10,000 persons by about 8 cases with a 95 per cent credible interval from 2 to 20 cases. For age at intake of 1, the number of radiation-related cases is assessed to be higher by a factor of about 2. Thyroid surveillance plays an important role in the number of detected thyroid cancer, and care has to be taken in transferring observations from a study to other populations;

(h) After exposures resulting in an absorbed dose below 1 Gy, much less is known about radiation-risks for cardiovascular diseases, as compared with cancer. Thus, the Committee used observations in the life span study to estimate risk in a scenario of a Japanese population exposed at age 30 to external radiation with an absorbed dose to the colon of 1.5 Gy. In addition to about 930 baseline mortalities per 10,000 persons from heart diseases up to age 90, the Committee assessed about 160 radiation-induced cases per 10,000 persons with a confidence interval from 30 to 300 cases. The Committee did not have enough information to judge the credible intervals that would have to take into account all known sources of uncertainty. The uncertainty of cerebrovascular mortality risk was even greater. These results are in line with the conclusions drawn in annex B to the UNSCEAR 2006 report;¹⁵

(i) Although much is known about radiation risks, considerable uncertainty remains regarding their quantification. In order to reduce that uncertainty, it is important to improve and continue epidemiological studies of health effects from exposures to ionizing radiation and to develop methods to quantify and combine the various sources of uncertainties.

B. Lung cancer from exposure to radon

56. At its sixty-sixth session, the Scientific Committee approved a document summarizing the findings of its scientific evaluation of lung cancer from exposure to radon and its decision regarding the dose conversion factor for radon exposure. The following was concluded:

(a) The Committee considered the issue of sources and effects of exposure to radon (^{222}Rn) and its progeny as well as thoron¹⁶ (^{220}Rn) with regard to workers and the public and confirmed its previous conclusions that inhalation of radon and its

¹⁵ *Effects of Ionizing Radiation: United Nations Scientific Committee on the Effects of Atomic Radiation 2006 Report to the General Assembly*, vol. I (United Nations publication, Sales No. E.08.IX.6), annex B ("Epidemiological evaluation of cardiovascular disease and other non-cancer diseases following radiation exposure").

¹⁶ As thoron (^{220}Rn) dosimetry studies are limited and the absence of thoron epidemiological studies, the evaluation covered the dose conversion factor for radon (^{222}Rn) exposure.

decay products is carcinogenic mainly for the lungs and that doses to other organs and tissues were at least an order of magnitude smaller than the doses to the lungs;

(b) The Committee acknowledged in its previous evaluations that conversion factors for calculating the dose from a given exposure to radon (^{222}Rn) were needed for the following:

- (i) For radiation protection purposes, which is in the mandate of other international bodies;
- (ii) For comparison purposes with other sources of radiation exposure, which is related directly to the mandate of the Committee;

(c) Two approaches for deriving radon dose conversion factors are in use to express effects from exposure to radon. These are a “dosimetric approach”, estimating the dose from a given exposure based on atmospheric conditions, breathing characteristics and lung modelling relevant for radon and its decay products; and an “epidemiological approach”, based on using the ratio of the risk of lung cancer per unit radon exposure studied mostly in miners and the nominal risk related to effective dose of all cancers derived mostly from survivors of the atomic bombings;

(d) The Committee reviewed recent published dosimetry assessments for exposures in homes, indoor workplaces and mines and found for exposures in homes the range of the assessed effective doses per unit of exposure of equilibrium equivalent concentration (EEC) of ^{222}Rn are from 7 to 34 nSv per (h Bq m⁻³) with an arithmetic mean of 18 nSv per (h Bq m⁻³), and a geometric mean of 16 nSv per (h Bq m⁻³). These values are consistent with those previously estimated by the Committee for average indoor conditions on the basis of dosimetric evaluations;

(e) The Committee also reviewed articles reporting on epidemiological studies (residential and occupational) of lung cancer risk from radon exposure published since 2006. For the residential studies, the excess relative risk estimates for lung cancer varied from -0.13 to 0.73 per 100 Bq m⁻³ for exposure to radon gas, with the mean excess relative risk of 0.13 per 100 Bq m⁻³;

(f) Occupational studies of miners published since 2006 were based mainly on extended follow-up of earlier cohort studies. Substantial variability in the excess relative risk estimates for lung cancer was observed in the updated occupational studies, with values ranging from 0.19 to 3.4 per 100 working level month (WLM),¹⁷ without adjustment for modifying factors. Based on a statistical weighting procedure,¹⁸ the combined excess relative risk estimated from the entire cohorts was 0.60 (95 per cent CI: 0.34, 0.87) per 100 WLM, in close agreement with the Committee’s previous combined estimate of 0.59 (95 per cent CI: 0.35, 1.0) per 100 WLM in annex E to the UNSCEAR 2006 report. A higher combined excess relative risk estimate of 1.53 (95 per cent CI: 1.11, 1.94) per 100 WLM was obtained when restricting the analysis to more recent work periods and lower exposures. Preference was given to the latter estimate due to improved radon exposure assessments in more recent periods and to these radon exposures being more reflective of current mining conditions. However, this estimate is less precise due to smaller sample sizes;

(g) Residential and occupational risk estimates can be compared in a simple manner by converting a residential radon concentration to a cumulative exposure. The Committee’s current estimate of lung cancer excess relative risk for residences of 0.16 per 100 Bq m⁻³, adjusted for exposure uncertainty, can thus be expressed as 1.21 (95 per cent CI: 0.38, 2.35) per 100 WLM, an estimate which is between the previously stated combined risk estimate of 0.60 for the entire miner cohorts and 1.53 for combined subcohorts for more recent work periods. The risk of lung cancer

¹⁷ A working level month refers to the exposure to one working level for 170 hours per month. A working level is the concentration of short-lived decay products of radon in equilibrium with 3,700 Bq/m³ (100 pCi/L) in air.

¹⁸ A random-effects meta-analysis with inverse-variance weighting.

from exposure to radon is not expected to be the same for residents and miners because of the different conditions under which they are exposed;

(h) A notable limitation of the combined estimates is that they ignore the modifying factors of exposure rate and attained age across studies, which reduce the comparability of individual results. In studies that did report on modifying factors, the lung cancer excess relative risk was observed to decrease with increasing attained age, with increasing time since exposure and with increasing exposure rate, albeit only for cumulative exposures above 50 to 100 WLM. Gender could not be investigated in the occupational studies as a modifying factor. It was concluded that models that included modifying factors were preferred for better comparability across studies and improved risk transfer to specific combinations of such factors;

(i) Lifetime risk was estimated by applying the BEIR VI¹⁹ exposure-age-concentration model to selected Czech,²⁰ Wismut²¹ and Eldorado²² miner studies, where information was available, and the combined 11 miner studies used in the BEIR VI report. The estimates of lifetime excess absolute risk were 2.4 per 10,000 persons per WLM for the newly published large Wismut study, 3.9 for the updated Czech study and 7.5 for the updated Eldorado study. For the BEIR VI studies, the estimated lifetime excess absolute risk was 5.5 per 10,000 persons per WLM. The totality of this evidence is compatible with the Committee's previous assessment of lung cancer risk due to radon;

(j) Analyses of miner studies show largely a sub-multiplicative joint effect of radon and smoking on lung cancer risk. An assumption of synergistic effect of smoking and radon would mean that the lifetime absolute risk from radon would depend on the prevalence of smoking in the population: when the prevalence decreases, the risk decreases;

(k) Even though extensive research has been conducted on dosimetric and epidemiological evaluations, uncertainties remain large. The main uncertainties in the assessment of dose by using the dosimetric approach are due primarily to the uncertainty and variability of model parameter values and uncertainties associated with the assumptions built into the particular model, including over-simplification of the underlying processes. Both the miner studies and the residential studies of lung cancer risk from radon are subject to limitations arising mainly from uncertainties in estimates of radon exposure, particularly in early mining periods, and subject to confounding by other exposures, such as smoking. Limitations in evaluation of differences in risk across subgroups of the population include low precision due to small numbers of lung cancer cases among non-smokers, women and younger age groups. As outlined in the UNSCEAR 2012 report, annex B, on uncertainties in risk estimates for radiation-induced cancer, uncertainties are likely to underestimate excess relative risk estimates in studies of residential radon by 50 to 100 per cent. Since thoron and its decay products can be a significant component of the total exposure in some specific situations (workplaces or dwellings), it can be an additional source of error in radon studies that do not distinguish radon and thoron contributions

¹⁹ National Research Council, Committee on Health Risks of Exposure to Radon, *Health Effects of Exposure to Radon*, BEIR Series, No. VI (Washington, D.C., National Academies Press, 1999).

²⁰ Based on a database established in 1969 with approximately 100,000 Czechoslovak uranium miners, the Czech cohort includes approximately 10,000 miners (4,364 miners first employed underground since 1948 for at least four years, and 5,625 miners first employed since 1969 for at least one year). The last report included 1,141 lung cancers observed in the cohort by 2010.

²¹ The German Wismut cohort includes approximately 59,000 miners employed for at least six months between 1946 and 1989 at the Wismut uranium mining company in the former German Democratic Republic. The latest available information included 3,942 lung cancers observed in the cohort by 2013.

²² The Canadian Eldorado cohort includes approximately 17,600 workers employed at the Beaverlodge mine between 1948 and the final shutdown of the mine in 1982, at the Port Radium uranium mine between 1942 and 1960, and at the Port Hope radium and uranium refining and processing between 1932 and 1980. The available information included 618 lung cancers observed in the cohort by 1999.

to the total exposure. Thoron contamination in radon measurements could have an impact on the assessment of lung cancer risk following radon exposure;

(l) Given that the uncertainties from both dosimetric and epidemiological studies give rise to a broad range of risk estimates and the fact that values from the current dosimetry and epidemiological reviews are consistent with those used in previous UNSCEAR reports, the Committee recommends the continued use of the dose conversion factor of 9 nSv per (h Bq m⁻³) EEC of ²²²Rn, which corresponds to 1.6 mSv (mJ h m⁻³)⁻¹ for estimating radon exposure levels to a population;

(m) The evidence reviewed by the Committee is compatible with the available data in the Committee's previous assessment of lung cancer risk due to radon. Therefore, it is concluded that there is no reason to change the established dose conversion factor. The Committee will continue its general review of population exposure to radon, with a focus on the consequent risk of lung cancer.

Appendix I

Members of national delegations attending the sixty-third to sixty-sixth sessions of the United Nations Scientific Committee on the Effects of Atomic Radiation in the preparation of its scientific reports for 2019

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China	S. Liu (Representative), Z. Pan (Representative), L. Chen, L. Dong, T. Fang, D. Huang, Z. Lei, Y. Li, X. Lin, J. Liu, L. Liu, S. Liu, J. Mao, S. Pan, Q. Sun, X. Xia, M. Xu, S. Xu, D. Yang, F. Yang, H. Yang, X. Wu, G. Zhou, P. Zhou
Egypt	M.A.M. Gomaa (Representative), W. M. Badawy (Representative), T. M. Morsi
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Indonesia	N.R. Hidayati (Representative), Z. Alatas (Representative), E. Hiswara (Representative)
Japan	M. Akashi (Representative), Y. Yonekura (Representative), K. Akahane, S. Akiba, H. Fujita, R. Kanda, I. Kawaguchi, K. Kodama, M. Kowatari, K. Ozasa, S. Saigusa, K. Sakai, K. Tani, H. Yasuda, S. Yoshinaga
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Pakistan	R. A. Khan (Representative), Z. A. Baig (Representative)
Peru	A. Lachos Dávila (Representative), B. García Gutiérrez
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Appendix II

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J. Chen	K. Furukawa
C. Kaiser	D. Laurier
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B. Smith	L. Tomášek

Members of the Committee's ad hoc working group on the effects of radiation exposure and the biological mechanisms by which they occur established at the sixty-fifth session

P. Jacob, Chair (Germany)	A. Auvinen, Rapporteur (Finland)
J. R. Jourdain (France)	L. Lebaron-Jacobs (France)
K. Ozasa (Japan)	K. M. Seong (Republic of Korea)
A. Akleev (Russian Federation)	S. Bouffler (United Kingdom)
D. Pawel (United States)	

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

- B. Batandjieva-Metcalf (sixty-sixth session)
- M. J. Crick (sixty-third and sixty-fourth sessions)
- F. Shannoun (sixty-third to sixty-sixth sessions)

ANNEX A

EVALUATION OF SELECTED HEALTH EFFECTS AND INFERENCE OF RISK DUE TO RADIATION EXPOSURE

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I. INTRODUCTION

1. The United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) in its UNSCEAR 2012 Report, annex B summarized the current methodologies to estimate uncertainties in risk estimates for radiation-induced cancer [U8]. A key outcome was realizing the need to go beyond purely statistical uncertainties and to consider, as far as possible, other sources of uncertainty,¹ e.g. those due to dose estimates, or choice of model* for analysing epidemiological data.

2. The Committee agreed at its sixty-second session (1–5 June 2015) to conduct initial feasibility work on a proposal to perform evaluations of selected health effects and inferences of risk from exposure to ionizing radiation. The risk evaluations for the present report were carried out according to three criteria:

- (a) Importance for decisions involving the safe use of ionizing radiation or addressing public controversy;
- (b) Availability of a sufficient amount of information to allow a meaningful assessment of uncertainties;
- (c) Existence of one or more recent epidemiological studies related to the topic of the risk evaluation.

3. Risk evaluations that meet these criteria fulfil an important part of the mandate of the Committee, which is to assess and report levels and effects of exposure to ionizing radiation. Evaluations of key health risks from low-dose and low-dose-rate exposures, such as those caused by the accident at the Fukushima Daiichi nuclear power station, are of particular interest. The present state of knowledge of these health risks after such exposures is limited. Great care has to be taken in extrapolating health effects from acute-, moderate- or high-dose exposures to health risks from low-dose and low-dose-rate exposures.

4. The aim of the present annex was not to perform an exhaustive review of the literature about risks at low doses and dose rates, nor to perform a meta-analysis* or a combined analysis of results available for specific health risks at low doses, but rather to identify the most pertinent information to assess risks for key health risks in specific situations of exposure to ionizing radiation.

5. This annex provides evaluations of those health effects that meet the three criteria mentioned above, with a view to quantifying the risks of those effects at lower doses and dose rates than was possible before. The quantitative risk evaluations of these selected health effects are based on specific situations involving low to moderate doses for which meaningful assessments of the uncertainties in the risk estimates can be made. Low and moderate doses are defined as about 10 to about 100 mGy and as about 100 mGy to about 1 Gy, respectively [U8]. The Committee expects that the results will improve the application of risk models to other exposure situations.

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

6. The global approach used can be broken down into five main steps with some interrelation between steps 1 and 2:

- *Step 1*: Definition of specific scenarios and the motivation behind their choice;
- *Step 2*: Literature search for information to enable the calculation of cumulative excess risk;
- *Step 3*: Calculation of cumulative excess risk for each scenario and comparison with the risk derived from the Life Span Study (LSS) applied to the scenario (“risk transfer”);
- *Step 4*: Discussion of further uncertainties;
- *Step 5*: Identification of the preferred risk inference, which is the one that best fits the characteristics of the considered scenario, based on an expert judgement on the magnitude of all the uncertainties associated with it.

1. Step 1: Definition of specific scenarios and the motivation behind their choice

7. Five specific scenarios have been elaborated, corresponding to realistic situations of exposure to radiation, for which enough information is currently available to allow quantitative assessments of radiation risk to be made:

- (a) Risk of leukaemia after low-dose exposure during childhood with a total absorbed dose* to the red bone marrow (RBM) of 20 mGy.² Recent results from relevant epidemiological studies have been reviewed. A scenario has been elaborated to reflect possible exposure to repeated computed tomography (CT) scans during childhood;
- (b) Risk of leukaemia after a moderate dose (200 mGy to the RBM) during adulthood with special emphasis on possible differences between acute* and protracted exposure* and on transfer of risk estimates to other populations. Recent results from relevant epidemiological studies have been reviewed. A scenario has been elaborated to reflect possible prolonged occupational exposure of a population of workers in the nuclear industry;
- (c) Risk of solid cancer after a dose at the borderline of low to moderate doses (100 mGy) to the whole-body during adulthood with special emphasis on possible differences between acute and protracted exposure and on transfer of risk estimates to other populations. Recent results from relevant epidemiological studies have been reviewed. A scenario has been elaborated to reflect possible prolonged occupational exposure of a population of workers in the nuclear industry;
- (d) Risk of thyroid cancer after exposure to a moderate dose (500 mGy) to the thyroid during childhood and adolescence. New studies of the impact of ultrasonography screenings and dose uncertainties in the dose response were considered. Other focuses are on the dependence on time since exposure by considering studies of thyroid cancer after exposure due to radioiodine released by the Chernobyl accident and among the Japanese atomic bombing survivors, and on the transfer of risk estimates among different populations;
- (e) Risk of circulatory disease after acute whole-body exposure (1.5 Gy) was estimated. New studies of the atomic bombing survivors were considered and risks of different disease types

² If not stated otherwise absorbed doses refer to low-LET radiation.

(cerebrovascular diseases and heart diseases) were considered. A focus was on the form of the dose–response relationships.* To mitigate various concerns arising in assessments of the risk of circulatory disease, the risks estimated from the LSS at a relatively high dose (1.5 Gy low-linear energy transfer (LET)* radiation) were applied to the entire population in Japan, rather than transferring those risks to another population with different characteristics.

2. Step 2: Literature search for information to enable the calculation of cumulative excess risk

8. The aim of the present annex was not to perform an exhaustive review of the literature, but just to identify the main epidemiological studies able to provide the needed information and risk models for the elaboration of the scenarios and the calculation of cumulative excess risk.

9. For each of the five scenarios, a comprehensive literature review was performed in PubMed to identify articles providing information on the quantification of risk for the selected health effect, and for the specific situation of exposure considered. Those publications were reviewed that appeared after the most recent UNSCEAR publication on the specific topic (leukaemia, solid cancer, thyroid cancer, circulatory diseases). Any articles published after June 2017 were only considered if they were crucial for the conclusions of this annex. The sections dealing with the review of the literature are limited to those studies presenting original epidemiological results with quantitative dose–risk relationships pertinent to the selected health effects and the specific exposure situation. As a minimum requirement, only those publications that mentioned a dose–risk coefficient (relative risk, excess relative risk* or excess absolute risk* per unit dose) were included.

10. The reviews of epidemiological studies were conducted according to the UNSCEAR 2017 Report, annex A [U10]. Further, as there has been a special emphasis on low-dose-rate studies in annex B of the UNSCEAR 2017 Report [U10], only key publications on this topic were included in this annex. Biological aspects were not addressed in this annex as the Committee is preparing a separate annex on “Biological mechanisms relevant for the inference of cancer risks from low-dose radiation”.

3. Step 3: Calculation of cumulative excess risk for each scenario and comparison with the risk derived from the Life Span Study applied to the scenario (“risk transfer”)

11. For each of the five scenarios, calculation of cumulative excess risk was performed using risk models derived from a study based on the same population as considered in the scenario. A parallel calculation of cumulative excess risk was performed using risk models derived from the LSS, so that a comparison of the results could be made.

12. The details of the scenario (reference rates, age at exposure, age at the end of follow-up, sex, etc.) were defined based on the study providing the risk model. Expressions like “exposure at age 1” mean that the exposure took place in the year before the first birthday. Similarly, “up to age 30” means up to the 30th birthday.

13. The indicators of health risk used in this annex are defined as follows:

- *Cumulative baseline risk (CBR)*, which is the cumulative baseline risk* of a specific disease (incidence or mortality) occurring up to a given age in the absence of the particular exposure under consideration [W6];

- *Cumulative excess risk (CER)*, which specifies the cumulative risk of a specific disease (incidence or mortality) occurring up to a given age, attributable to a given dose; excess is understood in comparison to a population group not exposed to radiation;
- *Cumulative fractional risk (CFR)*, which reflects the relative increase in the cumulative excess risk (CER) in relation to the cumulative baseline risk (CBR) given by the ratio CER/CBR;
- *Survival fraction*, which is the fraction of a population that is still alive at a given time point (here age).

14. To calculate the CER, the methodology of risk of exposure-induced death/risk of exposure-induced cases (REID/REIC) was used. The REID/REIC gives an estimate of the probability that an individual will die from (or be diagnosed with) a specific disease associated with the exposure [T7]. The Committee has usually used it as a measure of lifetime risk. However, in this annex, the REID/REIC has also been used as an indicator of cumulative risk up to a given age at the end of follow-up (varying from 30 to 90 years according to the scenario).

15. Both additive transfer of risk estimates (based on the transfer of the excess absolute risk (EAR)) and multiplicative transfer (based on the transfer of the excess relative risk (ERR)) were used to calculate the CER for each scenario. The additive transfer assumes that the excess risk of a cancer is given directly by the EAR model, thus the baseline rates* of cancer for the population are not included in the calculation. A multiplicative transfer of risk assumes that the excess risk of a cancer due to exposure to radiation is proportional to the baseline rate of that cancer in the population and is obtained by multiplying the baseline rate by the ERR model for the dose of interest. Differences between risks inferred by the additive and multiplicative transfers provide an indication of the magnitude of uncertainty in the transfer of radiation effects in an epidemiological study to risk estimates in a population of interest.

16. Estimated CERs are associated with 95% confidence intervals* (95% CI). Confidence intervals were calculated using Monte Carlo uncertainty propagation.* In this annex, the term “credible intervals”* was developed to account for the impact of sources of uncertainties that required quantification by use of professional judgement. The term “credible interval” is frequently thought to be used in the context of a Bayesian approach only. However, this is not the case, because the definition is much broader. The credible interval refers 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. 95%) representing the assessor’s degree of belief that the true value of a quantity of interest falls within the interval. Credible intervals were calculated as described in appendix A. Latency period* (lag time, the minimum time between exposure and occurrence of an excess risk in an exposed population) was modelled using different methods according to the scenario.

4. Step 4: Discussion of further uncertainties

17. Seven major sources of uncertainties were considered systematically for each of the scenarios, as determined in annex A of the UNSCEAR 2017 Report [U10]:

- (a) *Selected populations*: A clear definition of the criteria used to select the study population (inclusion and exclusion criteria) is needed. Also detailed description of the source population characteristics should be available: in particular, age, sex, start of exposure, duration of follow-up, percentage lost to follow-up. Data to assess the possibility of a selection bias* should be available;

(b) *Exposure assessment*: The determination of radiation dose for epidemiological studies is notoriously difficult to do. The uncertainty depends on the quality of the methods used to estimate individual exposures, and on assumptions needed to estimate the doses. The nature, type and magnitude of measurement errors can play a role on the potential impact of these uncertainties on the estimated dose–risk relationship. Other points that may need to be considered, when discussing uncertainties in radiation exposure, include the possibility of other sources of radiation exposure, the quality of the radiation, consideration of possible internal exposures, and the distribution of dose within the body;

(c) *Health outcome assessment*: Problems may arise because of diagnostic errors, so that wrong diseases are reported to registries or are mentioned in death certificates. Another potentially serious problem is related to modifications of the International Statistical Classification of Diseases and Related Health Problems (ICD) over the course of time;

(d) *Study design*: Each epidemiological design has inherent limitations. There are always crucial questions to be answered: Was there any potential design specific bias* in the considered studies? Was the follow-up reasonably complete? Was follow-up related to exposure or outcome? Were the comparison groups appropriate?

(e) *Confounding factors*:* Confounding occurs when a third factor is associated both with the exposure under study and the health outcome of interest and is not on the causal pathway between exposure and effect. It can lead to bias in the results pertaining to the exposure–disease association. Among others, smoking, alcohol or chemicals (like benzene) are potential confounders for the effect of radiation exposure on cancer risk. Again, important questions have to be addressed: Were all important confounders assessed in the study? Were other carcinogens considered that can be associated with radiation exposure? Since all factors influencing cancer risk are not known, unknown confounding factors need to be borne in mind, although the potential effect of these cannot be quantified;

(f) *Statistical methods and model uncertainties*: Many uncertainties can be linked to the risk models, including the shape of the dose–risk relationship, the quantification of modifying effects (such as sex, age, time since exposure and duration of radiation exposure for chronic exposures*) and the determination of the latency period between exposure and effect. Usually, several options for risk models exist, and it may be difficult to decide which provides the best description of the situation. Using the wrong model may result in serious misjudgements. One way out of this problem is to use the technique of multi-model inference* that has been proposed to account for model uncertainty.* Another main element is the transfer of risk between populations. Two populations can differ substantially with respect to specific characteristics that are relevant for the expression of cancer risk and are difficult to account for, for example, ethnicity, social status, industrialization, and background cancer spectrum. Therefore, the determination of the transfer of risk, additive (using an EAR model) or multiplicative (using an ERR model) can have an important impact on the estimated cumulative risk;

(g) *Other sources of uncertainty*: Incidence or mortality baseline rates of specific diseases are essential for the estimation of the respective cumulative excess risks. Baseline rates, especially baseline rates of cancer have been collected for many modern populations and they are usually based on large numbers of cases, leading to good statistics. Uncertainties in the cumulative risk related to baseline rates most often occur when such rates are not available for the target population of interest. For example, baseline rates may not be available for subgroups of a modern population, or for populations exposed many decades ago. Also, current baseline rates for some diseases may change markedly in the future because of, for example, changes in environmental factors or

lifestyle, or improvements in diagnostic and/or therapeutic measures. In particular, uncertainties can arise from a more thorough diagnosis of health effects in the exposed population (such diagnoses are frequently triggered by a specific event, like a nuclear reactor accident). This so-called “screening effect” may be even more serious when more sensitive diagnostic techniques are used than in the past (for example, for the detection of thyroid cancer).

18. The following sources of uncertainty were not considered:

(a) *Individual susceptibility*: The data used for the quantification of uncertainties in this annex were obtained from epidemiological studies of populations. Individual susceptibility is covered by the risk coefficients obtained from these studies. As the uncertainties mentioned in this annex refer to populations and not to individual persons, individual susceptibility is not explicitly addressed here. This aspect, however, might play a role, when the selected populations differ in the number of susceptible individuals;

(b) *Dose and dose-rate effectiveness factor (DDREF)*: The DDREF is a concept that is used in radiation protection. The Committee concluded in its UNSCEAR 2017 Report, annex B [U10] that “on the basis of the possible risk estimates derived from studies of low-dose and low-dose-rate radiation exposures and the new scientific developments in understanding of the mechanisms of radiation-induced cancer, the Committee intends to continue not to use the concept of a single reduction factor for its future radiation risk estimates at low doses and low dose rates”. Thus, DDREF is not applied in this annex.

5. Step 5: Identification of the preferred risk inference

19. In this annex, for all five scenarios, the preferred risk inference has been defined as the one that best fits the characteristics of the considered scenario, based on an expert judgement of the magnitude of the associated uncertainties. Nevertheless, other routes of determination could have been considered. For example, one could have looked for the estimate which answers best the expectation of the targeted population. To illustrate this, it is likely that a worker exposed to radiation throughout his or her professional career would consider as “more informative” (“more preferable”) to know their lifetime risk of developing cancer, a risk estimate up to the attained age* of 90, whereas the criteria in this annex lead to preference of a risk estimate up to the age of 60, because this is the age until which solid epidemiological observations are available. The aim was neither to identify the most reliable risk estimate for a specific person (a kind of “individualized approach”), nor to determine the risk estimate most suitable to very different situations of exposure (a kind of “overarching approach” such as that used in radiation protection). The aim was to evaluate the ability of the recent scientific literature to provide elements to quantify risks for key health effects in specific situations of exposure to ionizing radiation. The preferred risk inferences identified in this annex may therefore not be the best ones to infer risk in another context.

20. For each scenario, the preferred risk inference was identified, and the motivation for this choice was explained. The most important criterion was a minimum of assumptions needed to transfer the effect per unit dose observed in an epidemiological study to the risk per unit dose in the scenario. The widths of the confidence intervals in the different risk projections were also considered.

21. An attempt was made to quantify the potential impact of the different sources of uncertainty on the estimated cumulative excess risk. The impact of the different sources of uncertainty, besides the

statistical uncertainty,³ was classified into four categories according to the variation they are expected to induce on the reported confidence interval of the CER: (a) very small—less than a factor of 1.1 (or a variation of 10%); (b) small—between a factor of 1.1 to 1.5 (or a variation between 10 and 50%); (c) moderate—between a factor of 1.5 to 2 (or a variation between 50 and 100%); and (d) large—greater than a factor of 2 (or a variation of more than 100%). As the statistical uncertainties range up to a factor of 5 or substantially more, the nomenclature (very small, small, moderate and large) is deemed to be appropriate. From this evaluation of the different sources of uncertainty on the preferred risk inference of the CER, credible intervals (also called “credibility intervals”) were assessed, based on the procedure described in appendix A. These credible intervals are intended to reflect both the statistical uncertainty and the potential impact of the additional sources of uncertainty considered to be multiplicative.

II. LEUKAEMIA INCIDENCE AFTER REPEATED LOW-DOSE EXPOSURE DURING CHILDHOOD

A. Motivation

22. The risk of leukaemia related to low levels of radiation exposure during childhood is of particular interest, because there is substantial information of increased risk from epidemiological studies. Specific attention is given to the exposure of children and young adults (below 20 years of age), because current knowledge indicates that, for the same dose, the increase in risk is higher than that after exposure during adulthood.

23. The primary epidemiological basis for estimating leukaemia risk from exposure to ionizing radiation is the LSS cohort of survivors of the atomic bombings in Japan. Within a few years of the bombings, there was evidence of an excess incidence of leukaemia among the survivors. For the same dose, the relative increase in incidence appeared to be larger than that observed for most of the solid cancers, and the minimum latency period between exposure and occurrence of disease appeared to be shorter. A strong decrease in the slope of the dose–response relationship with increasing age at exposure and with increasing attained age was also observed.

24. This evidence is mostly derived from acute exposure* situations with moderate-to-high doses. However, the risks associated with repeated low-dose exposures are more relevant to patients with more than one CT scan. CT scan imaging provides substantial medical benefits for the diagnosis of many diseases. It is widely used in health care, but effective doses* from CT scans may be at least 5–20 times higher than those from routine conventional radiology. Consequently, CT scans contribute a large portion of overall exposure currently received during medical diagnostic procedures [U3]. The magnitude of this exposure has raised concerns about its potential adverse effects, particularly for the risk of leukaemia after exposure during childhood.

³ Random or statistical uncertainties arise from random fluctuations in an outcome of a measurement or a study. In the context of this annex, the statistical uncertainty is expressed by the uncertainty distributions of the calculated cumulative baseline and excess risks, and especially by their confidence intervals.

25. Myelodysplastic syndromes (MDS) are rare bone marrow diseases in childhood and often progress to acute myeloid leukaemia (AML). In the past, MDS was sometimes referred to as pre-leukaemia or smoldering leukaemia. Clinical classification of MDS was only defined in the 1980s, and it is likely that some cases identified as AML in the early years would have been classified as MDS today. Additional information on MDS is provided in section II.F.1(c). Therefore, in the present section, the literature providing information about radiation and the risk of leukaemia or leukaemia +MDS⁴ in the recent years was considered.

B. Recapitulation of previous UNSCEAR publications

26. Annex A of the UNSCEAR 2006 Report [U3] included a comprehensive review of studies providing results on the risk of leukaemia after exposure to ionizing radiation. A model derived from the LSS was available to estimate both the ERR and EAR of leukaemia per unit dose. No specific analysis was proposed for exposure during childhood, but this model integrated the modifying effect of age at exposure: for exposure below 20 years of age, the ERR per unit dose was 8.3 (90% CI: 4.9, 13.7) Sv⁻¹, approximately 2 to 3 times higher than the coefficient estimated after exposure during adulthood. The EAR per 10,000 person-years per unit dose was 2.8 (90% CI: 2.0, 3.7) Sv⁻¹, similar to the coefficient estimated after exposure during adulthood [P8, U3].

27. The most recent relevant UNSCEAR report for leukaemia risks associated with external exposure during childhood is the UNSCEAR 2013 Report, annex B [U6]. This annex presented a review of the results from studies of populations or exposure situations including persons exposed to natural background radiation, the atomic bombing survivors, persons exposed to deposited radionuclides (from the Chernobyl accident and weapon tests), persons living near nuclear facilities, persons undergoing diagnostic radiology and persons undergoing radiotherapy.

28. The Committee concluded in the UNSCEAR 2013 Report, annex B [U6] that there is little doubt that leukaemia (other than chronic lymphocytic leukaemia, CLL) is induced by radiation, with a minimum latency period of approximately two years. The risk estimates at low doses were based on mathematical models, because the observational studies had not shown a statistically significant increase in leukaemia incidence at doses to the RBM of less than about 400 mGy [U6]. A linear-quadratic dose-response model appeared to provide a better fit to the data than a linear non-threshold model, with allowance for dependencies on sex, age at exposure and time since exposure. Overall, the risk of leukaemia associated with an exposure during childhood appeared to be three to fivefold greater than that with the same exposure during adulthood [U6].

C. Review of recent epidemiological literature

29. A comprehensive literature review was performed to identify articles providing information of the quantification of the risk of leukaemia or leukaemia+MDS associated with radiation exposure, published since the UNSCEAR 2013 Report, annex B [U6]. Selection was based on the presence of the following keywords in the title or abstract: leukaemia and (radiation or radiologic) and cohort and

⁴ The expression “leukaemia+MDS” describes the sum of leukaemia and MDS cases.

publication date from 2012 onwards. Using these criteria, case-control studies providing estimates of leukaemia risk associated with radiation exposure were also identified. This research did not separate articles according to age at radiation exposure, so the same literature review was used for both sections II and III. A total of 181 references were obtained, and three additional articles were added after a complementary search. Populations or exposure situations considered included the atomic bombing survivors, persons undergoing diagnostic radiology, persons undergoing radiotherapy, persons exposed to natural background radiation, and persons living near nuclear facilities.

30. Not all these publications provided original results allowing the estimation of a dose-risk relationship after exposure during childhood or provision of information in the low-dose range. For instance, two cohorts of children exposed to radiation following the release of radionuclides from the Chernobyl nuclear power plant accident observed elevated standardized incidence ratios for leukaemia (1.7 and 1.9, respectively, in Belarus and Ukraine), but did not provide estimates of the dose-risk relationship [H2, O4]. Several other studies considered the relationship between exposure to natural background radiation and leukaemia risk but were ecological studies and therefore not based on individual data [S14]. Another example is about studies of the incidence of leukaemia among children living near nuclear facilities. Many studies were published in recent years [C8, J2, L5, M11, N10], but these studies are not able to provide an estimate of the dose-risk relationship.

31. The following review is limited to studies presenting original epidemiological results, based on individual data, with a quantitative dose-risk relationship for populations exposed during childhood to moderate- or low-level external radiation. A total of 13 articles were selected.

1. Studies of the Japanese atomic bombing survivors

32. The most comprehensive publication detailing results on leukaemia incidence among the Japanese atomic bombing survivors was published in 2013 by Hsu et al. [H4]. This article presents analyses of the increased incidence of leukaemia, lymphoma and multiple myeloma from radiation, updated with additional data obtained during the 14 years since the last comprehensive report on these malignancies. These analyses were based on incidence data in the tumour and leukaemia registry for 113,011 cohort members with 3.6 million person-years of follow-up from the late 1950s to the end of 2001. A total of 312 cases of leukaemia other than CLL or adult T-cell leukaemia (ATL) (neither of which appear to be radiation-related) was observed, among them 183 received less than 100 mGy.

33. The article provided analyses of the excess risk for all types of leukaemia, other than CLL or ATL, and also provided analyses of specific leukaemia subtypes (acute lymphoblastic leukaemia (ALL), CLL, AML, chronic myeloid leukaemia (CML) and ATL). For all types of leukaemia other than CLL or ATL, models considering a linear-quadratic relationship between dose to the RBM and incidence were fitted, with a modifying effect of sex, age at exposure, and time since exposure. Much of the evidence for this non-linearity arose from data on AML. The increased incidence of leukaemia generally declined with attained age or time since exposure. Nevertheless, the radiation-associated excess incidence of AML had persisted throughout the follow-up period (55 years after the bombings). MDS was not specifically considered in the analyses by Hsu et al. [H4]. Indeed, MDS cases were diagnosed in the early years, and were probably categorized as AML. But as misdiagnosis of MDS as AML was likely to be independent of dose, it should not affect the estimate of the estimated dose-risk relationship [H4]. More details on the risk models are given in section II.D.3.

2. Studies of children exposed due to medical procedures

34. Five epidemiological studies of cancer risks after CT examinations during childhood were published between 2012 and 2015, in the United Kingdom [P1], Australia [M1], China (Taiwan) [H5], France [J6, J7] and Germany [K26]. For leukaemia, the results of these studies are consistent and show an increased incidence in children who had been exposed to several CT scans (table 1). A second analysis of the UK study was published in 2016 [B4]. For leukaemia+MDS, the results of these studies are consistent and show an increased incidence in children who had been exposed to several CT scans (table 1).

Table 1. Excess relative risk estimates obtained in childhood CT scan studies

ERR: Excess relative risk; MDS: Myelodysplastic syndromes; CI: Confidence interval

<i>Pathology definition</i>	<i>Number of cases</i>	<i>ERR per 100 mGy</i>	<i>95% CI</i>	<i>Source</i>
All leukaemia+MDS	74	3.6 ^a	(0.5, 12.0)	[P1] ^b
All leukaemia+MDS	246	3.9 ^a	(1.4, 7.0)	[M1]
All leukaemia+MDS	19	5.7 ^a	(−7.9, 19.3)	[J6]
All leukaemia	12	0.9 ^c	(−1.9, 3.7)	[K26]
All leukaemia+MDS	72	3.3 ^a	(0.4, 11.4)	[B4] ^b

^a Linear ERR model, with 2-year lag time.

^b Successive analyses of the same UK CT-scan data.

35. Approximation of the ERR from the published hazard ratio* per mGy=1.009 (95% CI: 0.98, 1.04). However, methodological limits due to retrospective assessment of radiation exposure from CT scans and lack of statistical power* need to be taken into consideration. For CT scans, the most discussed limitations are denominated as “reverse causation*” (when a CT scan is ordered due to symptoms of a cancer which has not yet been detected, but ends up being detected sometime later) and “confounding by indication” (when a CT scan is ordered due to a condition which itself increases cancer risk) [B9, B13, W5]. Especially, there was some discussion about the potential impact of cancer predisposing factors on the estimated dose–risk relationship [C7, J5, J7, M14]. In addition, due to the identification of cases with previous history of malignancy, a potential for selection bias is also possible.

36. Due to its design characteristics, size and duration of follow-up, the most important study published in recent years is of children in the United Kingdom who were subjected to CT scans (the UK childhood CT-scan cohort) [B4, P1]. This retrospective cohort study* included 178,364 patients without previous cancer diagnoses who were first examined with CT between 1985 and 2002, when they were younger than 22 years of age. Absorbed doses to the RBM, according to age, sex, examination type and year of scan, were estimated on the basis of typical machine settings for CT scans in the United Kingdom at the time. The total number of person–years over the period 1985–2008 was 1.7 million. The mean cumulative dose to the RBM was about 12 mGy. Cancer incidence data were obtained by linkage with the NHS Central Registry (NHSCR). The first analysis included 74 cases of leukaemia +MDS. The estimated linear ERR per unit absorbed dose for leukaemia+MDS was 0.036 (95% CI: 0.005, 0.118) mGy^{−1}. The estimated ERR for leukaemia excluding MDS (65 cases) was 0.019 (95% CI: −0.012, 0.079) mGy^{−1}, whereas the estimated ERR per unit dose for MDS only (9 cases) was 6.098 (95% CI: >0, 145.4) mGy^{−1} [P1].

37. A second analysis was published in 2016 after consideration of additional sources of medical information. This verification led to the exclusion of 2 cases and 104 non-cases with previously unreported cancer [B4]. Based on 72 cases of leukaemia+MDS, the updated analysis showed an estimated linear ERR per unit absorbed dose for leukaemia+MDS of 0.033 (95% CI: 0.004, 0.114) mGy^{-1} [B4]. No results were provided for leukaemia and MDS separately. For comparison, the corresponding estimated linear ERR per unit absorbed dose derived from the cohort of atomic bombing survivors was 0.045 (95% CI: 0.016, 0.188) mGy^{-1} (excluding MDS) [P1]. A dose to the RBM of greater than 30 mGy was associated with a significantly increased incidence of leukaemia+MDS compared to a dose of less than 5 mGy (relative risk, $\text{RR}=2.63$; 95% CI: 1.09, 6.24) [B4].

38. The roles of radiotherapy and chemotherapy in the occurrence of subsequent leukaemia after childhood cancer were investigated in a recent case–control study in France. The study involved 35 cases and 140 controls, selected from the cohort of French Childhood Cancer Survivors Study (FCCSS). The doses to the RBM were estimated individually, as well as the doses of chemotherapy drugs. A significant positive trend in the incidence of secondary leukaemia with radiation dose was observed, after accounting for heterogeneity in the dose to the RBM, but was no longer significant after adjustment for chemotherapy [A2]. The application of data from cancer survivors to the general public requires some caution as there may be a role of cancer predisposing factors in the survivors.

3. Other studies

39. A population-based case–control study investigated whether acute leukaemia is increased among children who were less than six years of age at the time of the Chernobyl accident, living in contaminated regions of Belarus, the Russian Federation and Ukraine up to the year 2000. Two controls were matched to each case on sex, birth year and residence. The median dose to the RBM was less than 10 mGy. For all three countries combined, the incidence of leukaemia increased significantly with increasing radiation dose; the estimated ERR per unit dose was 32.4 (95% CI: 8.78, 84.0) Gy^{-1} . This was largely accounted for by the significant dose–response in Ukraine, in which the estimated regression coefficient was roughly five times greater than the estimate for Belarus. The dose–response was not statistically significant in either Belarus or the Russian Federation. The authors considered that the dose–response observed in Ukraine might be overestimated. They concluded that their study provided no convincing evidence of an increased risk of childhood leukaemia as a result of exposure to radiation from the Chernobyl accident [I3]. Another case-control study* was later conducted in the most radioactively contaminated territories of Ukraine, including 246 leukaemia cases and 492 randomly selected controls. Ninety-two per cent of the persons had cumulative doses of less than 10 mGy. The association between dose of radiation exposure and leukaemia risk was statistically significant among those with doses ranging from 10 to 314 mGy. The estimated ERR per unit dose was 20.9 (95% CI: 5.6, 43.2) Gy^{-1} [N8].

40. Several studies of the incidence of childhood leukaemia related to exposure to natural background radiation were published in Europe in recent years. In the United Kingdom, a population-based record-based case–control study comparing 9,058 cases of childhood leukaemia and 11,912 controls showed an association with gamma radiation ($\text{ERR per unit dose}=0.12$ (95% CI: 0.03, 0.22) mSv^{-1}), but not with radon concentrations in the areas of residence at birth [K11]. The expanded Swiss cohort study (530 cases) found a statistically significant association between the estimated cumulative exposure to gamma radiation and leukaemia [S15]. In Finland, a nationwide register-based case–control study observed a positive association between exposure to natural background radiation and incidence of childhood leukaemia, but this was not significant (1,093 cases) [N5]. In France, a study combined a geographical approach (9,056 cases of acute leukaemia) and a case–control approach (2,763 cases of

acute leukaemia and 30,000 controls). The incidence of acute leukaemia was not associated with the levels of exposure to radon or gamma radiation in municipalities or with cumulative dose to the RBM [D5]. These studies were limited mainly by the quality of the exposure reconstruction. Especially, calculation of RBM dose due to radon is particularly uncertain. Efforts are ongoing to improve exposure and dose assessment. Also, some studies were limited by a low statistical power and lack of control of other potential risk factors. Up to now, the results from these studies do not provide conclusive results nor do they allow derivation of a dose–risk relationship.

4. Synthesis of studies

41. In recent years, new results have been published from studies of children exposed for medical reasons (CT scans or therapy) or to environmental exposures (natural background or post-accidental settings). Results from these studies complemented those obtained from the cohort of atomic bombing survivors. These results are largely consistent with the existence of a dose–risk relationship for the risk of leukaemia or leukaemia+MDS after exposure during childhood, with a higher risk coefficient than estimated from studies considering exposure during adulthood. This is consistent with previous knowledge [U6]. Results from studies of natural background exposure are less clear, but this could be related to limitation in the reconstruction of individual exposure.

42. As leukaemia is a relatively rare disease [K1], most studies have been based on small numbers of cases, often only several tens. Thus, such studies may have limited statistical power, especially to determine the impact of modifiers of the dose–risk relationship, such as age at exposure or time since exposure, or to quantify a dose–risk relationship for specific leukaemia subtypes. Collaborative research projects aiming to perform pooled analyses of individual data have been launched to cope with this limitation, such as the EPI-CT European project (Epidemiological study to quantify risks for paediatric CT and to optimize doses) [B10, W7].

43. Based on a comprehensive review of the incidence of childhood leukaemia following exposure to ionizing radiation, Wakeford proposed an estimation of the ERR per unit dose for childhood leukaemia of about 50 Sv^{-1} [W1]. The author considered that this ERR estimate was broadly applicable to circumstances of low-dose exposure.

44. More recently, Little et al. [L17] published the results of a pooled analysis* of the association between leukaemia incidence and low-dose radiation exposure in childhood. The pooled analysis included data from nine eligible cohorts from Canada (the Canadian tuberculosis fluoroscopy cohort), France (the French haemangioma cohort), Japan (the LSS), Sweden (the Gothenburg haemangioma cohort and the Stockholm haemangioma cohort), the United Kingdom (the UK CT-scan cohort), and the United States (the Massachusetts tuberculosis fluoroscopy cohort, the Rochester thymus enlargement cohort and the US scoliosis cohort). The pooled database included 262,573 people who had been exposed to less than 100 mSv before 21 years of age and enrolled before 2005. The mean follow-up was 19.6 years and the mean cumulative dose to the RBM was 19.6 mSv. Overall, the number of leukaemia cases (excluding CLL) was 221, including 79 AML, 8 MDS, 36 CML and 40 ALL. The relative rate at 100 mSv was reported as 2.56 (95% CI: 1.09, 5.06) for AML, 3.09 (1.41, 5.92) for AML+MDS and 5.66 (1.35, 19.71) for ALL. However, the relative rate of CML did not appear to increase 0.36 (95% CI: 0.00, 2.36). There were few indications of between-cohort heterogeneity or departure from linearity. For AML and MDS combined and for ALL, the dose responses remained significant when analyses were restricted to doses <50 mSv. Excess absolute rates* at 100 mSv were in the range of 0.1–0.4 cases or deaths per 10,000 person–years.

D. Definition of scenario

45. The scenario selected was of repeated exposure to CT scans during childhood, for which pertinent results on the risk of leukaemia+MDS had been published in recent years. As risk models and data on baseline rates of incidence were available, assessment of the risk of leukaemia incidence was considered, in contrast to the adulthood analyses, which concentrated on mortality (see section III).

1. Exposure scenario

46. The scenario was designed to reflect the characteristics of the UK childhood CT-scan cohort [B4, P1]. This cohort considered the incidence of leukaemia+MDS. In this cohort, age at CT exposure ranged from 0 to 21 years. Estimated doses to the RBM per scan varied between 2 and 9 mGy for a head scan, between 3 and 4 mGy for a chest scan and between 2 and 4 mGy for an abdomen scan. Most children underwent only one scan, but some received several. The mean cumulative dose to the RBM was about 12 mGy. Follow-up for leukaemia began two years after the first CT. Age at the end of follow-up ranged from 6 to 45 years. The mean duration of follow-up was 10 years.

47. The defined scenario has the following characteristics:

- (a) UK population;
- (b) Population composed of 50% males and 50% females;
- (c) Exposure to four CT scans during the same year, either at age 1 or 10;
- (d) Mean dose to the RBM of 5 mGy per CT scan, leading to a cumulative dose of 20 mGy received in a single year;
- (e) Alive two years after the first CT scan (i.e. at ages 3 and 12, respectively);
- (f) Follow-up of leukaemia+MDS incidence to age 30 (approximately the mean attained age at the end of the follow-up) or age 40 (approximately the maximum attained age at the end of the follow-up).

2. Reference data

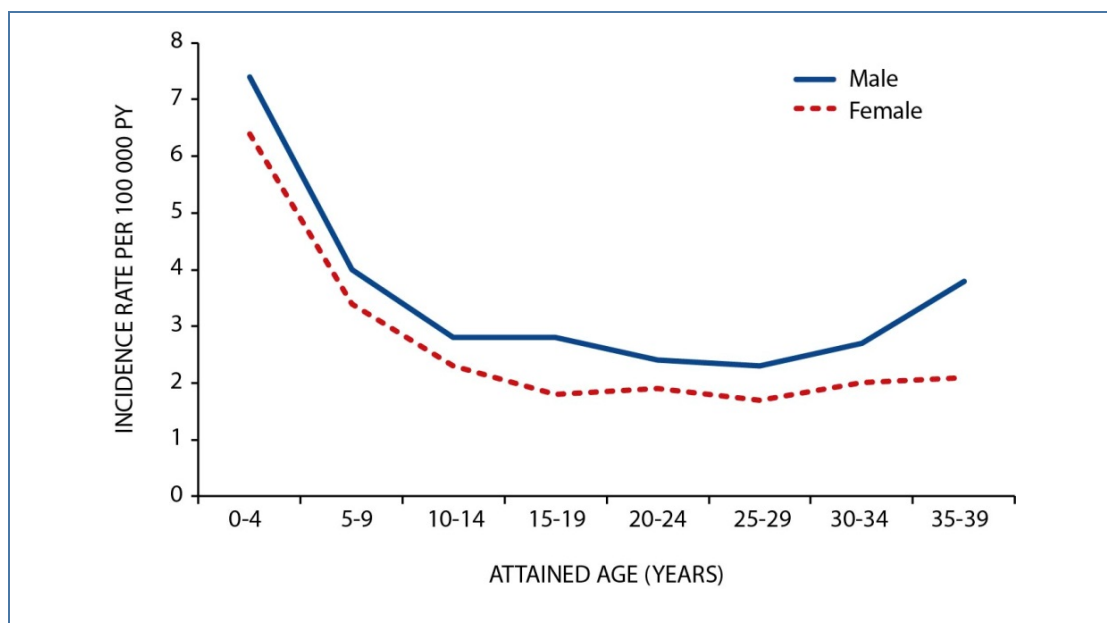
48. For the calculations of the survival function and baseline risk of leukaemia, the following data sources were used:

- (a) *Survival function*: age- and sex-specific death rates per 1,000 population registered in England and Wales in 2010 [O3];
- (b) *Baseline risk of leukaemia*: age- and sex-specific incidence rates per 100,000 population in the United Kingdom for years 2011–2013 [C2]. Leukaemia was defined according to the ICD-10 codes as C91–C95 [W10]. As the estimated incidence of paediatric MDS in Europe is very low (1 to 4 cases per million per year) compared to leukaemia incidence, MDS incidence has not been considered in the baseline rates used for the scenario.

49. Leukaemia baseline incidence rates decrease between birth and age 20, and then increase with age, maximum rates being reached after 85 years of age. Figure I presents the evolution of leukaemia incidence baseline rates in the United Kingdom over the age range considered in the scenario.

Figure I. Baseline rates of leukaemia incidence in the United Kingdom in the period of 2011–2013 per category of attained age

PY: person–years



3. Risk models

50. Risk models considered leukaemia or leukaemia+MDS. No model for specific leukaemia subtype has been considered. MDS cases were not specifically diagnosed before the 1980s and not systematically before 2000. It is likely that some cases identified as AML in the early years would have been classified as MDS, if they had been diagnosed with modern criteria [H4]. Therefore, it has been considered that the best way to ensure consistency in risk comparison was to use models of leukaemia risk when based on olden exposure (as the models derived from the LSS [H4]) and a model of leukaemia+MDS risk when based on recent exposures (as the model derived from the UK CT-scan study [B4]).

51. Risk models derived from the cohort of Japanese atomic bombing survivors were those published by Hsu et al. [H4] for the risk of leukaemia other than CLL or ATL. Both ERR and EAR models were considered.

52. The ERR model (denoted thereafter as the LSS ERR model) was linear–quadratic in dose with a log–linear effect modification* depending on attained age and time since exposure (TSE), but not on sex:

$$\text{ERR} = (\beta_1 d + \beta_2 d^2) \exp(\alpha \ln(\text{age}/70) + \gamma \ln(\text{TSE}/40))$$

where d is the absorbed dose to the RBM, and $\beta_1=0.79$ (95% CI: 0.03, 1.93) Gy^{-1} ; $\beta_2=0.95$ (95% CI: 0.34, 1.80) Gy^{-2} ; $\alpha=-1.09$ (95% CI: $-2.01, -0.27$); and $\gamma=-0.81$ (95% CI: $-1.31, -0.28$).

53. The EAR model (denoted thereafter as the LSS EAR model) was linear–quadratic in dose with log–linear effect modification depending on attained age and age at exposure (AE), with different dose coefficients for males and females:

$$\text{EAR} = (\beta_1 d + \beta_2 d^2) \exp(\alpha_1 (\text{AE}-30)/10 + \alpha_2 \cdot \ln(\text{age}/70) + \tau \cdot \text{sex})$$

where d is the absorbed dose to the RBM; $\text{sex}=0$ for males and 1 for females, and $\beta_1=1.06$ ($\text{Gy } 10,000 \text{ PY}^{-1}$); $\beta_2=1.09$ ($\text{Gy}^2 10,000 \text{ PY}^{-1}$); $\alpha_1=0.41$; $\alpha_2=-1.45$; and $\tau=-0.42$.

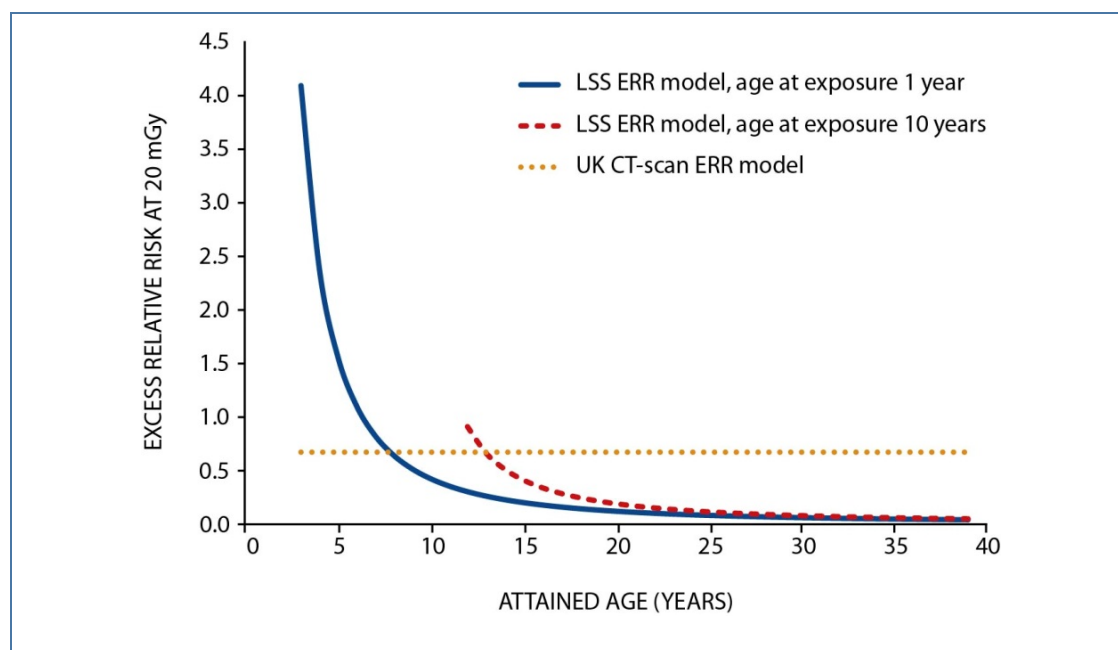
54. The risk assessment was also conducted using the ERR model derived from the UK childhood CT-scan cohort [B4] for the incidence of leukaemia+MDS. The model was a linear ERR model. Model parameters are indicated below:

$$\text{ERR} = \beta d$$

where d is the cumulative dose to the RBM, and $\beta=33$ (90% CI: 4, 114) Gy^{-1} .

55. The risk model behaviour is presented in figure II, for the age characteristics considered in the scenario. Based on the LSS ERR model, the decrease of the ERR with age appears steeper after exposure at age 1 than after exposure at age 10, whereas no variation with age is considered in the UK childhood CT-scan model.

Figure II. Excess relative risk of leukaemia+MDS at 20 mGy as a function of attained age, for age at exposure of 1 and 10 years obtained from LSS [H4] and UK childhood CT-scan [B4]



4. Risk-transfer methods

56. For the transfer of risk from the atomic bombing survivors population to the scenario, both multiplicative (based on the LSS ERR model) and additive (based on the LSS EAR model) risk transfers were used.

57. For the application of all models (derived from the cohort of atomic bombing survivors or from the UK childhood CT-scan cohort) to the scenario, a minimum lag time was considered between exposure and effect. This lag time was modelled as a sigmoid function, varying between 0 and 2 years and centred on 1.5 years, similarly as applied in the *Interactive RadioEpidemiological Program* (IREP) package [K14].

E. Results

58. The estimated cumulative risk of leukaemia up to ages 30 and 40, associated with the childhood CT-scan scenario at ages 1 and 10 are presented in tables 2 and 3, respectively. The survival fraction was 99% at age 30 and 98% at age 40, which indicates that most of the population was presumed to be alive at the end of follow-up. The CBR was about 9 to 12 per 10,000 persons from age 1 to 30, or 40, and about 4 to 7 per 10,000 persons from age 10 to 30, or 40, respectively. This difference can be explained by the peak in the baseline rates of ALL between age 2 and 7.

59. The estimated CFR varied between 0.16 and 0.60, according to the models used. This means that the estimated CERs represent an important proportion of the CBR (about one sixth to two thirds), even if the cumulative dose to the RBM considered in the scenario was small (20 mSv). This large percentage was due to the high excess relative risk of leukaemia among children (figure II).

60. Results indicate a CER between 1.8 and 7.0 after exposure at age 1 and between 0.8 and 4.4 after exposure at age 10; the CER associated with an exposure at age 1 was 1.5 to 5 times higher than that associated with an exposure at age 10. The CER estimated from the LSS ERR model was higher than that estimated from the LSS EAR model, however, the associated confidence interval was systematically larger with the ERR model.

61. After exposure at age 1 and follow-up to age 30, the agreement in the estimated CER between the LSS ERR model and the CT-scan ERR model was very good: CER=5.0 (95% CI: -0.6, 30) and 5.3 (95% CI: 0.6, 18.3) per 10,000 persons, respectively. For follow-up to age 40, the difference in the estimated CER was less than 40%.

62. After exposure at age 10, the estimated CER was 3 to 4 times higher with the CT-scan ERR model. The agreement between the LSS ERR model and the CT-scan ERR model was better with a follow-up to age 30 than to age 40. This may reflect a greater difficulty of the CT-scan ERR model to take into account the variation of risk with age, as this model does not integrate any modifying effect of attained age and age at exposure (figure II).

63. Comparison of the confidence intervals associated with the CER estimates between the LSS ERR model and the CT-scan ERR model shows that the CT-scan ERR model leads to a narrower confidence interval in the scenario with exposure at age 1, but a comparable confidence interval in the scenario with exposure at age 10 years.

Table 2. Cumulative risk of leukaemia incidence for a scenario of a child receiving 20 mGy to the RBM from CT scans at 1 year of age

CBR: Cumulative baseline risk; CER: Cumulative excess risk, estimated using the REIC methodology;

CFR: Cumulative fractional ratio; CI: Confidence interval; LSS: Life Span Study

Risk model	Cumulative baseline risk ^a		Cumulative leukaemia risk associated with the exposure scenario ^b	
	All-cause mortality per 10 000 persons	Leukaemia incidence per 10 000 persons	CER per 10 000 persons (95% CI)	CFR (CER/CBR)
EXPOSURE AT 1 YEAR OF AGE, FOLLOW-UP TO 30 YEARS OF AGE ^{b c}				
LSS incidence models [H4]				
ERR transfer	76	9.1	5.0 (−0.6, 30)	0.55
EAR transfer			1.8 (0.1, 4.4)	0.19
CT-scan incidence model ^d [B4]				
ERR transfer	76	9.1	5.3 (0.6, 18.3)	0.58
EXPOSURE AT 1 YEAR OF AGE, FOLLOW-UP TO 40 YEARS OF AGE ^{b c}				
LSS incidence models [H4]				
ERR transfer	164	12	5.1 (−0.8, 30)	0.43
EAR transfer			1.9 (0.0, 4.6)	0.16
CT-scan incidence model ^d [B4]				
ERR transfer	164	12	7.0 (0.9, 24)	0.60

^a United Kingdom population, unweighted average of males and females—without exposure—alive at exposure age.^b Cumulative dose to RBM of 20 mGy due to four CT scans received in the same year.^c Up to 30 (40) years of age means up to the 30th (40th) birthday.^d Including MDS.

Table 3. Cumulative risk of leukaemia for a scenario of a child receiving a dose of 20 mGy to the RBM from CT scans at 10 years of age

CBR: Cumulative baseline risk; CER: Cumulative excess risk, estimated using the REIC methodology;

CFR: Cumulative fractional ratio; CI: Confidence interval; LSS: Life Span Study

Risk model	Cumulative baseline risk ^a		Cumulative leukaemia risk associated with the exposure scenario ^b	
	All-cause mortality per 10 000 persons	Leukaemia risk per 10 000 persons	CER per 10 000 persons (95% CI)	CFR (CER/CBR)
EXPOSURE AT 10 YEARS OF AGE, FOLLOW-UP TO 30 YEARS OF AGE ^{b c}				
LSS incidence models [H4]				
ERR transfer	66	4.4	1.0 (–0.2, 3.5)	0.23
EAR transfer			0.8 (0.0, 1.6)	0.18
CT-scan incidence model ^d [B4]				
ERR transfer	66	4.4	2.7 (0.3, 9.3)	0.60
EXPOSURE AT 10 YEARS OF AGE, FOLLOW-UP TO 40 YEARS OF AGE ^{b c}				
LSS incidence models [H4]				
ERR transfer	154	7.1	1.2 (–0.1, 3.9)	0.17
EAR transfer			1.0 (0.0, 1.9)	0.14
CT-scan incidence model ^d [B4]				
ERR transfer	154	7.1	4.4 (0.5, 15)	0.62

^a United Kingdom population, unweighted average of males and females—without exposure—alive at exposure age.^b Cumulative dose to RBM of 20 mGy due to four CT scans received in the same year.^c Up to 30 (40) years of age means up to the 30th (40th) birthday.^d Including MDS.

F. Discussion of scenario calculations

1. Sources of uncertainties

(a) Selected populations

64. The scenario was designed to reflect the characteristics of the United Kingdom childhood CT-scan cohort [B4, P1]. The pattern of exposure (4 scans in 1 year, at age 1 or 10) was driven by descriptive data from the UK childhood CT-scan cohort. The level of cumulative dose (20 mGy) was a rounded value, intended to be realistic, even if a little bit higher than the mean cumulative dose to the RBM (12 mGy). To be coherent with the age at the end of follow-up of the UK childhood CT-scan cohort, the cumulative leukaemia risks up to attained ages 30 and 40 were calculated.

65. The LSS cohort included a large portion of the atomic bombing survivors who were within 2.5 km of the hypocentres at the time of the bombings, an age- and sex-matched sample of people who were between 2.5 and 10 km from the hypocentres, and a sample of about 27,000 persons who were registered as residents of either Hiroshima or Nagasaki in 1950, but were not in the cities at the time of the bombings. The cohort members were recruited on the basis of the 1950 Japanese National Census and of additional information collected by the Atomic Bomb Casualty Commission (ABCC). The risk model for leukaemia was based on the 113,011 cohort members in the LSS for whom dose estimates were available. Almost 60% of the cohort members were females and 41% were less than 20 years of age at the time of the bombings [H4].

66. The UK childhood CT-scan study included patients without previous malignant disease who were first examined with CT between 1985 and 2002 when they were younger than 22 years of age. Patients were scanned at hospitals within 81 National Health Service (NHS) regional services in Great Britain (England, Wales and Scotland). The cohort was assembled from historical data from computerized information systems from the participating hospitals and, for a small number of patients in five hospitals, from paper or film records. Cancer incidence, mortality and loss-to-follow-up data were obtained by linkage with the NHSCR from 1 January 1985 to 31 December 2008. In order to reduce the possibility of inclusion of patients who had CT scans because a cancer was suspected, patients who had an exit date of less than two years after the first scan were excluded from the analysis of the incidence of leukaemia+MDS. Patients who could not be traced by the NHSCR were also excluded, as well as those who had missing information or inaccurate information on the date of CT scan [P1].

67. In the UK CT-scan cohort, the collection of additional clinical information from radiology information system databases and underlying causes of death reports led to the exclusion of two cases (out of a total of 74 patients with leukaemia+MDS) and 104 non-cases with previously unreported cancer [B4]. These 106 patients should not have been included in the initial cohort, as they did not respect the selection criteria. Furthermore, children with previous cancer are susceptible to have more CT scans and higher cumulated doses, and their inclusion may therefore bias the estimated risk. Indeed, exclusion of these patients led to a reduction in the estimated ERR of about 8% compared to the initial estimate, from 0.036 (95% CI: 0.005, 0.118) mGy⁻¹ [P1] to 0.033 (95% CI: 0.004, 0.114) mGy⁻¹ [B4]. Furthermore, the collection of additional clinical information has been possible only for about 40% of the cohort, so it cannot be ruled out that other cases should have been excluded due to previous unreported cancer. Nevertheless, it is unlikely that the global impact on the confidence interval could be more than 50%, and the uncertainty associated to this factor is considered to be small.

68. It should be noted that the model derived from the UK CT-scan study was based on a population with a range of age at exposure and attained age much narrower than the LSS. One option would have been to use a model derived from an LSS subset limited to children at the time of the bombings. Indeed, about a third of the leukaemia cases were diagnosed in survivors who were exposed as children. Nevertheless, it is not clear if such a model would have been able to quantify the modifying effect of age at exposure and attained age.

(b) Exposure assessment

69. The exposure parameters and doses considered in the present scenario are fixed and considered without uncertainty. Nevertheless, uncertainties and measurement errors exist in the cohorts used to derive the scenario and the risk models.

70. In the LSS, the following points have to be considered while discussing uncertainty in the exposure assessment:

(a) The radiation dose received by each survivor was estimated based on location, orientation and other information at the time of the bombings. Some uncertainties remain about, for example, the sizes and locations of explosions, radiation emitted and shielding. While continuing efforts have been made to improve the dosimetry [C9, C10], much of the information provided for the dosimetry system was collected through interviews 5–10 years after the exposure;

(b) Dose estimates were adjusted for possible biases based on a statistical method of regression calibration* with a plausible error model which assumes a 35% multiplicative error [P3]. Pierce et al. [P3] found that the excess cancer-risk estimates in the LSS could increase by 6–17% if allowance was made for dose estimation errors, while the standard errors of the parameter estimates remained essentially unchanged. This result reflects the fact that the additional variation in the data due to dose errors was small;

(c) The current approach to dose uncertainty in the LSS deals with the classical errors* that arise primarily from errors in each survivor's reported location and shielding. But another type of error, Berkson errors,* can arise from the data used to characterize the explosion (height, power, location, radiation emitted) [P4, P5]. This approach made adjustments on both gamma and neutron doses. More recently, to account for the uncertainty involved in the assumed true-dose distribution, a new approach involving simulation-extrapolation under a mixture of classical and Berkson errors has been considered and applied to the cancer-incidence analysis in the LSS [M9], where the risk estimates appeared to be fairly comparable to those by the conventional adjustment;

(d) There is additional uncertainty in the LSS dose estimates due to sources other than errors in the survivors' reported exposure data, including some shared errors* due to parameters in the dose calculations such as the heights above ground, yields and locations of the hypocentres of the explosions, but uncertainty from these sources is thought to be small compared to that from inaccuracies in the input data for survivors [K8];

(e) There are also concerns about additional uncertainties potentially linked to the consideration of internal contamination, or exposure to the "black rain" that contained radioactive materials and fell after the atomic bombings. However, up to now, there has been no clear evidence for long-term deleterious health effects from such exposures [S1] and, thus, they are unlikely to have a large impact on the current risk evaluations.

71. In the childhood CT-scan cohorts, the following points have to be considered in the discussion of uncertainty in the exposure assessment:

(a) The reconstruction of doses to organs associated with past CT scans requires taking account of different types of CT scanners, different CT-scan technologies, and details of the CT examinations and protocols over the last decades. Most studies, including the UK CT-scan study, used rather crude data, including date of the scan, body region scanned, sex and date of birth [B4, P1]. In early childhood, age is only a crude proxy for the relevant anatomical characteristics that influence dose as the distribution of height and weight for the same age can be broad;

(b) The variability* of examinations, types of scan and protocols makes it difficult to reconstruct doses, and the level of detail available for dose reconstruction differs in different periods. Doses due to CT-scan examinations decreased in the recent years, while the doses from the United Kingdom cohort reflect doses before 2000 and did not take into account variability of doses linked to protocols and CT machines. Missing information on examinations or on the characteristics of the

children is also a source of uncertainty. Due to the method of dose reconstruction, measurement errors should be mainly of the Berkson type, but they are shared among members of a group (for example, for patients at a specific hospital). Such uncertainties and measurement errors could be important and affect the reliability of risk estimates. Up to now, models derived from CT-scan studies did not consider dose uncertainties. Improvement in the strategy of dose reconstruction and consideration of uncertainties are intended to be conducted in the frame of the EPI-CT European research project, an epidemiological study to quantify risks for paediatric CT [T5]. Due to the reconstruction scheme for individual doses, it is likely that measurement errors will be mostly of the Berkson type. Nevertheless, as uncertainties are not all truly Berkson type, the potential impact on the estimated dose–risk relationship and on the confidence intervals will depend on the degree and the magnitude of errors;

(c) Missing information about CT-scan characteristics and possible repeated scans may lead to missing doses and therefore, to underestimation of the cumulative doses;

(d) The absence of consideration of any doses linked to other medical examinations (e.g. CT nuclear medicine procedures, catheterization) also constitutes a source of uncertainty.

(c) *Health outcome assessment*

72. Leukaemia is a group of cancers belonging to a broader group known as cancers of the haematopoietic and lymphoid tissues. There are four main types of leukaemia: ALL, AML, CLL and CML, as well as several less common types, such as ATL. Classification of leukaemia evolved over time, with the definition of the disease becoming more and more precise. This evolution may lead to discrepancies in the composition of the “leukaemia category” considered by different data sources (registries for baseline rates) or epidemiological studies. Also, the frequency of specific subtypes varies between countries. For example, Japan is known to have lower rates of CLL but higher rates of ATL than many other industrialized countries. Little evidence exists of an association between ionizing radiation exposure and CLL or ATL risk. The analysis by Hsu et al. showed that the dose–risk relationship may vary according to leukaemia subtypes. The shape of the dose response appeared to depend on subtype, but also modification by age at exposure appeared to be greater for some subtypes than others, and the age-dependence for baseline rates also differed by subtype [H4]. If the proportion of childhood leukaemia subtypes is different in the United Kingdom than in Japan, then this may be a source of bias when transferring the risk from the LSS population to a United Kingdom population. In the future, consideration of separate leukaemia subtypes for such comparison of estimated cumulative risks is warranted.

73. In the scenarios, United Kingdom age- and sex-specific incidence rates for all types of leukaemia (defined according to the ICD-10 codes C91–C95) were used [W10]. The model derived from the cohort of Japanese atomic bombing survivors considered the risk of leukaemia other than CLL or ATL [H4]. Nevertheless, this difference should not cause problems in the assessment of risk. Indeed, CLL occurs in the population only at old ages; the CLL rate before age 40 is almost zero and appears mainly at older ages. Furthermore, ATL, which is infection-based and can be endemic in some areas of Japan (especially near Nagasaki), is very rare in the United Kingdom. As the maximum age at the end of follow-up in the scenario is only 40, using reference rates excluding CLL would have little impact on the estimated risk.

74. Both MDS and leukaemia are due to abnormalities in the bone marrow. The classification of AML and MDS includes clinical data (previous history, age) and biological characteristics

(morphology, cytochemistry, immunophenotype, cytogenetic and molecular biology). MDS is a rare condition in childhood and often progresses to AML. MDS in children may be consecutive to radiotherapy treatment for a previous cancer, so care is required to ensure that patients with a previous cancer are excluded from any analysis. The estimated incidence of paediatric MDS in Europe varies from 1 to 4 cases per million per year and is equal in males and females, whereas the leukaemia incidence among children under 15 years of age is about 40 to 50 cases per million per year. Thus, whether children with MDS are included does not have an important impact on estimated baseline rates.

75. Risk assessment was conducted using the ERR model derived from the UK childhood CT-scan cohort [B4], which considered incidence of both leukaemia and MDS. The article did not present results for leukaemia only. Nevertheless, even if MDS cases represented only a small fraction of the total number of cases (9 MDS cases for 65 leukaemia cases), the impact on the estimated dose–risk relationship might be important. In the previous analysis in the UK childhood CT-scan cohort, the estimated ERR for leukaemia excluding MDS was reduced to 0.019 (95% CI: –0.012, 0.079) mGy^{-1} , whereas the estimated ERR per unit dose for MDS only was 6.098 (95% CI: >0, 145.4) mGy^{-1} , but associated with a very large confidence interval due to the small number of cases [P1].

76. One study investigated the incidence of MDS among the atomic bombing survivors and the associated dose–response relationship [I7]. The results demonstrated a significant linear dose–response relationship over 40 to 60 years after radiation exposure. The estimated ERR per unit dose was 4.3 (95% CI: 1.6, 9.5; $p < 0.001$) Gy^{-1} . The incidence of MDS was significantly greater for those exposed when young. MDS was not specifically considered in the analyses by Hsu et al. [H4], but the authors discussed the potential impact of MDS on the estimated risk of leukaemia, and especially of AML. They stated that it was likely that some cases identified as AML in the early years would have been classified as MDS, if they had been diagnosed with modern criteria. As misdiagnosis of MDS as AML was likely to be independent of dose, they concluded that it would not affect the estimate of ERR for the risk of AML, although it would tend to increase the EAR estimate [H4].

77. Classification of MDS evolved in the recent years. In the past, cases were not identified as MDS and were often misdiagnosed as AML. In addition, MDS is a rare pathology, regrouping heterogeneous diseases. For these different reasons, the assessment of MDS risk associated with radiation exposure is very uncertain today. Nevertheless, the estimated ERR per unit dose estimated specifically for MDS in the UK childhood CT-scan cohort, based on 9 cases [P1], appears to be particularly high. This result makes it questionable to include MDS in the assessment of leukaemia risk. Indeed, the relative impact of the inclusion or not of MDS in the estimated ERR per unit dose is close to 50% (estimated ERR per unit dose decreased from 0.036 to 0.019 mGy^{-1}). Ongoing studies should provide information to better determine the risk of MDS associated to radiation exposure, and its potential impact of the dose–risk relationship estimated for leukaemia+MDS.

(d) *Study design*

78. Two to three years after the atomic bombings of Hiroshima and Nagasaki, a number of physicians in Hiroshima and Nagasaki noted a markedly increased incidence rate of leukaemia in children living near the hypocentres [H4]. Nevertheless, before 1950 some cases may have been missed because of death from infectious disease before leukaemia diagnosis. Therefore, in the early 1950s, the Atomic Bomb Casualty Commission researchers together with haematologists in Hiroshima and Nagasaki launched the Leukaemia-Registry to ascertain all potential cases of leukaemia and other haematological malignancies in the two areas, including cases that occurred in the late 1940s. The Leukaemia Registry remained active until the late 1980s, when it was replaced by the city and prefecture population-based

Tumour Registries. Study of the incidence of leukaemia, lymphoma and multiple myeloma among the survivors of the atomic bombings began on 1 October 1950. The end of follow-up was the earliest date of diagnosis of the first primary malignancy (of any type), the date of death, the date of loss to follow-up or 31 December 2001. There is no nationwide cancer registration system in Japan. So, people who moved from the Hiroshima/Nagasaki regions may have been lost to follow-up due to migration out of the catchment areas of the local registry. The followed-up person-years are consolidated from the contact records in the Adult Health Study (AHS). For the last publication on leukaemia risk with follow-up to 2001, the percentage of cohort members lost to follow-up was estimated to be less than 1% [H4].

79. In the UK CT-scan study, cancer incidence, mortality and loss-to-follow-up data were obtained by linkage with the NHSCR from 1 January 1985 to 31 December 2008. A total of 33,372 patients (about 30% of the initial dataset) were excluded because they could not be traced by the NHSCR because their names or dates of birth in the Radiology Information System (RIS) databases were incomplete. According to the authors, the availability of information on persons is considered to be independent of the dose received and incidence of leukaemia, so this relatively high percentage of persons excluded from the study should not bias the estimated risk. Altogether, 178,604 persons were included in the analyses of the incidence of leukaemia [P1].

(e) *Confounding factors*

80. The established risk factors for childhood leukaemia are Down syndrome, sex (it occurs more frequently with boys than with girls), chemotherapeutic drugs and exposure to ionizing radiation. Exposure to 50 Hz electric and magnetic fields (ELF-EMF) has also been suggested as a risk factor for childhood leukaemia [I1], but the evidence remains controversial [A3]. Many other factors have been suggested, such as genetic and infectious risk factors, maternal reproductive history, birth characteristics, exposure to hydrocarbons and pesticides, alcohol use, cigarette smoking and illicit drug use, but, to date, most of them have been found to be weakly and inconsistently associated with childhood leukaemia [B1, W8].

81. A major limitation of CT-scan studies is the potential bias by reverse causation [B9, U6, W5]. Reverse causation implies that it is the early symptoms of undetected cancer, that are the indication for the CT scans, rather than the CT scans per se that are causing the apparent excess incidence of cancer. In the literature, two circumstances of such a bias are differentiated:

(a) The previously unreported cancer of interest has only been reported after the first CT scan. In most CT-scan studies, the possibility for such a bias has been considered through the application of different latency periods between the CT scan and occurrence of the cancer (from 1 year to more than 10 years), but most of the published studies were limited by their duration of follow-up. Whereas such a bias appears possible for brain tumours [B9], it is much more unlikely for leukaemia, as most of the leukaemia cases occurring during childhood or young age are acute, with no known early symptoms occurring more than one year before diagnosis;

(b) A type of cancer different from the cancer of interest in the study had not been reported. This may introduce a systematic bias, because cancer therapy may cause leukaemia and may have been the clinical indication for several CT scans [B4].

82. Several CT studies are under way, such as the EPI-CT study in Europe, which hopefully should be able to establish the reasons for the CT examinations in subgroups of patients, and then to better assess the potential effects of reverse causation [W5, W7].

83. Confounding by indication is another potential source of bias of CT-scan studies [B13]. Indeed, some conditions, such as infections or neurological conditions, may require CT examinations for the purpose of diagnosis but also involve increased susceptibility to leukaemia and the prevalence of leukaemia predisposing factors among children undergoing CT-scan examinations (for example, Down syndrome or Crohn's disease) may modify the estimated dose–risk relationship. In the UK CT-scan study the collection of additional clinical information on leukaemia related conditions from radiology information system databases, underlying causes of death and pathology reports, led to a change in the estimated ERR per unit dose from 0.036 (95% CI: 0.005, 0.118) mGy^{-1} to 0.037 (95% CI: 0.005, 0.126) mGy^{-1} [B4] compared to the previous estimate [P1]. In the French CT-scan cohort, the ERR related to CT exposure differed in persons with or without predisposing factors. The authors concluded that predisposing factors were acting as modifying factors of the dose–risk relationship rather than as confounding factors [C7, J5, M14]. Nevertheless, as the risk estimates in patients without predisposing factors were close to the unadjusted ERR in the overall cohort, the impact of predisposing factors appeared limited. Another recent study based on simulation in the Netherlands concluded that associations between radiation exposure from paediatric CT scans and leukaemia reported in previous studies are unlikely to be substantially confounded by unmeasured cancer susceptibility syndromes [M6]. A new analysis in the Netherlands concluded that indication bias is likely to be negligible or small among adults [M7]. Nonetheless, the absence of information on the reasons for CT scans in most published studies remains a problem, and collection of such data when possible is recommended for future studies.

(f) *Statistical methods and model uncertainties*

84. Many uncertainties can be linked to the risk models, including the shape of the dose–risk relationship, the quantification of modifying effects related to age and time since exposure, the latency period between exposure and risk, and the nature of the risk transfer (EAR or ERR).

85. In the scenarios considered, the statistical uncertainty associated with risk coefficients was considered through confidence intervals, and, where available, both EAR and ERR models were considered. Uncertainty remains in the modelling of effect modification depending on age at exposure, attained age or time since exposure, of the dose–response relationship or of the latency. Especially, the risk model derived from the UK CT-scan study does not consider a modifying effect of age at exposure [B4], whereas the LSS model demonstrated a strong decrease of the estimated ERR per unit dose with increasing age at exposure. Between exposure at ages 1 and 10, the reduction in the ERR is higher than a factor two [H4]. The mean age at exposure of the cases in the UK CT-scan study being about 10 years, it is probable that the ERR estimated for age at exposure of 1 year is expected to be higher than the age-independent value used in these calculations.

86. The risk models derived from the LSS are based on a large population (113,011 cohort members) and a long duration of follow-up (from 1950 to 2001). This large database allowed a detailed analysis of the excess risk for all types of leukaemia other than CLL or ATL [H4]. The models were linear–quadratic in dose with effect modification depending on attained age and time since exposure. Both ERR and EAR models were derived. Uncertainty in the risk estimates at low doses was thought to originate from various sources, including variation of estimated baseline rates, uncertainty in the dose estimates, residual confounding and interaction, potential confounding due to uncontrolled risk factors, and exposure to other sources of radiation [O6]. In addition, due to the late beginning of follow-up (1950, which was five years after the bombings), a greater uncertainty is associated with the risk estimated in the first years after exposure. As the estimated risk coefficients are very high at very young ages at exposure, this point may impact especially the estimated risk in the scenario with exposure at 1 year of age.

87. To assess the impact of model selection on the estimates of the ERR, Walsh and Kaiser [W4] refitted nine previously published leukaemia-risk models to the LSS mortality data from the period 1950–2000. For a comprehensive characterization of the model uncertainties, Akaike Information Criterion* (AIC)-weighted risk averages were calculated using the multi-model inference technique. The authors considered several exposure scenarios, including childhood exposure at ages 2, 7, 12 and short times since exposure of 5 and 10 years. For young age at exposure and short time since exposure, the number of leukaemia cases was very low for attained age up to 25. Less than 30 cases have been recorded in the dose range 0–4 Gy. Hence, risk estimation at doses below 100 mGy for the above-mentioned scenarios was mainly based on extrapolation of the model results. The 95% CI of the ERR estimates using the multi-model inference technique were very large (upper bound up to four times larger than the combined estimate), and always included the value zero (absence of increasing risk per unit dose) [W4]. The central ERR estimates based on multi-model inference agreed with that estimated in the UK childhood CT-scan study [B4].

88. The uncertainties associated with risk estimates based on the UK childhood CT-scan cohort model have so far not been fully quantified. The confidence intervals associated with the risk coefficients only reflect a portion of the complete uncertainty. The main limit of the CT-scans studies is the absence of estimates for age-modifying effects, due to the current limited power. A second limit is that, up to now, no study has provided estimates of the EAR; only ERR estimates are available.

(g) Other sources of uncertainty

89. The calculation of risk is based on the assumption that the risk of leukaemia over a given period of follow-up can be predicted [W6]. One major underlying assumption is that the selected reference rates are stable over the whole period of risk assessment, which here is up to a duration of 39 years (scenario of exposure at age 1 with a follow-up to age 40).

90. Statistics available for recent periods do not show a strong variation of leukaemia rates at young ages over time [I2]. Nevertheless, the evolution of mortality rates and of leukaemia incidence in the future is very difficult to predict, but the evolution of diagnostic practices and of treatment during the last decades clearly indicate that the assumption of stability over time is uncertain. This uncertainty applies to the estimation of the CBR and CER.

91. For the estimation of the baseline risk for leukaemia, age- and sex-specific incidence rates per 100,000 population in the United Kingdom for the period 2011–2013 were used. These rates were assumed to present no uncertainty in the considered scenarios. Furthermore, the survival function was considered known and not affected by uncertainties.

2. Preferred risk inference

(a) Selection of the preferred risk inference

92. The preferred risk inference for the selected scenario of repeated exposure to CT scans in the United Kingdom is the one derived from the UK childhood CT-scan cohort for exposure at the age of 1 year with a dose to the RBM of 20 mGy and follow-up to 30 years [B4]. The estimated CER for leukaemia+MDS is 5.3 per 10,000 persons (95% CI: 0.6, 18.3) with a CFR of 0.58.

93. This estimate was derived from a study which had been used as the basis to determine the characteristics of the scenario. Thus, no further assumption was required. Therefore, this estimate is preferred to the one derived from the LSS study for which assumptions were needed regarding the transfer of risk estimates obtained from another population, the extrapolation from high doses, and the transposition from a different dose-rate pattern. Nevertheless, several sources of uncertainties can have a non-negligible impact on this estimate.

94. The estimation of risk up to 30 years of age is preferred as the more informative scenario compared to that up to 40 years of age, as 30 years corresponds approximately to the mean age at the end of follow-up of the UK childhood CT-scan study. The model based on the UK study does not take into account the decrease of the relative rate with age attained (figure II).

(b) *Discussion of the impact of sources of uncertainty*

95. The main sources of uncertainties associated with this risk estimate are summarized in table 4. The subsequent paragraphs give the reasons for the grading of the uncertainties (very small, small, moderate or large).

96. *Selected populations:* The impact of population selection is considered to be small, especially because the scenario was determined to mimic the characteristics of the UK childhood CT-scan study, from which the risk model is derived. Exclusion of cases with previous cancer is an imperative selection criterion. Exclusion of 2 cases due to the collection of additional clinical information in the UK childhood CT-scan study demonstrated the importance of this criterion. Nevertheless, the impact of erroneous inclusions appears to be quantitatively small as far as it remains limited to a small number of cases.

97. *Exposure assessment:* The reconstruction of organ doses associated with past CT scans in the UK study was rather crude as it did not consider specific data on the body size of the patients. Due to the reconstruction of individual doses, it is likely that measurement errors will be mostly of the Berkson type, but not all of them truly Berkson. The potential impact on the estimated dose–risk relationship and on the confidence intervals will also depend on degree and magnitude of shared errors. The impact of uncertainty linked to exposure reconstruction has not yet been estimated in published CT-scan studies.

98. *Health outcome assessment:* CLL is very rare before the age of 40, and therefore exclusion of CLL is considered to be of very small impact. The rate of MDS in the United Kingdom population before age 40 is very low compared to leukaemia rates, and would be of negligible impact on the estimated (absolute) risk. In the LSS, analyses suggested a relation between radiation exposure and the ERR of MDS of the same order of magnitude as for leukaemia [I7]. Conversely, in the UK childhood CT-scan study, the ERR estimated for MDS appears to be very high (and very uncertain, based on only nine cases) and much higher than that estimated for leukaemia alone [P1]. Inclusion of MDS cases in addition to leukaemia cases appears to change the estimated ERR per unit dose from 3.6 to 1.9 Gy⁻¹, so a reduction by about a factor of 1.9. Thus, the potential impact of outcome assessment in the case of leukaemia is considered to be moderate.

99. *Study design:* About 30% of the initial dataset of the UK CT-scan study was excluded because of missing data for linkage with the NHSCR. Nevertheless, the probability of missing data is independent of the dose, and the potential impact of study design on the estimated risk is therefore considered as small.

100. *Confounding factors:* Two major sources of bias have been discussed in the context of CT-scan studies; reverse causation and confounding by indication [B13, W5]. Whereas a bias due to reverse causation appears possible for brain tumours, it is much more unlikely for leukaemia, as most leukaemia cases occurring during childhood or young age are acute, with no known early symptoms

occurring more than one year before diagnosis. Indeed, the persistence of the relationship after excluding the data for the first one or two years after CT-scan seems coherent with this. The possibility of a bias due to confounding by indication cannot be ruled out, but several recent results suggested that predisposing factors are unlikely to substantially confound the estimated dose–risk relationship [J5, M6]. The impact of these two confounding factors is therefore considered to be small.

101. *Statistical methods and model uncertainties*: The model derived from the UK CT-scan study is a simple linear risk model. At the present time, the model does not allow consideration of a potential modifying effect of age at exposure and time since exposure on the estimated risk. The potential impact of this limitation is considered small for attained age as the scenario is designed to mimic the characteristics of the study population (which will not be true if one considers an older age at the end of follow-up). For age at exposure, the model derived from the UK CT-scan study does not allow considering a decrease of the ERR per unit dose with increasing age at exposure, which may lead to an underestimation of the risk for very young ages at exposure. The impact of this limitation for the scenario of exposure at age 1 is considered to be potentially large (higher than a factor two).

102. *Other sources of uncertainty*: The scenario relies on the hypothesis that the baseline risk of leukaemia is stable over time, up to the end of follow-up. Based on the recent statistics for the United Kingdom, which do not show a large variation of leukaemia baseline rates since 2000, the impact of this assumption is considered to be small.

Table 4. Characterization of the main sources of uncertainty associated with the preferred risk inference of leukaemia following repeated exposure to CT scans during childhood

Source	Characterization of source	Judged impact ^a
Selected populations	Scenario based on the UK childhood CT-scan study	Very small
	Erroneous inclusion of a limited number of cases with previous cancer	Small
Exposure assessment	Crude estimation of dose to the RBM based on protocols, lack of individual information	Small
	Existence of missing data	Small
Health outcome assessment	Inclusion of CLL—very rare before age 30	Very small
	Consideration of MDS in baseline rates—low rate compared to leukaemia	Very small
	Impact of MDS cases on the estimated ERR	Moderate
Study design	Linkage with the UK NHSCR	Very small
Confounding factors	Higher rate of predisposing factors among children with CT-scan	Small
	Reverse causation	Small
Statistical methods and model uncertainty	Latency	Small
	Absence of assessment of the modifying effect of age at exposure and time since exposure	Large
Other sources of uncertainty	Hypothesis of stability of the baseline risk up to the end of follow-up	Small

^a The impact of the different sources of uncertainty is classified into four categories according to the variation that they are expected to induce on the reported CER: very small—less than a factor of 1.1; small—between a factor of 1.1 to 1.5; moderate—between a factor of 1.5 to 2; and large—greater than a factor of 2.

(c) *Concluding remarks on the preferred risk inference*

103. The preferred risk inference has been derived from a study in which the characteristics of the population, the exposure situation and the period of follow-up to the study are very similar to the scenario. The ERR associated with a dose to the RBM of 20 mGy (the basic quantity in the risk estimation) of about 0.7 is supported by a number of childhood CT-scan studies (table 1), a recent pooled analysis of low-dose studies [L17] and a review of childhood leukaemia studies in various exposure conditions [W1].

104. Three systematic errors* in the preferred risk inference for leukaemia+MDS after CT scans during childhood scenario may be moderate or even large. Two (the inclusion of MDS in the risk model classified as moderate, the inclusion of patients with previous cancer classified as small) may lead to an overestimation of the CER, whereas the third one (mean age at exposure in the study cohort of [B4] considerably higher than one, classified as large) may lead to an underestimation of the risk.

105. The Committee judged the credible interval for the preferred risk inference of the CER based on the consideration of the sources of uncertainties in table 4 which are additional to the statistical uncertainty in table 2. The sources of uncertainties listed above are considered to essentially compensate each other in the preferred estimate but question the significance of the result. Monte Carlo calculations were performed to estimate the impact of small stochastic uncertainties (appendix A). Leukaemia incidence up to age 30 after CT scans at age 1 with a total dose to the RBM of 20 mGy is estimated to be five cases among 10,000 persons with a 95% credible interval from about 0 to 20 cases.

106. Very few estimations of leukaemia CER over a limited period are available in the literature. An assessment of the health risk from the nuclear accident after the Great East Japan earthquake and tsunami in 2011 was performed by an expert group of the World Health Organization (WHO), based on hypothetical lifetime dose to the RBM. The cumulative risk of leukaemia attributable to estimated RBM doses due to the accident was calculated for the residents of the different villages of the Fukushima Prefecture, considering either a follow-up of 15 years after the accident or a follow-up to the attained age of 89 years old [W9]. Table 5 presents the results of the WHO health risk assessment and those of the preferred risk inference in the present report for the same dose level (20 mGy). Based on the results of the LSS (figure II) it is expected that all major contributions to the CER accumulate within the first 29 years after exposure. Thus, the results for CER in the preferred risk inference may be compared to the WHO estimate for a follow-up to 89 years of age. The estimated CERs appear to be of the same order of magnitude: the preferred risk inference of the present report appears to be slightly higher (factor of two) than the one in the WHO report. The good agreement is obtained in spite of larger differences in the scenarios and calculations. The WHO assessment is based on baseline rates in Japan, whereas the present report used baseline rates in the United Kingdom. WHO used a mortality model to calculate incidence [W9], whereas the present report used the Hsu et al. [H4] incidence model, which was not available at the time of the WHO report. Also, WHO [W9] used the mean of the ERR and EAR models for risk transfer, whereas the preferred risk inference in the present report is based on a study of a population similar to the one in the scenario and thus avoiding large uncertainties in the transfer of observed effects from the study population to another population.

107. For age at exposure of 10, again the present estimation of CER based on Berrington de González et al. [B4] (table 3) is larger than the WHO result by a factor of two. According to the discussion of systematic errors, the present estimation of CER is expected to be slightly too large. Thus, there is a very good agreement between the present analysis and the WHO report [W9] for leukaemia risk after exposure at age of 10 years.

Table 5. Comparison of estimates of cumulative leukaemia incidence (per 10,000 persons) after exposure at age of 1 with a dose to the RBM of 20 mGy

CBR: Cumulative baseline risk; CER: Cumulative excess risk; EAR: Excess absolute risk; ERR: Excess relative risk

Source	WHO [W9] ^a	Present report	WHO [W9] ^a
Follow-up time	15 years after the accident	29 years	Up to 89 years of age
CBR	3.0	9.1	52
CER			
Preferred model	1.6	5.3 ^b	2.6
ERR transfer from LSS	2.7	5.0 ^c	3.8
EAR transfer from LSS	0.54	1.8 ^c	1.3

^a Risk estimate from the work of the WHO expert group on the assessment of the health risk from the nuclear accident after the Great East Japan earthquake and tsunami in 2011 based on hypothetical RBM doses [W9]. ERR and EAR risk models derived from the LSS mortality data ([W9], annex J). Preferred model is an unweighted average of ERR and EAR transfer. Baseline incidence rates derived from the recent Japanese population, sex averaged absolute risk scaled from about 26 mGy (mean RBM dose in region 1 in the WHO report) to 20 mGy.

^b Risk estimate from the present report. ERR risk model derived from the UK CT-scan incidence study [B4]. Baseline rates derived from the current United Kingdom population.

^c Risk estimate from the present report. ERR risk model derived from the LSS incidence study [H4]. Baseline rates derived from the current United Kingdom population.

G. Conclusions

108. Rather consistent results were obtained for leukaemia+MDS up to age 30 after CT scans at age 1 with a total dose to the RBM of 20 mGy. Among 10,000 persons with an assumed cumulative baseline incidence of 9 cases, a cumulative excess incidence of about 5 cases of leukaemia+MDS was estimated with a 95% credible interval from about 0 to about 20 cases. Larger uncertainties exist for longer times after exposure.

109. The agreement in the estimated CER between the LSS ERR model and the CT-scan ERR model after exposure at age 1 and follow-up to age 30 is very good (less than a 10% difference). The confidence interval associated with the CER appears to be larger when using the LSS ERR model than when using the UK CT-scan ERR model.

110. For exposure during early childhood and follow-up until young adulthood, CT-scan studies provide a pertinent source of information to assess the risk associated with medical diagnostic exposure. The use of risk models derived from CT-scan studies requires no extrapolation or transfer, whereas using risk models derived from the atomic bombing survivors rely on uncertain assumptions (because of a different situation of exposure, higher doses, different dose rate and ages at exposure). At the present time, the calculation of the CER associated with radiation exposure based on risk models derived from either the LSS or from a CT-scan study, appears to be coherent when scenarios focus precisely on the characteristics of the CT-scan study population (low dose, exposure at young age, short duration of follow-up). This strengthens the confidence in the method used to assess radiation risks based on a transfer of the estimates derived from the LSS to other populations and exposure conditions. Nevertheless, sources of uncertainty in the childhood CT-scan studies are not negligible and can have a moderate to large impact on the preferred risk inference.

111. Extrapolation of the results of the CT-scan study to exposures received at different ages of exposure or longer follow-up embracing a larger part of adulthood is questionable, because they do not deal with age dependencies. Under these conditions, it seems that the use of transfer risk models derived from the LSS remains a method of choice for risk estimations. In the future, methods should be extended to combine information from several studies in the development of risk models better suited to transfer risks between different populations or extend predictions beyond the observed age range.

112. Some of the limitations of the CT-scan studies may be reduced in the future. Extension of the duration of follow-up would allow a better assessment of the modifying effect of age. Additional information on any predisposing factors and the medical reasons for scans will help to clarify potential biases. Analyses based on larger numbers of cases should allow specific analyses of leukaemia subtypes, and better distinction of the risk associated to leukaemia and to MDS. Also, the development of studies in different countries will provide better knowledge about the coherence of the estimated ERR and EAR risks between countries. Other studies are ongoing in Spain [B11] and in the Netherlands [M5]. International projects such as EPI-CT (Epidemiological study to quantify risks for paediatric CT and to optimize doses), with a large statistical power (includes nine national European cohorts with a total of about 1 million children), and with a focus on dosimetric reconstruction and minimization of bias, are expected to provide more precise results [B10, O2, T5, V1, W7].

III. LEUKAEMIA MORTALITY AFTER REPEATED LOW-DOSE EXPOSURE DURING ADULTHOOD

A. Motivation

113. Leukaemia related to repeated radiation exposure during adulthood is of particular interest, because there is a substantial amount of information on an increased incidence of the disease from epidemiology. There is however much uncertainty about the risks of leukaemia after repeated or protracted low-dose exposure. Since the beginning of the nuclear industry in the mid-1940s, occupationally-exposed workers were usually monitored individually with dosimeters. Some of these workers were exposed to low-dose protracted or intermittent radiation exposure over their whole occupational life, and some of these workers have accumulated moderate or even high cumulative doses. In some countries, large populations of such workers have been included in epidemiological cohorts and followed up for up to 60 years.

B. Recapitulation of previous UNSCEAR publications

114. The UNSCEAR 2006 Report, annex A [U3] included a comprehensive review of studies providing results on the incidence of leukaemia after exposure during adulthood. The most informative studies regarding the demonstration of a dose–risk relationship was considered to be those of the cohort of the atomic bombing survivors, workers involved in the nuclear industry, radiologists and other medical X-ray workers, ankylosing spondylitis patients and other medically exposed groups, and the

Techa River residents. The report concluded that the available information confirmed the evidence of a curvilinear dose–response relationship. Little indication existed of an association between the incidence of leukaemia and uranium or plutonium exposure. Based on the LSS [P8], the ERR per unit dose estimated for exposure at 20–40 years of age was 3.6 (90% CI: 2.0, 6.0) Sv^{-1} , and the EAR per 10,000 person–years per unit dose was 2.7 (90% CI: 1.7, 3.9) Sv^{-1} [U3].

115. The UNSCEAR 2012 Report, annex B [U8] was aimed at reviewing the sources of uncertainty and methodology of risk assessment. Leukaemia risk was not considered in the selected risk evaluations, but leukaemia was considered in the general review of sources of uncertainties.

116. The UNSCEAR 2013 Report, annex A [U7] on the health effects of the Fukushima accident similarly reviewed the available results for leukaemia incidence after exposure during adulthood, especially in a post-accident context. The estimated risks for the workers at the Fukushima Daiichi nuclear power station by the Committee and those from WHO [W9] were in good agreement. The workers at the Fukushima Daiichi nuclear power station who incurred the highest external exposure received doses to the RBM of at most 200 mGy. Owing to the small number of workers involved, the conclusion of the UNSCEAR 2013 Report was that no discernible effect of the radiation exposure on leukaemia incidence was expected [U7].

C. Review of recent epidemiological literature

117. A literature review was performed to identify articles providing information on the quantification of the risk of leukaemia associated with radiation exposure. The same research procedure as described in section II.C was applied.

118. Articles providing results for leukaemia risk after exposure during adulthood were considered. However, not all these publications provided original results allowing estimation of a dose–risk relationship after exposure during adulthood in the low to moderate dose range, or were able to derive an estimate of the dose–risk relationship. For instance, an analysis of cancer mortality in a cohort of 43,763 radiologists in the United States, published by Berrington de González et al. [B3] estimated a relative risk were through a comparison with a cohort of 64,990 psychiatrists. An increased death rate was observed among the radiologists for AML and MDS ($n=41$; $\text{RR}=1.62$; 95% CI: 1.05, 2.50). These rates were dominated by those persons who had graduated before 1940 ($\text{RR}=4.68$; 95% CI: 0.91, 24.18). The authors concluded that the excess risk of AML and MDS mortality in radiologists who had graduated before 1940 was likely to have been due to occupational radiation exposure. Nevertheless, due to a lack of information on individual radiation doses, no dose–risk relationship could be derived. Another study by Rajaraman et al. [R2] based on a prospective cohort of 90,957 radiological technologists in the United States showed no elevated incidence of leukaemia among workers who performed fluoroscopically guided interventional procedures, however no dose–risk relationship could be derived as no individual data on radiation doses were available.

119. The following review was limited to studies presenting original epidemiological results, based on individual data, with a quantitative dose–risk relationship for populations exposed to moderate- or low-level ionizing radiation during adulthood. Fourteen articles were selected, related to the atomic bombing survivors, to workers exposed due to their occupation (nuclear workers, miners and Chernobyl liquidators), and to environmental exposures (residents of the Techa River).

1. Life Span Studies of the Japanese atomic bombing survivors

120. A comprehensive publication on cancer mortality among the atomic bombing survivors was published in 2012 [O5]. The study included 86,611 persons, followed up over the period 1950–2003. Dose estimates were based on the DS02 dosimetry system. There were 318 registered deaths from leukaemia. Models considering a linear–quadratic relationship between dose to the RBM and risk of leukaemia provided a better fit than linear models. The sex-averaged ERR of leukaemia was 3.1 (95% CI: 1.8, 4.3) at 1 Gy and 0.15 (95% CI: –0.01, 0.31) at 0.1 Gy with the linear–quadratic model, with a modifying effect of attained age. No specific results were provided for adults at the time of exposure. More details on the risk models are given in section III.D.3.

121. Several articles were recently published proposing methodological improvements in the quantification of the dose–response relationship for leukaemia. In particular, Walsh and Kaiser [W4] applied a model-averaging procedure to nine published leukaemia-risk models, developed from the epidemiological data on mortality from the studies of the Japanese atomic bombing survivors. The model-averaged ERR at 1 Sv was not found to be statistically significant for attained ages of 7 and 12, but was statistically significant for attained ages of 17, 22 and 55. This approach was further developed by extending the number of considered models to 40, and developing a rigorous selection approach [K3]. Compared to the previous analysis, the ERR for leukaemia mortality from the multi-model inference was similar for doses between 0.5 and 2.5 Sv, but at lower doses, the ERR estimates were markedly reduced. The multi-model inference produced risk estimates with a positive 2.5% percentile, only above doses of some 300 mGy. A detailed analysis of leukaemia incidence among the Japanese atomic bombing survivors was also published in 2013 [H4]. The main results of this study are presented in section II.C.1.

2. Studies of workers exposed to radiation

122. The most important study published in recent years on repeated exposure over the working lives of occupationally-exposed workers is the International Nuclear Workers Study (INWORKS) [R5, R6]. The cohort included 308,297 workers monitored for exposure and employed for at least one year by the French Atomic Energy Commission (CEA), AREVA Nuclear Cycle (formerly COGEMA), and Electricité de France (EDF) (the French cohort); workers employed by the British Atomic Weapons Establishment, British Nuclear Fuels Limited (BNFL), the UK Atomic Energy Authority, British Energy Generation, the UK Ministry of Defence, and other organizations providing data to the UK National Registry for Radiation Workers (NRRW) (the United Kingdom cohort); and workers employed by the US Department of Energy's Hanford Site, Savannah River Site, Oak Ridge National Laboratory, Idaho National Laboratory, and the Portsmouth Naval Shipyard (the United States cohort). Analyses of leukaemia risk were published previously for each of the three national cohorts separately: using a linear model, the estimated ERRs per unit dose for leukaemia excluding CLL were 3.96 Gy^{-1} ($n=60$; 90% CI: <0, 16.82) [M4], 1.71 Gy^{-1} ($n=198$; 90% CI: 0.06, 4.29) [M12], and 1.7 Gy^{-1} ($n=369$; 95% CI: –0.22, 4.7) [S5], respectively, for the French, United Kingdom and United States cohorts. The INWORKS used recorded photon doses only, excluding neutron doses and doses from internal emitters. The absorbed dose to the RBM was calculated for each worker based on the results of their individual monitoring for external exposure. Cumulative doses were lagged by 2 years. The exposure period ranged from 1945 to 2005. The total follow-up over the period 1945–2005 was 8.2 million person–years. The mean duration of follow-up was 27 years. The mean cumulative dose to the RBM was 16 mGy (maximum 1.2 Gy), accrued at very low rates (mean 1 mGy per year). The total number of leukaemia deaths (excluding CLL) was 531. For the whole cohort, the estimated linear ERRs of leukaemia mortality per unit absorbed dose was 1.95 (90% CI: 0.50, 3.73) Gy^{-1} and 2.96 (90% CI:

1.17, 5.21) Gy^{-1} after excluding CLL. The strongest association was observed for CML, with an ERR per unit dose of 10.45 (90% CI: 4.48, 19.65) Gy^{-1} [L7].

123. A sensitivity analysis involved fitting the same model to restricted ranges of cumulative dose. This analysis allows excluding person-years with the highest cumulative doses, to assess their impact on the estimated dose–risk relationship. In the dose range 0–300 mGy, the estimated linear ERR of leukaemia mortality per unit dose was 2.52 (90% CI: 0.70, 4.73) Gy^{-1} and 3.31 (90% CI: 1.13, 6.00) Gy^{-1} after excluding CLL [L7]. When restricted ranges within the dose range 0–300 mGy (e.g. 0–250, 0–200 ...) were used, the estimated ERR per unit dose was no longer significantly different from zero. The confidence intervals obtained for the subcohort corresponding to the restricted dose range 0–300 mGy were only slightly wider than those obtained for the whole cohort, because the number of cases excluded was very small. In the dose range 0–300 mGy, the estimated linear ERR of CML mortality per unit dose was 8.68 (90% CI: 2.44, 18.4) Gy^{-1} [L7].

124. Complementary analyses of the INWORKS dataset were performed using a nested case–control approach in order to investigate further the impact of time since exposure and age at exposure on the estimated ERR per unit dose. A significant positive dose–response association was confirmed using a fixed lag model for non-CLL leukaemia mortality; ERR was 2.80 (90% CI: 0.96, 5.10) Gy^{-1} . The fitted lag was estimated to be about 13–17 years, but the difference was not significant. A non-significant time-since-exposure effect was suggested for non-CLL leukaemia mortality. A higher ERR per unit dose was confirmed for CML mortality [D1].

125. More recently, a comprehensive analysis of the French cohort of nuclear workers was published, on a subset similar to the one included in the INWORKS. The cohort included 59,004 workers followed up to 2004. Estimates of dose–mortality associations were obtained using linear ERR models. For non-CLL leukaemia, the estimated ERR per unit dose was 3.52 (90% CI: <0, 16.0) Gy^{-1} , but was not statistically significant, due to the small number of cases (57 deaths) [L8].

126. An analysis of leukaemia incidence has been performed in the cohort of Mayak workers (the Russian Federation) [K28]. The cohort included 22,373 workers employed at the Mayak Production Association main facilities between 1948 and 1982 and followed up to the end of 2004. The cohort included 25% females. A total of 535,877 person-years was accumulated in the study cohort. Information on tobacco-smoking was obtained from medical records for 89% of the workers in the cohort. The doses to the RBM were estimated using the Mayak Workers Dosimetry System 2008. The mean cumulative external gamma-dose to the RBM was 0.39 Gy (0.41 Gy for males and 0.33 Gy for females) while 90% of the workers received doses below 1.15 Gy. The analysis included 77 cases of leukaemia, comprising 24 cases with AML, 21 cases with CLL and 13 cases with CML. The estimated linear ERR for leukaemia incidence per unit dose to the RBM from external gamma exposure was 1.89 (90% CI: 0.89, 3.74) Gy^{-1} and 3.46 (90% CI: 1.57, 7.65) Gy^{-1} after excluding CLL. After adjustment for internal exposure, a significant effect modifier of time since exposure and age at exposure was observed.

127. An analysis of leukaemia risk has been performed on the cohort of Eldorado uranium miners and processors, based on both incidence and mortality data [Z4]. The cohort included 92% of males. The mortality analysis included 17,660 workers first employed in 1932–1980 and followed up over 1950–1999 and 16,770 workers followed up over 1969–1999 for the incidence analysis. The mean cumulative gamma doses weighted by person-years and lagged by 5 years for the Eldorado cohort among males was 52.2 mSv (from 0 to 3,420.0 mSv) in the mortality and 41.5 mSv (from 0 to 2,921.0 mSv) in the incidence analysis. The number of leukaemia deaths was 34 in the mortality analysis and of leukaemia cases 53 in the incidence analysis. No statistically significant association between gamma doses and leukaemia mortality or incidence was found. Nevertheless, interpretation of the results was limited by

the small numbers of cases and the fact that the main exposure was due to radon. Within the Eldorado cohort, Port Hope workers were predominantly exposed to external gamma radiation. The mean cumulative person–year weighted mean cumulative radon exposure was 15.9 working level month (WLM)* and the mean cumulative whole-body gamma dose was 134.4 mSv. ERRs for radon exposure and gamma doses were calculated separately. There was no significant association between leukaemia mortality and gamma dose, radon exposure, or a combination of both [Z3].

128. The risk of death from leukaemia in relation to occupational exposure to prolonged low-level external and internal radiation was analysed by Kreuzer et al. [K25] in the cohort of the former Wismut uranium miners. The cohort included 58,972 miners with mortality follow-up from 1946 to 2013. The dose to the RBM from low-LET (mainly external gamma radiation) and high-LET (mainly due to radon gas and radon decay products) radiation was estimated. The mean cumulative low-LET and high-LET doses to the RBM among exposed miners were 48 and 9 mGy, respectively. A linear model was used for analyses, as the linear-quadratic model provided no statistically significantly better fit. No significant dose–risk relationships were observed for non-CLL leukaemia ($n=120$) in relation to both low-LET (ERR per unit dose of 2.18 (95% CI: $-0.41, 6.37$) Gy^{-1}) and high-LET radiation (ERR per unit dose of 16.65 (95% CI: $-1.13, 46.75$) Gy^{-1}). A significant positive dose–risk relationship was found for CML ($n=31$) with low-LET radiation (ERR per unit dose of 7.20 (95% CI: $0.48, 24.54$) Gy^{-1}) and for all myeloid leukaemia ($n=99$) with high-LET radiation (ERR per unit dose of 26.02 (95% CI: $2.55, 68.99$) Gy^{-1}). No association with death from CLL ($n=70$) with either type of radiation was observed [K25].

129. A nested case–control study of incidence was conducted on a cohort of 110,645 Ukrainian clean-up workers of the 1986 Chernobyl nuclear power plant accident [Z2]. Absorbed doses to the RBM were estimated individually by the Realistic Analytical Dose Reconstruction with Uncertainty Estimation (RADRUE) method. A significant linear dose–response was observed for all types of leukaemia (137 cases) with a linear non-threshold (LNT) model resulting in an ERR per unit dose of 1.26 (95% CI: $0.03, 3.58$) Gy^{-1} . Non-significant positive dose–responses were noted for both CLL and non-CLL (ERR per unit dose of 0.76 (95% CI: $<-0.38, 3.84$) Gy^{-1} and 1.87 (95% CI: $-0.02, 6.54$) Gy^{-1} , based on 79 and 58 cases, respectively). The authors concluded that the estimated dose–risk relationship was statistically consistent with the estimates for the Japanese atomic bombing survivors. However, the exposure estimates were based on proxy interviews, which imply a high uncertainty and potential for bias [U7].

3. Other studies

130. Leukaemia incidence has been analysed for the Techa River cohort, including persons residing in riverside villages between 1950 and 1961, when the releases from the plutonium-production complex of the Mayak Production Association contaminated the river. The cohort included 28,233 persons. Doses to the RBM due to internal and external exposure were estimated individually using the Techa River Dosimetry System (TRDS)-2009. Over the period 1953–2007, 72 leukaemia cases (excluding CLL) were observed. The estimated ERR per unit dose was 1.2 (95% CI: $0.4, 2.5$) Gy^{-1} for all types of leukaemia and 2.2 (95% CI: $0.8, 5.4$) Gy^{-1} for non-CLL leukaemia. The data were consistent with a linear dose–response relationship with no evidence of modification. There was no evidence of a dose–response for CLL [K18].

4. Synthesis of studies

131. In recent years, new results were published from the studies of adults exposed to external radiation due to their occupation (nuclear workers, miners and Chernobyl liquidators) or their environment (residents of the Techa River). The results from these studies complemented those obtained from the cohort of atomic bombing survivors.

132. These results are mostly consistent with a dose–risk relationship for leukaemia risk after exposures during adulthood, with a lower risk coefficient than that estimated in studies considering exposure during childhood. This is coherent with previous knowledge [U6]. Furthermore, these studies improve the knowledge about the leukaemia risk associated with low-dose-rate exposure. Recent studies did not suggest the existence of a threshold dose for the risk of radiation-induced leukaemia.

133. One main limitation is that most of these studies (except the UK occupationally-exposed worker study, the Mayak worker study, the Ukrainian clean-up workers, the Eldorado study and the Techa River cohort) consider mortality rather than incidence data. This is mainly due to the retrospective nature of these studies, which include early periods during which no leukaemia incidence data were available. The development of cancer registries in some countries or regions should allow the development of more incidence studies in the future.

D. Definition of scenario

134. A scenario of repeated exposure over the occupational lifetime of workers in the nuclear industry was chosen, for which pertinent results have been published in recent years. As most risk models for adult exposures only cover mortality, assessment of the risk of leukaemia mortality was considered. This contrasts with the childhood analyses, which concentrated on incidence (see section II). Risk assessment considered both the risk of mortality from leukaemia and leukaemia excluding CLL.

1. Exposure scenario

135. The scenario was designed to reflect the characteristics of the INWORKS cohort [L7]. The INWORKS was a mortality study. This cohort consisted of 85% males. Only those who were monitored for external exposure for one year or more were included. The mean age was 29 at first monitoring and 43 at last monitoring (i.e. a mean duration of radiation monitoring of 14 years). The mean duration of follow-up was 27 years and the mean age at the end of follow-up was 58. The mean cumulative dose to the RBM was 16 mGy, accrued at very low dose rates (mean 1 mGy each year).

136. The defined scenario has the following characteristics:

- (a) United States population;
- (b) Population composed of males only;
- (c) Prolonged exposure from ages 30 to 45 (duration of 15 years);
- (d) Constant dose rate to the RBM of 13.3 mGy each year, leading to a cumulative dose of 200 mGy;
- (e) Alive at the first monitoring (i.e. at age 30);
- (f) Follow-up ranging from ages 30 to 60 (approximately the mean attained age at the end of the follow-up) or 90 (approximately the maximum attained age at the end of follow-up).

2. Reference data

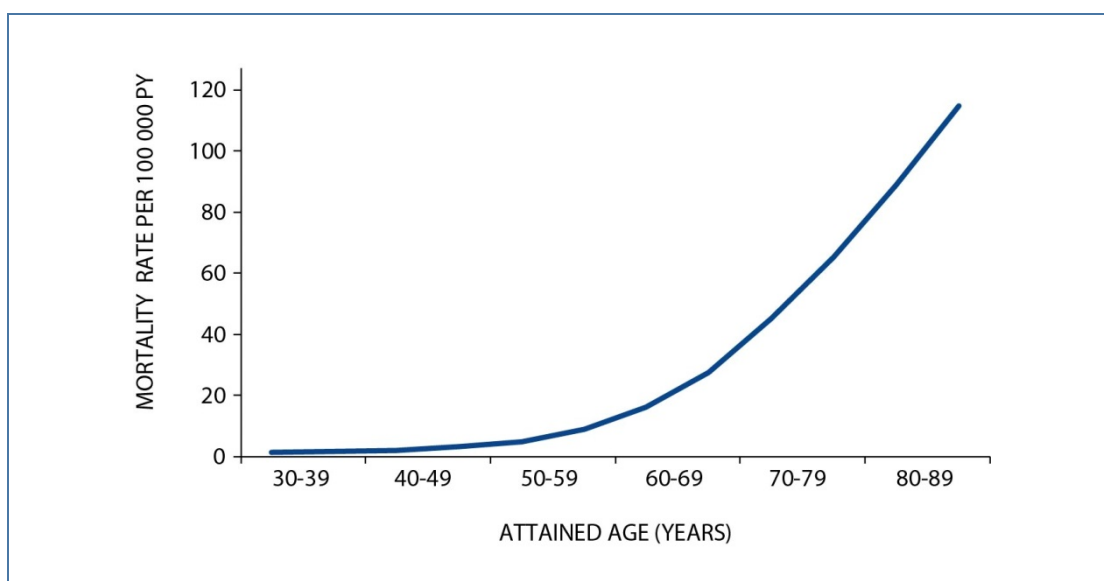
137. For the calculation of the survival function and of the baseline risk of leukaemia, the following sources of data were used:

- (a) For the calculation of the survival function, age- and sex-specific mortality rates were based on data from the United States in 2000 [A4];
- (b) For the estimation of baseline mortality risk of leukaemia and leukaemia excluding CLL, age- and sex-specific rates per 100,000 were based on data on leukaemia mortality derived for the United States from the Surveillance, Epidemiology, and End Results (SEER) program of the National Cancer Institute (NCI) for the period 2000–2005 [N6].

138. Leukaemia baseline mortality rates increase sharply with age. Figure III presents the evolution of leukaemia mortality baseline rates in the United States over the age range considered in the scenario.

Figure III. Baseline rates of leukaemia (all leukaemia including CLL) mortality among males in the United States in 2000–2005 per category of attained age [N6]

CLL: Chronic lymphocytic leukaemia, PY: Person-years



3. Risk models

139. Assessment of radiation-associated risk was performed using the models for all leukaemia mortality derived from the cohort of Japanese atomic bombing survivors by Kaiser and Walsh [K3]. The cohort included 86,611 persons, with 318 deaths from leukaemia observed between 1950 and 2003 [O5]. Both the ERR and EAR models were considered. The ERR model (denoted thereafter as the LSS ERR model) considered a linear–quadratic function with the dose to the RBM and a modifying effect of attained age [K3]:

$$\text{ERR} = (\beta_1 d + \beta_2 d^2) \cdot \exp(\alpha \cdot \ln(\text{age}/55))$$

where d is the dose to the RBM, and $\beta_1=1.38 \text{ Gy}^{-1}$; $\beta_2=1.33 \text{ Gy}^{-2}$; $\alpha=-1.63$. In contrast to the ERR model of Ozasa et al. [O5], the ERR model of Kaiser and Walsh [K3] provided a significant age dependence which ensures a decreasing risk contribution to the CER with increasing attained age. Without this age dependence the CER estimate would exceed plausible limits at old age.

140. The EAR model (denoted thereafter as the LSS EAR model) was linear–quadratic in dose with log–linear effect modification depending on time since exposure (TSE), with different dose coefficients for males and females:

$$\text{EAR} = (\beta_1 d + \beta_2 d^2) \cdot \exp(\gamma \cdot \ln(\text{TSE}/40) \pm \alpha_s)$$

where d is the dose to the RBM, and $\beta_1=1.75 (\text{Gy } 10,000 \text{ PY})^{-1}$; $\beta_2=1.53 (\text{Gy}^2 10,000 \text{ PY})^{-1}$; $\gamma=-0.50$ and $\alpha_s=0.54$ using the positive, negative sign for males and females, respectively. Since no EAR model has been reported by Ozasa et al. [O5], the above EAR model has been developed by refitting the LSS cohort data used in Kaiser and Walsh for the calculation presented in this annex; for the fit, the functional form of the baseline model like that one for the ERR model of Kaiser and Walsh has been applied [K3]. The dependence of time since exposure was significant ($p<10^{-2}$), but measured by the AIC goodness-of-fit was about 10 points lower compared to the ERR model.

141. Risk was also assessed using ERR models derived from the INWORKS cohort, for all leukaemia and leukaemia excluding CLL [L7]. The risk coefficient for all leukaemias obtained from a sensitivity analysis on a restricted group with a dose range 0–300 mGy was also considered. The models considered a linear association with dose to the RBM, with no modifying factor. Model parameters are indicated below:

$$\text{ERR} = \beta \cdot d$$

where d is the cumulative dose to the RBM. For all leukaemia, β was equal to 1.95 (90% CI: 0.50, 3.73) Gy^{-1} over the whole dose range and 2.52 (90% CI: 0.70, 4.73) Gy^{-1} over the restricted range 0–300 mGy. For leukaemia excluding CLL over the whole dose range, β was equal to 2.96 (90% CI: 1.17, 5.21) Gy^{-1} .

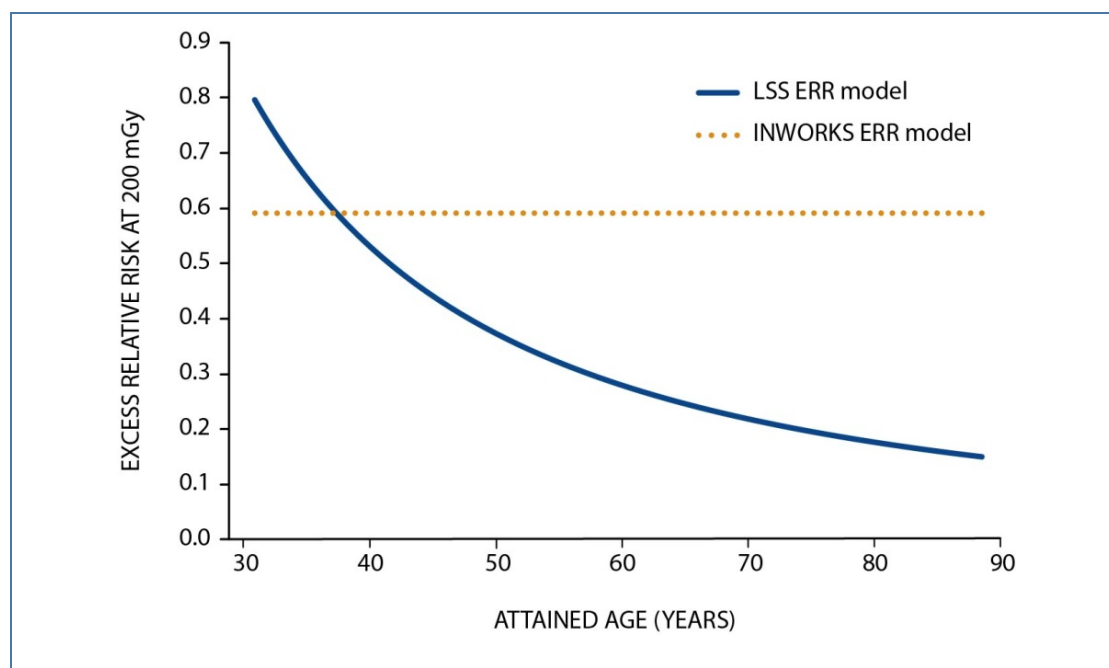
142. For the purpose of this annex, an EAR model was also fitted from the full INWORKS cohort for leukaemia excluding CLL, using a baseline parametric model that was adjusted for country, sex, birth year, birth year squared, log age and log age squared [R4]. The model considered a simple linear association with dose to the RBM but did not allow assessment of the potential impact of modifying factors. Model parameters are indicated below:

$$\text{EAR} = \beta \cdot d$$

where d is the 5-year lagged cumulative dose to the RBM, and $\beta=2.25$ (90% CI: 0.69, 4.1) per 10,000 person–years Gy^{-1} over the whole dose range.

143. The variation of the risk coefficients with attained age, for a dose of 200 mGy received at the age of 30 years is presented in figure IV. Based on the risk derived from the LSS, the ERR decreases sharply with attained age, whereas no variation with attained age is considered in the ERR model derived from the INWORKS.

Figure IV. Excess relative risk at 200 mGy as a function of attained age, for age at exposure of 30 years obtained from the LSS model [K3] and the INWORKS model [L7]



4. Risk-transfer methods

144. No correction was applied to extrapolate from high to low dose. Indeed, a reduction of the strength of the dose–risk relationship at low dose is implicitly considered in the linear–quadratic shape of the models derived from data on the atomic bombing survivors.

145. Because the follow-up of the cohort of atomic bombing survivors began only in 1950, no mortality data are available for the period between 1945 and 1949. This lack of data led to a large uncertainty in the estimated risk for the years just following exposure, when models derived from the LSS were used. To avoid this problem, risk coefficients were capped for the first five years after the bombings in the LSS models, i.e. for each year between exposure and 5 years later the ERR value was the one estimated.

146. To transfer the data from the atomic bombing survivors to the scenario, both multiplicative (based on an ERR model) and additive (based on an EAR model) risk transfers were used. For the application of all models (derived from the cohort of atomic bombing survivors or from the INWORKS cohort) to the scenario, a minimum lag time was considered between exposure and risk. This lag time was modelled as a sigmoid function, varying between 0 and 2 years and centred on 1.5 year.

E. Results

147. The results of the estimated cumulative leukaemia risk associated with the worker scenario for a follow-up to age 60 and 90 are presented in table 6. The survival fraction was 88% at age 60 and 15% at 90. The CBR for leukaemia was 10 per 10,000 persons from ages 30 to 60 years (9.1 for leukaemia other than CLL), and 84 per 10,000 persons from ages 30 to 90 (65 for leukaemia other than CLL). The estimated CFR varied between 18 and 58%, using the ERR model, and up to 135% with the LSS EAR model and follow-up to age 60 years.

148. For the INWORKS cohort, the CER obtained using the ERR model based on the restricted dose range below 300 mGy is slightly higher than that obtained using the ERR model based on the full dose range (a difference of about 30%). Application of the ERR model to leukaemia or leukaemia other than CLL leukaemia makes little difference in the estimation of CER; slightly higher values are obtained in the case of leukaemia other than CLL (a difference of about 30%).

149. For the follow-up from ages 30 to 60, the CER for leukaemia due to the cumulative dose to the RBM estimated from the EAR models was systematically higher than that estimated from the ERR models for both the LSS and INWORKS cohorts, but were associated with a much wider confidence interval. This difference was no longer observed for follow-up from ages 30 to 90.

150. For the follow-up to age 60, the estimated CERs for all leukaemias derived from the ERR model for the LSS and INWORKS cohorts were close and had similar confidence intervals (2.8 (95% CI: -0.1, 5.6) Gy⁻¹ and 3.5 (95% CI: 0.8, 8.0) Gy⁻¹, respectively). But when a follow-up to age 90 was considered, the CER estimated from the ERR model for the LSS cohort was about half that estimated for the INWORKS cohort (15 (95% CI: 0.1, 31) Gy⁻¹ and 32 (95% CI: 6.9, 73) Gy⁻¹, respectively) and the confidence interval for the INWORKS cohort was wide. This wide confidence interval may reflect an overestimation of the risk to the INWORKS cohort, due to the absence of correction for the modifying effect of attained age.

Table 6. Cumulative risk of leukaemia mortality for a scenario of a population of workers receiving a dose of 200 mGy to the RBM over their occupational life

CBR: Cumulative baseline risk; CER: Cumulative excess risk, estimated using the REIC methodology; CFR: Cumulative fractional ratio; CLL: Chronic lymphocytic leukaemia; LSS: Life Span Study

Model	CBR ^a		Cumulative leukaemia risk associated with exposure scenario ^b	
	All-cause mortality per 10 000 persons	Leukaemia incidence per 10 000 persons	CER per 10 000 persons (95% CI)	CFR (CER/CBR)
PROTRACTED EXPOSURE FROM AGES 30 TO 45, FOLLOW-UP TO AGE 60 ^{c,d}				
LSS mortality models [K3]				
ERR transfer—whole dose range— all leukaemia	1 294	10	2.8 (–0.1, 5.6)	0.27
EAR transfer—whole dose range— all leukaemia			14 (–3.0, 32)	1.35
INWORKS mortality model [L7]				
ERR transfer—whole dose range— all leukaemia	1 294	10	3.5 (0.8, 8.0)	0.34
ERR transfer—restricted dose range 0–300 mGy—all leukaemia			4.5 (1.1, 10)	0.43
ERR transfer—whole dose range— leukaemia excluding CLL	1 294	9.1	4.6 (1.5, 9.6)	0.50
EAR transfer—whole dose range— leukaemia excluding CLL			8.8 (2.3, 19)	0.97

Model	CBR ^a		Cumulative leukaemia risk associated with exposure scenario ^b	
	All-cause mortality per 10 000 persons	Leukaemia incidence per 10 000 persons	CER per 10 000 persons (95% CI)	CFR (CER/CBR)
PROTRACTED EXPOSURE FROM AGES 30 TO 45, FOLLOW-UP TO AGE 90 ^{c,d}				
LSS mortality models [K3]				
ERR transfer—whole dose range— all leukaemia	8 716	84	15 (0.1, 31)	0.18
EAR transfer—whole dose range— all leukaemia			20 (–4.2, 43)	0.24
INWORKS mortality model [L7]				
ERR transfer—whole dose range— all leukaemia	8 716	84	32 (6.9, 73)	0.38
ERR transfer—restricted dose range 0–300 mGy—all leukaemia			42 (9.7, 93)	0.49
ERR transfer—whole dose range— leukaemia excluding CLL	8 716	65	37 (12, 78)	0.58
EAR transfer—whole dose range— leukaemia excluding CLL			16 (4.2, 35)	0.25

^a United States male population—without exposure—alive at exposure age.

^b Cumulative dose to RBM of 200 mGy due to external exposure at 13.3 mGy each year from ages 30 to 45.

^c Workers exposed to 13.3 mGy during 15 years from ages 30 to 45.

^d Up to age 60 (90) means up to the 60th (90th) birthday.

F. Discussion of scenario calculations

1. Sources of uncertainties

(a) Selected populations

151. The scenario was designed to reflect the characteristics of the INWORKS cohort [L7]. The INWORKS was a mortality study, and therefore the whole scenario was based on mortality: use of mortality reference data for baseline rates and use of a risk model based on mortality from the LSS. As 85% of the INWORKS workers were males, the scenario was focused on males only. The pattern of exposure (200 mGy cumulative over 15 years of activity) was considered to be realistic. The duration of exposure corresponds to the mean duration observed in the INWORKS cohort. The level of exposure is clearly higher than the mean cumulative dose (16 mGy), however was chosen to be closer to the range where significant results had been observed. This level of dose is realistic, as some workers from the cohort received doses of more than 200 mGy.

152. The LSS cohort included a large portion of the atomic bombing survivors who were within 2.5 km of the hypocentres at the time of the bombings, and an age- and sex-matched sample of people who were between 2.5 and 10 km from the hypocentres. The people were recruited on the basis of the 1950 Japanese National Census and of additional information collected by the Atomic Bomb Casualty Commission. Comprehensive mortality follow-up began in October 1950. Unavoidably, leukaemia cases occurring before 1950, the number of which could have been appreciable, were lost to the study [F1]. The number of persons included was 120,321 (82,214 from Hiroshima and 38,107 from Nagasaki). Among them, 123 persons were unavailable for the study because of misidentification or insufficient information, and another 7,058 survivors did not have dose estimates, mainly due to insufficient or uncertain information on their location and shielding at the time of the bombings. About 27,000 were not in the city at the time of the bombings and, thus, were not exposed. The dose–risk analyses were therefore based on a total of 86,611 persons [O5].

153. The INWORKS cohort consisted of the pooling of three pre-existing cohorts of occupationally-exposed workers in France, the United Kingdom and the United States. The selection criteria were that the workers should have been employed in the nuclear industry for at least one year and to have been monitored for external radiation exposure. The selection criteria were independent of the studied health outcome, namely the risk of leukaemia death. Workers entered the study either one year after the date of first employment or on the date of first dosimetric monitoring, whichever was later. In France, follow-up began only on 1 January 1968, as no information on individual causes of death is available from the National Death Registry before. In France, workers were given the opportunity to refuse participation, which is required by the French Data Protection Authority; however, none did. In the United States, worker information was taken from existing records, with no direct contact with any participants; because there is minimal risk to participants, the Institutional Review Board of the National Institute for Occupational Safety and Health waived the requirements for informed consent. In the United Kingdom, less than 1% of the workers refused to participate in the NRRW study.

154. It should be noted that the risk model derived from the INWORKS is based on a population with a range of age at exposure and attained age much narrower than the LSS. It is not sure that a risk model derived from an LSS subset limited to adults at the time of the bombings would be able to quantify the modifying effect of age at exposure and attained age.

(b) *Exposure assessment*

155. The exposure parameters and doses considered in the present scenario are fixed and considered without uncertainty. Nevertheless, uncertainties and measurement errors exist in the cohorts used to derive the scenario and the risk models. In the LSS, the main points to be considered while discussing uncertainty in the exposure assessment are detailed in section II.F.1(b).

156. The reconstruction of cumulative doses due to occupational exposure is associated with uncertainties, detailed in [T6]. The absorbed dose to the RBM was calculated for each worker based on the results of their individual monitoring for external exposure. The main sources of uncertainties were due to incomplete dosimetric records, limit of detection of dosimeters, and non-consideration of neutron and internal exposure. In the INWORKS, it was not possible to estimate doses due to neutron or internal contamination, but it was possible to flag workers with such potential exposures. Sensitivity analyses based on these flags proved not to change the main conclusions of the INWORKS [L7, S5]. Nevertheless, one cannot exclude the possibility that the highest doses were received by earlier workers whose dose records could be most suspect and be most susceptible to missing doses. A thorough investigation of the impact of neutron doses and doses from internal emitters, as well as the possibility of unrecorded occupational external radiation doses has yet to be performed.

(c) *Health outcome assessment*

157. In the scenarios, age- and sex-specific rates per 100,000 population for leukaemia mortality for the United States were used. This choice was made to ensure coherence between the reference data and risk models from the LSS and the INWORKS. Either rates for all leukaemias or for leukaemia excluding CLL were used to coincide with the model used.

158. The total number of leukaemia deaths in the LSS cohort was 318. The sex-averaged ERR for all leukaemia was 3.1 (95% CI: 1.8, 4.3) Gy^{-1} [O5]. Since only seven deaths were attributed to CLL (2%) in the LSS, no separate dose-response analysis was performed for CLL [R3]. No model was derived for leukaemia mortality excluding CLL. Nevertheless, due to the small percentage of deaths, exclusion of CLLs should have little impact on the estimated ERR.

159. The total number of leukaemia deaths in the INWORKS cohort was 669, including 138 CLL deaths (21%). The estimated linear ERR for leukaemia mortality per unit absorbed dose was 1.9 (90% CI: 0.5, 3.7) Gy^{-1} and 3.0 (90% CI: 1.1, 5.2) Gy^{-1} after excluding CLL [L7, L8]. The ERR per unit dose for CLL was -1.1 (90% CI: not estimable, 1.8) Gy^{-1} [L7].

(d) *Study design*

160. In the LSS, information on vital status and cause of death has been collected continually since the cohort's inception in 1 October 1950 until 31 December 2000. Mortality follow-up was facilitated by the family registry system (*koseki*), which covers the whole of Japan and is 99% complete. Classification of decedents was by the underlying cause of death coded according to the International Classification of Diseases. Only a very small number were lost to follow-up due to migration out of the country [O5, R3].

161. The INWORKS gathered data from three cohorts. Follow-up ranged from 1943 to 2005. In the United Kingdom, follow-up commenced in 1955 with updates of mortality information obtained on an ongoing basis from central registries for England, Wales and Scotland, as well as at intervals from regional offices for workers resident in the Channel Islands, the Isle of Man or Northern Ireland. In the United States, follow-up commenced with the start of operations at each facility (1944 for the earliest nuclear facility in the United States), and cause of death was obtained from the National Death Index (from 1979 onwards, and from US State and multiple other sources before that year) [H1]. The cause of death was confirmed through periodic searches of social security administration records conducted by the US National Institute for Occupational Safety and Health. In France, follow-up commenced in 1968 because the French National Death Registry has only recorded information on individual causes of death since 1968; follow-up is updated biannually with cause of death obtained from the French National Institute for Medical Research. The number of deaths in the INWORKS was 66,632. Underlying causes of death were coded according to the International Classification of Diseases. Because information was obtained from employers and national registries, loss to follow-up is minimal: only 0.22, 2.56 and 0.83% of employees were lost to follow-up or emigrated from the French, United Kingdom and United States cohorts, respectively [H1, L6].

(e) *Confounding factors*

162. Risk factors for and causes of leukaemia are largely unknown. Therefore, there are few known confounders of the association between leukaemia and radiation. Age and sex are controlled in the analyses. Other known risk factors include genetic diseases, exposure to benzene and some

pesticides, and history of treatment for cancer. Smoking is associated with myeloid leukaemia; however, the size of this association is relatively small and therefore would require large differences in smoking frequency across levels of cumulative dose to cause substantial confounding of the radiation–leukaemia association.

163. In the LSS, differences in the baseline mortality rates for leukaemia were reported between proximal and distal survivors, particularly in the first decade after the bombings [R3]. Adjustment for proximal or distal location at the time of the bombings affected the estimates of the association between radiation dose and leukaemia mortality. Differences in baseline mortality rates by location at the time of the bombings may also reflect the selective survival among proximal survivors. Adjustment for baseline differences in mortality rates between proximal and distal survivors minimizes the problems of confounding by proximal or distal location, but does not address concerns that the survivors of the atomic bombings may be a selected group of people who are relatively less susceptible to radiation-induced leukaemia than the general population [R3].

164. In the INWORKS, adjusting the risk analyses by socio-economic status was considered to substantially reduce confounding by smoking. Adjustment for socio-economic status, however, resulted in little change in the risk estimate for leukaemia excluding CLL. Exposure of nuclear workers to other causes of leukaemia such as benzene cannot be excluded as a potential source of bias [L7]. A previous analysis of the United States nuclear workers reported weak evidence of confounding by benzene exposure in an analysis of the leukaemia risk associated with external radiation exposure [S5]. Benzene exposure could not be assessed for the INWORKS cohort. Nevertheless, results from sensitivity analyses and the use of indirect arguments suggest that confounding did not have a large impact on estimates derived from INWORKS [S5].

(f) *Statistical methods and model uncertainties*

165. Many uncertainties can be linked to the risk models, including the shape of the dose–risk relationship, the quantification of modifying effects (age, time since exposure), the latency period between exposure and risk, and the type of risk transfer (EAR or ERR based transfer).

166. In the scenarios used, the statistical uncertainty associated with the risk coefficients was considered through confidence intervals, and, where available, for both the EAR and ERR models.

167. The mortality risk models derived from the LSS are based on a large population (more than 86,000 persons) and long duration of follow-up (from 1950 to 2003). There were 318 registered deaths from leukaemia. Uncertainty in the risk estimates at low doses was thought to originate from various sources, including different estimates of risk at background levels, uncertainty in the dose estimates, residual confounding and interaction, other risk factors, and exposure to residual radiation and/or medical radiation [O6]. In addition, due to the late beginning of follow-up (1950, which was five years after the bombings), a greater uncertainty is associated with the risk estimated in the first years after exposure. This lack of information was managed by applying a 5-year cap to the risks estimated in the five years after the bombings. Both the ERR and EAR models were considered. The models considered a linear–quadratic function with dose to the RBM and a modifying effect of attained age. There is no evidence for modifying effects of sex, age at exposure, or time since exposure [K3]. Neglecting such possible modifying effects may introduce a small uncertainty.

168. In the INWORKS cohort, additional analyses considered possible modification of the ERR by time since exposure and age at exposure. Compared to the risk coefficient estimated using a fixed lag of two years, the estimated ERR for non-CLL leukaemia increased nearly twofold using a fitted lag of

19 years (ERR per unit dose of 4.68 (90% CI: 1.26, 9.37) Gy⁻¹). The analysis of a combined temporal effect on the risk of non-CLL leukaemia due to radiation exposure showed that the highest significantly positive ERR estimates were observed for age at exposure of 35 years or older and time since exposure of 20 or more years. Significant risk heterogeneity was observed for CML with time since exposure, with increased ERR estimates shortly after exposure (2–10 years) and again later (20–30 years). Delayed effects were observed for AML although the estimates were not statistically significant. Additional sensitivity analyses considered different lag times. Using a 10-year lag time, the estimated linear ERR for leukaemia mortality per unit absorbed dose was 2.5 (90% CI: 0.8, 4.5) Gy⁻¹ (instead of 1.9 (90% CI: 0.5, 3.7) Gy⁻¹ in the main analysis using a 2-year lag) [D1].

(g) *Other sources of uncertainty*

169. The estimation of baseline risk relied on the baseline mortality risk for leukaemia, age- and sex-specific rates per 100,000 population for the United States for the period 2000–2005. Baseline mortality rates could change, if, for example, an effective treatment could be developed for some types of leukaemia. Nevertheless, for the purpose of the present risk assessment, it was assumed that uncertainty associated with baseline rates in the United States would be small. The survival function was also considered known and not affected by uncertainties.

170. One major assumption was that the selected reference rates were considered stable over the whole period of the risk assessment, which is here up to a period of 60 years (scenario of exposure at age 30 with a follow-up to age 90). Evolution of leukaemia mortality rates in the future is very difficult to predict. The assumption of stability is even more critical based on mortality than on incidence in view of the evolution of treatment. Uncertainty exists in the level of reference rates, but also a potential shift of rates with attained age cannot be excluded. This uncertainty applies to the estimation of both the CBR and CER.

171. Another potential source of bias is related to the healthy worker effect. This effect, however, is more applicable to solid cancer than to leukaemia risk and is discussed in detail in section IV.F.1(g).

2. Preferred risk inference

(a) *Selection of the preferred risk inference*

172. The preferred risk inference for the selected scenario of repeated exposure over the occupational life of a United States male worker in the nuclear industry is the one derived from the INWORKS for leukaemia excluding CLL [L7]. For exposure from ages 30 to 45 and follow-up to 60 years of age, the estimated CER is 4.6 per 10,000 persons (95% CI: 1.5, 9.6) for a dose to the RBM of 200 mGy.

173. Given that the selected scenario refers to the exposure of a modern population of United States male workers exposed over a prolonged period, the CERs based on the INWORKS are thought to be more representative than the CERs obtained using models from the LSS. Indeed, this estimate is derived from a study which has been used as the basis to determine the characteristics of the scenario. There is no need to transfer the exposure from another population, or extrapolate from high doses, or transpose from a different dose-rate pattern. Therefore, this estimate is preferred to the one derived from the LSS study for which assumptions for these three aspects are needed.

174. As CLL does not seem to be associated with radiation exposure, the ERR for leukaemia excluding CLL was the preferred one derived from the INWORKS [L7]. The confidence interval associated with the CER is narrow, and of similar width to the one associated with the CER estimated for all leukaemias, for both the full dose range and the restricted dose range below 300 mGy.

175. Estimation of risk up to 60 years of age is preferred to 90 years of age, as 60 years corresponds approximately to the mean age at the end of follow-up in the INWORKS. As no age-dependency could be derived for the ERR and EAR obtained from the INWORKS, the CERs cumulated up to age 90 probably lead to an overestimation of the risk, as they do not reflect a potential reduction of the strength of the association with attained age (as illustrated by the results in table 6).

176. Up to now, only ERR models have been published from the INWORKS [L7]. Simple EAR coefficients derived from the INWORKS were provided especially for this annex to allow comparison. The estimated CER up to age 60 for leukaemia excluding CLL for the INWORKS cohort was higher with the EAR model than that with the ERR model, and associated with a much wider confidence interval. It is noted, however, that the quality of fit of the INWORKS EAR model was lower than that of the ERR model. If multi-model inference was to be implemented, the results would be very close to the risk estimates based on the ERR model with negligible influence of the EAR model. This is a result of the negligible weight for the EAR model in multi-model inference.

(b) *Discussion of the impact of sources of uncertainty*

177. The main sources of uncertainties associated with this risk estimate are summarized in table 7. The subsequent paragraphs give the reasons for the grading of the uncertainties (very small, small, moderate or large).

178. *Selected populations:* The INWORKS includes a contemporary population of mostly males (87%) from several countries (France, United Kingdom and United States) with similar lifestyles to those in the selected scenario (United States male workers). The potential impact of population selection is therefore considered to be very small.

179. *Exposure assessment:* The primary source of exposure of the members of the INWORKS cohort was external low-LET radiation received at the workplace. However, some INWORKS workers had additional exposures to neutrons at the workplace, internal emitters (caesium, tritium, plutonium), environmental sources (radon and decay products and terrestrial gamma radiation) and job-related medical exposures (i.e. chest X-rays). Leuraud et al. showed that adjustment for neutron led to a decrease in the ERR estimated for leukaemia excluding CLL of about 40% [L7]. The other sources of dosimetric uncertainties (e.g. missing dose records) were not assessed but are also expected to be small. A reanalysis of Canadian nuclear energy workers allowed considering separate terms for tritium and gamma doses. The mean cumulative person-time weighted lung dose from tritium was about 3 mSv. Risks were due solely to gamma doses and the addition of tritium doses did not improve the fit of the model [Z5].

180. *Health outcome assessment:* The impact of sources of uncertainty related to outcome assessment is considered to be small or very small because of the good quality of ascertainment of cancer cases. Choosing all leukaemias instead of only leukaemia excluding CLL makes a difference of 24% in the estimated CER. In the future, if possible, from available data, analysis by leukaemia subtypes is recommended.

181. *Study design*: The completeness of follow-up was very good in the three countries involved in the INWORKS. Certification of death was of good quality, and considered to be independent of dose. The potential impact of study design on the estimated risk is therefore small to very small.

182. *Confounding factors*: Adjustment for socio-economic status resulted in a decrease of only 2% in the estimated ERR for leukaemia excluding CLL in the INWORKS [L7]. Furthermore, no evidence of confounding by benzene exposure was suggested in a previous analysis of US nuclear workers [S5]. Thus, the potential impact of confounding is considered to be small to very small.

Table 7. Characterization of the main sources of uncertainty associated with the preferred risk inference of leukaemia following prolonged exposure over the occupational life of a US male worker in the nuclear industry

Source	Characterization of source	Judged impact ^a
Selected populations	Scenario based on the INWORKS	Very small
Exposure assessment	Exposures to radiation not specifically accounted for in the INWORKS	
	Neutrons	Small
	Internal emitters	Small
	Missed doses	Small
	Job-required chest X-rays	Small
	Uncertainty in external doses	Small
Health outcome assessment	Quality of causes of death	Very small
	Inclusion of CLL	Small
Study design	Competing causes of death	Small
	Loss to follow-up	Very small
Confounding factors	Socio-economic status	Very small
	Exposure to other leukaemogens at the work place (benzene, hydrazine ...)	Small
Statistical methods and model uncertainty	Assumed latency period	Small
	Curvature of the dose–risk relationship	Small (at such level of doses)
	Transfer (ERR versus EAR)	Small ^b
	Absence of assessment of the modifying effect of age and time	Small (as the scenario is like the study characteristics)
Other sources of uncertainty	Hypothesis of stability of the baseline risk up to the end of follow-up	Small

^a The impact of the different sources of uncertainty is classified into four categories according to the variation they are expected to induce on the reported CER: very small—less than a factor of 1.1; small—between a factor of 1.1 to 1.5; moderate—between a factor of 1.5 to 2; and large—greater than a factor of 2.

^b The judged impact is “small” in all situations, except when using the INWORKS EAR model, which presents a limited quality of fit compared to the INWORKS ERR model.

183. *Statistical methods and model uncertainties*: A sensitivity analysis of the impact of the lag period (10-year instead of 2-year lag) indicated an increase of 21% in the ERR per unit dose estimate for leukaemia excluding CLL [L7]. Furthermore, even though additional analyses of the INWORKS cohort observed risk heterogeneity with age or time since exposure for CML or AML, they did not identify age at time of exposure, time since exposure or attained age dependencies for leukaemia excluding CLL [D1].

The risk models based on the INWORKS can be used to predict the risk for the population of interest in this scenario for a follow-up period ending at age 60, as this range of ages represents the centre of the data for the INWORKS cohort. The ERR per unit dose estimated for leukaemia in the INWORKS over the whole dose range is very similar to the one obtained for the restricted dose range 0–300 mGy. A difference of about a factor of 1.9 is observed between the CERs estimated using an ERR- and an EAR-based model. The impact of the choice of model transfer therefore seems to be a source of uncertainty of moderate magnitude. However, due to the limited quality of fit of the INWORKS EAR model, its impact on risk estimates based on multi-model inference would be negligible.

184. *Other sources of uncertainty:* In the present scenario, the estimated risk is valid under the assumption that the baseline rates apply without change to the whole period of the scenario. This hypothesis of stability of baseline rates for a period of 30 years (from age 30 at first exposure to attained age 60) is indeed a strong hypothesis. Nevertheless, the evolution of leukaemia mortality rates in the United States has shown a decrease of about 25% over the last two decades. It is therefore unlikely that variation of baseline rates could have more than a small impact on the estimated risks. Other sources of uncertainty not taken into account explicitly are expected to have only a minor impact on the preferred estimates and credible intervals.

(c) *Concluding remarks on the preferred risk inference*

185. The selected risk estimate was applied to a scenario similar to the population from which it was derived. The characteristic limits any uncertainties associated with transfer to a different population or exposure situation.

186. Different sources of uncertainty apply to such cumulative analysis of the risk estimates. None of the sources of uncertainty not considered in the calculations is expected to lead to a large or even moderate impact on the estimated radiation risk. Those considered include selection of the study population, exposure assessment, health outcome classification, latency period, potential confounders, transfer of effect-per-unit-dose estimates to risk of the population in the scenario, and the evolution of baseline rates.

187. Based on the analysis of the different sources of uncertainty presented in table 7, and the statistical uncertainty estimated in table 6, the Committee judged the credible interval for the “preferred” risk estimate of the CER. Leukaemia mortality up to age 60 after occupational exposure with a total whole-body dose of 200 mGy is estimated to be about 5 cases among 10,000 persons with a 95% credible interval from about 1 to about 10 cases (table 24).

G. Conclusions

188. For exposure to a dose to the RBM of 200 mGy from 30 to 45 years of age with a follow-up to 60 years of age, the INWORKS provides a much more pertinent source of information to assess leukaemia mortality risk among male workers than the LSS. For the present scenario, the use of the ERR per unit dose derived from the INWORKS cohort requires no extrapolation or transfer, whereas using risk models derived from the atomic bombing survivors relies on uncertain assumptions (related, for example, to a different situation of exposure, higher doses and different dose rates). Based on the INWORKS, a CER of about 5 per 10,000 persons with a credible interval from about 1 to 10 per 10,000 persons was derived.

189. Calculation of cumulative leukaemia excess risk associated with radiation using risk models, derived either from LSS or INWORKS ERR risk models, appears to be coherent, when scenarios focus precisely on the characteristics of the INWORKS population (repeated low doses over several years). This supports the validity of using risk models derived from the LSS to transfer risks to other exposed populations. In the future, consideration of leukaemia subtypes in such comparisons of the ability of different risk models to predict risk for a similar scenario would be worthwhile.

190. The agreement in the estimated CER between the LSS ERR model and the INWORKS ERR model with follow-up to age 60 was good. However, for follow-up to age 90, the agreement was less good. This may be due to the inability of the INWORKS model to estimate risk over a long lifespan. Indeed, the mean age at the end of follow-up in the INWORKS is 58, and prediction* up to age 90 lies at the edge of the covered age span. In addition, the considered model did not include any modifying effect of age.

191. In this analysis, it was considered that the preferred estimate was for the follow-up period up to age 60, because the scenario was elaborated on the characteristics of the INWORKS population. Nevertheless, it is likely that the excess risk for cancer before age 60 from occupational exposures accounts for a relatively small portion (presumably, less than 25%) of the CER for cancer at age 90.

192. Currently, risk models derived from the INWORKS are not so reliable when a longer duration of follow-up is considered. For such a prediction, a risk model derived from the LSS and considering the modifying effect of age may be preferred. The limitations of the INWORKS should be reduced in the future, because of an extended follow-up, which should allow a better assessment of the modifying effect of age on the dose–risk relationship. Furthermore, comparison between cohorts will provide a better knowledge about the coherence of the ERR and EAR risks estimated between countries.

IV. SOLID CANCER MORTALITY AFTER ACUTE AND PROTRACTED EXPOSURE

A. Motivation

193. Studies of radiogenic solid cancer are essential to understand the societal impact on health from exposure to ionizing radiation, and to develop risk assessment tools that can be used in retrospective or prospective analyses of radiation-exposure situations. After a uniform whole-body exposure to low-LET radiation, the excess lifetime risk of cancer is dominated by the excess lifetime risk of solid cancers (more than 90% in males and 95% in females, of the excess risk of all cancers combined [N9, U3]). Studies providing dose–response relationships for individual solid cancer types are, in particular, useful for estimating the risk from non-uniform exposure (e.g. X-ray exposures of particular organs or tissues, and radionuclides that accumulate in certain organs [U2, U3]). Studies of solid cancers as a group (e.g. ICD-9 codes 140–199; ICD-10 codes C00–C80) are useful when all organs are exposed to doses of similar magnitude, which is often the case for workers or members of the public exposed externally to penetrating gamma radiation. Dose–response relationships for solid cancers as a group are based on a larger number of cases than for individual cancers, and they normally have lower uncertainties. However, they represent a mixture of dose responses that could be biologically different from cancer to cancer and could need different mathematical approaches.

194. An important part of the mandate of the Committee is to analyse the risk of adverse health effects for workers exposed to radiation during typical day-to-day activities. This section describes an evaluation of solid cancer mortality for a hypothetical scenario of workers in the United States assumed to be exposed over a prolonged period to low doses of low-LET radiation. This evaluation is based on the most recent relevant epidemiological studies for solid cancers, and is intended to:

- (a) Provide estimates of the magnitude of radiogenic risk for solid cancers at low doses and low dose rates;
- (b) Provide a meaningful assessment of uncertainties in the risk estimates;
- (c) Enhance understanding of the application of risk models derived from one exposure situation (e.g. LSS) to estimate the risk in a different exposure situation (e.g. occupationally-exposed workers).

195. The scenario described in this section focuses on solid cancer mortality at the borderline of low to moderate dose exposures (100 mGy). Since the publication of the Committee's previous report on the subject (annex B of the UNSCEAR 2012 Report [U8]), two major epidemiological studies of all solid cancers for the LSS cohort have been published: Ozasa et al. [O5] for cancer mortality, and Grant et al. [G8] for cancer incidence based on a revised dosimetry (DS02R1 [C10]). Furthermore, a significant number of epidemiological studies of cancer incidence and mortality in workers and in members of the public exposed to radiation have been published. All of these studies (see section IV.C) yield significant developments and a sufficient amount of information to allow meaningful assessments of radiological cancer risk and its uncertainties.

B. Recapitulation of previous UNSCEAR publications

196. The UNSCEAR 2006 Report, annex A [U3] reviewed dose responses for all solid cancers as a group and for individual solid cancers. For all solid cancers in the LSS cohort, the report included mortality data with follow-up until the end of 2000, using the DS02 dosimetry system. The report included risk estimates for solid cancer derived from other cohort studies, mainly among workers in the nuclear industry, for comparison. The UNSCEAR 2006 Report [U3] also presented a series of estimates of lifetime cancer risk based on mortality and incidence data from the LSS cohort of the atomic bombing survivors. Projected lifetime cancer mortality risks (i.e. the REID) were calculated at three test doses: 0.01 Sv, 0.1 Sv and 1 Sv (assuming no threshold in dose), and they were reported separately for males, females and both sexes combined, for different ages at exposures, for populations of five countries/territories (China, Japan, Puerto Rico, United Kingdom and United States), and for different ERR and EAR risk models with different dependencies on dose, age at exposure and time since exposure. Risk estimates were presented as single values for each combination of factors (age, sex, population). Probability distributions of the REID obtained using Bayesian Markov Chain Monte Carlo approaches (MCMC) were included for selected endpoints. Their main results were for a dose of 100 mSv (0.1 Sv). For the United States population (table 60 of [U3]), the point estimates* of the REID from a test dose of 100 mSv from various models varied from 3.8 to 7.9% Sv^{-1} for males and from 5.0 to 12.9% Sv^{-1} for females.

197. The UNSCEAR 2012 Report, annex B [U8] focused on the characterization of uncertainties in the estimation of risk of cancer due to exposure to radiation and stated that proper estimation and communication of uncertainties is essential for gaining confidence among the public, decision-makers and professionals. The report identified the main sources of uncertainty in risk estimation and separated

them into (a) uncertainties in different aspects of radio-epidemiology (dosimetry, health data, model choice and statistical analysis); and (b) uncertainties associated with the application of epidemiological data to different populations and exposure situations (different exposure rates or radiation types). The report provided guidance regarding methods to propagate and combine uncertainties (e.g. Monte Carlo techniques; multi-model inference) and provided uncertainty ranges for important parameters of the risk assessment models.

198. The UNSCEAR 2012 Report, annex B [U8] developed an example of an assessment of risk of solid cancers in workers exposed to low-LET radiation from ages 30 to 44, at cumulative whole-body doses of 100 mGy above typical natural background exposure. The scenario was based on typical exposures observed among occupationally-exposed workers included in the UK's NRRW study [M12, M13]. Lifetime expected cancer cases (baseline) and excess cases (radiation-associated), as well as years of life lost and life expectancy, were estimated. Radiation-associated risks of cancer incidence were determined using risk models derived from the NRRW study [M12, M13] and risk models derived from studies of the atomic bombing survivors [N9]. The NRRW-based estimate of risk was 96 excess cases in 10,000 persons (95% CI: 7, 197), while the LSS-based estimate of risk was 81 excess cases in 10,000 persons (95% CI: 32, 160).

C. Review of recent epidemiological literature

199. A significant number of epidemiological studies on the relationship between incidence or mortality of solid cancers and exposure to radiation have been published since the publication of the UNSCEAR 2012 Report [U8]. A comprehensive literature search was performed to identify original peer-reviewed epidemiological studies using the quality criteria described in the UNSCEAR 2017 Report [U10]. The literature search covered the period from January 2012 to July 2017, producing a total of 249 unique references. Since this section focuses on cohort studies dedicated to all solid cancers as a group from (external) exposure of workers to low-LET radiation, selection criteria were set such that preference was given to studies that included exposures of healthy adults (representative of a worker population) and studies which report dose-dependent risk models for all solid tumours (ICD-9 codes 140–199). Studies reporting risks for all cancers excluding leukaemia were preserved as well (ICD-9 codes 140–203). Studies of single cancer types (e.g. breast, lung), those dedicated only to exposures to high-LET radiation (e.g. radon and its decay products), those concerned with exposures in childhood, and those concerned with radiation treatment of people with cancer were not included. After applying the selection criteria, a total of 21 publications were selected, some describing the same epidemiological cohort. Several studies published since 2009 and after July 2017 were included after the literature search was completed. The studies were grouped into three categories: (a) the LSS of the Japanese atomic bombing survivors; (b) studies of occupationally-exposed workers; and (c) studies of members of the public. A summary of the studies of risk of solid cancer from exposure to low-LET radiation is provided at the end of this section. References other than epidemiological studies (e.g. publications describing details of dosimetry for exposed workers) were used as supporting documents and cited as needed.

1. Life Span Studies of the Japanese atomic bombing survivors

(a) *Cancer mortality in the Life Span Study cohort*

1950–2003 follow-up

200. The publication of Ozasa et al. [O5] represents the 14th Radiation Effects Research Foundation (RERF) report on the LSS cohort. It provides an analysis of mortality due to cancer and non-cancer diseases in the cohort for 1950–2003 (3,294,210 person-years). Among the 86,611 persons with estimated DS02 doses, 58% had died during the follow-up period, 80% of those under age 20 at the time of exposure were still alive at the end of the period, and 99.6% of those of age 40 or older at the time of exposure had died. This study includes an additional 6 years of follow-up since the previous report, and provides substantially more epidemiological information, with 17% more deaths over the entire cohort and 58% more deaths among those under 10 years of age at the time of exposure.

201. Weighted doses were expressed in Gy and they were estimated as the gamma dose plus 10 times the neutron dose, to allow for the greater biological effectiveness of neutron doses. DS02 doses have been estimated for 15 tissues, and analyses of mortality from all solid tumours combined have been carried out using the dose to the colon as representative of the whole-body dose, as was done in previous LSS studies. For individual dose estimates, shielded kerma estimates above 4 Gy (317 persons) have been truncated at 4 Gy, because they are likely to reflect incorrect information on shielding or exact location. Out of 86,611 persons with known doses to the colon, 38,509 had doses lower than 0.005 Gy (44.5%), 68,470 had doses lower than 0.1 Gy (79.1%), and 84,224 had doses lower than 1 Gy (97.2%). The mean dose to the colon was 0.117 Gy [P12]. The dose estimates in the LSS cohort have been corrected for classical errors using a statistical method of regression calibration which assumed a plausible 35% multiplicative error [P3]. Pierce et al. [P3] found that the excess cancer risk estimates in the LSS are 6–16% greater than estimates obtained without accounting for classical errors in dosimetry.

202. The risk of all causes of death was positively associated with radiation dose. The risk of all solid cancers combined was modelled with linear, linear-quadratic and quadratic dose-response relationships, with the linear model providing the best fit for the full dose range, but with the linear-quadratic model having a better fit when the dose range was limited to 0–2 Gy. The ERR and EAR dose-response relationships for all solid cancers combined with modifiers for sex, age at exposure and attained age were developed (table 8). The EAR per unit dose for all solid cancers was found to increase throughout life with a linear dose-response relationship, having a value of 26.4 (95% CI: 20.3, 32.8) excess cancer cases per 10^4 person-years per Gy at attained age 70 after an exposure at age 30, based on a linear model. For the same ages, the sex-averaged ERR at 1 Gy was 0.42 (95% CI: 0.32, 0.53). These ERR and EAR models were obtained based on the analysis of the entire cohort (full range of doses and all ages; table 8) and are the models preferred by Ozasa et al. [O5].

203. The analyses of the LSS cohort data [O5] restricted to those who had received doses less than 1 Gy and 0.5 Gy indicate ERRs per unit dose (at attained age 70 after an exposure at age 30) that are similar to those from the full dose-range analysis. However, the uncertainty in the ERRs at 1 Gy and in the modifiers increases as the dose range becomes more restricted, and only an ERR model was capable of fitting the restricted LSS data (table 8).

204. Estimates of ERR at 1 Gy based on a simple linear model (i.e. without modifiers) were also derived (table 9) by restricting the analysis to people in the LSS cohort aged 30 to 44 years at the time of exposure [O5] (similar to the age range of workers included in the INWORKS cohort [R5]).

The ERR at 1 Gy for the restricted ages is compatible with that for the full range of doses in the whole cohort, but is more uncertain. The uncertainty in the ERR at 1 Gy increases even further if the cohort aged 30 to 44 years is more restricted to persons with doses less than 1 Gy. However, when the cohort of people aged 30 to 44 years is restricted to persons receiving doses less than 0.5 Gy, the ERR at 1 Gy is reduced significantly, with a wide uncertainty range in which the lower bound is negative and the upper bound is positive (table 9). Thus, the dose response for adults exposed to doses less than 0.5 Gy cannot be used reliably for the purposes of risk assessment.

205. The risk of cancer mortality increased significantly for most major cancer sites, including the stomach, lung, liver, colon, breast, gallbladder, oesophagus, bladder and ovary [O5]. For these cancer sites, dose responses with positive ERR at 1 Gy have been observed. Analyses of cancer mortality for rectum, pancreas, uterus, prostate and kidney parenchyma did not result in ERR values that indicate a significantly increased risk to these organs.

206. Revised individual radiation dose estimates for the LSS (DS02R1) have been recently published by Cullings et al. [C10]. The DS02R1 system is the same as the previous DS02 system, but with updated input parameters regarding the location of survivors and shielding, based on a thorough review of the original materials collected for dosimetry purposes. Although changes have been made for many persons, about 90% of the survivors stayed in the same kerma category. Cullings et al. [C10] compared dose responses obtained using DS02 and DS02R1 individual dose estimates using the LSS mortality (not incidence) data for all solid tumours combined [O5]. For the full dose range, the estimated sex-averaged ERRs at 1 Gy based on a linear model were virtually identical; 0.42 (95% CI: 0.32, 0.53) in the Ozasa et al. analysis and 0.43 (95% CI: 0.32, 0.53) in the Cullings et al. analysis. Estimates of the ERR based on the full dose range were also very similar in the two analyses for males and females separately, and when a linear–quadratic model was considered. Some differences in curvature between males and females were observed when the data was analysed by restricting the doses to <2 Gy.

207. The LSS mortality data are one of the most comprehensive sources of information on radiation-induced effects, with a large cohort and number of cases, long follow-up, good cancer ascertainment, good information about smoking, and in-depth analyses of dose–response relationships, with age and sex modifiers. The LSS cohort received a single acute exposure to radiation. This aspect is a strength, if the risk from acute exposures is to be estimated, but it can be a weakness, if the risk from prolonged exposures is required. Another possible weakness is the “healthy survivor effect” (i.e. cohort members had to survive until the commencement of the LSS in October 1950), particularly for persons exposed to high doses.

Table 8. Excess relative risk and excess absolute risk mortality risk models, with effect modifiers, for all solid cancers as a group, for the LSS cohort [O5]

Risk model coefficient	Symbol	Dose range for LSS cohort					
		Full dose range ^{a,b}		<1.0 Gy ^c		<0.5 Gy ^c	
		Estimate	95% CI	Estimate	95% CI	Estimate	95% CI
ERR MODEL ^d							
Sex-averaged ERR per unit dose (Gy ⁻¹)	β	0.42	(0.32, 0.53)	0.40	(0.24, 0.55)	0.41	(0.14, 0.67)
Modifiers							
Sex (ERR ratio: female/male)	σ	2.1	(1.4, 3.1)	1.7	(0.84, 4.2)	2.2	(0.72, 13.1)
Age at exposure	τ	−0.29	(−0.41, −0.17)	−0.18	(−0.4, 0.07)	−0.35	(−0.66, 0.05)
Attained age	ν	−0.86	(−1.6, −0.06)	−0.73	(−1.9, 0.67)	0.16	(−1.66, 2.88)
EAR MODEL ^d							
Sex-average EAR per unit dose (10 ⁴ person–year Gy)	β	26.4	(20.3, 32.8)	— ^e		— ^e	
Modifiers							
Sex (EAR ratio: female/male)	σ	1.1	(0.80, 1.74)	— ^e		— ^e	
Age at exposure	−τ	−0.19	(−0.31, −0.07)	— ^e		— ^e	
Attained age	ν	3.4	(2.7, 4.1)	— ^e		— ^e	

^a This is the preferred model selected by Ozasa et al. [O5].

^b All persons in the cohort were included in the analyses, but 317 persons with shielded kerma greater than 4 Gy were assigned a truncated kerma of 4 Gy. Estimates of kerma of >4 Gy are likely to represent misinformation on exposure factors such as shielding or exact location [O5].

^c Derived for this report base on the LSS data used by Ozasa et al. [O5].

^d Risk models are defined as ERR or EAR = $\beta d \cdot \exp(T E^* + \nu \ln(A^*)) \cdot (1 + \sigma s)$, where d is the dose, s is the sex, $E^* = (E - 30)/10$ and e is the age at exposure, $A^* = a/70$ and a is the attained age, and σ , τ and ν are coefficients for effect modification. For sex, variable s is -1 for males and +1 for females, and the sex ratio presented in the table relates to the coefficient σ , as follows: sex ratio = $(1+\sigma)/(1-\sigma)$. For the ERR model, coefficient β represents the sex-averaged ERR per unit dose (Gy) at attained age 70 after an exposure at age 30. For the EAR model, coefficient β represents the sex-averaged EAR per unit dose (10⁴ person-year Gy) at attained age 70 after an exposure at age 30.

^e No reliable estimates could be derived because of lack of convergence.

Table 9. Excess relative risk per unit dose (Gy^{-1}) for mortality due to all solid cancers as a group, obtained using a simple linear model, with no effect modifiers, for the LSS cohort restricted to adults exposed between 30 and 44 years of age [O5]

Dose range for LSS cohort ^{a,b}	ERR per unit dose (Gy^{-1})	95% CI
Full dose range	0.32	(0.19, 0.47)
<1.0 Gy	0.27	(0.055, 0.50)
<0.5 Gy	0.0048	(−0.33, 0.38)

^a To obtain the ERR per unit dose reported in this table, the cohort was restricted to persons exposed between ages 30 and 44. Then the cohort was further restricted to persons with doses to the colon of <1 Gy and <0.5 Gy [O5].

^b If persons of all ages at exposure are kept in the cohort, an ERR per unit dose for a simple model linear in dose of 0.56 (95% CI: 0.15, 1.04) is obtained for a range of doses to the colon restricted to 0 to 0.2 Gy [O5].

(b) Cancer incidence in the Life Span Study cohort

1958–1998 follow-up

208. Analyses of the cancer incidence data from the LSS with a follow-up from 1958 to 1998 were published by Preston et al. [P11]. These analyses were based on the DS02 dosimetry and included 17,448 first primary cancers (including non-melanoma skin cancer) diagnosed among 105,427 cohort members, with individual dose estimates for those who were alive and not known to have had cancer prior to 1958. The same data were analysed by the US National Academy of Sciences to derive the risk models for different types of solid cancers included in the BEIR VII report [N9]. The BEIR VII risk models estimated ERR and EAR for 11 cancer types: stomach, colon, liver, lung, breast, prostate, uterus, ovary, bladder, thyroid and leukaemia based on the cancer cases in the LSS cohort.

209. Berrington de González et al. [B5] provided an extension of the analyses of radiogenic cancer incidence in the LSS cohort carried out by BEIR VII, to include risk models for seven additional cancer types (oral, oesophagus, gallbladder, pancreas, rectum, kidney and brain/central nervous system (CNS) cancers), using the same dataset and the same basic model formulation for the risk of solid cancer. The new cancers included at least 100 incident cases available and had been evaluated in detail in the LSS cancer incidence report [B5, P11].

210. The ERR and EAR models for solid cancers other than 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 Gy, γ is the age at exposure parameter, e^* is $(e-30)/10$ for $e < 30$ and zero for $e \geq 30$, where e is age at exposure in years, η is the attained age parameter and a^* is $(a/60)$, where a is the attained age in years. For breast and thyroid cancer, detailed pooled analyses were carried out based on a combination of data from the LSS and from medically exposed populations. The risk of thyroid cancer was based on the ERR model derived from the pooled data of seven studies described by Ron et al. [R8], as analysed by Land et al. [L2] and modified for sex-dependency by BEIR VII [N9]. The ERR thyroid model is similar in form to the standard model for solid cancers, however, depends only on age at exposure and not on attained age (i.e. η is equal to zero). The preferred model for breast cancer was the EAR model from the pooled analysis of four cohorts by Preston et al. [P9]. That model has the same form as the standard model for solid cancers, but e^* is $(e-25)/10$ for all ages, e , at exposure and a^* is $(a/50)$.

211. A new risk model for a remainder category of cancers (different from that in the BEIR VII report) was developed to include all solid cancers except the 17 solid cancers modelled separately [B5]. The

risk models for the new remainder category had a mathematical form similar to that applicable to most solid cancers and a sex-specific risk coefficient, β . When the total cancer risk is estimated, the risk for the remainder category needs to be added to the risk estimates for individual cancer types.

1958–2009 follow-up

212. The third analysis of solid cancer incidence among the LSS cohort of atomic bombing survivors [G8] includes an additional 11 years of follow-up (since the previous analysis) in which 5,090 new incident cancers were observed, an updated dosimetry system (DS02R1 [C10]) and improved adjustments for smoking (similar to those from Furukawa et al. [F5]). The cohort included 111,917 persons (45,864 males and 66,053 females) who were alive and cancer free at the beginning of the follow-up on 1 January 1958. After eliminating 6,473 persons for whom doses could not be estimated, analyses have been carried out for a cohort of 105,444 eligible persons, which included 80,205 survivors with dose estimates and 25,239 persons who were not in either city at the time of the bombings. By the end of the follow-up (31 December 2009), 42,138 persons (37.7% of the cohort) were still alive. This study provides 3,079,484 person-years of follow-up during the period 1958–2009.

213. After excluding lymphopoietic cancers and cancers diagnosed only at autopsy, a total of 22,538 eligible solid cancer cases were counted during the follow-up period (10,473 in males and 12,065 in females), with 5,918 cases (26%) occurring in the 11 years (1999–2009) since the end of the previous follow-up period. For 76.7% of the cases, cancer diagnosis was verified histologically.

214. Of all persons with known doses (80,205), 44.9% had weighted doses to the colon less than 0.005 Gy, 79.2% had doses less than 0.1 Gy and 97.4% had doses less than 1 Gy. Only 495 people received doses higher than 2 Gy. Doses were the DS02R1 revised individual dose estimates [C10]. This dosimetry system is unchanged from the previous DS02 system, but information regarding the location of survivors and shielding had been refined based on a reanalysis of the original material. Although changes had been made for many persons, about 90% of the survivors stayed in the same kerma category.

215. The modelled sex-averaged ERR per unit dose for all solid cancers was 0.50 (95% CI: 0.42, 0.59) Gy^{-1} , representative of an exposure at age 30 and follow-up to age 70. Only a small difference in the radiation risk estimate occurred when account was taken of smoking through the use of a joint multiplicative smoking–radiation model: ERR per unit dose of 0.47 (95% CI: 0.39, 0.55) Gy^{-1} . These values are very similar to that observed in the previous LSS analysis of 0.47 Gy^{-1} [P11].

216. Grant et al. [G8] estimated a significantly higher ERR per unit dose for females (0.64 (95% CI: 0.52, 0.77) Gy^{-1}) than for males (0.27 (95% CI: 0.19, 0.37) Gy^{-1}), when a linear model over the entire dose range was applied. While for females, the dose response was consistent with linearity, for males, a significant upward curvature was observed, and the modelled dose response was compatible with a linear–quadratic dependency on dose with an ERR of 0.2 (95% CI: 0.12, 0.28) at 1 Gy, and an ERR of 0.01 (95% CI: –0.0003, 0.021) at 0.1 Gy.

217. The EAR per 10,000 person-years at 1 Gy for males was estimated from the linear–quadratic relationship provided by Grant et al. [G8] (table 10) as $21.7 \times 1 \text{ Gy} + 21.2 \times 1 \text{ Gy}^2 = 42.9$. This value is rather similar to the EAR at 1 Gy of 54.7 for females. However, the EAR for males at 0.1 Gy was only 2.4 compared to that for females of 5.5, because of the significant quadratic component of the male risk model.

218. The lowest dose range that showed a statistically significant dose response using the sex-averaged linear ERR model was 0 to 100 mGy with an estimated ERR per unit dose of 0.49 (95% CI: 0.026, 1.01) Gy^{-1} ; $p=0.038$; table 11), virtually identical with the estimate of 0.50 over the full dose range [G8]. For the sexes combined, over the full dose range the linear–quadratic model fits the data better

than the pure quadratic model ($p < 0.001$), indicating that there is a positive slope at low doses. Statistical tests did not indicate a dose threshold significantly different from zero ($p = 0.18$ for females, $p = 0.49$ for males).

219. The interpretation of the sex-related differences in curvilinearity is complex, and no mechanistic explanation exists at this time. This result is surprising especially because such differences were not observed in the previous analysis of the LSS incidence data [P11]. Statistically, the differences in magnitude of risk between males and females could be attributed, in part, to the higher baseline cancer rates in males. Another potential reason for the observed curvilinearity is the revision of individual doses (DS02R1). Cullings et al. [C10] compared dose responses obtained using individual doses of DS02 and DS02R1 and the LSS mortality (not incidence) for all solid tumours [O5]. For the full dose range, no statistically significant curvature for either sex was observed, and the best estimates were nearly identical for both original and updated doses. For the dose range 0–2 Gy, a statistically significant curvature was obtained for females for the updated DS02R1 individual doses ($p = 0.02$), but not for the original DS02 doses. No curvature was observed for males for the dose range 0–2 Gy with either the revised or the original dose estimates. These results are at odds with the results reported by Grant et al. [G8] for new incidence data which indicated a dose–response curvature for males, but not for females. Further studies are necessary to explain the curvilinearity observed by Grant et al. [G8] in the data on the incidence of solid cancers, and to answer the more fundamental question of why the shape of the dose response for males should be different from that for females.

220. Aside from the differences in curvilinearity between males and females, the data for the period 1958–2009 on solid cancer incidence from the LSS cohort of atomic bombing survivors, with its large number of person–years of follow-up and cancer cases, offers high statistical power for the estimation of radiation risk, and it provides evidence of a statistically significant dose response over the dose range of 0 to 100 mGy.

Table 10. Parameter estimates and 95% confidence intervals for the preferred excess relative risk and excess absolute risk models for all solid cancer incidence: LSS cohort, 1958–2009 [G8]

<i>Dose–response model</i>	<i>Males</i>			<i>Females</i>		<i>Both sexes</i>
	<i>Dependency on dose^a</i>		<i>Attained age</i>	<i>Dependency on dose^a</i>	<i>Attained age</i>	<i>Age at exposure^b</i>
	<i>Linear</i>	<i>Quadratic</i>	<i>Power</i>	<i>Linear</i>	<i>Power</i>	
ERR	0.094 (<0.02, 0.23)	0.11 (0.04, 0.20)	−2.70 (−3.58, −1.81)	0.64 (0.52, 0.77)	−1.36 (−1.86, −0.84)	−22% (−30%, −13%)
EAR	21.7 (<−1.7, 47.7)	21.2 (6.8, 37.6)	2.89 (2.14, 3.68)	54.7 (44.7, 65.3)	2.07 (1.64, 2.53)	−30% (−37%, −22%)

^a The linear parameter is the ERR (per Gy) or the EAR per 10,000 person–years (per Gy), respectively. The quadratic parameter is the ERR or EAR per Gy². Parameters represent the risk at attained age 70, from an exposure at age 30.

^b Percentage change per decade increase in age at exposure (same value applies to both males and females).

Table 11. Excess relative risk per unit dose (Gy^{-1}) for incidence due to all solid cancers as a group, obtained using a simple linear model: LSS cohort, 1958–2009 [G8]

Dose range (Gy) LSS cohort ^{a,b}	Females		Males		Both sexes	
	ERR per unit dose (Gy^{-1}) ^a	95% CI	ERR per unit dose (Gy^{-1}) ^{a,b}	95% CI	ERR per unit dose (Gy^{-1})	95% CI
Full range	0.64	(0.52, 0.77)	0.27	(0.19, 0.37)		
<2.0	0.65	(0.52, 0.78)	0.25	(0.17, 0.36)		
<1.0	0.58	(0.44, 0.47)	0.19	(0.09, 0.30)		
<0.5	0.53	(0.34, 0.75)	0.07	(<−0.05, 0.22)		
<0.25	0.55	(0.24, 0.92)	0.02	(<−0.18, 0.25)		
<0.1	0.39	(−0.27, 1.1)	0.33	(<−0.10, 0.89)	0.49	(0.026, 1.01)

^a Estimated sex-specific excess relative risks per Gy were based on a linear dose–response model that included radiation effect modification by attained age (sex-specific) and age at exposure (common to both sexes) and adjusted for smoking using a multiplicative ERR model for the joint effect of radiation and smoking [G8].

^b Statistically significant curvature in the dose response was observed for males (table 10) over the full range of doses. Statistically significant linear–quadratic dose responses for males were also determined for dose ranges 0–2 Gy and 0–1 Gy. For a dose range 0–0.5 Gy, a negative range was observed. No linear–quadratic dose responses or significant curvatures were observed for lower dose ranges [G8].

2. Studies of workers exposed to radiation

(a) Cancer mortality in the INWORKS cohort

221. The INWORKS [R5, R6] focused on mortality in the cohorts of occupationally-exposed workers from France [M4], the United Kingdom [M12, M13] and the United States [S5]. INWORKS continued the idea of pooling data of exposed workers which was previously used by the 15-country worker study [C4, C5], and did so with updated data from the three countries, as they hold much of the epidemiological information contained in the 15-country study. The INWORKS cohort included 308,297 workers in the nuclear industry (87% males) with detailed monitoring data for external exposure to ionizing radiation and a total follow-up of 8.2 million person–years. Out of 66,632 known deaths by the end of follow-up, 19,748 were identified to be due to cancer (17,957 solid cancers). The follow-up period was from 1944 to 2005, the mean follow-up per worker was 27 years (median of 26 years), the mean attained age at the end of the follow-up was 58, the mean length of employment was 15 years (median 12 years), and the mean age at the beginning of employment was 28.

222. External exposures of the workers in the INWORKS included photons of energies between 100 and 3,000 keV. Recorded doses from neutrons and internal emitters, including inadvertently missed external gamma doses, were not quantified for all members of the cohort and were not used in the analysis directly, although their potential impact on the dose response was assessed at least for some of the missing components and judged to be modest (section IV.F.1). The ERR per unit dose for mortality from solid cancers was estimated using absorbed doses to the colon. Among the 257,166 workers with a positive recorded dose, the average cumulative dose for the cohort was 20.9 mGy (France, 17.6 mGy; United Kingdom, 22.5 mGy; United States, 20 mGy), and the distribution of doses was skewed (median dose 4.1 mGy; 90th percentile, 53 mGy; maximum dose 1.3 Gy) [R5, T6].

223. Dose responses were quantified using a Poisson regression model for the relative rate, defined as $1+\beta D$, where D is the cumulative dose in Gy, lagged by ten years, and β is the ERR per unit dose. A statistically significant ERR at 100 mGy for solid cancers of 0.047 (90% CI: 0.018, 0.079) was derived based on 17,957 cancer deaths in the entire cohort. One test for the effect of smoking on the risk estimate was performed by estimating the risk of solid cancer, other than lung cancer, and was based on 12,155 cases. The ERR at 100 mSv for this grouping was 0.046 (90% CI: 0.011, 0.085). These estimates do not include any dependencies on the age at exposure, age at diagnosis or time since exposure. A separate analysis of risk dependency of age at exposure and time since exposure as categorical variables [D1] was performed using piecewise constant models (age at exposure groups: <35, 35–50, 50+; time-since-exposure groups: 10–20, 20–30, 30+ years). Trends were not statistically significant, although a decrease of the ERR per unit dose with increasing time since exposure was observed when a 10-year lag was imposed.

224. The preferred ERR at 100 mGy for solid cancers of 0.047 (90% CI: 0.018, 0.079) represents the entire dose range in the cohort, with the largest dose group having an average dose of 631 mGy [R5]. Dose responses for lower cumulative doses were not reported for solid cancers (ICD-9 codes 140–199), but for all cancers other than leukaemia, as a cancer grouping (ICD-9 codes 140–203). The number of deaths in the cohort from all cancers other than leukaemia was 19,064. For the entire dose range, the ERR at 100 mGy for this cancer grouping was 0.048 (90% CI: 0.02, 0.079). For the restricted dose ranges (table 12), the observed ERRs at 100 mGy for dose ranges 0–200 mGy, 0–150 mGy and 0–100 mGy were 0.104 (90% CI: 0.055, 0.156), 0.069 (90% CI: 0.010, 0.13) and 0.081 (90% CI: 0.001, 0.164), respectively. The uncertainty in the ERR per unit dose increases substantially with the decreasing upper bound of the dose range, but the statistical significance and the consistency of the estimated ERRs indicate an approximately linear dose response.

Table 12. Estimates of excess relative risk at 100 mGy and excess absolute risk per 10,000 person–years at 100 mGy for cancer mortality derived using data of specific dose ranges [R5]

Dose range (mGy)	ERR or EAR	
	Estimate	90% CI
SOLID CANCERS (ICD-9 CODES 140–199)		
	ERR at 100 mGy	
Entire dose range	0.047	(0.018, 0.079)
	EAR per 10 000 PY at 100 mGy	
Entire dose range	0.48	(0.021, 1.03)
ALL CANCERS OTHER THAN LEUKAEMIA (ICD-9 CODES 140–203)		
	ERR at 100 mGy	
Entire dose range	0.048	(0.020, 0.079)
0–200	0.104	(0.055, 0.156)
0–150	0.069	(0.010, 0.130)
0–100	0.081	(0.001, 0.164)

225. Models for EAR for solid cancers were fitted using a baseline parametric model that was adjusted for country, sex, birth year, birth year squared, log of age and log of age squared. The fits were based on the full INWORKS cohort. The EAR coefficient resulting from the fit for solid cancers, based on a 5-year lagged dose to the colon, is 0.48 (90% CI: 0.02, 1.03) per 10,000 person–years per 100 mGy.

226. Site-specific solid cancer mortality analyses for the INWORKS cohort by Richardson et al. [R6] showed positive point estimates of ERR per unit dose for oral, oesophagus, stomach, colon, rectum, pancreas, peritoneum, larynx, lung, pleura, bone and connective tissue, skin, ovary, testis and thyroid cancer. In addition, negative point estimates of ERR per unit dose were observed for cancer of the liver and gallbladder, prostate, bladder, kidney and brain. However, the estimated coefficients exhibited substantial imprecision. A second type of dose-response analysis (i.e. using hierarchical Poisson regression) had little impact on the estimated associations for the most commonly observed outcomes. However, for less frequent cancer types, the estimates obtained using this second method tended to take fewer extreme values and, thus, have less uncertainty than estimates obtained with maximum-likelihood Poisson regression.

227. The INWORKS is based on a large cohort, with long follow-up and good dosimetry for external doses. The dose-response analyses indicate a statistically-significant association of mortality from all solid cancers combined with increasing dose. Estimates of ERR and EAR per unit dose for a linear dose response can be considered reliable for assessing risk in workers exposed to low-LET radiation. The INWORKS, however, includes mostly adult males (with only a relatively small fraction of females and no children), and thus cannot be used for cases of childhood exposure and is less reliable for assessing radiogenic risk in adult females. Dose responses for all solid cancers are based on recorded external gamma doses, with unaccounted or missed neutron and internal emitter doses potentially affecting reported results. Mortality dose responses for site-specific solid cancers have been derived, but they are affected by substantial imprecision.

(b) *Cancer mortality in German uranium millers*

228. Extensive uranium mining and milling were in operation from 1946 until 1990 in the southern part of the former German Democratic Republic. The mining operations were conducted by a company named “Wismut”. Workers were exposed primarily to radon decay products, external gamma radiation, long-lived radionuclides from uranium ore, and silica and arsenic dust. Other occupational exposures include asbestos, diesel, sulfuric acid and ammonia. In 1993, a cohort was established to include 58,982 male workers who had been employed by Wismut for at least six months between 1946 and 1989.

229. A study by Kreuzer et al. [K24] focused on a cohort of 4,054 uranium millers, a subgroup of the Wismut workers, who had never worked in underground or opencast mining. Uranium millers differ from uranium miners because they were exposed to (a) appreciably lower mean cumulative radon daughter exposures (8 versus 328 WLM); (b) lower average cumulative exposures to external gamma radiation (26 versus 50 mSv) and silica dust (4.9 versus 7 mg m⁻³ per year); and (c) additional exposure to a variety of chemicals. In contrast, both millers and miners were exposed to similar amounts of long-lived internally-deposited radionuclides (3.9 versus 4.1 h kBq m⁻³).

230. The cohort of German uranium millers includes males who worked between 1946 and 1989. Workers were employed for an average of 15 years (range 0.5–44). The mean age at first employment was 25 years (range 14–61). Mortality was followed up from 1946 to 2008 (62 years), accumulating 158,383 person-years at risk. The mean duration of follow-up was 39 years.

231. Their cumulative exposure included: (a) inhalation of radon decay products (mean 8; median 5; maximum 127 WLM); (b) inhalation of long-lived radionuclides (mean 3.9; median 0.97; maximum 132.1 h kBq m⁻³); (c) inhalation of silica dust (mean 4.9; median 2.5; maximum 37 mg m⁻³ per year); and (d) exposures to external gamma radiation (mean 26; median 11; maximum 667 mSv). Effective doses from external exposure to gamma radiation were calculated based on measurements of ²²⁶Ra in rocks. Only 4.2% of the cohort had received external doses larger than 100 mSv. The mean, median and

maximum duration of exposure was 11, 8 and 43 years, respectively. Exposures to silica occurred over a longer period (mean 15; median 12; maximum 43 years).

232. Statistical analyses of the cohort included (a) external comparisons with a compatible general male population in Eastern Germany expressed as standard mortality ratios (SMR); and (b) determination of dose responses expressed as relative rates, using Poisson regression, with both RR and ERR being reported. A linear dose response was used independently for each contaminant of interest (radon, long-lived radionuclides, gamma, silica) and the exposure was lagged by five years to account for the minimum latency period.

233. The external comparisons, for a follow-up from 1970 to 2008, showed that all-cause mortality was lower in the exposed cohort (SMR=0.85; 95% CI: 0.81, 0.90; O=1,539; statistically significant). All-cancer mortality in the exposed cohort was also lower than in the general population (SMR=0.92; 95% CI: 0.8, 1.00; O=437; not statistically significant).

234. Although the average cumulative radon daughter exposure was rather low, the ERR for all solid cancers combined was significant (ERR at 100 WLM=1.74; 95% CI: 0.24, 3.23) with the largest contributor being lung cancer (ERR at 100 WLM=3.39; 95% CI: -0.01, 6.78). The central estimate ERR per unit exposure for lung cancer is much larger than the value derived for the complete Wismut cohort (ERR at 100 WLM=0.19; 95% CI: 0.16, 0.22) [W3], although the confidence limits overlap. However, the two central estimates become compatible when taking into account that the ERR per unit exposure for the full Wismut cohort was strongly modified by the exposure rate, with the ERR per unit exposure being about 10 times lower at higher exposure rates than at low exposure rates. Also, among 2,148 Port Hope uranium processors in Canada with low radon exposure levels, similar to those in the present report, a lower mortality risk was reported ($n=78$; ERR at 100 WLM=0.39; 95% CI: <-1.22, 4.52) [Z3].

235. No significant increase in risk of all solid tumours as a group was observed for exposures to long-lived radionuclides: ERR at 100 h kBq m⁻³ of -0.04 (95% CI: -0.80, 0.72), although a relatively high, but not statistically significant ERR at 100 h kBq m⁻³ was observed for stomach 2.61 (95% CI: -1.60, 6.81) and kidney 7.38 (95% CI: -11.2, 26.0). Exposures to silica indicated a low ERR per unit exposure for all solid tumours (mg m⁻³ per year) of 0.011 (95% CI: -0.010, 0.032) for all solid cancers as a group.

236. The dose response for all solid tumours from exposure to external gamma radiation had an ERR per unit dose of 1.86 (95% CI: -0.08, 3.8) Sv⁻¹; $p=0.06$, with the highest contributors to the risk being stomach cancer: ERR per unit dose of 10 (95% CI: -2.65, 22.6) Sv⁻¹; $p=0.12$, and lung cancer: ERR per unit dose of 2.55 (95% CI: -0.97, 6.07) Sv⁻¹; $p=0.16$. Given that the members of the cohort were also exposed to radon, silica and long-lived radionuclides, analyses were carried out to adjust the ERR from gamma radiation for the effect of radon or silica. When adjusted for the effect of radon, the ERR at 1 Sv for solid tumours decreased from 1.86 to 0.26 (95% CI: -2.47, 2.98) and the ERR at 1 Sv for lung cancer was reduced from 2.55 to -1.1. No analyses have been carried out to adjust for both radon and silica. Furthermore, no adjustments of the ERR from gamma radiation due to the effect of exposure to long-lived radionuclides were carried out.

237. The results of this study provide only suggestive evidence for a dose response for solid tumours for external gamma exposure to doses under 100 mSv. The study has a number of limitations as follows: (a) low statistical power due to low exposures, small population size (4,054 males) and a small number of deaths in specific subgroups (457 from cancer; 717 cardiovascular diseases; 111 non-malignant respiratory disease); (b) magnitude of the observed risks influenced by several correlated sources of exposure; (c) unaccounted for uncertainties in exposure assessment, including missing-dose calculations; (d) missing information on potential confounders such as smoking and chemicals; and (e) some issues with ascertainment of the cause of death (e.g. cause of death was missing for a small

number of persons ($n=47$) who died prior to 1970; however sensitivity analyses showed that results restricted to 1970–2008 period are similar to results for the full follow-up period).

(c) *Cancer mortality in German nuclear power plant workers*

238. A study of risk of cancer mortality in a cohort of workers from 11 nuclear power plants in Germany was conducted by Merzenich et al. [M3]. This study included 8,972 workers and was an extension of an earlier study of 4,844 workers from 10 power plants in Germany. The extended cohort comprised 8,746 males (97.5%) and 226 females (2.5%) who (a) were employed on 1 January 1991 or started employment before 31 December 2008; (b) were employed for at least three months in a job category with exposures expected to exceed an annual effective dose of 6 mSv; (c) were monitored for external exposure; and (d) were directly employed by the nuclear power plant.

239. The follow-up of vital status started on 1 January 1991. The end of follow-up was defined as the date of death, last information date (for workers lost to follow-up) or 31 December 2008. The average age at the end of the 17 years of follow-up was 50. The average follow-up duration per worker was 14.6 years. By 2009, 310 males, but no females, had died (120 persons had died from a solid cancer), 70 persons (67 males) were lost to follow-up, and 8,592 persons (8,369 males) were alive on 31 December 2008. The mortality follow-up accumulated 130,737 person-years at risk (128,570 person-years at risk for males).

240. The workers were monitored with film badges for external photon radiation (X-rays and gamma radiation), with detection thresholds varying from 0.1 to 0.4 mSv during different time periods of measurement. Effective annual doses for males ranged from 0 to 31.8 mSv, with 98% being below 6 mSv. At the end of the follow-up period, the mean cumulative effective dose for males was 29.5 mSv (median 5.7 mSv), with 48% of the population having doses less than 5 mSv and 90% of the population having doses less than 100 mSv. The mean cumulative dose among the 226 females was 0.64 mSv (median 0.0 mSv). Given that, for females, the number of persons was small, doses were very low, and no deaths have been recorded during the follow-up period, the dose-response analysis was limited to the male subgroup of the cohort.

241. Based on a representative general population of males from Germany for the period 1991–2008, the expected number of deaths would have been 627.1 with 188.7 from solid tumours. The SMR for the cohort of workers is 0.5 (95% CI: 0.45, 0.56) for all causes of death and 0.64 (95% CI: 0.50, 0.81) for solid cancers. It was not possible to adjust for smoking and alcohol consumption for this cohort. Instead, analyses were carried out by grouping causes of deaths related to these two risk factors. Thus, the SMR for tobacco-related solid cancers was 0.50 (95% CI: 0.35, 0.71), the SMR for solid cancers excluding tobacco-related cancers was 0.80 (95% CI: 0.58, 1.10) and the SMR for alcohol-associated causes was 0.31 (95% CI: 0.19, 0.50).

242. The statistical analysis was based on Cox regression models fitted to estimate hazard ratios as a function of cumulative radiation dose for selected causes of death. A latency period of two years for leukaemia and 10 years for solid cancers was assumed. Poisson regressions were not carried out and ERR or EAR dose responses have not been derived. A hazard ratio per mSv for all solid cancers of 0.999 (95% CI: 0.996, 1.001) was determined, with hazard ratios per mSv for individual cancer sites being almost indistinguishable from 1.0.

243. The cohort of German nuclear power plant workers is still young, with a relatively small number of persons 8,972 workers compared to 308,297 workers included in the INWORKS [R5]; 59,201 workers in the French cohort [M4]; 119,195 workers in the United States cohort [S5]; 174,541

workers in the United Kingdom cohort [M12]; and a small number of observed deaths due to solid cancers with 120 deaths compared to 17,957 in the INWORKS; 2,312 in the French cohort; 10,877 in the United States cohort from all cancers except leukaemia; and 8,107 in the United Kingdom cohort.

(d) *Cancer incidence in nuclear power plant workers in the Republic of Korea*

244. A large-scale epidemiological investigation of nuclear power workers was launched in the Republic of Korea in 1992 [J4]. Between 1992 and 2005, workers participated in questionnaire surveys and clinical health check-ups. Given the relatively small number of females in the workforce, the epidemiological investigation was focused on males. A cohort of 16,236 male workers was formed, with persons identified as radiation workers (8,429) or non-radiation workers (7,807). The first category included persons who were issued with thermoluminescent dosimeters (TLD) and who have external or internal exposure data recorded in a nationwide database. The second category comprised persons with no dosimetry records. Given that radiation monitoring of nuclear workers is strictly applied in the Republic of Korea, persons with no dosimetry records were assumed to have had negligible radiation doses. The survey results indicated that 1,995 persons (23.7%) never smoked, 1,846 persons (21.9%) were former smokers, and 4,553 persons (54.0%) were current smokers. The remaining 35 persons did not provide responses regarding smoking history.

245. The radiation workers (8,429) and non-radiation workers (7,807) accumulated 63,503 and 48,301 person-years at risk, respectively, calculated from the date of the questionnaire or the first exposure date, whichever occurred later. The average length of follow-up was 7.53 years for radiation workers and 6.19 years for non-radiation workers. The mean ages at the end of follow-up for the exposed and unexposed categories were 41.3 and 46.2, respectively. A total of 99 cancer incidence cases and 43 deaths were observed among the radiation workers, compared to 104 incident cases and 39 deaths in the non-radiation workers. Cancer ascertainment relied on data from the Korean Central Cancer Registry, based on ICD-10 codes. The linkage was deterministic based on an identification number unique to each person. Cancer and vital status were checked for the period between 1992 and 2005 [J4].

246. The dose recorded in the database for the Korean workers included in this study [J4] was, in principle, a total effective dose from both external and internal exposure. The majority of recorded doses came from external exposures to high-energy photons (>100 keV). External exposure to neutrons occurred for 7.8% of the radiation workers (657 persons), who had received less than 10% of their total dose from neutrons. The mean dose from neutrons was 0.44 mSv. Internal exposures were recorded for 25.9% of the radiation workers (2,182 persons; mean dose 0.82 mSv). Doses from neutrons and internal emitters were considered too small for separate dose-response analyses. The main indicator selected to assess risk of cancer was the total cumulative dose estimated from the recorded total annual doses between the date of first exposure and the date of exit (date of cancer diagnosis, death or study end, whichever occurred first). Total cumulative doses ranged from 0 to 480.5 mSv, with a mean dose of 19.9 mSv (median 2.93 mSv). Doses to 19.9% of the radiation workers (1,678) were recorded as zero and 95% had doses less than 100 mSv. The cumulative dose was lagged by two years for leukaemia and 10 years for solid cancers. The mean dose lagged for leukaemia was 18.4 mSv and the mean dose lagged for solid cancers was 12.05 mSv [J4].

247. Poisson regression was used to determine the ERR as a linear function of the cumulative lagged dose, after adjusting the baseline risk for age, birth year and smoking status. Standardized incidence ratios (SIR) were derived for both radiation and non-radiation workers by comparisons with the national baseline rates. For leukaemia, and stomach, lung, thyroid, all cancers (as a group) and all cancers excluding leukaemia (as a group), the SIRs were greater than 1.0, indicating higher rates of cancer incidence in the radiation workers than in the general population, although this was not

statistically significant. For all cancers excluding leukaemia, the SIR was 1.064 (95% CI: 0.86, 1.29) for the radiation workers, compared to an SIR of 0.86 (95% CI: 0.70, 1.05) for the non-radiation workers. The ERR at 1 Sv for all cancers excluding leukaemia was positive at 2.06, but with a large uncertainty range (95% CI: -1.91, 9.0). For all cancers combined, the ERR at 1 Sv was 1.69 (95% CI: -2.07, 8.21) [J4].

248. Although the study by Jeong et al. [J4] was well organized and conducted, the size of the cohort was small, leading to a low statistical power. Dosimetry relied on TLD measurements for each person, but similar to other studies no consideration was given to medical exposures or to prior exposures in other workplaces, and no attempt was made to correct for potential underestimation of doses recorded as zero below the limit of detection (0.1 mSv for TLD badges).

(e) *Cancer incidence in Chinese medical diagnostic X-ray workers*

249. The Chinese medical X-ray workers study included 27,011 persons (radiologists and radiological technicians) who were employed between 1 January 1950 and 31 December 1980 at major hospitals in 24 provinces of China [S16]. The median duration of employment was 26 years and the mean age at entry into the cohort was 26.4. Another cohort comprising 25,782 physicians (surgeons, otolaryngologists etc.), who did not use X-ray equipment, was established as a control. The mean age at entry of this population was 25.1.

250. Cancer ascertainment relied on information through 1995, which included date, diagnosis and other details related to diagnosis from medical records. Histological confirmation was available for 70% of all cancer cases. All neoplasms (excluding leukaemia) were included and cancers were classified according to ICD-9 codes. The vital status of the cohort was checked first in 1980, then in 1985 and again in 1990 and the follow-up ceased in 1995. Out of the 27,011 persons in the cohort (21,571 males and 5,440 females), 95% were still alive on 31 December 1995. The mean follow-up for the cohort was 25.7 years (683,425 person-years at risk). The mean follow-up for the comparison population was 29.6 years. A total of 1,643 of solid cancer cases were observed during the follow-up period among all workers (52,793 persons), with 795 in the exposed group and 848 in the unexposed group [S16].

251. Most, if not all, members of the cohort were exposed to 25 to 40 keV X-rays, with no or negligible exposures to other types of radiation. Estimated doses represent annual averages, for each year from 1949 until 1995. For calendar years prior to 1949, it was assumed that doses were equal to the annual average for 1949. Doses were estimated by simulating measurements for multiple types of X-ray machines, workplaces and working conditions, including the use of lead aprons and work history for 3,805 of the workers (14% of the cohort). Mathematical models were used to determine year-specific personal dose equivalent (Sv) at a tissue depth of 10 mm, $H_p(10)$, from the dosimeter measurements. The dose to the colon, used as a proxy for the dose to all organs, was determined by converting $H_p(10)$ using conversion coefficients representing exposures to 35 keV X-rays in an anterior-posterior geometry. The mean reconstructed cumulative dose to the dosimeter was 0.25 Gy (250 mGy) with a median of 0.12 Gy (120 mGy). The distribution of cumulative doses to the colon was very skewed, with 60% of the medical workers having a dose to the colon less than 0.05 Gy (50 mGy) and 99% of workers having a dose less than 0.5 Gy (<500 mGy). The mean cumulative dose to the colon was 0.086 Gy (86 mGy), while the median dose was 0.042 Gy (42 mGy) [S16].

252. Poisson regression methods were used to fit ERR and EAR models for all cancers excluding leukaemia, based on 5-year lagged doses to the colon. The ERR and EAR models were set as functions of dose (linear response), sex, age at exposure and attained age. The ERR at 1 Gy for an attained age of

50 was 0.87 (95% CI: 0.48, 1.45) for both sexes, 0.82 (95% CI: 0.46, 1.32) for males and 0.93 (95% CI: 0.35, 1.84) for females. The EAR for an attained age of 50 was 22 (95% CI: 14, 32) per 10,000 person-years Gy for both sexes, 25 (95% CI: 16, 36) per 10,000 person-years Gy for males, and 18 (95% CI: 8, 33) per 10,000 person-years Gy for females. Neither the ERR nor the EAR models seem to indicate a dependency of risk on age at exposure, a fact that is not surprising since the workers were adults, with many of similar ages at the time of employment. However, both the ERR and the EAR risk models seem to indicate a statistically significant increase of risk with increasing attained age. While this is normal for an EAR model, such behaviour is curious for ERR and is at odds with the dependencies on attained age observed in the LSS cohort [S16].

253. The study by Sun et al. [S16] included a large number of persons with similar exposures (i.e. X-rays only), had a long follow-up and used cancer incidence rather than mortality. However, the study has a number of limitations. There are several issues related to dosimetry: (a) group-level data were used to impute dosimetry parameters, since individual data were not available for more than 14% of the cohort; (b) dose to the colon was used as a proxy for doses to specific organs; and (c) assumptions made about the energy of X-rays being constant over the years and about prevalent exposure orientation (e.g. anterior-posterior). These are important sources of uncertainty. While the limited potential for substantial confounding by other occupational exposures than radiation is a strength of this study, the completeness of cancer ascertainment is uncertain, with 30% of cancers not confirmed histologically. Finally, the reported attained-age dependency dose-response relationship is unclear, and, for the ERR model, it predicts an increase of ERR with attained age.

(f) *Cancer mortality and incidence in the United Kingdom's BNFL workers*

254. Gillies and Haylock [G6] provided an updated analysis of cancer mortality and incidence in nuclear workers formerly employed by BNFL in the United Kingdom. The BNFL cohort is only a portion of the larger NRRW cohort, representing around 50% of the collective dose in the NRRW study [M12]. The cohort comprises 64,956 employees, out of which 136 were excluded because of incompleteness of data. Thus, analyses were performed on 64,820 workers (53,821 males, 83% and 10,999 females, 17%) who accumulated 1,894,069 person-years at risk. Cohort members were classified either as radiation workers or as non-radiation workers, according to whether they were monitored for external radiation exposures using film badges. The cohort had 42,431 radiation workers (38,785 males, 91% and 3,646 females, 9%) and 22,389 non-radiation workers (15,036 males, 67% and 7,353 females, 33%).

255. The radiation workers were separated into those only exposed externally and those also exposed internally, according to the source of radiation exposure for which they were monitored. Those exposed internally were exposed to systemically distributed plutonium, tritium, or uranium or a combination of the three elements, in addition to external exposure to gamma radiation and possibly neutrons. These workers, monitored for internal exposures, tended to accumulate higher external doses than workers exposed only externally, because they had, in general, longer lengths of service, longer exposure histories and job assignments prone to higher external exposures. The mean annual external dose for the entire cohort was 4.9 mSv. The cumulative external dose among all radiation workers had a mean of 53 mSv and a median of 12 mSv, and the 99th percentile of the dose distribution was 590 mSv. The average cumulative external dose was 90 mSv for workers exposed either to plutonium or to tritium, and 31 mSv for workers exposed to uranium, while workers exposed to multiple internally deposited radionuclides received an average external cumulative dose of 212 mSv.

256. Workers in the cohort were employed between the beginning of 1946 and the end of 2002. The vital status was followed to 31 December 2005 starting from 1 January 1971 for cancer incidence

(i.e. 34 years of follow-up; 1,894,069 person-years). Altogether 5,511 solid cancers were diagnosed among the radiation workers (2,535 in the externally exposed group and 2,976 in the internally exposed group). Non-radiation workers had 3,524 solid cancer diagnoses during the period of follow-up. The number of recorded cancer deaths from solid cancers was 3,026 in the group of radiation workers (1,363 in the externally exposed group and 1,663 in the internally exposed group) and 2,223 in the non-radiation workers.

257. The SIRs for solid cancers were 0.95 (95% CI: 0.91, 0.98) for those externally exposed, 1.01 (95% CI: 0.97, 1.05) for those internally exposed, and 1.00 (95% CI: 0.97, 1.04) for the non-radiation workers. The SMRs were 0.86 (95% CI: 0.81, 0.90) for those externally exposed, 0.94 (95% CI: 0.89, 0.98) for those internally exposed, and 0.98 (95% CI: 0.94, 1.03) for the non-exposed workers.

258. Poisson regression was used to fit ERR models for incidence and mortality, as a function of the total cumulative external radiation dose lagged by 10 years. For solid cancer incidence, the ERR at 1 Sv for all radiation workers was 0.28 (90% CI: 0.08, 0.49). Estimates of the ERR for smoking-related cancers and for non-smoking related cancers were 0.11 (90% CI: -0.22, 0.50) and 0.35 (90% CI: 0.11, 0.62), respectively. When the cohort was analysed separately, the ERR at 1 Sv of cumulative external dose (lagged by 10 years) was 0.87 (90% CI: 0.36, 1.44) for the externally exposed workers and 0.13 (90% CI: -0.07, 0.36) for those exposed internally.

259. For solid cancer mortality, the ERR at 1 Sv for all radiation workers was 0.29 (90% CI: 0.02, 0.59). Estimates of the mortality ERR for smoking-related cancers and for non-smoking-related cancers were very similar to the ERR for all solid cancers, but with slightly larger uncertainty ranges. When the cohort was analysed separately for externally and internally exposed workers, the ERR at 1 Sv was 1.03 (90% CI: 0.37, 1.81) for those exposed externally and 0.06 (90% CI: -0.02, 0.37) for those exposed internally, for external dose lagged by 10 years.

260. The BNFL cohort is an important component of the larger NRRW cohort. Possible limitations of this study are: (a) radiation doses from internally incorporated radionuclides have not been included explicitly; (b) unrecorded neutron doses could be a source of bias in the reported dose responses; and (c) external doses for workers at the plutonium plant in Sellafield could have been overestimated from the 1960s onwards, leading to a potential underestimation of the risk per unit dose. Further work would be necessary to investigate the full effect of internal radiation worker exposure.

(g) Cancer mortality among nuclear workers in Japan

261. A cohort study of Japanese nuclear workers was started in 1990 by the Institute of Radiation Epidemiology of the Radiation Effects Association [A1]. The cohort included 200,583 male Japanese workers followed up from 1991 to 2000, with an average follow-up duration of 6.8 years. The cohort had an accumulated 1,373,000 person-years at risk. A total of 2,636 deaths from cancers other than leukaemia were observed during the follow-up period, a value very close to that expected for in the general population. About a quarter of the members of the cohort (48,281 males) responded to a questionnaire survey used to determine occupational history and lifestyle characteristics such as alcohol and tobacco consumption.

262. The radiation exposure of the Japanese nuclear workers in this cohort was almost exclusively external. Individual external doses were recorded using film badges, and in recent years, TLD. The mean individual cumulative dose was 12.2 mSv, with 75.4% of the cohort having received doses less than 10 mSv and 97.4% of the cohort received doses less than 100 mSv. Poisson regression was used to derive the ERR per unit dose for leukaemia and for other cancer mortality. Statistical analyses of the

dose response were carried out using cumulative doses lagged by 2 years for leukaemia and 10 years for cancers other than leukaemia.

263. The ERR at 1 Sv for all cancers except leukaemia was 1.26 (95% CI: -0.27, 3.0). To investigate the potential confounding effect of alcohol consumption, a dose-response analysis was carried out by grouping alcohol-related cancers. The ERR at 1 Sv for alcohol-related cancers only was 4.64 (95% CI: 1.13, 8.91), while the ERR at 1 Sv for all cancers excluding those related to alcohol and excluding leukaemia was 0.2 (95% CI: -1.42, 2.09). The ERR at 1 Sv for smoking-related cancers was also increased 1.9 (95% CI: -0.28, 4.47), compared to the ERR for all cancers except leukaemia.

264. Alcohol consumption and smoking are suspected to have been important confounding factors that may have influenced the results. The risk of death from alcohol-related cancers is strongly related to the cumulative dose. Mortality from liver cancer was not found to be statistically related to the cumulative dose. However, no unequivocal explanation is available to clarify why. Furthermore, a more recent study by Kudo et al. [K27] examined the confounding effect of smoking in a differently constructed cohort of Japanese nuclear workers followed up from 1999 to 2010 and determined that, when adjusting for smoking, the ERR at 1 Sv for all cancers except leukaemia declined compared to the ERR at 1 Sv obtained without adjusting for smoking.

(h) *Cancer incidence and mortality in Canadian uranium processing workers*

265. The retrospective cohort study of uranium workers from Port Hope, Ontario, Canada included 3,000 males and females with dates of first employment between 1932 and 1980, who were followed up for cancer mortality from 1950 to 1999 and for cancer incidence from 1969 to 1999 [Z3]. The cohort included workers that processed uranium (2,472) and radium (528), however did not have a history of work in uranium mines. The average age at first employment was 30 and the average duration of employment was 6.4 years. Out of all the workers 2,645 were males of whom, 2,148 processed uranium, and 497 processed radium. Given the low number of females and their low exposures, analyses were carried out for males only. This study provides 82,999 person-years of follow-up for mortality and 55,493 person-years for incidence (males only).

266. The members of this cohort were exposed to external gamma radiation and to radon decay products, but also to long-lived radionuclides (e.g. concentrated forms of uranium sulphites, nitrates, oxides and fluorides) and other chemicals. Exposure was characterized separately for external gamma radiation and radon decay products, with external exposures being represented by effective doses (reported in mSv) and internal exposures represented in terms of WLM. Gamma radiation was the primary type of radiation exposure at Port Hope. Measured doses by individual dosimeters were available for all workers starting after 1970. For earlier years, gamma doses were calculated using estimated average dose rates and time on the job. Exposures to radon decay products were determined based on monitoring data including radiochemical analyses of urine and whole-body counting. Doses from external gamma exposure to the end of follow-up, for males, had a mean of 116.4 mSv (range 0–5,099 mSv). Radon decay products produced an exposure, for males, with a mean of 13.3 WLM (range 0–628 WLM) [Z3].

267. Cancer incidence and mortality were lower among the members of this cohort when compared to the general Canadian population. A total of 418 cancer cases were observed during the period of follow-up, when 453.52 cases were expected (SIR=0.92; 95% CI: 0.84, 1.01). Similarly, 266 cancer deaths were observed compared to 282.5 expected cancer deaths (SMR=0.94; 95% CI: 0.83, 1.06). Analyses using a linear dose response resulted in a mortality ERR per unit dose for solid cancers of 0.12 (95% CI: <-0.35, 0.98) Sv⁻¹. Because radon decay products primarily affect the lung tissue,

separate dose–response analyses were carried out for lung cancer, resulting in a mortality ERR at 1 WLM of 0.21 (95% CI: <–0.45, 1.59) and an incidence ERR at 1 WLM of 0.77 (95% CI: <–0.19, 3.4). Other dose responses for either incidence or mortality were not statistically significant [Z3].

268. The study by Zablotska [Z3] included both cancer incidence and mortality and a relatively long follow-up period (especially for mortality). However, the cohort was small (2,645 males) and the statistical power low. Dose responses were provided separately for external gamma radiation and radon decay products and analyses for cancer other than lung were performed, all showing non-significant dose responses. A confounding effect of exposure to radon decay products on cancers other than lung could not be addressed by the existing data.

(i) Cancer incidence and mortality in Chernobyl emergency and recovery workers

269. Emergency workers from the Russian Federation who responded after the 1986 Chernobyl accident have been followed up to assess radiological health effects. Solid cancer incidence and mortality data were collected by the Russian National Medical and Dosimetric Registry. A retrospective epidemiological study of solid cancers has been carried out on a cohort of 67,568 male workers who worked in the Chernobyl Exclusion Zone in the period 1986–1987 [K5]. The follow-up period of the cohort for this study was 1992–2009. A total of 4,002 solid cancers were diagnosed and a total of 2,442 solid cancer deaths were recorded during the follow-up period. However, many of the cancers were diagnosed as a result of the mandatory annual health examinations that started in 2003. The study has a follow-up of 972,659 person–years for cancer incidence, and 993,423 person–years for mortality.

270. The members of the cohort were aged between 18 and 70 at the time of entry into the exclusion zone, with a mean age of 34 years (median 35). Dosimetry was based on recorded dates of arrival and departure from the Chernobyl Exclusion Zone. The majority of doses (85%) were measured using individual dosimeters, while the remaining doses were determined from group dosimeters or estimated [P7]. Cumulative absorbed doses to each group member from external exposure to gamma radiation during the working period ranged from 0.0001 to 1.24 Gy (median 0.102 Gy; mean 0.132 Gy), with 46% of the persons having received doses less than 0.1 Gy and 99% of the persons' doses less than 0.3 Gy. Uncertainties in individual doses ranged between factors of 0.5 to 3, depending on the method used (individual dosimeter, group dosimeter or calculations based on dose rate).

271. Cancer incidence was about 18% larger in the emergency workers, compared to the baseline rates among males in the Russian Federation, as indicated by the observed SIR of 1.18 (95% CI: 1.15, 1.22). However, this result could have been influenced by the screening effect introduced by the mandatory annual health examinations. Cancer mortality, on the other hand, was not statistically different from the mortality baseline cancer incidence rate (SMR=0.95; 95% CI: 0.92, 0.99).

272. Statistically significant linear dose responses were observed for both incidence and mortality. The ERR per unit dose for solid cancer incidence was 0.47 (95% CI: 0.03, 0.96) Gy^{–1}, and this value was obtained when an attempt was made to adjust for the screening effect that may have produced the increased cancer incidence compared to the baseline risk (SIR=1.18). For solid cancer mortality, the ERR per unit dose was 0.58 (95% CI: 0.002, 1.25) Gy^{–1}.

273. The strengths of this study include a large cohort with 85% of doses measured by individual dosimeters; and availability of both incidence and mortality data. However, this study (a) has a fairly young cohort, with a relatively short follow-up period 1992–2009 available to date; (b) does not have information

on smoking or alcohol consumption; (c) includes no investigation of non-linear dose responses; and (d) has results possibly influenced by the screening effect of mandatory annual medical examinations.

(j) *Cancer incidence and mortality in Mayak workers*

274. The Mayak Production Association located in Ozyorsk in the Chelyabinsk oblast of the Russian Federation was an industrial complex dedicated to the production of plutonium for the Soviet nuclear weapons programme. The Mayak Production Association began operations in 1948 and has included nuclear reactors, radiochemical and plutonium production plants and a number of auxiliary departments. Studies of radiological health effects in Mayak workers started in the 1980s when the Mayak workers cohort was first established. Occupational radiation exposure was complex as members of the Mayak cohort worked at five different facilities, where operations and radiological protection measures had changed with time (resulting mostly in a reduction of dose over time). Workers experienced external exposure to gamma radiation, internal exposure due, mostly, to inhalation of plutonium and other alpha emitters, or a combination of both external and internal exposure. Lung, liver and bone are particularly affected by the internal exposure to plutonium and other alpha emitters and they have been studied separately [G2, G3, G5, K15, K16, S13]. This section focuses on the newest studies of risk from external exposure to low-LET radiation for incidence and mortality of solid cancers other than lung, liver and bone (“non-LLB cancers” [H6, S11, S12]).

275. Dosimetry for studies of incidence [H6] and mortality [S12] of solid cancers other than lung, liver and bone was based on the 2008 version of the Mayak worker dosimetry system (MWDS-2008) [K12]. External doses were mainly from gamma radiation and were monitored by the Radiation Protection Department of the Mayak Production Association. Estimates of doses to specific organs from external sources were obtained either from individual film badge measurements or from reconstructed badge readings based on individual work histories. Film badge measurements were corrected to account for energy and angular variation, using information on the nature of the radiation fields at various workplaces. Measurements of cumulative external exposures are expressed as personal equivalent dose* at a tissue penetrating depth of 10 mm.

276. The cohort for analysis of solid cancer incidence [H6] includes 22,366 workers (75% males; 25% females) first employed between 1948 and 1982, with 6,699 workers with known plutonium exposure, 5,154 workers confirmed to have had no plutonium exposures, and 10,513 potentially exposed to plutonium (but unmonitored). The cohort is restricted to Ozyorsk residents, as data on diagnosed cases could not be collected for persons who migrated out of the area. The follow-up period includes 535,932 person-years.

277. For the incidence study cohort, the mean cumulative external dose was 0.51 Gy (range of 0 to 6.8 Gy; mean dose to males of 0.54 Gy; mean dose to females of 0.44 Gy). The mean dose was substantially higher for people who started to work between 1948 and 1958 (0.81 Gy) compared to those who started to work between 1959 and 1982 (0.15 Gy).

278. A total of 1,447 solid cancers other than lung, liver and bone were diagnosed during the follow-up period. Non-melanoma skin cancer was not included among these cases because of incomplete registration. Dose-response analyses for cancer incidence were conducted using Poisson regression, with cohort data classified by sex, attained age, calendar year, smoking status, alcohol consumption, plant where the person received the exposure, and estimated cumulative dose. Different latency periods (0, 5, 10, 15 and 20 years) were considered. An ERR model linear in dose was selected as the main type of dose response for cancer incidence, with a linear-quadratic fit as a potential alternative. Dose responses for incidence of all solid cancers except lung, liver and bone as a group and cancer-specific dose responses were investigated.

279. A statistically borderline significant relationship with cumulative dose from external gamma exposure was observed for non-LLB solid cancer incidence on a basis of a zero-year lag for cumulative doses (ERR per Gy=0.07; 95% CI: 0.01, 0.15; $p=0.06$) after adjusting for age, sex and smoking status. A non-statistically significant association was obtained after adjusting for internal plutonium exposure (ERR per Gy=0.06; 95% CI: -0.01, 0.14; $p=0.12$). Alternative lag periods (5, 10, 15 and 20 years) were used, but the resulting estimates or their statistical significance did not change substantially. There was also no evidence of non-linearity with external dose, based on a linear-quadratic model.

280. The mortality cohort [S11, S12] includes 25,757 persons, of whom 25% are females. Cohort members started employment in the period 1948–1982 and they have been followed up for cancer mortality from 1948 until 2008. The mean age of entry into the cohort was 24.8 and the mean age of exit was 61.7 (average follow-up of 36.9 years). The follow-up period includes 950,896 person-years.

281. Cigarette smoking was recorded among the mortality cohort, with 50% of the cohort being smokers, 37% never smokers and the remaining 14% having an unknown smoking status. Smoking was more prevalent in males than in females. Among males, 65% were smokers and 22% were never smokers, compared to 3% smokers and 80% never smokers among females.

282. Epidemiological analyses of mortality for solid non-LLB cancers were carried out using 5-year lagged cumulative external doses to the colon up to the end of follow-up. Doses ranged from zero to more than 3 Gy. The mean external dose was 0.354 Gy [S11]. People with doses to the colon of less than 100 mGy contributed 54% of the follow-up expressed in person-years, while those with doses less than 1 Gy contributed 90% of this.

283. Statistical analyses for the mortality cohort were carried out using Poisson regression. Analysed models included linear and non-linear dose responses, with and without attained age modifiers. The studies also analysed the possible effect of internal exposures to alpha particles on the mortality risk of solid, non-LLB cancers as a function of the doses from external gamma exposure. These analyses were carried out for the entire cohort using time-dependent indicators of exposure to alpha particles [S11] and for subcohorts of persons who did not work in areas where intakes of alpha-emitting radionuclides were likely (table 13) [S12].

284. Linear dose responses with no age modifiers produced the best statistically significant fits to the data. The ERR per unit dose for mortality from all solid cancers other than lung, liver or bone from exposure to external gamma radiation was 0.16 (95% CI: 0.07, 0.26) Gy^{-1} , when unadjusted for plutonium exposure and 0.12 (95% CI: 0.03, 0.21) Gy^{-1} , when adjusted for plutonium exposure. These results represent the dose response for the entire cohort. The dose response for a subcohort that does not include plutonium workers produced a similar ERR per unit dose: 0.14 (95% CI: 0.04, 0.25) Gy^{-1} , while the dose response for reactor workers only was higher: 0.25 (95% CI: 0.01, 0.59). Analyses for other subcohorts (table 13) also produced comparable ERRs, indicating that the observed dose response from exposure to external gamma radiation was not influenced by the exposures to alpha particles. Male and female smokers showed significantly elevated risks of death from non-LLB compared to non-smoking males and females with estimated ERRs per unit dose of 1.53 (95% CI: 1.33, 1.76) Gy^{-1} and 1.60 (95% CI: 1.01, 2.40) Gy^{-1} , respectively [S12].

285. The major strength of the Mayak studies is a relatively large cohort with long follow-up of good quality, with individual doses from external exposure from measurements and detailed work histories. Multiple dose-response models have been studied and the effect of smoking has been assessed. Alcohol consumption has not yet been accounted for explicitly. The current risk models for the Mayak cohort are based on the 2008 version of the dosimetry system (MWDS-2008). A new, updated Mayak workers dosimetry system, labelled MWDS-2013, has recently been published [N3, V4] and is already being

updated by MWDS-2016 [V5]. The MWDS-2013 dosimetry system incorporates a Bayesian approach to determining plutonium intake from historical urinalysis samples, and a revised set of models for the estimation of doses from external sources of radiation, adapted and expanded to account for uncertainties in the exposure scenarios, measurements and other parameters. Revised dose–response analyses based on MWDS-2013 or MWDS-2016 have not been published.

Table 13. Excess relative risk per Gy from external gamma exposure for solid cancers other than lung, liver and bone observed in the Mayak worker cohort [H6, S11, S12]

<i>Cohort/subcohort</i>	<i>Number of workers</i>	<i>Cases^a</i>	<i>ERR per Gy</i>	<i>95% CI</i>
INCIDENCE				
Full cohort	22 366	1 447	0.07	0.01, 0.15
MORTALITY				
Full cohort	25 757	1 825		
No adjustment for effect of ²³⁹ Pu			0.16	0.07, 0.26
Adjusted for effect of ²³⁹ Pu			0.12	0.03, 0.21
No plutonium workers	17 944	1 281	0.14	0.04, 0.25
No plutonium or radiochemical workers	8 800	593	0.20	−0.0002, 0.46
Reactor workers only	5 416	405	0.25	0.01, 0.59
Plutonium versus non-plutonium workers				
Reactor + auxiliary	NA	NA	0.19	0.022, 0.39
Radiochemical + plutonium production	16 957	1 232	0.15	0.063, 0.25

^a Incident cases or death cases, respectively, from solid cancers other than lung, liver and bone.

(k) *Cancer mortality in Rocketdyne workers*

286. Rocketdyne was a rocket engine testing facility in the United States. In 1950, Rocketdyne merged with Atomics International. It was located in California at the Santa Susana Field Laboratory, Canoga Park and Do Soto sites, where ten research reactors and seven criticality facilities were operated. Other radiation-related activities included fabrication of enriched uranium and plutonium fuel (from 1958 to 1983) for research, space and power reactors, decladding spent nuclear fuel, storing radioactive material, and disassembling and decontamination of reactor facilities.

287. A cohort of Rocketdyne workers has been set up to analyse radiogenic cancer mortality. The first analysis followed up the cohort from 1948 until 1999 [B6], and an updated analysis added nine years of follow-up (1948–2008) [B8]. The cohort now includes 46,970 workers, out of which 5,801 were involved in radiation-related activities. While at Rocketdyne, workers were monitored for external exposure (3,569), internal exposure (58) or both external and internal exposures (2,174). There were 1,833 (32%) workers who were monitored for radiation either before or after employment at Rocketdyne. Among the 2,232 workers monitored for internal exposures, 87% (1,941) had negligible intakes. The remaining 41,169 members of the cohort were engaged in activities not involving radiation exposure. Most of the workers were males (92%). Vital status of workers has been ascertained from 1 July 1948 (or six months after the date of first hire, whichever came later) up to 31 December 2008 (or age 95, whichever came first), producing a total of 196,674 person–years of follow-up.

288. Whole-body doses from external gamma exposure were obtained in two ways: from abstracted dosimeter records from Rocketdyne/Atomics International radiation files or by linking Rocketdyne workers with various nationwide databases to determine exposures before and after employment at Rocketdyne [B7]. Doses were cumulated through end of follow-up for those alive and to the date of death for those who died. The mean dose from external exposure was 13.5 mSv with a maximum of 1 Sv, with approximately 87% of persons having doses less than 100 mSv. A small number of workers (665 workers) received neutron doses from Rocketdyne/Atomics International or other employment. The mean dose from neutrons was 1.2 mSv, with 93% having received doses less than 5 mSv and 98% less than 30 mSv (maximum 55.8 mSv). Internal doses to 16 organs from intakes of 14 radionuclides were estimated based on bioassay data recorded on 11 different bioassay forms. The most important contributors to internal exposure were isotopes of uranium (^{234}U , ^{235}U and ^{238}U), plutonium (^{239}Pu), strontium (^{90}Sr), thorium (^{232}Th), polonium (^{210}Po), americium (^{241}Am) and cerium (^{144}Ce). Lung was the organ with the largest internal exposure. The mean dose to lung from external and internal radiation combined was 19 mSv.

289. Out of the 5,801 monitored persons, 2,382 died during the period of observation, with 684 deaths due to malignant neoplasms [B8]. A number of 778.2 solid cancer deaths from radiation were expected, indicating an SMR of 0.88 (95% CI: 0.81, 0.95). Relative risks were estimated by Cox proportional hazard modelling techniques. The relative risk at 100 mSv for all cancers except leukaemia from exposure to external radiation was 0.98 (95% CI: 0.82, 1.17). This converts into an ERR at 1 Sv of -0.2 (95% CI: -1.8 , 1.7). The RR at 100 mSv for lung cancer was 1.01 (95% CI: 0.89, 1.16) or an ERR at 1 Sv of 0.1 (95% CI: -1.1 , 1.6). Relative risks from internal exposures for organs other than lung have been calculated. As for solid tumours and lung, no statistically significant increases in risk were seen for any individual solid cancer types.

290. Strengths of this study include the cohort design with a large number of non-exposed workers from the same facilities, estimation of doses both before and after employment at Rocketdyne and a long period of observation of up to 60 years (mean: 33.9 years). Limitations include (a) a small number of exposed workers ($n=5,801$), leading to low statistical power; (b) no possibility of analysing the joint effect of external and internal exposures, because of small number of cases (only six lung cancers) among workers with more than 5 mSv from both external and internal exposures; (c) possible errors in dosimetry which are unaccounted for; (d) no analyses of non-linear dose responses; and (e) incomplete knowledge about confounding factors such as smoking.

3. Studies of members of the public exposed to radiation

(a) *Cancer incidence and mortality in Techa River cohort*

291. From 1949 to 1956, the radiochemical plant that operated at the Mayak Production Association in support of the Soviet nuclear weapons programme released large amounts of radionuclides into the Techa River, creating significant exposures of a population of about 30,000 residents of 41 rural villages along 250 km of this river. The exposed residents are members of the Techa River cohort which includes males and females of all ages. This cohort has been followed to study cancer mortality from 1950 to 2007 [S4] and cancer incidence from 1956 to 2007 [D3], accumulating 927,743 person-years for mortality and 472,788 person-years for incidence.

292. The cohort for cancer mortality includes 29,730 persons, out of which 42% are males (12,487) and 58% are females (17,243), with 80% Slav and 20% Tatar and Bashkir ethnicities. Of all members of the cohort, 40% were exposed before age 20, 28% at ages 20–40 and 32% after age 40.

293. The cohort for cancer incidence includes 17,435 persons, out of which 43% are men (7,521) and 57% are females (9,914), with 68% Slav (11,810) and 32% Tatar and Bashkir (5,625) ethnicities. The distribution of the cohort by age at entry is: 7,353 (less than 20 years of age), 5,876 (20–40 years of age) and 4,206 (more than 40 years of age).

294. Members of the cohort were exposed externally to penetrating gamma radiation from river sediments and flood-plain soil, and internally through ingestion of water and food products contaminated primarily with ^{89}Sr , ^{90}Sr and ^{137}Cs , but also with ^{144}Ce , ^{95}Zr and ^{95}Nb . Estimates of the doses to organs were based on the most recent Techa River Dosimetry System (TRDS)-2009 [D4]. Analyses of incidence and mortality for solid cancer as a group were performed using the 5-year lagged cumulative doses to the stomach, which varied from 0 to 960 mGy.

295. Analyses of solid cancer mortality based on 2,303 solid cancer deaths (1,188 males and 1,115 females) indicated a statistically significant linear trend with an ERR at 100 mGy of 0.061 (95% CI: 0.004, 0.127). No EAR analyses have been carried out for this study. The reported ERR per unit dose represents a total of 927,743 person-years of follow-up, out of which 92.3% were for persons that received less than 100 mGy (99.9% less than 500 mGy) [S4] with a mean dose to the cohort of 35 mGy.

296. Analyses of solid cancer incidence based on 1,933 cases (963 males and 970 females), with a mean age at diagnosis of 63, indicated a linear dose response with an ERR at 100 mGy (adjusted for the effects of smoking) of 0.077 (95% CI: 0.013, 0.15). The ERR at 100 mGy unadjusted for the effects of smoking was similar: 0.09 (95% CI: 0.02, 0.16). The reported ERR represents 472,788 person-years of follow-up, out of which 89.1% were for persons who had received less than 100 mGy (97.7% less than 300 mGy). The mean dose to the stomach was reported as 52 mGy, with a mean dose to the persons diagnosed with cancer (dose to the cases) of 55 mGy.

297. The ERRs observed for the Techa River cohort are not suitable to estimate risks in a population of adult workers, because it includes children (40% of the cohort received exposures under age 20). No ERR values are available for adults only.

298. The Techa River studies provide important insights into the radiation-related health risks in the case of accidental or routine prolonged radiation exposure of the general population (of both sexes, all age groups and different health status). The strength of these studies is the relatively large and unselected cohort of males, females and children with a long follow-up. The cohort includes persons who lived along the river at some time during the period 1950–1960, out of which about 75% have died. For the mortality study, a limitation is introduced by the lack of complete histopathological verification of the cancer deaths and by missing cause of death for about 9% of deaths. The results of both mortality and incidence studies could have been affected by the relatively large fraction (~20%) of the population lost to follow-up because of migration out of the area, by the potential medical screening bias, by unaccounted radiation exposure due to medical diagnostic examinations (e.g. fluoroscopy) and by issues with cancer ascertainment [D3, K10, K17, S4]. In addition, there are still concerns about uncertainties related to the estimated doses [D3, S4].

299. A study to revise the Techa River Dosimetry System (TRDS)-2009 with the purpose of quantifying the uncertainties in dosimetry is ongoing and revised dose–response analyses accounting for the uncertainties in dose are expected.

(b) *Cancer incidence in India's high natural background area*

300. Epidemiological studies on cancer in high level natural radiation areas provide useful information on chronic low dose and low dose rate radiation exposure on human populations. The population residing in Karunagappally Taluk of Kerala state in southwest India gives a unique opportunity to evaluate health effects of low dose and low dose rate chronic exposure prevailing in this area because of its vast population size and varied range of background radiation exposure due to the patchy distribution of ^{232}Th containing monazite sand. Radiation levels in this area vary from less than 1.0 to 45 mGy per year and some places are reported to be as high as 70 mGy per year.

301. A comprehensive survey was conducted in this area and a population cancer registry was established in 1990. Data on cancer incidence and cancer deaths were collected during 1990–1996 and the preliminary study did not reveal any increase in cancer incidence due to the level of external gamma radiation [N1].

302. A more recent study [N2] was conducted that examined 69,958 residents (32,085 males and 37,873 females) with age range between 30–84 years, an average follow-up period of 10.5 years, and which accumulated 736,586 person–years of observation. A total of 1,349 cases of cancer (747 males and 602 females) and 30 leukaemia cases were identified by the end of 2005. Data obtained were evaluated with respect to sex, attained age, follow-up interval, sociodemographic factors and smoking.

303. Cumulative radiation doses to colon were estimated for all members of the cohort, lagged by 10 years for analyses of risk of solid tumours. Doses to bone marrow lagged by two years were used for leukaemia analyses. Doses are based on TLD measurements in indoor and outdoor environments combined with occupancy factors describing the fraction of time spent in each environment and converted to colon or bone marrow dose. For solid tumours, the portion of the cohort including persons with a cumulative dose to colon less than 50 mGy was used as reference. Persons with doses less than 500 mGy account for 98% of all solid cancer cases (21% of cases in the reference group with doses less than 50 mGy, and 77% of cases for the group with doses between 50 and 500 mGy). Also, persons with doses less than 500 mGy account for 99% of person–years of follow-up, while those with doses less than 100 mGy account for 60% of the person–years.

304. The ERR per Gy for incidence of all cancers except leukaemia was estimated to be -0.13 (90% CI: $-0.58, 0.46$; $p > 0.5$) [N2]. The incidence of leukaemia excluding CLL was not significantly related to high level natural radiation. The cancer incidence among the residents in high level natural radiation areas of Karunagappally Taluk in Kerala state, India suggests that the ERR per unit dose for solid cancer after chronic radiation exposure is significantly lower than that associated with acute exposure in other studies [N2].

305. A recent follow-up study on the Karunagappally cohort showed that bidi smoking (larger amounts of bidi smoked a day and longer durations) increases the risk of hypopharyngeal and laryngeal cancer. Tobacco chewing was found not related to the risk of hypopharynx or larynx cancer [J3].

306. This study includes persons exposed to very low doses who have been followed up only for a relatively short time period. Thus, the study may not have adequate power to detect a dose response, despite the relatively large size of the exposed population. Environmental and social factors such as tobacco use and bidi (local tobacco) smoking, income difference, access to health care and migration of population may also affect the dose response [N2]. Overall, this study indicates that it is unlikely that the risk from exposure at these levels of natural radiation is substantially higher than currently believed.

(c) *Cancer mortality in China's high natural background area*

307. The Yangjiang region in the Guangdong province, China, is known for its high levels of background radiation, with an average annual dose from external radiation from natural sources, including thorium, of 2.1 mSv, compared to levels of 0.77 mSv in a control area. Yangjiang has two high background radiation areas, Tongyou and Donganling, with 21,838 and 44,786 residents, respectively, during the 1979 census. The control area is located in the eastern part of Yangjiang and had 25,924 residents during the same census.

308. To study the effect of the high background radiation, a cohort of 31,604 persons (16,045 males and 15,559 females) was established [T3]. The members of the cohort attained the age of 30 to 74 years during the follow-up period 1979–1998. It was decided to exclude persons younger than 30 years of age because the baseline cancer risk is low for those in this age group. Persons aged 75 years or older were not included because they were less likely to seek medical care for cancer or other diseases, and this could result in inaccurate diagnosis and cause of death. The mean attained age of persons from the high background area was 54, while the mean attained age in the control group was 57.

309. In the follow-up period 1979–1998, the study accumulated 736,942 person–years at risk (528,429 in the high background radiation group and 208,513 person–years in the control group). A total of 6,005 deaths were recorded, with 956 deaths from cancer (941 from cancers other than leukaemia, and 15 deaths from leukaemia). The most common cancer types resulting in death were liver (202 males, 73 females) and oropharynx (159 males and 49 females) followed by lung, stomach, colon-rectum and uterus. To determine cancer ascertainment, trained local census workers visited hospitals in the study area and reviewed the medical records of the deceased persons and extracted the relevant information.

310. Doses were based on indoor and outdoor measurements of gamma dose rates (at a height of 1 m, with the contribution from cosmic rays being subtracted) and on sex- and age-specific occupancy factors, the fraction of time spent indoors. Outdoor measurements were taken in each village and community, on main roads, in alleys, in open recreational areas, on rice paddies, in areas adjacent to wells, and on banks of ponds. Indoor measurements were carried out in about one third of homes in each village or community, 8,028 households in total. House occupancy factors were based on a questionnaire survey of 5,291 persons (aged 0–92 years, mean age 32.3) in 88 villages and communities. Cumulative doses to the colon lagged by 10 years were used in the risk analysis. The mean individual cumulative dose was 21.6 mGy in the control area. In the Tongyou and Donganling high background areas, the mean doses were 88.5 and 81.7 mGy, respectively. Among the 941 cases of cancer death (excluding leukaemia), 81% received cumulative doses less than 100 mGy, and 95.6% received doses less than 125 mGy. Among all members of the cohort, 28,009 persons (88.6%) received doses less than 100 mGy.

311. Statistical analyses were carried out by Poisson regression using linear dose–response models with no age modifiers [T3]. The ERR per unit dose for all cancers excluding leukaemia was -1.01 (95% CI: $-2.53, 0.95$) Gy^{-1} . Liver cancer was the most commonly observed cancer type leading to death, but there were difficulties of accurately diagnosing and establishing liver cancer as a cause of death, and the liver cancer data are suspected to have contained errors. Only six cases of liver cancer deaths had pathological confirmation. Thus, an analysis was also carried out for all cancers excluding both leukaemia and liver cancer. The resulting dose response was positive, however had a negative lower bound: ERR per unit dose of 0.19 (95% CI: $-1.87, 3.04$) Gy^{-1} .

312. The strengths of this study [T3] include a stable population with exposed and controls from areas with similar life styles. The limitations include (a) the dosimetry does not include contributions from internal doses (due to inhalation of radon decay products), a contribution that would affect at least the

risk of lung cancer; (b) indoor measurements have been carried out in an only limited number of households, although they did show a rather uniform distribution; and (c) cancer ascertainment of liver cancer is questionable, and this is important because this cancer type is responsible for most of the deaths in the cohort.

4. Summary of studies of solid cancer risk from low-LET radiation

313. A significant number of epidemiological studies of risk of solid cancers from exposure to low-LET radiation have been published since the UNSCEAR 2012 Report [U8], covering a wide variety of exposure situations (table 14). Cancer incidence and mortality studies of the Japanese atomic bombing survivors have been updated with a longer follow-up of the LSS cohort and a revised dosimetry system (DS02R1, fully applied to the solid cancer incidence data so far). New or updated cancer incidence and mortality studies of radiation workers from nine countries (Canada, China, France, Germany, Japan, Republic of Korea, Russian Federation, United Kingdom and United States) cover nuclear power plant workers, uranium processing workers, X-ray technicians, emergency workers and others.

314. The reviewed studies have several common characteristics. Low-LET radiation (X-rays and gamma radiation) was the primary cause of exposure for all cohorts, although exposure to high-LET radiation (alpha particles, neutrons) has occurred in some cohorts and this may have induced biases in the reported dose response for low-LET exposures. Aside from the Japanese atomic bombing survivors (LSS cohort), the other studied cohorts received chronic or fractionated exposures, at low doses and dose rates. For all cohorts, more than 50% of the members received doses less than 100 mGy, with most cohorts having the majority of their members being exposed to doses lower than 100 mGy (i.e. ~90% or more). Table 14 presents the risk as the ERR at 100 mGy (or mSv), instead of the customary ERR at 1 Gy, since risks at ~100 mGy (or mSv) are of interest for radiation protection purposes and they are relevant for the discussed cohorts.

315. In most studies, the best estimate of the ERR at 100 mGy (or mSv) was greater than zero and less than 0.1. However, not all positive ERRs per unit dose were statistically significant. Many of the studies are small (i.e. small number of people and small number of diseases) and have negligible power to detect radiogenic risk (at the present), but studies that are well conducted should be followed up in the future, as they may be informative as the workers age. In addition, smaller studies should be pooled with other studies to create larger cohorts. The worker studies often showed a healthy worker effect indicated by cancer incidence or mortality rates in the exposed group that were lower than those in a comparable general population (i.e. the SIRs or SMRs were less than 1.0); thus, internal analyses within the exposed group are required to assess a risk per unit dose, and determine if the risk for workers with low doses is different from the risk for workers with high doses.

316. The LSS cohort is unique because it includes a large number of persons of all ages and both sexes, it has been carefully characterized and followed up, and it relies on high quality dosimetry. The LSS studies provide information on the age dependence of radiogenic health effects, allowing derivation of dose responses that depend explicitly on age at time of exposure, time since exposure and attained age.

317. Among the workers studies, the recent information from the INWORKS is exceptional because of the long observation time (more than 8 million person-years), the large number of solid cancer deaths analysed (nearly 18,000), and the high quality of data. Worker studies provide data that are relevant to exposure of adults, mostly males. Thus, dose responses from worker studies cannot be reliably applied to childhood exposure (e.g. children exposed as members of the public, or paediatric medical exposures) or to exposure of adult females. None of the worker studies reviewed provided reliable

information on the dependency of risk with age at exposure or attained age within the adult age group. However, the dose response from the worker studies could be applied to the estimation of risk in other workers exposed to radiation.

318. The ERR at 100 mGy for mortality from all solid tumours from studies of the LSS and INWORKS cohorts are compatible with the ERR at 100 mGy from the rest of the studies (figure V). While some of the studies have statistically non-significant ERRs, the central values are within a range of 0 and 0.07 per 100 mGy (0 to 0.7 per Gy) for all studies except those on the Rocketdyne workers, which has a slightly negative ERR at 100 mGy.

Figure V. Excess relative risk at 100 mGy for solid tumours from recent mortality studies of cohorts with prolonged, long-term exposures, except the LSS cohort which represents an acute exposure

ERRs for LSS [O5], INWORKS [R5], BNFL [G6], Mayak [S11], Chernobyl [K5], Port Hope [Z3], Rocketdyne [B8] and Wismut [K24] represent exposures of adults only, while for Techa River [S4] and Yangjiang region [T3] children are included. The study of nuclear workers in Japan [A1] is not included because of strong confounders (alcohol and smoking)

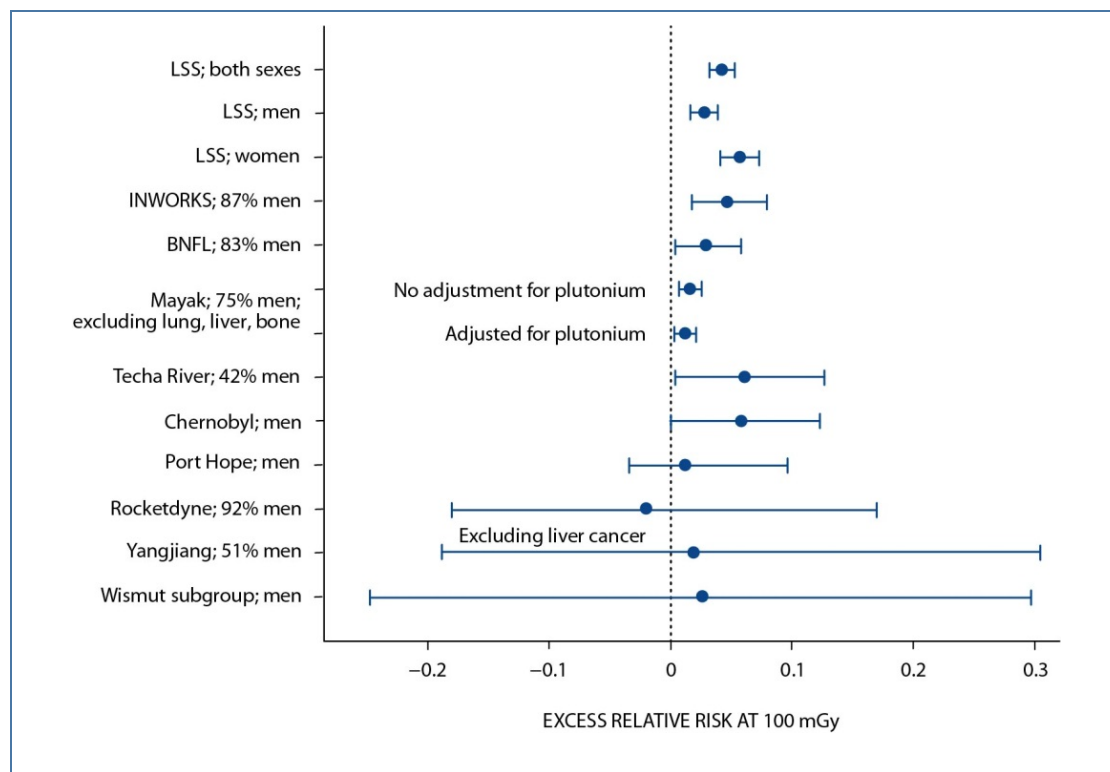


Table 14. Summary of recent studies of solid cancer incidence and mortality

Included are studies published between 2009 and 2017. Previous studies are included in previous UNSCEAR reports

<i>Study</i>	<i>Cohort</i>	<i>Cases</i>	<i>Follow-up</i>	<i>Person-years</i>	<i>Dosimetry^a</i>	<i>Dose response (95% CI)^b</i>
JAPAN Mortality Atomic bombing survivors [O5]	Exposed (DS02 doses) 86 611 persons 35 687 males 50 924 females Entire cohort 120 321 persons 50 175 males 70 146 females All ages	Exposed (DS02 doses) 50 620 deaths 10 929 deaths from solid cancer	Total follow-up 1950–2003 (53 years)	Exposed (DS02 doses) 3 294 210 PY	External exposure Mean weighted dose to colon=117 mGy 79.1% of cohort had doses <100 mGy	ERR at 100 mGy Sex-averaged 0.042 (0.032, 0.053) Males 0.028 (0.018, 0.039) Females 0.057 (0.042, 0.072)
JAPAN Incidence Atomic bombing survivors [G8]	Exposed (DS02R1 doses) 80 205 persons Entire cohort 105 444 persons 42 910 males 62 534 females All ages	Exposed (DS02R1 doses) 22 538 cases 10 473 in males 12 065 in females	Total follow-up 1958–2009 (51 years)	Exposed (DS02R1 doses) 2 317 915 Entire cohort 3 079 484 PY	External exposure Mean weighted dose to colon=114 mGy 79.2% of cohort had doses <100 mGy	ERR at 100 mGy Sex-averaged, linear 0.050 (0.042, 0.059) Males, linear quadratic ERR at 1 000 mGy=0.20 (0.12, 0.28) ERR at 100 mGy=0.01 (–0.0003, 0.024) Females, linear 0.064 (0.052, 0.077) Sex-averaged, linear With smoking adjustment ERR at 100 mGy=0.047 (0.039, 0.055)

<i>Study</i>	<i>Cohort</i>	<i>Cases</i>	<i>Follow-up</i>	<i>Person-years</i>	<i>Dosimetry</i> ^a	<i>Dose response</i> (95% CI) ^b
UNITED KINGDOM, FRANCE, UNITED STATES Mortality INWORKS Occupationally-exposed workers [R5]	Entire cohort 308 297 workers 268 262 males 40 035 females	Solid cancer 17 957 deaths All cancers 19 748 deaths All causes 66 632 deaths	Total follow-up 1944–2005 (61 years) Mean follow-up duration 27 years	Entire cohort 8.2 million PY	External gamma exposure Dose to colon (10-year lag) Mean=20.9 mGy Median=4.1 mGy 90th percentile=53.4 mGy	ERR at 100 mGy 0.047 (90% CI: 0.018, 0.079)
GERMANY Mortality Uranium millers [K24]	4 054 males	Solid cancers 457 deaths Cardiovascular disease 717 deaths Non-malignant respiratory disease 111 deaths	Total follow-up 1946–2008 (62 years) Mean follow-up duration 39 years	158 383 PY	Effective dose from external gamma radiation (5-year lag) Mean=26 mSv Median=11 mSv 95.8% of cohort had doses <100 mSv Radon daughter exposure Mean=8 WLM Median=5 WLM Long-lived radionuclides exposure Mean=3.9 h kBq m ⁻³	External gamma exposure ERR at 100 mSv Solid cancers 0.186 (–0.008, 0.38) Adjusted for radon 0.026 (–0.247, 0.298) Radon daughter exposure Solid cancers ERR at 1 WLM=0.0174 (0.0024, 0.0323) Adjusted for gamma ERR at 1 WLM=0.0163 (0.0034, 0.036)
GERMANY Mortality Nuclear power plant workers [M3]	8 972 workers 8 746 males 226 females	Males Solid cancers 120 deaths All causes 310 deaths Females No deaths	Total follow-up 1991–2008 (17 years) Mean follow-up duration 14.6 years	Males 128 570 PY Entire cohort 130 737 PY	Effective dose from external gamma exposure (10-year lag) Mean=29.5 mSv Median=5.7 mSv 90% of cohort had doses <100 mSv	No reported ERR or EAR dose response Hazard ratio/mSv Solid tumours 0.999 (0.996, 1.001) All cancers excluding leukaemia 0.999 (0.996, 1.001)

<i>Study</i>	<i>Cohort</i>	<i>Cases</i>	<i>Follow-up</i>	<i>Person-years</i>	<i>Dosimetry^a</i>	<i>Dose response (95% CI)^b</i>
KOREA, Republic of Incidence Nuclear power plant workers [J4]	Exposed 8 429 workers Males only Entire cohort 16 236 workers	Males Exposed workers 96 cases All workers 197 cases All cancers excluding leukaemia	Total follow-up 1992–2005 (13 years) Mean follow-up duration 7.53 years exposed workers	Exposed 63 503 PY Entire cohort 111 804 PY	Total effective doses (external and internal) (10-year lag) Mean=19.9 mSv Median=2.93 mSv 95% of cohort had doses <100 mSv	ERR at 100 mSv All cancers excluding leukaemia 0.21 (–0.19, 0.9) All cancers 0.17 (–0.21, 0.82)
CHINA Incidence Medical X-ray technicians [S16]	Exposed 27 011 workers 21 571 males (80%) 5 440 females (20%) Unexposed 25 782 workers Entire cohort 52 793 workers	Exposed 795 cases Unexposed 848 cases Entire cohort 1 643 cases	Total follow-up 1950–1995 (45 years) Mean follow-up duration 25.7 years	Exposed 683 425 PY Unexposed 762 950 PY Entire cohort 1 446 375 PY	External gamma exposure Dose to colon (10-year lag) Mean=86 mGy Median=42 mGy 60% of cohort had doses <50 mGy 99% of cohort had doses <500 mGy	At attained age 50 years ERR at 100 mGy 0.087 (0.048, 0.145) EAR at 100 mGy 2.2 (1.4, 3.2) per 10 000 PY Gy
UNITED KINGDOM Incidence and mortality BNFL nuclear workers [G6]	Exposed 42 431 workers 38 785 males (91%) 3 646 females (9%) Unexposed 22 389 workers Entire cohort 64 820 workers	Exposed 5 511 cases 3 026 deaths Unexposed 3 524 cases 2 223 deaths	Total follow-up 1971–2005 (34 years)	Exposed 1 164 960 PY Unexposed 729 109 PY Entire cohort 1 894 069 PY	External gamma exposure (10-year lag) Mean=53 mSv Median=12 mSv 99% of cohort had doses <590 mSv	ERR at 100 mSv Solid cancers Incidence 0.028 (90% CI: 0.008, 0.049) Mortality 0.029 (90% CI: 0.002, 0.059)

<i>Study</i>	<i>Cohort</i>	<i>Cases</i>	<i>Follow-up</i>	<i>Person-years</i>	<i>Dosimetry</i> ^a	<i>Dose response</i> (95% CI) ^b
JAPAN Mortality Nuclear workers [A1]	200 583 males	All cancers excluding leukaemia 2 636 deaths	Total follow-up 1991–2002 (11 years) Mean follow-up duration 6.8 years	Entire cohort 1 373 000 PY	Effective dose from external gamma exposure (10-year lag) Mean=12.2 mSv 97.4% of cohort had doses <100 mSv 75.4% of cohort had doses <10 mSv	ERR at 100 mSv 0.126 (–0.027, 0.30) All cancers excluding leukaemia 0.020 (–0.142, 0.21) Excluding alcohol-related cancers and leukaemia 0.464 (0.113, 0.891) Alcohol-related cancers only –0.002 (–0.265, 0.304) Excluding smoking-related cancers and leukaemia
CANADA Incidence and mortality Port Hope Uranium millers [Z3]	3 000 workers 2 645 males 355 females Analyses for males only	418 cases 266 deaths	Total follow-up Incidence 1969–1999 (30 years) Mortality 1950–1999 (49 years)	Entire cohort Mortality 82 999 PY Incidence 55 493 PY	Effective dose from external gamma exposure (5-year lag) Mean=116.4 mSv Range=0–5 099 mSv Radon decay products Mean=13.3 WLM Range=0–628 WLM	External gamma ERR at 100 mSv Mortality, solid cancers 0.012 (<–0.035, 0.098) Radon decay products ERR at 1 WLM, lung cancer Incidence: 0.0077 (<–0.0019, 0.034) Mortality: 0.0021 (<–0.0045, 0.016)
RUSSIAN FEDERATION Incidence and mortality Chernobyl emergency workers [K5]	67 568 males	4 002 cases 2 442 deaths	Total follow-up Incidence 1992–2009 (17 years)	Entire cohort Mortality 993 423 PY Incidence 972 659 PY	External gamma exposure Whole-body doses Mean=132 mGy 46% of cohort had doses <100 mGy 99% of cohort had doses <300 mGy	ERR at 100 mGy Incidence: 0.047 (0.003, 0.096) Mortality: 0.058 (0.0002, 0.125) Screening effect

<i>Study</i>	<i>Cohort</i>	<i>Cases</i>	<i>Follow-up</i>	<i>Person-years</i>	<i>Dosimetry</i> ^a	<i>Dose response</i> (95% CI) ^b
RUSSIAN FEDERATION Incidence Mayak workers [H6]	22 366 workers 16 679 males 5 687 females	1 447 cases All solid cancers, except lung, liver and bone; Non-melanoma skin not included	Total follow-up 1948–2004 (56 years)	Entire cohort 535 932 PY	External gamma exposure Hp(10) doses (0-year lag) Mean=510 mGy Range: 0–6 800 mGy 90% of person-years had doses <1 000 mGy	ERR at 100 mGy Solid cancers Excluding lung, liver and bone Adjusted for age, sex, smoking status (0-year lag) 0.007 (0.001, 0.015) Unadjusted for Pu exposure 0.006 (–0.001, 0.014) Adjusted for Pu exposure
RUSSIAN FEDERATION Mortality Mayak workers [S11, S12]	25 757 workers 19 318 males 6 439 females	1 825 deaths All solid cancers, except lung, liver and bone	Total follow-up 1948–2008 (60 years) Mean follow-up duration 36.9 years	Entire cohort 950 896 PY	External gamma exposure Dose to colon (5-year lag) Mean=354 mGy 54% of person-years had doses <100 mGy 90% of person-years had doses <1 000 mGy	ERR at 100 mGy Solid cancers Excluding lung, liver and bone 0.016 (0.007, 0.026) Unadjusted for Pu exposure 0.012 (0.003, 0.021) Adjusted for Pu exposure
UNITED STATES Mortality Rocketdyne nuclear workers [B8]	Exposed 5 801 workers 5 335 males 466 females Unexposed 41 169 workers 31 677 males 9 492 females Entire cohort 46 970 workers	684 deaths	Total follow-up 1948–2008 (60 years) Mean follow-up duration 33.9 years	Exposed workers 196 674 PY	External gamma exposure Whole body dose (10-year lag) Mean=13.5 mSv External and internal dose to the lung Mean=19.0 mSv 87% of cohort had doses <100 mSv	ERR at 100 mSv All cancers excluding leukaemia –0.02 (–0.18, 0.17) Lung cancer 0.01 (–0.11, 0.16)

<i>Study</i>	<i>Cohort</i>	<i>Cases</i>	<i>Follow-up</i>	<i>Person-years</i>	<i>Dosimetry</i> ^a	<i>Dose response</i> (95% CI) ^b
<p>RUSSIAN FEDERATION</p> <p>Incidence and mortality Members of public Techa River region</p> <p>Incidence [D3] Mortality [S4]</p>	<p>Incidence 17 435 persons 7 521 males 9 914 females</p> <p>Mortality 29 730 persons 12 487 males 17 243 females</p> <p>Age at entry <20 years for 40% of cohort</p>	<p>1 933 cases 2 303 deaths</p>	<p>Total follow-up</p> <p>Incidence 1956–2007 (51 years)</p> <p>Mortality 1950–2007 (57 years)</p>	<p>Incidence 472 788 PY</p> <p>Mortality 927 743 PY</p>	<p>External gamma + internal beta exposure Doses to stomach (5-year lag)</p> <p>Incidence Mean=60 mGy</p> <p>89.1% of person-years had doses <100 mGy</p> <p>Mortality Mean=35 mGy</p> <p>92.3% of person-years had doses <100 mGy</p>	<p>ERR at 100 mGy</p> <p>Incidence 0.077 (0.013, 0.15)</p> <p>Mortality 0.061 (0.004, 0.127)</p>
<p>INDIA</p> <p>Incidence Members of public</p> <p>High background radiation area [N2]</p>	<p>Incidence 69 958 persons 32 085 males 37 873 females</p>	<p>All cancers excluding leukaemia</p> <p>1 349 cases 747 males 602 females</p>	<p>Total follow-up 10.5 years</p>	<p>Entire cohort 736 586 PY</p>	<p>External gamma Doses to colon (10-year lag)</p> <p>99% of person-years had doses <500 mGy</p> <p>60% of person-years had doses <100 mGy</p>	<p>ERR at 1 000 mGy</p> <p>Incidence all cancers excluding leukaemia –0.13 (90% CI: –0.58, 0.46)</p>

<i>Study</i>	<i>Cohort</i>	<i>Cases</i>	<i>Follow-up</i>	<i>Person-years</i>	<i>Dosimetry</i> ^a	<i>Dose response</i> (95% CI) ^b
CHINA Mortality Members of public High background radiation areas [T3]	High background group 31 604 persons 16 045 males 15 559 females Control group 25 924 persons Adults only Ages 30–74	All cancers excluding leukaemia 941 deaths All causes 6 005 deaths	Total follow-up 1979–1998 (19 years)	High background group 528 429 PY Control group 208 513 PY Entire cohort 736 942 PY	External gamma exposure Doses to colon (10-year lag) High background area Mean=84.8 mGy Control area Mean=21.6 mGy 88.6% of cohort had doses <100 mGy 81% of the 941 deaths had doses <100 mGy	ERR at 100 mGy All cancers excluding leukaemia and liver 0.019 (–0.187, 0.304) All cancers excluding leukaemia –0.101 (–0.253, 0.095)

^a Doses from studies involving acute or short-term exposures (e.g. LSS cohort) represent the total dose received during the exposure event. Doses from studies involving prolonged exposures represent the total cumulative dose lagged by either 5 or 10 years.

^b 95% confidence interval, unless otherwise specified.

D. Definition of scenario

1. Exposure scenario

319. The purpose of this scenario is to understand the long-term risk of solid cancer mortality for workers exposed to low doses and low dose rates of low-LET radiation and to assess the predictive capabilities of the risk models, including a meaningful assessment of the uncertainties in the estimates of risk. This section provides the details of the exposure scenario, discusses the models and methodology used to estimate risk and describes the sources and magnitude of the uncertainties considered in this risk assessment.

320. A scenario involving a hypothetical case of occupational exposure to low-LET radiation for male workers from the United States population was considered. The exposure is assumed to have occurred over a period of 15 years, starting at age 30 and ending at age 45. The scenario assumes that workers are alive and cancer free at the beginning of the period of exposure (i.e. at age 30). The risks of cancer mortality are estimated up to age 60 and 90 (i.e. over the first 30 years and 60 years, respectively, after the beginning of exposure). The total cumulative uniform whole-body dose is assumed to be 100 mGy, received in annual increments of about 6.67 mGy.

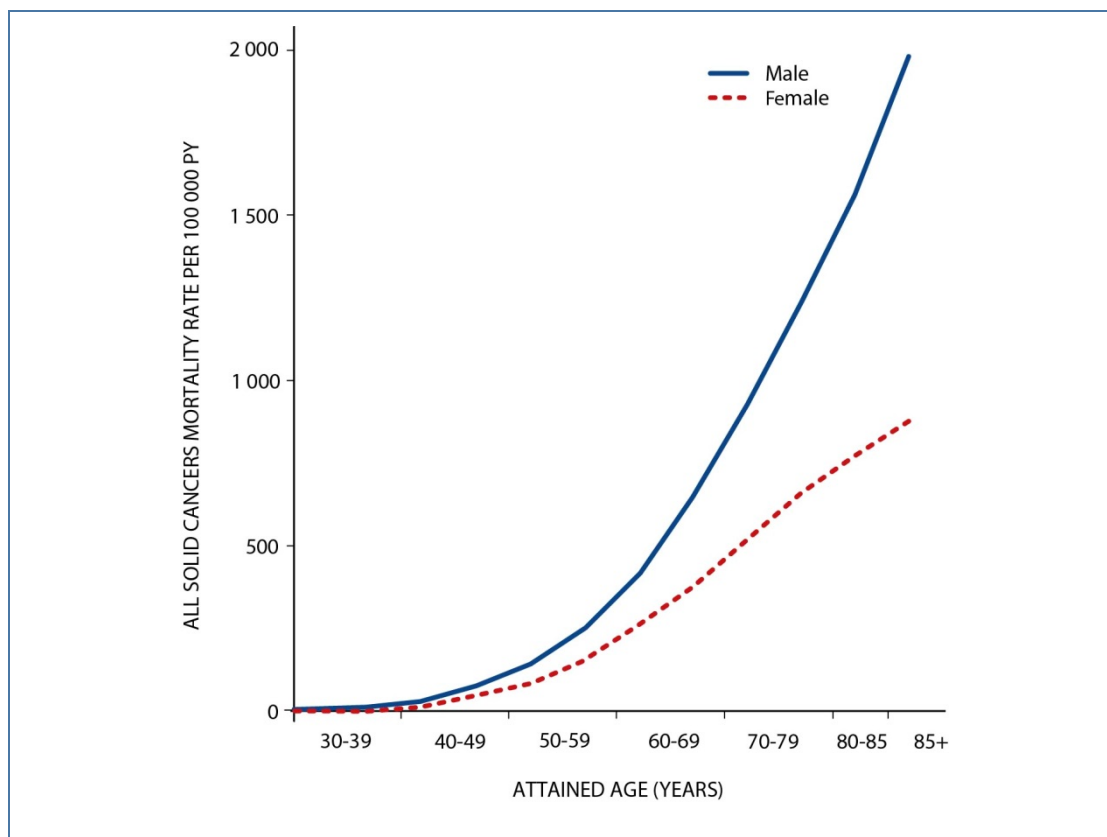
321. This exposure scenario is similar to the exposure situation encountered by the occupationally-exposed workers included in the INWORKS [H1, R5, T6], who had a mean duration of employment of 15 years, starting at an average age close to 30. The mean attained age at the end of the follow-up for members of the INWORKS cohort was approximately 60, with a maximum attained age at the end of the follow-up of 90.

322. The majority of the members of the INWORKS cohort are males (87% males, 13% females) and the persons with the highest doses are males as well. Thus, the dose response provided by the INWORKS is representative for males and therefore representative for the given exposure scenario.

2. Reference data

323. The population of the United States workers was described by baseline rates of cancer obtained from the Surveillance, Epidemiology, and End Results Program of the US National Cancer Institute (NCI) for 2000–2005 and by survival functions based on the US Decennial Life Tables for the period 1999–2001 [A4]. The baseline rates and survival functions are presented in figure VI. By definition, the United States baseline rates and survival functions are considered to be representative for the population of workers for which the risk is estimated, with no uncertainties.

Figure VI. Baseline mortality rates for all solid cancers in the United States (2000–2005) [N6]



3. Risk models

324. The risk models from the mortality study of the INWORKS workers [R5] and from the mortality analyses of the LSS cohort [O5] are considered to be the most relevant for the estimation of risk of all solid cancer mortality for the occupational exposure scenario defined above. These two studies are well designed and include large cohorts, large numbers of cancer-related deaths, long follow-up, high statistical power, good dosimetry and good case ascertainment.

325. Estimates of risk were obtained using the linear risk model from the INWORKS for the full dose range described by an ERR at 100 mGy of 0.047 (90% CI: 0.018, 0.079) for all solid cancers. A second set of risk estimates based on the INWORKS was estimated using the ERR at 100 mGy of 0.081 (90% CI: 0.001, 0.164) derived from the result obtained by restricting the dose range to 0–100 mGy (this ERR is for all cancers except leukaemia) [R5]. These ERR values were assumed to apply to all ages at exposure and all attained ages (figure VII). Weibull probability distribution functions were used, with the mode set equal to the best estimate and the 5th and 95th percentiles set to the limits of the reported 90% confidence interval.

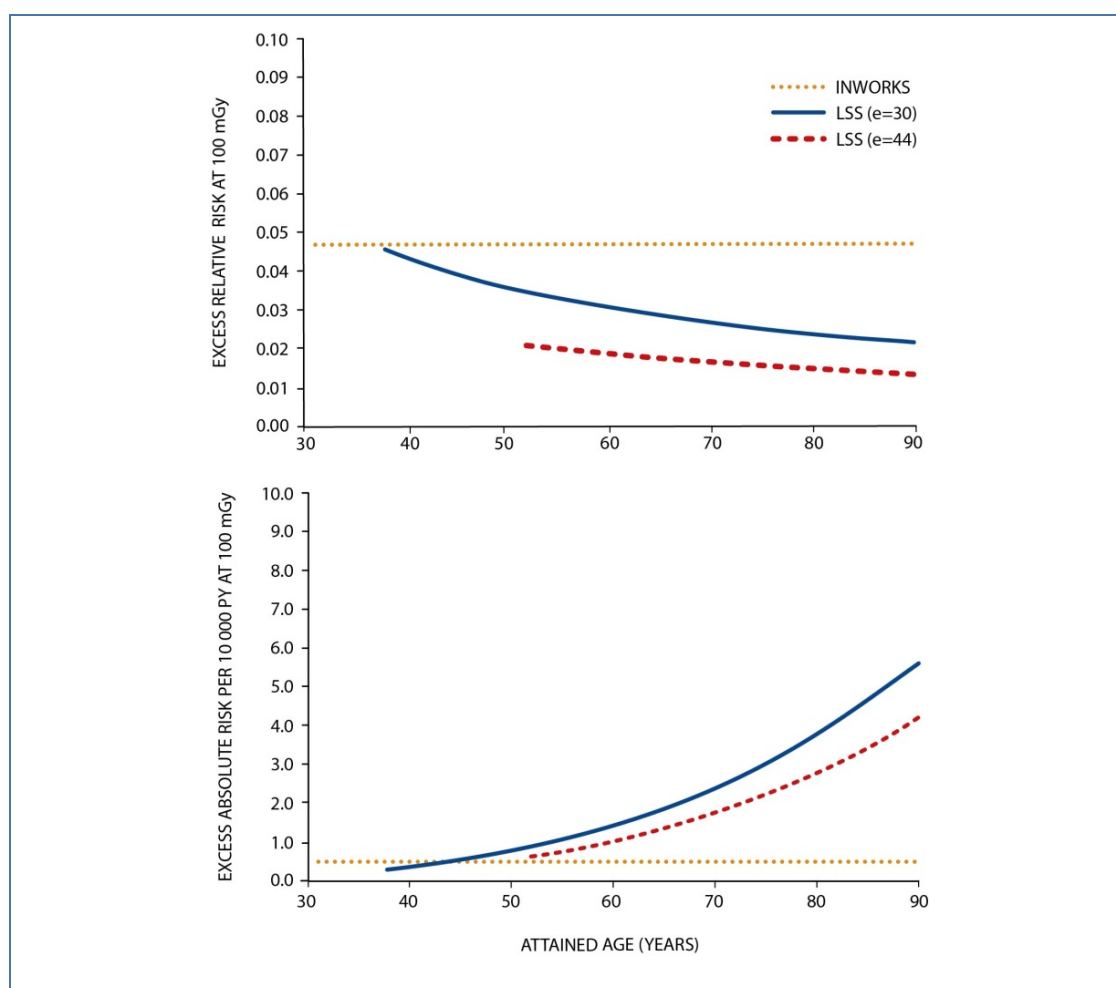
326. Risk estimates were obtained using the preferred Ozasa et al. linear models for all solid cancers [O5], based on the LSS data for the full dose range (table 8). These ERR and EAR models account for the dependency of risk on age at exposure and attained age. The ERR and EAR models are defined as:

$$\text{ERR or EAR} = \beta d \cdot \exp(\tau e^* + v \ln(a^*)) \cdot (1 + \sigma s)$$

where d is the dose, s is the sex (with $s=-1$ for males), $e^* = (e - 30)/10$ and e is the age at exposure, $a^* = a/70$ and a is the attained age, and σ , τ and ν are coefficients for effect modification. The parameter values and uncertainty distributions are presented in table 8. For the ERR model, the parameter β represents the ERR per unit dose (Gy) at attained age 70 after an exposure at age 30 (0.42 per Gy sex-averaged; 0.27 per Gy males and 0.57 per Gy females; female:male ERR ratio=2.1). For the EAR model, the parameter β represents the sex-averaged EAR per unit dose (10^4 person-year per Gy) at attained age 70 after an exposure at age 30 (26.4 per 10^4 PY/Gy sex-averaged; 24.6 per 10^4 PY/Gy males; 28.2 per 10^4 PY/Gy female; female:male EAR ratio=1.1). Figure VII shows ERR at 100 mGy and EAR per 10,000 person-years at 100 mGy obtained from the INWORKS and LSS studies, as a function of attained age, for adult males.

327. The REID was estimated using the methods described in annex A of the UNSCEAR 2006 Report (appendix B) [U3], with the difference that the risk was cumulated up to age 60 and 90, as opposed to being cumulated up to the end of the expected lifetime. The reported CBR and CER represent all solid cancers. In a few cases, the risk for all cancers except leukaemia was estimated, as noted in table 15.

Figure VII. Excess relative risk at 100 mGy and excess absolute risk per 10,000 person-years at 100 mGy for all solid cancer mortality from the INWORKS [R5] and from the LSS (males; [O5])



4. Risk-transfer methods

328. The term “risk transfer” refers to the application of the risks observed in a given population (e.g. the LSS cohort) to another population (e.g. United States workers). The risk of cancer in the population of the United States workers was estimated using both a purely multiplicative projection and a purely additive projection of risk [U8].

329. The purely multiplicative projection of risk assumes that the excess risk of cancer due to exposure to radiation is proportional to the baseline cancer rates in the population of workers. That is, the multiplicative projection is obtained by multiplying the baseline rates by the ERR indicated by each risk model for the dose of interest. Age- and sex-specific mortality baseline rates for all solid cancers were used to estimate the REID based on the models from Ozasa et al. [O5] and the INWORKS [R5].

330. The purely additive projection assumes that the excess risk of cancer is given directly by the EAR indicated by each risk model, thus being independent of the baseline rates of cancer for the population of workers. The differences observed between the risks predicted by the multiplicative and the additive projections represent the magnitude of uncertainty in the risk transfer model.

331. Risk estimates based on both the multiplicative and the additive projections were produced using risk models from the INWORKS [R5] and the LSS [O5] cohorts. The two projections for each model provide a range of possible values of risk based on the data from the two cohorts [U8].

5. Accounting for the minimum latency period of cancer

332. In an epidemiological study, the minimum latency period is accounted for by using a lag time during which no health effect is expected. In the INWORKS, their preferred estimate for the ERR at 100 mGy for all solid cancers mortality was obtained using an assumed fixed lag of 10 years [D1, R5]. Sensitivity analyses were carried out by allowing the lag time to vary. The best fit was three years [D1] and, for this fitted lag time, the observed ERR at 100 mGy was similar to that observed for a fixed 10-year lag.

333. Ivanov et al. [I6] estimated a minimum latency period of four years (95% CI: 3.3, 4.9) for the induction of solid cancers as a group based on studies of 59,770 emergency workers followed up during the first 10 years after the Chernobyl accident. The minimum latency period is expected to differ with cancer type, and perhaps to change with age at exposure, but information is limited to only a few cancers. For the incidence of thyroid cancer after the Chernobyl accident, a minimum latency period of three years was suggested by Heidenreich et al. [H3] based on childhood thyroid cancer incidence in Belarus. A minimum latency period to the time of surgery (not diagnosis) of about six years was observed by Williams et al. [W12] in children from Ukraine and Belarus. For lung cancer in the Colorado Plateau uranium miners, Gasparrini [G1] modelled the hazard ratio as an increasing function of lag time, reaching half of its maximum value at about five years and the maximum value at about 10 years. For breast cancer, Norton [N7] estimated an average of eight years of growth from one cell to clinical recognition size of one to five billion cells. Shorter times are now expected for the diagnosis of cancer, given the existence of more advanced diagnostic techniques, such as mammography.

334. The BEIR VII report [N9] used a minimum latency period of five years in their risk assessment for both cancer incidence and mortality of any solid tumours, which they described as a “threshold function”: that is, the risk was assumed to be zero for the first five years after exposure and changed abruptly to a non-zero risk after that. More realistic predictors of the dynamics of tumour growth are Logistic- or Gompertz-type S-shaped functions [L1, W13]. For risk assessment, Berrington de

González et al. [B5] adopted an S-shaped function that increases from 0 to 1 with increasing time after exposure. This function is used to adjust the risk estimated during the first years after exposure.

335. For the solid cancer scenario addressed in this section, the risk was phased using an uncertain adjustment factor described as an S-shaped function that increases with increasing time after exposure. The risk reaches 99% of its full value at about seven years after exposure and 99.9% of its full value about 10 years after exposure, compared with five years used in the BEIR VII report [N9]. The overall timespan of the minimum latency period is 2 to 7 years (1 and 99% of the full risk). The midpoint, defined as the time after exposure where risk is one half of its maximum value, is considered uncertain and varies from 3 to 4 years (i.e. described by a uniform probability distribution function between 3 and 4 years). This function is consistent with findings and assumptions used in the INWORKS. In the INWORKS, the preferred ERR risk model was derived using a 10-year lag time, but, when the lag time was allowed to vary and it was fitted to maximize the likelihood* function, lags as short as three years were indicated.

E. Results

336. The cumulative excess risk (CER) of solid cancer mortality in adult male workers was assessed based on the most recent epidemiological studies. The REID for all solid cancers for United States workers was estimated assuming an exposure to low-LET radiation, delivered from ages 30 to 45 with a total dose of 100 mGy (table 15). Risks were estimated using ERR and EAR models developed from the INWORKS, which included workers from France, the United Kingdom and the United States, and from studies of the LSS cohort of atomic bombing survivors. They were reported as risks cumulated up to age 60 and 90 years. The application of the ERR models from the INWORKS or LSS represents a multiplicative risk projection, as the ERR is multiplied by the baseline rates of cancer mortality in the exposed population of workers. The application of the EAR models assumes that the excess risk due to radiation is independent of the baseline rates of cancer mortality, and is given directly by the EAR from each respective risk model.

337. The results based on the ERR model from the INWORKS for all solid cancers and the full dose range [R5] give values of CER of 11 (95% CI: 3.1, 19.3) chances in 10,000 persons when cumulated up to age 60, and 86 (95% CI: 24, 151) chances in 10,000 persons when cumulated up to age 90 (table 15). These excess cases represent fewer than 5% of the number of solid tumour deaths expected to occur in the absence of exposure to radiation, for the same range of ages. The range of the confidence interval is about a factor of 1.5 larger than the central estimate.

338. The results based on the EAR model from the INWORKS for all solid cancers and the full dose range indicate a CER of 11 (95% CI: -1.1, 25) chances in 10,000 persons when cumulated up to age 60. The central estimate is similar to that obtained from the ERR risk model from the INWORKS. However, the confidence interval is considerably wider. When cumulated up to age 90, the CER is only 20 (95% CI: -1.9, 44) chances in 10,000 persons, substantially lower than the risk produced by using the ERR model. The ERR and EAR models from the INWORKS do not include attained age modifiers, and they represent average risks from the mean age at the beginning of employment (age 28) up to the mean age at the end of follow-up (age 58). Thus, the CER cumulated up to age 90 and obtained based on the ERR model from the INWORKS is likely to be an overestimate, while that obtained based on the EAR model is likely to be an underestimate. However, the CER cumulated from age 30 up to age 60 are consistent between the ERR and EAR models and they are reliable estimates.

339. The estimates based on the ERR model from the LSS [O5] give risks from an exposure to 100 mGy of 6.4 (95% CI: 4.0, 9.8) chances in 10,000 persons when cumulated up to age 60, and 39 (95% CI: 25, 58) chances in 10,000 persons when cumulated up to age 90 (table 15). The CER predicted based on the EAR risk models are larger: 12 (95% CI: 8.1, 18) when cumulated up to age 60 and 52 (95% CI: 34, 75) when cumulated up to age 90. These results were obtained without making any adjustments for differences in dose and dose rate between the exposure condition of the LSS cohort and that of the workers assumed for this scenario (i.e. no DDREF adjustment was used). The uncertainties in such estimates are a factor of 2 to 3.

Table 15. Cumulative risk of all solid cancers mortality for United States workers exposed to a total dose of 100 mGy of low-LET radiation delivered from ages 30 to 45, estimated using risk models from two epidemiological studies

The confidence intervals include only uncertainties explicitly discussed in the risk modelling section. The impact of further sources of uncertainties is considered in section IV.F

CBR: Cumulative baseline risk; CER: Cumulative excess risk, estimated using the REID/C methodology; CFR: Cumulative fractional ratio; CI: Confidence interval; LSS: Life Span Study. Unless otherwise noted, excess risks represent all solid cancers as a group; DDREF: Dose and dose-rate effectiveness factor

Risk models	Cumulative mortality baseline risk		Excess risk associated with exposure to radiation	
	All causes (per 10 000)	Cancer only (CBR) (per 10 000)	(CER (95% CI) ^a) (per 10 000)	CFR (CER/CBR)
FOLLOW-UP TO AGE 60 YEARS ^b				
LSS mortality models [O5]				
Full dose range, all solid cancers	1 294	229	6.4 (4.0, 9.8)	0.028
ERR transfer			12 (8.1, 18)	0.054
EAR transfer				
INWORKS mortality models [R5]				
Full dose range, all solid cancers	1 294	229	11 (3.1, 19.3)	0.048
ERR transfer			11 (−1.1, 25)	0.048
EAR transfer				
Dose range 0–100 mGy, all cancers except leukaemia				
ERR transfer			18.8 (−2.6, 41)	0.082
FOLLOW-UP TO AGE 90 YEARS ^b				
LSS mortality models [O5]				
Full dose range, all solid cancers	8 716	1 844	39 (25, 58)	0.022
ERR transfer			52 (34, 75)	0.028
EAR transfer				
INWORKS mortality models [R5]				
Full dose range, all solid cancers	8 716	1 844	86 (24, 151)	0.046
ERR transfer			20 (−1.9, 44)	0.011
EAR transfer				
Dose range 0–100 mGy, all cancers except leukaemia				
ERR transfer			148 (−20, 320)	0.080

^a No DDREF was applied. The uncertainty ranges were obtained using Monte Carlo methods for uncertainty propagation, using 1,000 iterations with values produced by Latin Hypercube sampling.

^b Risks are integrated up to 60th and 90th birthday, respectively.

F. Discussion of scenario calculations

1. Sources of uncertainties

340. The uncertainties in risks for solid cancer mortality were estimated using the Monte Carlo method for error propagation. This method is described in annex B (appendix A) of the UNSCEAR 2012 Report [U8]. The uncertainty in each component of the risk calculation was represented as a probability density function. In the Monte Carlo process, a computer algorithm carried out 1,000 simulations, and, in each simulation, one value of CER was estimated based on one sample obtained for the probability density function of each component. The CER and its uncertainty range were derived by statistical analysis of all Monte Carlo samples.

341. A comprehensive description of the components and sources of uncertainties that can potentially affect the results of any radiation risk assessment are described in annex B of the UNSCEAR 2012 Report [U8]. This section discusses the limitations and sources of uncertainties originating from the epidemiological studies used for estimation of the risk of mortality for all solid cancers as a group, for the worker exposure scenario.

(a) *Selected populations*

342. The LSS cohort [O5] includes 86,611 persons with estimated DS02 doses (35,687 males and 50,924 females) selected from among the atomic bombing survivors who were within 2.5 km of the hypocentres at the time of the bombings, combined with the age- and sex-matched sample of people who were between 2.5 and 10 km from the hypocentres. The cohort also includes approximately 27,000 additional people registered as residents of Hiroshima and Nagasaki in 1950, but who were not in the cities at the time of the bombings. The members of the cohort were selected from the 1950 Japanese National Census and include persons who had supplementary questionnaires about exposures to the atomic bombings and participated in surveys conducted by the Atomic Bomb Casualty Commission in 1950 and 1951 and in the resident surveys of Hiroshima and Nagasaki in 1953 and 1950, respectively. The entire cohort accounts for 120,321 persons of all ages (50,175 males and 70,146 females). A potential limitation of the LSS cohort is that the persons survived physical injuries and burns from the bombings, biological injuries due to the deterministic effects,* and poor nutrition and hygiene in the post-war period. These conditions could have led to selective exclusion of vulnerable people. Nevertheless, estimation of the magnitude of stochastic health effects* such as solid cancer is not likely to be affected by such selection bias as supported by negligible discrepancies in the dose–response curves between the early and late periods for all solid cancers [O5, P11].

343. The INWORKS is a retrospective cohort study of workers employed by: the CEA, AREVA Nuclear Cycle (formerly COGEMA) and the EDF in France; five installations from the Departments of Energy and Defense in the United States; and the nuclear industry in the United Kingdom (i.e. those in the NRRW). The INWORKS cohort includes 308,297 workers in the nuclear industry (87% males) with detailed monitoring data for external exposure to ionizing radiation [H1, R5]. The inclusion criteria were based on the completeness, quality of monitoring and dose data, and the start of facility operations. Workers who were employed in the nuclear industry for less than one year were excluded from the study. Uranium miners and private contractors were not included. The mean age at the beginning of employment was 28 years and the mean age at the end of the follow up was 58 years.

(b) *Exposure assessment*

344. Doses for the members of the LSS cohort went through several major revisions. Doses for the members of the LSS cohort were estimated for 15 organs/tissues and represent the gamma dose plus 10 times the neutron dose, to allow for the greater biological effectiveness of neutrons. Analyses of all solid cancer mortality were carried out using the doses to the colon [O5]. An important source of error in dosimetry is the exact location and orientation of each survivor, because this information was obtained from interviews that took place five to ten years after the bombings [C10]. Shielded kerma estimates were truncated at 4 Gy (this applies to 317 persons), because they are likely to reflect misinformation on location and shielding. The doses were adjusted for possible biases based on a statistical method of regression calibration with a plausible error model assuming a 35% multiplicative error, to eliminate a 6–16% possible bias in the estimated excess risk [P3]. The current dosimetric approach deals with both classical errors in doses (originating from uncertainty in each survivor's location and shielding), and Berkson errors (related to assumed input parameters used to estimate the effectiveness of shielding [P5, P6]. Most recently, a mixed classical-Berkson error* model has been introduced to account for uncertainties in the true dose* distribution, and applied to the cancer-incidence analyses [M9]. The effect of shared errors in parameters common to many survivors (height of the two detonations, yield of the two bombings, or location of the hypocentres) is considered to be a negligible source of uncertainty in the estimated risks. The potential effect of internal contamination of survivors with radionuclides deposited in the environment after the bombings was analysed, but no clear evidence of long-term health effects was found [S1].

345. Workers in the INWORKS cohort were exposed mainly to external radiation, usually gamma radiation, and doses were measured routinely using individual dosimeters, with records being kept as early as the 1940s [H1, R5, T6]. The main sources of errors in the recorded doses from external exposure were quantified to account for the evolution of technology and differences in practice between facilities and countries. Correction factors were derived by dosimeter type and applied to eliminate biases. The recorded doses were converted into doses to organs. Analyses of risk for all solid tumours were carried out using the absorbed dose to the colon. The analyses included workers with potential exposure to neutrons and adjustment was made for neutron monitoring status when possible. Measurement of neutron doses has been a challenging task, because the energy of neutrons could range from 1 eV to around 20 MeV and detectors were not able to measure all energies, especially during the earlier years. Thus, it was not possible to estimate doses from neutron exposures for all workers and some persons might have had unrecorded or missed neutron exposures. For these reasons, estimates of risk in relation to external radiation dose were analysed by grouping workers with regard to neutron-monitoring status (16,651 deaths among workers with no neutron dose, 1,570 deaths among people with a neutron dose less than 10% of the gamma dose, and 843 deaths among people with a neutron dose greater than 10% of the gamma dose). The ERR for all cancers except leukaemia was 0.048 at 100 mGy for the entire cohort, but 0.055 for persons with no recorded neutron exposure, 0.036 for persons who had neutron doses less than 10% of their gamma doses, and 0.062 for persons who had neutron doses greater than 10% of their gamma doses. Although the number of persons with positive neutron records is small, accounting for neutron exposures demonstrates an additional uncertainty in the ERR per unit dose from the INWORKS. However, this uncertainty is small, being less than 30% above and below the reported ERR per unit dose [R5].

346. In addition, among the members of the INWORKS cohort there was the possibility of unrecorded doses and of “missed” photon doses in the early years of operations due to high limits of detection, frequent change of dosimeters, and doses below the limit of detection being recorded as zero. Excluded doses (due to neutron and internal exposure) and “missed” doses could be positively correlated with

recorded photon doses, but the level of correlation is likely to be different among different sources of missed or unaccounted exposures (neutrons, internal emitters and missed gamma radiation).

347. The effect of exposure to internal emitters, environmental exposures (radon and terrestrial external exposures) and job-related medical exposures (e.g. screening chest X-rays; fluoroscopy in early years) was studied by Fournier et al. [F2] among French workers, who are part of the INWORKS cohort. No substantial effect on the reported ERR per unit dose was found for exposures to internal emitters and for environmental exposures. Job-related medical exposures are not well known, especially for early time periods, but several medical exposure scenarios have been investigated, indicating that the ERR risk coefficient may be reduced by medical exposures by up to 30 to 55%, depending on the assumed scenario.

(c) *Health outcome assessment*

348. The outcome of interest for the scenario discussed in this section is all solid cancers as a group. Epidemiological studies for all solid cancers as a group include a larger number of cases (or deaths, in mortality studies) than the number of cases for any individual cancer type in the same cohort and thus are expected to produce risk estimates with lower uncertainties than those for individual cancer types from the same cohort. However, large cancer groupings, such as all solid cancers, cannot be used to determine the risk from highly non-homogenous exposures (e.g. exposure from a CT scan with a narrow field). Also, it is unlikely that all cancers included in the all solid cancers grouping will have the same dose response. This could be problematical if populations with different spectra of cancer types are being compared.

349. The members of the LSS cohort have been followed up to 31 December 2003 [O5]. Mortality ascertainment was facilitated by the family registry system (*koseki*) which covers the whole of Japan and is more than 99% complete. The cause of death for cohort members was classified by trained staff in the ABCC/RERF according to the international classification of diseases (ICD). During the long follow-up period of the LSS cohort, the 7th to 10th editions of the ICD have been used. The all solid cancer grouping analysed by Ozasa et al. [O5] includes cancers with ICD-7, -8 and -9 codes 140–199, and with ICD-10 codes C00–C80.

350. In the INWORKS, the vital status was ascertained through 2001, 2004 and 2005 for the United Kingdom, French and United States cohorts, respectively. Information on the underlying cause of death was abstracted and coded according to the international classification of diseases, 9th revision (ICD-9). Currently, the main ERR estimate reported by the INWORKS is for all solid cancers (ICD-9 codes 140–199) and was obtained based on the entire range of doses in the cohort [R5]. For subgroups of the cohort with doses restricted to less than 100 mGy or less than 200 mGy, the INWORKS reports the ERRs only for all cancers except leukaemia (ICD-9 codes 140–203). However, a sensitivity analysis carried out for the entire cohort (i.e. entire dose range) showed no significant differences between the ERRs for all cancers, all cancers except leukaemia, all solid tumours, and all solid cancers other than lung (table A4 in [R5]).

(d) *Study design*

351. The study of mortality from all solid cancers in the Japanese atomic bombing survivors is not expected to include any significant bias due to individuals lost to follow-up. That is, the LSS cohort included 120,321 members, among whom 123 were excluded because of misidentification or insufficient information. Doses based on the DS02 system were available for 86,611 persons. A total of

50,620 deaths were observed up to the end of the follow-up period in 31 December 2003. Only a very small number of persons were lost to follow-up due to migration out of the country and were censored at the time of emigration [O5]. Nineteen persons were born before 1900 and were presumed to be alive as of 1 January 2004 (104 years of age and older). However, only five of them were documented as being alive and the rest were deleted from the database, had migrated out of the area, or had no information. Survivors with doses less than 5 mGy were selected as the control group, while the 26,529 persons who were not in the cities at the time of the bombings were not included in the analyses of risk because of concerns of compatibility of their mortality rates with those in the zero-dose cohort [O5]. The effect of selection of the control group for the analyses of risk in the LSS cohort has been analysed by French et al. [F4] for the incidence data. That study showed less than 10% variation in the estimated ERRs when the control group was changed from the not in the cities group to the zero-dose group.

352. For the INWORKS cohort, information on demographic variables, including sex and date of birth, as well as race for the United States workers, was obtained from the employment records. Information also included the period of radiation work, job titles, facilities of employment and classification according to socio-economic status. While information on date and cause of death was carefully collected, information on other factors that may have affected the health of the workers could not be recorded. The follow-up started in 1968 in France, 1955 in the United Kingdom and 1944 in the United States. Information about persons obtained from employers and national registries was reliable and produced a minimal loss to follow-up: only 0.22%, 2.56% and 0.83% of workers were lost to follow-up or emigrated from the French, the United Kingdom and the United States cohorts, respectively [H1].

(e) *Confounding factors*

353. Smoking, alcohol consumption and other factors can affect the rates of solid cancer incidence and mortality either by themselves or in interaction with exposures to radiation. A strong interaction between radiation and smoking was observed in the incidence of lung cancer in the LSS cohort [C1, F5]. The reported ERRs for smoking-related cancers might be too high because of such an interaction. The incidence of lung cancer increased with the degree of smoking as expressed in terms of the number of cigarette pack-years (equal to one packet of 20 cigarettes every day for one year) and decreased with time since quitting smoking at any level of radiation exposure. The ERR per unit dose for lung cancer was significantly higher for low to moderate smokers than for heavy smokers, with little evidence of any radiation-associated excess risk in heavy smokers [C1, F5]. Significant smoking effects were observed for both laryngeal and other respiratory cancers, but there was little evidence of a radiation effect for laryngeal cancer. A non-significantly elevated risk of other respiratory cancers was observed [C1]. All solid cancers as a group include cancers that are not associated with smoking and thus the effects of smoking on the dose response for this grouping are expected to be smaller than the effects on smoking-related cancer sites.

354. Analyses of the INWORKS cohort [R5] indicate that smoking did not have a significant effect in the reported ERR for all solid cancers. Although lung cancer incidence is affected by smoking, the ERR for all solid cancers group of 0.047 at 100 mGy (90% CI: 0.018, 0.085), is virtually identical to the ERR observed for all solid cancers other than lung of 0.046 at 100 mGy (90% CI: 0.01, 0.085). Eliminating all cancers that are potentially related to smoking (oral cavity and pharynx, oesophagus, stomach, colon, rectum, liver, gallbladder, pancreas, nasal cavity, larynx, lung, cervix, ovary, bladder, kidney and ureter) yielded an estimated excess relative rate of 0.37 per Gy (90% CI: -0.14, 0.95). This large group of smoking-related cancers constituted 70% of solid cancer deaths, and thus resulted in a reduced magnitude and precision of the estimated ERR per Gy. The effect of alcohol consumption was not assessed

specifically, however, it can be inferred as being small from analyses of the effect of stratification by socio-economic status of the INWORKS cohort, which, arguably, is correlated with alcohol consumption.

(f) *Statistical methods and model uncertainties*

355. Statistical uncertainties refer to the magnitude of uncertainty in the ERR or EAR estimated from the results of the epidemiological studies, as described by the uncertainty ranges in the coefficients of the risk model. For the risk assessment described in this section, the reported 90% or 95% CI of the risk coefficients (ERR or EAR per unit dose, with age and sex modifiers) were used to describe statistical uncertainties. The risks estimated by a typical epidemiological study can be affected by selection of cohort members, uncertainty in dosimetry, assessment of outcome, study design, or statistical methods employed. The two main studies (LSS and INWORKS) used in the risk assessment scenario for solid cancers were selected because the uncertainties associated with the results of these epidemiological studies and the statistical methods employed are not substantial relative to other studies.

356. Multiple models were used in this section of the annex to estimate the CER for solid cancers in workers. Values of the CER were estimated using linear ERR and EAR dose responses based on the full range of doses for the INWORKS or for the LSS (i.e. the entire cohort). This approach has the lowest statistical uncertainties, given that it is based on the largest number of cases. Estimates of risk (i.e. the ERR) for restricted dose ranges are presented in table 8 for the LSS and table 12 for the INWORKS. Table 9 presents estimates of risk for the LSS cohort for both restricted ranges of dose and restricted ranges of age at exposure. Statistically significant central-value estimates of risks for restricted ranges of dose seem to be within a factor of two of the risk estimates obtained for the full range of doses. Uncertainties in the CER estimates for restricted ranges of dose increase as the range becomes more limited.

357. To further investigate the effect of other risk models, organ-specific ERR and EAR risk models based on the LSS cancer-incidence data with a follow-up from 1958 to 1998 [B5, N9, P11] were used to generate organ-specific risks of cancer, which were then converted into risks of mortality using adjustments for lethality of cancer. Risk estimates were then summed across cancer sites to obtain the CER estimates for all solid cancers. Age- and sex-specific baseline rates for cancer incidence and mortality for specific organs were used to produce risk estimates using these risk models. Because these models represent risk of cancer incidence, estimates of CER were obtained by applying an adjustment for cancer lethality derived for each organ as the ratio of mortality to incidence baseline risks cumulated from the last exposure to radiation until the age limit (i.e. age 60 or 90). Lethality fractions estimated based on risks cumulated starting at any other of the 15 ages at exposure have very similar values to the lethality fractions obtained from risks cumulated starting at the last of the 15 exposures. Lethality fractions based on the risks from the last exposures were used in this exercise.

358. The approach based on the LSS cancer-incidence data for the period 1958–1998 described above produced CER values (for a dose of 100 mGy) of: (a) 11 (95% CI: 7.4, 15) chances in 10,000 persons when cumulated up to age 60; and (b) 54 (95% CI: 36, 78) chances in 10,000 persons when cumulated up to age 90. These estimates are comparable with those based on mortality data in the INWORKS [R5] and LSS [O5] (table 15).

359. A model uncertainty that is explicitly included is the approach for the transfer between populations, where multiplicative and additive projections of risk are used. While the uncertainty ranges for the multiplicative and additive projections overlap (table 15), the differences between the central values of the two projections vary by factors less than two for risks cumulated up to age 60, but by factors up to four, for risks cumulated up to age 90. In the latter case, the differences between

predictions using multiplicative and additive models from the INWORKS are not entirely due to the transfer between populations, but they are strongly affected by the lack of an attained age modifier. The transfer between populations can be an important source of uncertainty in the estimated CER, depending on the selection of models (INWORKS versus LSS) and on the age up to which the risk is cumulated.

(g) Other sources of uncertainty

360. The exposure parameters and dose rates received by workers were considered constant for the given exposure scenario. That is, the age of workers at the beginning (30 years) and end (45 years) of the defined exposure period, the total cumulative dose (e.g. 100 mGy), the annual dose rate (6.67 mGy per year for all years), and baseline rates of cancer mortality and survival functions were considered known and not affected by uncertainties.

361. *Evolution of future baseline rates:* The REID for solid cancers was estimated using the baseline rates for the period 2000–2005 and associated survival functions for the United States population. These REID estimates are representative for a population of exposed workers and followed up starting during the decades before and continuing after the period 2000–2005. However, for a prospective study which would assume that workers will be exposed and experience a radiation risk in the future, additional uncertainties associated with baseline rates need to be considered, because it is likely that future baseline rates will be different from the currently available rates (i.e. the 2000–2005 rates represent a modern existing population but not necessarily a future population). For example, future cancer mortality rates are expected to decrease with increasing treatment success, and be affected by changes in smoking habits. A similar situation would occur if a risk assessment were to be performed for historical exposures (e.g. patients or medical personnel exposed to X-rays in the 1930s and 1940s), meaning that additional uncertainty is introduced if current-day baseline rates were applied to earlier populations. Finally, uncertainties in baseline rates need to be considered in cases of risk assessments for populations for which reliable baseline-rate data is scarce (e.g. the population of Marshall Islands), as rates from nearby or surrogate populations need to be used in the calculations.

362. *Healthy worker effect:* The cumulative (e.g. lifetime) risk of cancer (mortality or incidence) from an exposure at given age and to a given dose depends on three elements: (a) the radiation dose response described by the ERR and EAR models; (b) the baseline rates of cancer (B); and (c) a survival function (S), which depends on the probability of death from all causes in the population of interest. The risk estimates presented in this section were obtained assuming the population of interest (i.e. United States workers) has baseline rates for all solid tumours and probabilities of death (i.e. survival functions) similar to those observed in the general United States population. The healthy worker effect occurs for a population of workers who are expected to be healthier and live longer than the general population. That is, the healthy worker effect accounts for a reduction in the baseline rates of cancer (B) and an increase of the probability survival (S) in the population of interest (United States workers in the example scenario), compared to the general (United States) population.

363. An indicator of the state of health in a selected population (e.g. occupationally-exposed workers) is the SMR, defined as the ratio of observed to expected deaths for an occupational cohort, where the number of expected deaths is determined by applying age–sex–birth cohort-specific person–years of follow-up to the relevant national mortality rates for the same age, sex and calendar period. SMRs are the most reliable metric for worker mortality when an internal control group of non-exposed employees is not available. SMR can be estimated using the number of deaths from all causes, deaths due to all cancers, deaths due to solid cancers as a group or deaths due to site-specific cancers (stomach, lung, etc.). Similarly, standardized incidence ratios (SIR) can be used as indicators of disease incidence. Section IV.C provides estimates of SMR and SIR from different studies of workers published since

2012. Other summaries of SMR for the purpose of evaluating the healthy worker effect can be found in the literature (e.g. [P2]).

364. If only the survival function (S) were to be adjusted for the healthy worker effect, estimates of the CER will be larger than estimates of cumulative risk unadjusted for the healthy worker effect. This would happen because healthier persons survive longer (longer lifespan) and thus they are alive for a longer period to experience the risk from radiation. However, if only the baseline rates (B) were to be adjusted for the healthy worker effect, estimates of the cumulative risk obtained using a multiplicative projection (ERR transfer) will always be lower than estimates of risk unadjusted for the healthy worker effect. This happens because healthier persons have lower baseline rates of cancer than the general population. When both S and B are adjusted for the healthy worker effect, the adjusted cumulative risk based on the ERR transfer can either increase or decrease. The decreasing effect introduced by the lower baseline rates (B) is generally stronger than the increasing effect introduced by the survival function (S). Thus, cumulative risks based on a multiplicative projection for which both B and S have been adjusted are expected to be lower than the unadjusted cumulative risks in most cases.

365. When the cumulative risk is estimated using an additive projection (EAR transfer), the excess absolute risk from the epidemiological study (e.g. the INWORKS) is assumed to apply directly to the population of interest (e.g. United States workers in the example scenario considered in this section), and thus the resulting cumulative risk does not depend on the differences between the baseline rates of cancer mortality in the population of interest and those in the general population. Thus, it is expected that resulting cumulative risk is affected at most by changes in the survival functions between the population of interest (United States workers) and the general population, with the adjusted risk for the healthy worker effect being higher than the unadjusted EAR-projected risk.

366. It is important to note that the impact of the healthy worker effect on estimated cumulative risk of cancer mortality or incidence depends on sex and on the age at time of exposure to radiation. The healthy worker effect refers to differences in rates of cancer between workers and general population observed during the adult, work-productive years of life (~30–60 years of age). No differences in baseline rates between the population of interest and the general population due to the healthy worker effect are expected for children and teenagers, and differences are expected to decrease towards zero for older ages (>60).

2. Preferred risk inference

(a) *Selection of the preferred risk inference*

367. Cumulative excess risks (CER) of solid cancer mortality were calculated in this annex for typical male workers in the United States who were exposed from age 30 to 45, to an assumed total cumulative dose of 100 mGy. Risks cumulated up to age 60 and up to age 90 were estimated using models obtained from epidemiological studies of the LSS and of the INWORKS cohorts, for different dose ranges and for two types of assumed transfer between populations (ERR or EAR; table 15).

368. For this scenario, the preferred risk inference is the CER cumulated up to age 60 obtained using the ERR transfer from the INWORKS [R5], which is equal to 11 chances in 10,000 persons (95% CI: 3.1, 19.3). Given that this scenario refers to the exposure of a modern population of United States male workers subject to prolonged exposure, the CERs based on the INWORKS are thought to be more representative than the CERs obtained using models from the LSS because (a) members of LSS cohort

had been exposed to acute, high-dose-rate radiation; and (b) the LSS cohort is representative of a mid-20th century Japanese population with different cancer rates, who survived the atomic bombings in 1945 and the subsequent difficult living conditions.

369. Among the risk estimates based on the INWORKS, the CERs cumulated up to age 60 are considered more reliable than the CERs up to age 90 because no age-dependency could be derived for the ERR and EAR per unit dose obtained from the INWORKS. The constant ERR and EAR per unit dose values are representative for attained ages 30 to 60, because this is the dominant age range in the current follow-up for the INWORKS cohort. In the calculation of the CERs cumulated up to age 90, it was assumed that the ERR and EAR per unit dose representative for ages 30 to 60 apply without modification. Based on the experiences in the LSS, it is expected that, when attained age increases from 60 to 90, the ERR would decrease, while the EAR would increase (figure VII). Thus, the CERs up to age 90 from the INWORKS (table 15) are expected to be too large for the transfer of the ERR and too low for the transfer of the EAR to the United States population, respectively.

370. Estimates of risk based on the INWORKS were obtained using either the ERR and EAR models derived for solid tumours using the full dose range, or the ERR derived for all cancers less leukaemia based on persons exposed to doses less than 100 mGy (no EAR estimates were available for solid cancer in this group). The CERs for solid cancers based on the full dose range are preferred because (a) the scenario considered in this section refers to solid cancers; (b) even when the full dose range is used, more than 95% of the INWORKS cohort has doses less than 100 mGy (90th percentile of dose in the cohort was 53 mGy [R5]), an exposure situation similar to the assumed exposure scenario; and (c) the CER for all cancers except leukaemia based on doses less than 100 mGy has a negative lower 2.5th percentile, although the ERR for the INWORKS cohort has a positive lower bound at the 5th percentile (table 12).

371. The CERs based on the INWORKS cumulated up to age 60 were obtained using either an ERR or an EAR transfer (or projection) of risk to the United States population. The central values of the two CERs are identical indicating that, in this case, the transfer from the INWORKS cohort to the United States population does not represent a major source of uncertainty, and that the INWORKS cohort is a good choice for performing risk assessments for the United States male worker population. Given that the INWORKS CER based on the EAR transfer has a negative lower bound, the INWORKS CER based on the ERR transfer and cumulated up to age 60 is the preferred risk inference for the scenario selected in this case.

(b) Discussion of the impact of sources of uncertainty

372. The main sources of uncertainties associated with this risk estimate are summarized in table 16. The subsequent paragraphs give the reasons for the grading of the uncertainties (very small, small, moderate or large).

373. *Selected populations:* The INWORKS cohort includes a population of mostly males (87%) from countries (France, United Kingdom and United States) with a lifestyle rather similar to that of the population of interest (United States male workers). The risk estimates obtained using the multiplicative (ERR) or additive (EAR) transfer models (table 15) are very similar, indicating that, in this case, the uncertainty associated with the transfer between populations is very small. Since the INWORKS cohort includes 87% males and 13% females, a potential bias may occur when the INWORKS ERR or EAR risk models are applied to a population of male workers. To assess the magnitude of such a bias, the CER was estimated using the LSS mortality data [O5] for a population with a mixture of 87% males and 13% females and was compared to the CER for 100% males for the LSS. The difference in CERs

was less than 4% in this case, with the risk for the mixed population being larger than the risk for males (due to the slightly larger risk for females indicated by the LSS cohort). Accounting for the fact that the INWORKS cohort is different from the LSS cohort, it is expected the CER based on the INWORKS cohort to be different from the risk in male workers by no more than 5–10%.

374. *Exposure assessment:* The primary source of exposure of the members of the INWORKS cohort was external low-LET radiation received in the workplace. However, some INWORKS workers also had exposure to neutrons in the workplace, exposure to internal emitters (caesium, tritium, plutonium), environmental exposure to radon and decay products and terrestrial radiation and exposure to job-related medical examinations (i.e. chest X-rays). Workers who were active during the early periods of time and who accumulated the highest doses are more prone to missed gamma, neutron or internal doses. The effect of exposure to neutrons has been evaluated based on the neutron monitoring status by Richardson et al. [R5], who found that, when accounting for neutron exposure, the ERR differed by less than 30% compared to the main reported ERR (table A5 in [R5]). A number of analyses of the effect of other exposures on the main reported ERR per unit dose were carried out for the French workers, who are part of the INWORKS cohort. The effect of exposure to internal emitters was studied by Fournier et al. [F2], based on a qualitative indicator of exposure, and their analysis indicated that no significant effect is expected on the observed ERR per unit dose. Fournier et al. [F3] analysed the effect of environmental exposures (radon and terrestrial external exposures) and the effect of job-related medical exposures (e.g. screening chest X-rays; fluoroscopy in early years) under different exposure scenarios. Adjusting for environmental radiation exposure did not substantially modify the ERR risk coefficient for the French cohort, but it was attenuated by medical exposure by 30 to 55% depending on the assumed exposure scenario.

375. Dose estimates rely largely on the results of individual monitoring. The errors associated with these measurements are unshared from person to person, and are of the classical as opposed to Berkson type [G4, S8]. However, doses could be larger if missed doses from external or other exposure types are to be explicitly included. The effect of uncertainties in the estimated external doses has not yet been addressed for the INWORKS cohort.

376. *Health outcome assessment:* Although outcomes are based on abstracted death certificates which can be inaccurate on a cancer by cancer basis, the uncertainty related to outcome assessment is expected to be very small when identifying all solid cancers as a group, given that whole-body irradiation can induce cancer at most, if not all sites. Also, no additional uncertainty related to the outcome assessment is introduced, because the preferred risk inference is based on the analysis of solid cancer mortality from the INWORKS, which matches the risk assessment selected for the scenario.

377. *Study design:* The INWORKS cohort comprises the French, United Kingdom and United States cohorts which are among the largest, oldest and most informative groups of occupationally-exposed workers in the world. They include workers who have been monitored for external exposure to radiation using individual dosimeters and have been followed up over decades to collect information on causes of death [R5]. While information on date and cause of death was carefully collected, information on other factors that may have affected the health of the workers or contributed to their death could not be recorded. Smoking, alcohol consumption and exposure to asbestos as potential causes of death are treated separately as confounding factors. The effects of any remaining cohort-wide causes of death that may compete with radiation have not been assessed. However, information about persons obtained from employers and national registries was reliable and produced a minimal loss to follow-up: only 0.22%, 2.56% and 0.83% of workers were lost to follow-up or emigrated from the French, the United Kingdom and the United States cohorts, respectively, with an average of 1.54% for the entire cohort [H1]. Thus, uncertainties in the ERR per unit dose reported by the INWORKS due to the minimal loss to follow-up are judged to be small.

378. *Confounding factors:* Smoking, alcohol consumption, and exposure to other carcinogens are potential confounding factors. In the INWORKS cohort, asbestos was identified as a possible carcinogen of concern. The effects of smoking and exposure to asbestos have been analysed [R5] and they were found to be less than 10% for smoking and less than 20% for asbestos. Effect of alcohol consumption was not assessed specifically, but the INWORKS cohort has been stratified by socio-economic status, which, arguably, is correlated with alcohol consumption. Given that consumption of alcohol is not known to be a major lifestyle consideration for the INWORKS cohort and given that the cohort has already been stratified by socio-economic status, it is expected that this impact of this source of uncertainty to be small.

379. *Statistical methods and model uncertainties:* An analysis of the dose responses for 5-year and 15-year lag for individual doses, in addition to the nominal 10-year lag [R5], indicate a potential variation in the risk estimate of less than 25%. The dose response for solid cancer mortality in the INWORKS cohort was linear, and no other dose response improved the fit to the data [R5].

380. Although attempted, analyses of the INWORKS cohort [D1] did not identify clear age at time of exposure, time after exposure or attained age dependencies. However, risk estimates based on the INWORKS are reliable to predict risk for the population of interest in this scenario for a follow-up period ending at age 60, as this represents the centre of the range of ages for the INWORKS cohort.

381. *Other sources of uncertainty:* The reported CERs are based on baseline rates for solid cancers averaged over a 5-year period (2000–2005), although the CERs represent the risk cumulated for 30 years (from ages 30 to 60). A potentially important source of uncertainty is the representativeness of the 5-year averaged baseline rates to the 30-year period of risk accumulation. This may be especially important for risk projection (as opposed to retrospective risk assessments), as the evolution of baseline rates in the future is unknown (e.g. cancer mortality rate may decrease with future increased effectiveness of treatment). The effect of this source of uncertainty will depend on the magnitude of the rate of change in baseline rates: a small expected change in baseline rates would translate into a small change in the estimated CER. An inspection of age-adjusted mortality rates for all cancers combined and for all solid cancers in the United States, as reported by SEER [N6], indicates variations less than 50% (less than a factor of 1.5) during time periods from 1970 to 2015. Thus, the uncertainty in the preferred CER due to evolution of baseline rates of solid cancer mortality is expected to be less than 50% (a factor of 1.5).

382. The CER estimates for this scenario are representative of a population of United States workers assumed to have baseline mortality rates and survival probabilities similar to those in the general United States population. Workers are often healthier and live longer than the general population. Lower cancer mortality rates and higher probabilities of survival will affect the estimated CERs. The impact of the healthy worker effect was assessed for the preferred risk inference (i.e. CER cumulated up to age 60 based on the ERR model from the INWORKS), by comparing the CER unadjusted for the healthy worker effect (11 chances in 10,000 persons (95% CI: 3.1, 19.3)), with a CER adjusted for the healthy worker effect. The adjustment for the healthy worker effect was based on the assumption that the baseline mortality rates of all solid cancers could be lower by an average of 20% for ages 20 to 60 in the population of interest compared to the rates in the general United States population (i.e. an SMR for all solid tumours of 0.8; range 0.6 to 1.0 [M12, P2]; uncertainty described by a triangular distribution, minimum=0.6, mode=0.8, maximum=1.0), with differences decreasing linearly to 0% (i.e. an SMR for all solid tumours of 1.0) for ages less than 15 and greater than 90. This adjustment is similar to that used by the UNSCEAR 2012 Report [U8]. In addition, the adjustment for the healthy worker effect also assumed that the mortality rates from all causes in the population of interest (which affect the survival function) could be lower by about 30% between ages of 20 and 60 compared to the general United States population (i.e. an SMR for all causes of death of 0.7; range 0.5 to 1.0,

uncertainty described by a triangular distribution), with differences decreasing linearly to 0% (i.e. an SMR for all causes of death of 1.0) for ages less than 15 and greater than 90. The CER cumulated up to age 60 and adjusted for the healthy worker effect was reduced by about 20% to 9 chances in 10,000 persons (95% CI: 2.5, 16). The uncertainty range (measured as the upper 97.5th percentile divided by the mean) increased from 1.77 in the CER unadjusted for the healthy worker effect to only 1.81 in the adjusted CER. Interestingly enough, the CER cumulated up to age 90 was unaffected by the healthy worker effect, because the decrease in risk introduced by the lower baseline rates of cancer mortality were largely offset by the assumed longer survival.

383. *Overall credible interval for the preferred risk inference:* The uncertainty in the CER cumulated up to age 60 obtained using the ERR transfer from the INWORKS, which is equal to 11 chances in 10,000 persons (95% CI: 3.1, 19.3; table 15), is dominated by the statistical uncertainty in the ERR per unit dose reported from epidemiological analyses performed for the INWORKS cohort [R5]. This section and table 16 summarize 19 other sources of uncertainties that may affect the estimated CER. These additional sources of uncertainty are small or very small and they can be considered statistically independent. Their combined effect is judged not to exceed a factor of 1.5 above and below the preferred estimate. Small shifts towards lowering the CER may be attributed to the effect of medical job-required chest X-rays [F3] and the healthy worker effect [P2]. To develop uncertainty intervals that would account for all envisioned sources of uncertainty, these additional sources of uncertainty were combined with the statistical uncertainty in the CER using a semi-analytical method for uncertainty propagation. The additional sources of uncertainty were characterized by a multiplicative judgement-based probability distribution for all additional uncertainties combined (e.g. defined by a factor of 1.5) and was considered to be probabilistically independent to the statistical CER. The limits and preferred estimate of the resulting credible intervals were rounded up or down to 1, 2, 3 or 5, or their products with 10 or 0.1. The most representative 95% credible interval for the CER up to age 60 for solid tumours was judged to be 2 to 20 chances in 10,000 persons, with a preferred estimate of 10 chances in 10,000 persons. The resulting uncertainty intervals are referred to as “credible” intervals.

(c) *Concluding remarks on the preferred risk inference*

384. Considering the additional uncertainties in table 16, the 95% credible interval of the preferred risk inference ranges from a factor of the preferred estimate of about a half to about two (i.e. $\pm 100\%$ from the preferred estimate, on a linear scale). These estimates may be compared to the credible interval of lifetime risk of radiation-induced solid cancer incidence of 81 (95% CI: 32, 160) chances in 10,000 persons estimated in the UNSCEAR 2012 Report [U8] for United Kingdom workers exposed to 100 mGy delivered from ages 30 to 44. This corresponds to a credible interval that ranges from a factor of about a third to about two (i.e. about -60% to $+100\%$ from the preferred estimate, on a linear scale). Roughly the ranges of the credible intervals are comparable, with a tendency that the lower boundary of the present preferred risk inference is a bit farther from the preferred estimate than in the UNSCEAR 2012 Report, and that there is a good agreement in the upper estimate (figure VIII). In the UNSCEAR 2012 Report, the Committee noted that “whether or not the credible interval is too narrow cannot be answered presently”. The preferred risk inference has confirmed the width of the credible interval. Also, the present lifetime risk estimate (up to age 90) is consistent with the result of the UNSCEAR 2012 Report [U8].

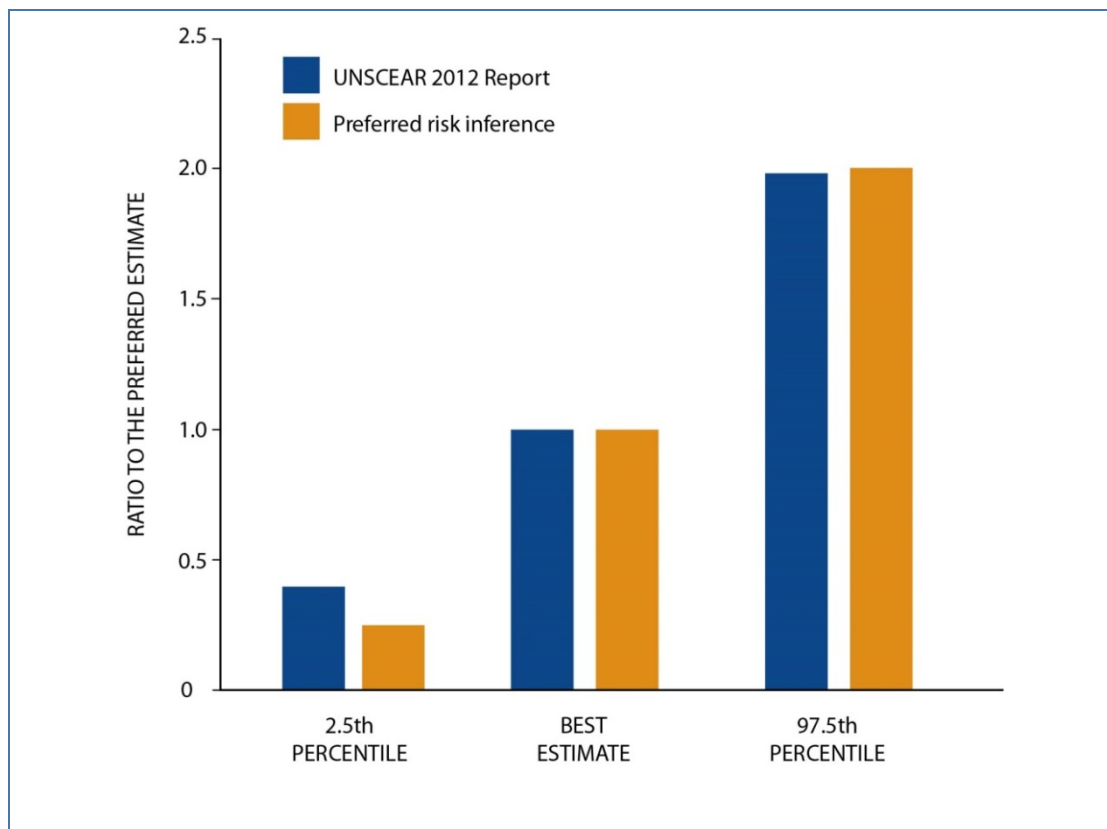
Table 16. Characterization of the main sources of uncertainty associated with the preferred risk inference of solid cancers

<i>Source</i>	<i>Characterization of source</i>	<i>Judged impact^a</i>
Selected populations	Transfer between populations	Very small
	Sex mixture (87% males in the INWORKS)	Small
Exposure assessment	Exposures to radiation not specifically accounted for in the INWORKS	
	Neutrons	Small
	Internal emitters	Very small
	Missed dose	Small
	Job-required chest X-rays	Small
	Uncertainty in external doses	Small
Health outcome assessment	Representativeness of outcome	Negligible
	Case ascertainment	Very small
Study design	Competing causes of death	Small
	Loss to follow-up	Very small
Confounding factors	Smoking	Very small
	Alcohol consumption	Small
	Exposure to other carcinogens in the workplace, e.g. asbestos	Small
Statistical methods and model uncertainties	Assumed latency period	Small
	Absence of assessment of modifying effect of age and time	Very small
Other sources of uncertainty	Evolution of future baseline rates	Small
	Healthy worker effect	Small

^a The impact of the different sources of uncertainty is classified into four categories according to the variation they are expected to induce on the reported CER: very small—less than a factor of 1.1; small—between a factor of 1.1 to 1.5; moderate—between a factor of 1.5 to 2; and large—greater than a factor of 2.

Figure VIII. Comparison of the magnitude of the credible intervals from the preferred risk inference (CER up to age 60 based on the INWORKS) and the credible interval for the lifetime risk from the UNSCEAR 2012 Report

The magnitude of the credible interval is depicted as the ratio between the upper and lower bounds to the respective preferred estimates



G. Conclusions

385. Cumulative risk of all solid cancer mortality in a population of United States male workers subject to prolonged exposure to low-LET radiation was estimated based on recently published epidemiological studies. Estimates of risk were obtained using risk models from the INWORKS and from the most recent mortality studies of the LSS cohort.

386. The preferred risk inference for the considered exposure scenario was the CER obtained using the ERR risk model obtained from the INWORKS. Data on workers from France, United Kingdom and United States have been successfully pooled in the INWORKS, leading to a large cohort with a long follow-up. The INWORKS is particularly suitable for estimation of risk of solid cancers in occupationally-exposed male workers because (a) the population of interest has similar characteristics to the INWORKS cohort; and (b) the population of interest was exposed to low-LET radiation at low doses and low dose rates.

387. The strengths of the LSS mortality study are: (a) a large, representative sample across all age groups of the atomic bombing survivors, using stratified sampling to enrich the higher-dose portion of the sample; (b) reasonably precise estimates of individual doses; (c) a wide range of doses in the cohort; (d) complete ascertainment of mortality and cause of death using the *koseki* system; and (e) a long observation period with a large number of deaths. Those strengths provide a high-quality, informative epidemiological study.

388. Pooling all solid cancers offers the advantage of large numbers to enhance the statistical precision in the assessment of the dose response, especially at low doses, and investigating effect modification of the radiation risk by age, time, sex and other factors. Pooling of all solid cancers is particularly relevant for the atomic bombing survivors, who received whole-body exposure and among whom radiation effects have been observed for almost all major organ sites. Aggregated solid-cancer risks have traditionally been reported in terms of both cancer incidence and cancer mortality from the LSS and other cohorts. However, there are also limitations to such an approach, because there may be real differences in the magnitude of the radiation risk and the nature of effect modification across different cancer sites. When developing a risk assessment system, it is advantageous to derive risk models and estimate risks on a cancer type by cancer type basis. As opposed to risk models for all solid tumours combined, a risk assessment system that relies on cancer-specific risk models would be suitable to handle cases of non-homogeneous exposures to radiation, such as medical diagnostic exposures involving CT scans of specific areas of the body (e.g. CT scan of the head).

389. Aside from the LSS, recently published epidemiological studies for all solid cancers rely on cohorts of (a) occupationally-exposed workers; or (b) members of the public from different countries. These cohorts include mostly males (except for the Techa River, the Yangjiang and the Kerala cohorts, which includes females). Many of these cohorts are either small or still young (short follow-up) and experienced small radiation doses leading to studies with low statistical power. It is expected that selected cohorts will be further followed up in the next decades allowing for accumulation of a larger number of cases over much of the lifespan of exposed persons. Cohorts including persons exposed as children have a better potential for detecting dose-response relationships.

390. Studies of workers or adult members of the public report radiation risks from prolonged or fractionated exposures. Typically, the risks are described in terms of the ERR per unit dose, and they are representative for the entire exposure period of the members of the cohort, without modifiers for age at exposure or attained age. Thus, these risks do not apply to exposures in childhood, and extrapolation of the risk to older ages needs to be interpreted carefully.

391. Risks obtained from epidemiological studies of workers or members of the public who have been subject to prolonged exposures can be directly applied to other groups of similar age and sex who have experienced chronic exposures to radiation of similar dose rates. However, they would need to be applied cautiously to estimate the risk for persons with acute exposures, even if such persons are of similar age and sex to the members of the studied cohort, as further adjustments may be necessary to account for possible differences between responses at high doses and dose rates and low doses and dose rates.

392. Epidemiological studies of persons subject to prolonged exposures can be further improved if designed to include larger groups of workers, and be combined (or pooled) with cohorts of members of the public, and other exposed groups (patients with long-term fractionated exposures).

V. THYROID CANCER RISK AFTER EXPOSURE DURING CHILDHOOD

A. Motivation

393. Probably the strongest evidence for the statistical association between internal radiation exposure and thyroid cancer (ICD-10:C73) has been produced by studies of children and adolescents who ingested radioiodine deposited after the Chernobyl accident in April 1986. Updated time trends for incidence of thyroid cancer in Ukraine and Belarus are published in [U9]. Kazakov et al. [K9] reported early evidence of the radiogenic origin of thyroid cancer six years after the accident. Other early studies were published about a decade after the event and these already observed a marked increase of thyroid-cancer incidence (reviewed in [C6]). In later studies on about 13,000 persons of the Ukrainian-American (UkrAm) cohort, which were exposed below age 19 and were subject to enhanced medical surveillance since 1998, the ERR per unit dose to the thyroid dropped from about 5.3 (95% CI: 1.7, 28) for prevalence at a mean age at operation of 16 to 1.91 (95% CI: 0.43, 6.34) for the incidence at the mean age at operation of 24 [B12, T11]. The estimate for a similar cohort from Belarus (BelAm cohort) is compatible with this decreasing trend of the relative risk with attained age [Z1]. Increased incidence in the LSS for exposure in childhood persisted for more than 50 years. For exposure in adulthood, the rates among the Japanese atomic bombing survivors are just marginally elevated [F6]. In the post Chernobyl cohorts UkrAm and BelAm “age at operation” of pathologically ascertained thyroid cancer cases determines age-risk patterns, while risk estimates are commonly related to “attained age”.

394. After the accident at the Fukushima Daiichi nuclear power station in March 2011, the Committee undertook an assessment of the health-related consequences. Radiation doses to the population were found to be much lower than those in the Chernobyl accident [U7]. A comprehensive summary of late health effects after exposure of children, which included the radiogenic origin of thyroid cancer, was provided in the UNSCEAR 2013 Report, annex B [U6]. A summary of radiation risk coefficients from pertinent thyroid cancer studies published until 2013 is given in table B7 of that report.

B. Recapitulation of previous UNSCEAR publications

395. In the UNSCEAR 2012 Report [U8] an assessment of risk and uncertainties for thyroid cancer after childhood exposure was performed for a hypothetical group of Ukrainians irradiated at age 10 with a dose to the thyroid of 200 mGy from ingested ¹³¹I. The attributable risk (AR) was calculated for age 28 in April 2004 and for the whole life. The choice of age 28 was possibly motivated by the mean age of operation of 27 in the study of Brenner et al. [B12]. Because thyroid cancer does not lead to death in most cases, the lifetime attributable risk (LAR) closely approximates the REIC [B2]. Two approaches for risk projection were applied.

396. The first approach was guided by risk estimates from studies conducted after the accident and used estimates from the LSS [P11] for risk projection to a hypothetical Ukrainian population. Both ERR and EAR models were applied for sex-specific transfer, but a thorough analysis of uncertainties was not performed. A transfer of ERR model estimates yielded considerably smaller AR and LAR than that using EAR model estimates.

397. The second approach was based on studies before the Chernobyl accident and did not take into account post-accident risk studies. The risk transfer was performed with the ERR model for thyroid cancer given in the BEIR VII report [N9]. The EAR for the Ukrainian population was generated by multiplying the recorded baseline incidence of thyroid cancer in Ukraine in 2009 and the ERR value of BEIR VII report. The BEIR VII model is based on the pooled analysis of Ron et al. [R8], which included the atomic bombing survivors' cohort and six other cohorts. Doses from ^{131}I were delivered as a prolonged exposure which prompted the application of the BEIR VII DDREF in risk transfer. The uncertainty in the LAR is dominated by the statistical uncertainty in the BEIR VII estimate of the ERR, followed by the BEIR VII uncertainty in the DDREF. However, DDREF was not applied in the present annex (see also section I.4).

398. A recent UNSCEAR white paper gives the latest data on the incidence of thyroid cancer after the Chernobyl accident for the most affected regions (defined as the whole of Belarus and Ukraine and the four most contaminated regions of the Russian Federation) [U9]. It contains a summary of the pertinent literature and provides an estimate of the fraction of the observed incidence that could possibly be attributed to radiation exposure. During the period 2006–2015, the crude incidence rate increased monotonically in all age groups for persons from the most affected regions who were younger than 19 years of age in 1986. Some 20,000 cases of thyroid cancer were recorded in this cohort during the period 1991–2015. The observed increase was attributed to (a) an increase in the sporadic incidence in this ageing cohort; (b) enhanced risk awareness after the accident; (c) enhanced effectiveness of medical surveillance; and (d) radiation exposure. The fraction of cases attributable to radiation exposure was estimated to be 0.25 with an uncertainty range from 0.07 to 0.5.

C. Review of recent epidemiological literature

399. The selection criteria developed by the Committee in its UNSCEAR 2017 Report [U10] were applied for the thyroid scenario. A literature search in PubMed with the query string “Search (((thyroid cancer[Title/Abstract]) AND radiation[Title/Abstract])) AND (""2011/01/01""[Date - Publication] : ""3000""[Date - Publication])) AND cohort[Title/Abstract]” resulted in 88 entries. However, not all of these 88 publications were relevant for the aim of this annex.

400. Furukawa et al. [F6] analysed long-term trends in the risk of thyroid cancer among the Japanese atomic bombing survivors up to 60 years after exposure. Using a linear dose–response model, the ERR for thyroid cancer at a dose of 1 Gy was estimated as 1.28 (95% CI: 0.59, 2.70) at age 60 after an acute exposure at age 10. The risk decreased sharply with increasing age at exposure and there was little evidence of increased rates of thyroid cancer for those exposed after age 20.

401. After the Fukushima accident, a large screening study for thyroid cancer in Fukushima Prefecture comprising about 300,000 residents below age 19 on 1 April 2011 was undertaken. The effort put in thyroid screening after the Fukushima accident was considerably higher than after Chernobyl [Y1]. At the onset of the screening study, an estimate of the prevalence of 0.027% (95% CI: 0.010%, 0.050%) for the first screening campaign was made by Jacob et al. [J1]. The underlying risk model for the prevalence estimate was derived from a reassessment of the incidence data for thyroid cancer in the LSS [P11]. The most recent observational study reported a prevalence of 0.037% from screening examinations between October 2011 and June 2015. The risk of thyroid cancer was not found to be associated with the radiation doses estimated by the Fukushima Health Management Survey and by WHO experts [I4, O1, W9]. This finding is at variance with claims that the excess thyroid cancers for years after the accident cannot be explained by ultrasound screening alone [T12]. Wakeford et al. [W2],

Williams [W11] and Suzuki [S17] disagreed with the conclusions of the study by Tsuda et al. [T12] for underestimating the impact of screening when comparing incidence rates of the Fukushima Prefecture with incidence rates in the general Japanese population.

402. An updated pooled analysis by Veiga et al. [V2] of 12 studies of thyroid cancer patients comprised 1,070 malignant thyroid tumours (66% females, 79% with papillary histology). The patients were exposed between 1920 and 2000 and followed up from 1935 to 2005. The time-related covariables were mean age at exposure of 5 (range 0–19), mean time since exposure 30 years, and mean age at diagnosis of 41 years. Patients were exposed to radiation with a mean (median) dose to the thyroid of 0.71 (0.07) Gy with a maximal dose of 76 Gy. Their study focused on the characterization of the shape of the dose response. Effect modifications of attained age, age at exposure and time since exposure were calculated in categories without considering combinations of age and time-related modifiers. Veiga et al. [V2] found an ERR at 1 Gy of 2.76 (95% CI: 0.94, 4.98) consistent with the result of Brenner et al. [B12]. The companion study of Lubin et al. [L18] investigated the same data sets but was especially interested in the shape of the dose response relation below 0.2 Gy. Lubin et al. reported no deviation from linearity with an ERR at 0.2 Gy of 2.2 (95% CI: 1.3, 3.3). In line with the findings of Furukawa et al. [F6], the ERR remains elevated more than 50 years after exposure in the studies of Veiga et al. [V2] and Lubin et al. [L18].

403. In contrast to the LSS cohort of Japanese atomic bombing survivors with maximal thyroid doses below 4 Gy, much higher doses up to 10 Gy have been reported in post Chernobyl studies of thyroid dosimetry [L9, L10, L11]. In the LSS risk reduction at higher doses with an exponential attenuation factor was marginally significant (p-value 0.07) [F6]. A significant risk attenuation for doses up to 10 Gy has been also observed in the Chernobyl studies [K4, Z1]. Veiga et al. [V2] observed a decrease of the ERR estimate only for doses above 20 Gy.

404. An analysis by Kaiser et al. [K4], using all of the 115 patients with papillary thyroid cancers in the UkrAm cohort, and a biologically based model of pathogenesis, reported an estimate for the ERR at 1 Gy of 1.6 (95% CI: 0.67, 2.6) for an attained age of 27, again in line with the result of Brenner et al. [B12]. However, the estimate of Kaiser et al. [K4] for the EAR at 1 Gy of 5.1 (95% CI: 3.5, 7.5) per 10⁴ person-years was markedly higher compared to that in the reference [B12]. But it was close to an older estimate from Ron et al. [R8] of 4.4 (95% CI: 1.9, 10.1) per 10⁴ person-years, which had been obtained in 1995 from a pooled analysis of seven studies of thyroid cancer patients as part of the updated analysis of Veiga et al. [V2]. The difference in the estimates of Brenner et al. and of Kaiser et al. is mainly related to the approach of adjusting for the effect of strongly varying incidence rates in different Ukrainian regions. Whereas Brenner et al. [B12] adjusted only the baseline rate, Kaiser et al. [K4] applied the adjustment on the total hazard, which resulted in a marked improvement in AIC based goodness-of-fit.

405. Tronko et al. [T10] reported an ERR estimate of 1.36 (95% CI: 0.39, 4.15) Gy⁻¹ for the fifth cycle of thyroid screening of the UkrAm cohort during the period 2012–2015. Nearly 30 years after the accident, 47 cases were detected at a mean age of screening of 35. The ERR estimate follows the decreasing trend with attained age, which was observed in the studies of Tronko et al. [T11] and Brenner et al. [B12]. Using an age dependence that is proportional to age⁻⁴ Kaiser et al. [K4] estimated an ERR of 0.75 (95% CI: 0.26, 1.3) Gy⁻¹ for a mean age of screening of 35. Their result obtained by extrapolation is compatible with the estimate of Tronko et al. [T10].

D. Definition of scenario

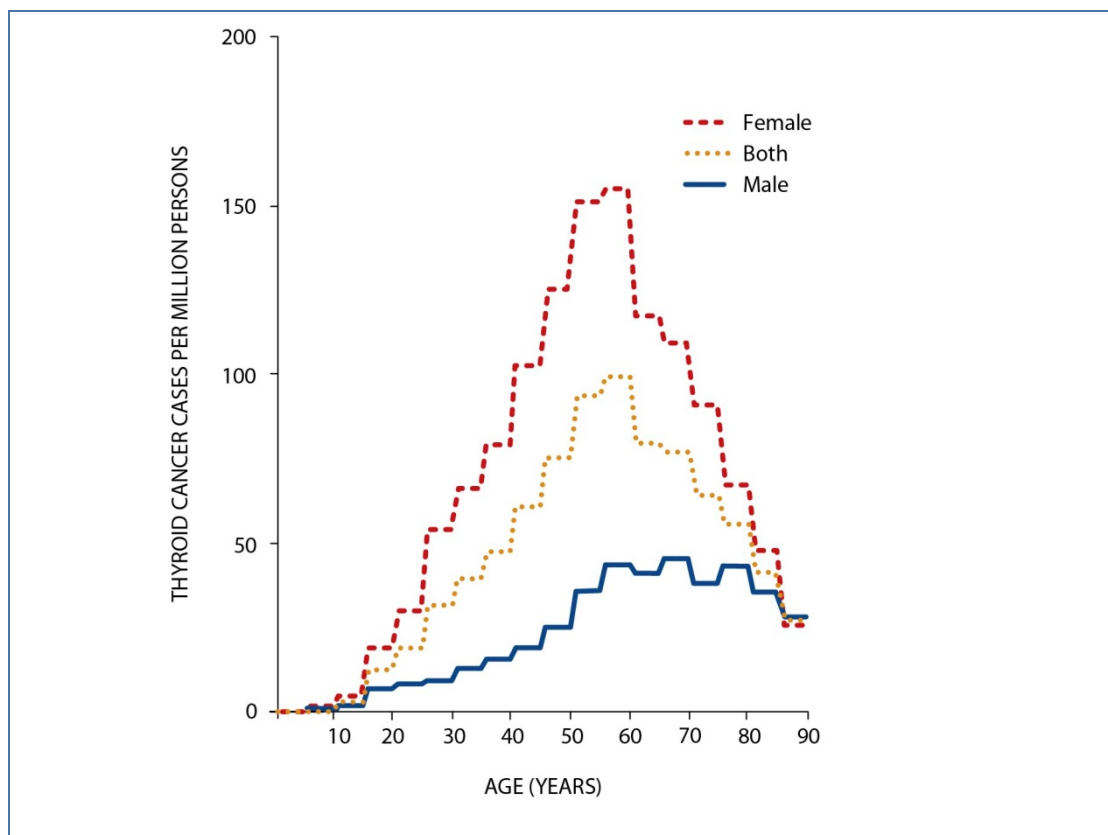
1. Exposure scenario

406. The design of the present scenario was inspired by the situation of the UkrAm cohort. The intention was to consider issues that had not been addressed in the previous scenario for thyroid cancer analysed in the UNSCEAR 2012 Report [U8]. Compared to the UNSCEAR 2012 scenario, which assumed an exposure of 200 mGy, it focuses on thyroid doses of about 500 mGy. The higher dose was chosen because the risk uncertainties appeared very large in the previous scenario. The risk was evaluated for ages 1 and 10 at exposure and ages 30 and 40 for the end of follow-up, in line with the scenario for leukaemia risk in children. Follow-up started at the first birthday and ended at the 30th and 40th birthday, respectively. In the UkrAm cohort [B12, K4], the oldest persons were operated on at age 35 in 2008. Provision of stable iodine and contamination of drinking water with nitrate are discussed below (see section V.F.1(e)) as possible confounding factors on risk estimates. In order to avoid any biases due to both factors, the target cohort was assumed to be the same as the UkrAm cohort in these aspects.

2. Reference data

407. To transfer the ERR estimates to the Ukrainian population, the combined incidence rates for thyroid cancer pertaining to the period 2001–2007 were applied, which were available in age groups of five years from the National Cancer Registry of Ukraine (figure IX). Data for 2005 on the Ukrainian population and deceased persons in age groups of five years were used from the State Statistics Service of Ukraine [U1]. With these data, the sex-specific and sex-averaged survival curves were calculated for age groups of five years up to age 75 in the standard way as negative exponentials of the cumulative incidence.

Figure IX. Thyroid cancer incidence in Ukraine for the period 2001–2007 [U1]



3. Risk models

408. Risk models derived from the LSS and UkrAm cohorts were applied for risk projection in the thyroid scenario. The most recent LSS incidence data set with follow-up from 1958 to 2005 has been analysed by Furukawa et al. [F6] for thyroid carcinoma >10 mm applying the ERR model:

$$\text{ERR} = \beta * \text{dose} * \exp(\alpha_a * \log(\text{age}/60) + \alpha_e * (\text{agex}-10)/10) * (1 + \alpha_s * m_{\text{sex}})$$

where $\beta=1.28$, $\alpha_a=-1.27$, $\alpha_e=-0.769$ and $\alpha_s=0.327$;

and the EAR model:

$$\text{EAR} = \beta * \text{dose} * \exp(\alpha_a * \log(\text{age}/60) + \alpha_e * (\text{agex}-10)/10) * (1 + \alpha_s * m_{\text{sex}})$$

where $\beta=2.95 \times 10^{-4}$, $\alpha_a=1.03$, $\alpha_e=-1.19$ and $\alpha_s=0.729$; $m_{\text{sex}}=1, -1$ for males, females, respectively. Covariables, age, agex and dose denote attained age, age at exposure and absorbed dose to the thyroid, respectively.

409. Jacob et al. [J1] have derived risk estimates from the LSS for all malignant tumours without size restrictions in the period 1958–1998 based on the ERR model:

$$\text{ERR} = \beta * \text{dose} * \exp(\alpha_a * \log(\text{age}/60) + \alpha_e * (\text{agex}-20)/10 + \alpha_s * m_{\text{sex}})$$

where $\beta=1.13$, $\alpha_a=-0.688$, $\alpha_e=-0.658$ and $\alpha_s=0.115$;

and the EAR model:

$$\text{EAR} = \beta * \text{dose} * \exp(\alpha_a * \log(\text{age}/60) + \alpha_e * (\text{age} - 20)/10 + \alpha_s * m_{\text{sex}})$$

where $\beta = 1.58 * 10^{-4}$, $\alpha_a = 1.04$, $\alpha_e = -0.802$ and $\alpha_s = 0.697$, $m_{\text{sex}} = -1, 1$ for males, females, respectively.

To calculate the CER from the risk models derived for the UkrAm cohort, the study of Kaiser et al. [K4] was used. They developed an EAR model:

$$\text{EAR} = \beta * \text{dose} * \exp(\alpha_{\text{exp}} * \text{dose} + \alpha_s * m_{\text{sex}})$$

where $\beta = 6.5 * 10^{-4}$, $\alpha_{\text{exp}} = -0.0891$ and $\alpha_s = 0.429$; $m_{\text{sex}} = -1, 1$ for males, females, respectively, and baseline $h_0 = b_0 * \exp(b_{\text{age}} * \log(\text{age}/25))$ where $b_0 = 0.935 * 10^{-4}$ and $b_{\text{age}} = 3.82$.

410. The EAR model of Kaiser et al. [K4] was used for the present analysis. It yielded almost identical results compared to those from their biologically based model. A multiplicative ERR model was derived from the EAR model by multiplication of the parametric baseline model for the UkrAm cohort.

411. The ERR estimates applied in thyroid scenario calculation for age at exposure of 10 are shown in figure X for attained age between 10 and 30. In this age interval, the majority of cases from the studies of Brenner et al. [B12] and Kaiser et al. [K4] have been recorded. As discussed below, the EAR models are less suitable in risk transfer calculations due to their higher sensitivity to differential screening regimes.

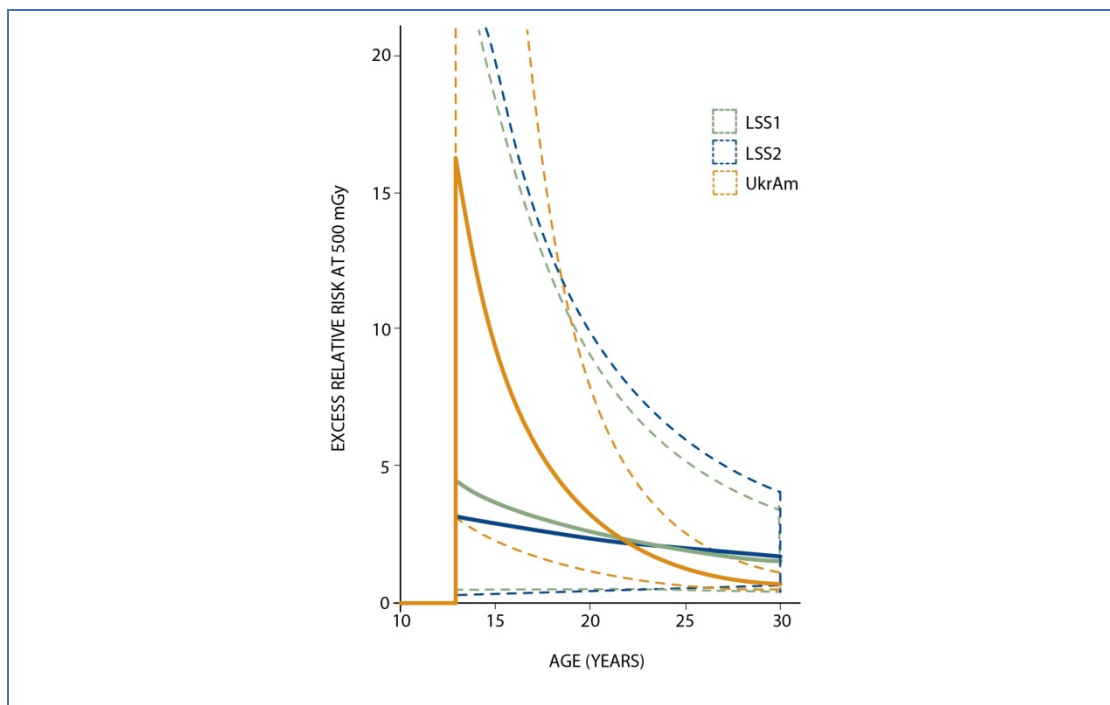
412. In the LSS, tumours of size <10 mm have been detected mainly in autopsy studies before 1970. The main difference between the UkrAm and LSS cohorts is the screening regime. With the LSS cohort, medical surveillance was not as intensive as with the UkrAm cohort even for persons participating in the adult health study. To assess the influence of tumour size on the risk projections, the models of the studies from Furukawa et al. [F6] and Jacob et al. [J1] were applied. Complete model parameter estimates and correlation matrices are given in the appendix. The sex dependence of the EAR estimates differed markedly between the LSS and UkrAm cohorts with female/male ratios of 6.4 (LSS) versus 2.4 (UkrAm) [K4] which may be related to ethnicity. Thus, to facilitate comparability only sex-averaged risk estimates are discussed in line with the scenario for leukaemia from CT scans in children. The studies of Tronko et al. [T11] and Brenner et al. [B12] report only sex-averaged risk estimates as their main results due to the small number of cases in each study.

413. The pooled study of Veiga et al. [V2] provides an alternative set of risk estimates. However, age-related dose-effect modifiers were presented in a form which did not allow risk estimates to be extracted that would be suitable for the scenario calculations.

414. For the CER calculation, a latency period of three years after exposure was assumed [H3]. During this period, the excess risk was set at zero. Smoothing of the latency period has been applied in the IREP software package [K13], but had negligible effect on the CER.

415. In the LSS, follow-up for thyroid-cancer incidence started in 1958, 13 years after exposure. Beyond a three-year latency period, the risk estimates for the 10 years before 1958 had to be inferred. This inference was accomplished by extrapolating the risk estimates pertaining to the time since exposure below 13 years based on age-related parameter estimates derived from cohort data for time since exposure exceeding 13 years.

Figure X. Sex-averaged excess relative risk estimates and 95% confidence intervals for the LSS cohort by Furukawa et al. [F6] (LSS1), by Jacob et al. [J1] (LSS2) and by Kaiser et al. [K4] for the UkrAm cohort using a latency period of three years after exposure at 10 years of age



4. Risk-transfer methods

416. Risk transfer was performed with an average risk coefficient for a population with an equal number of males and females. Sex-specific risk assessment was avoided for the thyroid scenario since sex-specific risk estimates and the baseline risk differed markedly between Japan and Ukraine.

417. The CER calculations with the ERR models were performed by applying the sex-averaged recorded incidence rates for thyroid cancer in the Ukrainian population for the period 2001–2007, which are shown in figure IX.

E. Results

418. In table 17, the estimates of the CBR, maximum-likelihood estimates (MLEs) and confidence intervals of the CER related to the scenario are given for the transfer of the ERR and the EAR at 0.5 Gy in the LSS based on the models in the references of Furukawa et al. [F6] and of Jacob et al. [J1], and from the UkrAm cohort based on the models of Kaiser et al. [K4]. To put disease-specific risks into perspective, cumulative risks for overall mortality are shown as well.

419. Although Furukawa et al. [F6] excluded tumours <10 mm from the analysis and Jacob et al. [J1] included all reported thyroid cancer cases, the central estimates and confidence intervals for the CER were very similar for all four combinations of age at exposure and age at the end of follow-up.

Table 17. Overall mortality in the follow-up period, CBR, maximum-likelihood estimates and 95% CIs of the sex-averaged CER of thyroid cancer incidence

Risks calculated per 10,000 persons exposed at age 1 or 10 to a thyroid dose of 500 mGy; LSS: Life Span Study; CBR: Cumulative baseline risk; CER: Cumulative excess risk; CFR: Cumulative fractional ratio; CI: Confidence interval

Method of transfer	Overall mortality and CBR		CER associated with the exposure scenario and CFR (i.e. CER/CBR)	
	Mortality per 10 000	CBR per 10 000	CER per 10 000 (95% CI)	CFR
EXPOSURE AT AGE 1, FOLLOW-UP TO AGE 30, DURATION OF FOLLOW-UP 29 YEARS				
LSS incidence models				
ERR transfer [J1]	383	3.3	13 (3.7, 40)	4.0
EAR transfer [J1]	383	3.3	31 (12, 90)	9.5
ERR transfer [F6]	383	3.3	16 (3.4, 59)	4.7
EAR transfer [F6]	383	3.3	30 (11, 91)	9.1
UkrAm incidence models				
ERR transfer [K4]	383	3.3	19 (3.2, 119)	5.6
EAR transfer [K4]	383	3.3	74 (46, 101)	23
EXPOSURE AT AGE 1, FOLLOW-UP TO AGE 40, DURATION OF FOLLOW-UP 39 YEARS				
LSS incidence models				
ERR transfer [J1]	831	7.4	25 (8.6, 69)	3.4
EAR transfer [J1]	831	7.4	55 (27, 119)	7.5
ERR transfer [F6]	831	7.4	26 (7.2, 79)	3.5
EAR transfer [F6]	831	7.4	53 (23, 126)	7.6
UkrAm incidence models				
ERR transfer [K4]	831	7.4	20 (4.4, 118)	2.7
EAR transfer [K4]	831	7.4	101 (62, 138)	14
EXPOSURE AT AGE 10, FOLLOW-UP TO AGE 30, DURATION OF FOLLOW-UP 20 YEARS				
LSS incidence models				
ERR transfer [J1]	258	3.3	6.8 (1.8, 19)	2.1
EAR transfer [J1]	258	3.3	13 (4.3, 33)	3.9
ERR transfer [F6]	258	3.3	7.0 (1.6, 23)	2.1
EAR transfer [F6]	258	3.3	8.6 (3.1, 24)	2.6
UkrAm incidence models				
ERR transfer [K4]	258	3.3	7.7 (2.4, 18)	2.4
EAR transfer [K4]	258	3.3	49 (31, 66)	15

Method of transfer	Overall mortality and CBR		CER associated with the exposure scenario and CFR (i.e. CER/CBR)	
	Mortality per 10 000	CBR per 10 000	CER per 10 000 (95% CI)	CFR
EXPOSURE AT AGE 10, FOLLOW-UP TO AGE 40, DURATION OF FOLLOW-UP 30 YEARS				
LSS incidence models				
ERR transfer [J1]	712	7.4	13 (4.5, 37)	1.8
EAR transfer [J1]	712	7.4	25 (11, 52)	3.3
ERR transfer [F6]	712	7.4	12 (3.2, 33)	1.7
EAR transfer [F6]	712	7.4	17 (7.6, 36)	2.3
UkrAm incidence models				
ERR transfer [K4]	712	7.4	9.3 (3.5, 20)	1.3
EAR transfer [K4]	712	7.4	76 (49, 103)	10

420. The central CER estimates based on the transfers of the ERR at 0.5 Gy in the LSS and UkrAm cohort agree well. However, estimates based on the transfer of the EAR at 0.5 Gy from the LSS cohort are markedly lower than those from the UkrAm cohort. This may be related to the intensive screening of the UkrAm cohort. The ERR estimates have been shown to be less sensitive to screening procedures than the EAR estimates when radiation-induced and sporadic thyroid cancers grow to similar size in similar timelines [K2].

421. Figure X shows that the ERR estimates from the UkrAm largely exceed those from the LSS cohort up to age 20. This discrepancy does not affect the CER calculations, since it is suppressed by the low thyroid cancer incidence at young age (figure IX). The width of the confidence intervals of the CER estimates are dominated by those of the transferred risk quantities. In the model of Kaiser et al. [K4], the EAR has a quite narrow confidence interval. The ERR derived from the EAR and the baseline risk has a huge uncertainty at age at exposure of 1 and a small one at age at exposure of 10. The small number of baseline cases at young age is driving this uncertainty.

F. Discussion of scenario calculations

1. Sources of uncertainties

(a) Selected populations

422. The LSS cohort includes about 93,000 atomic bombing survivors in Hiroshima and Nagasaki and about 27,000 people who were not in the cities at the time of the bombings. The incidence of cases of thyroid cancer in this cohort was identified from a study of the cancer registries in both cities. Histological materials collected from area hospitals and pathology laboratories were assessed by a panel of pathologists for diagnostic confirmation and histologic classification. The population-based cancer registries have been in operation since 1958 with a follow-up until 1998 [P11] or 2005 [F6].

423. For the UkrAm cohort, a list of persons born between 26 April 1968 and 26 April 1986 (the date of the accident), and who had had measurements made on the thyroid during May and June 1986 in the Chernihiv, Zhytomyr, or Kyiv oblasts in Ukraine was compiled. A sample of 32,385 persons was selected from this list. This number was reduced by applying several exclusion criteria and through loss to follow-up. Tronko et al. [T11] analysed 13,127 persons who were actually screened in the first cycle 1998–2000. Brenner et al. [B12] considered 12,514 persons who underwent up to four thyroid-screening examinations between 1998 and 2007. Tronko et al. [T10] considered 10,073 persons for the risk assessment in the fifth screening cycle.

424. The population in the scenario was assumed to have similar living conditions to those of the UkrAm cohort. Thus, the risk calculations based on a transfer of effect per unit dose estimates in the UkrAm cohort are not biased. On the other hand, there are possible biases in the transfer of effect per unit dose estimates in the LSS, because, for example, the provision of stable iodine is certainly different.

(b) *Exposure assessment*

425. The dose uncertainties in the LSS cohort have already been accounted for by the adjustment of the dose estimates (see section II.F.1(b)). For the UkrAm cohort, individual doses to the thyroid from ^{131}I and their uncertainties were estimated from the combination of thyroid measurements, data on dietary and lifestyle habits, and environmental transfer models using a Monte Carlo approach [L9, L10, L11].

426. Little et al. [L14] performed a thorough analysis of the impact of dose uncertainties on the risk estimates for the UkrAm cohort by applying two different methods of regression calibration and Monte Carlo simulation. The unadjusted ERR estimate per unit dose obtained by Tronko et al. [T11] was 5.3 (95% CI: 1.7, 28) Gy^{-1} . The first regression-calibration method yielded an ERR per unit dose of 5.8 (95% CI: 1.9, 27) Gy^{-1} , about 7% higher than the unadjusted ERR estimate. The second regression-calibration method gave an ERR per unit dose of 4.8 (95% CI: 1.6, 20) Gy^{-1} , about 11% lower than the unadjusted value. The Monte Carlo maximum-likelihood method produced an excess odds ratio* per unit dose of 4.9 (95% CI: 1.7, 20) Gy^{-1} , about 8% lower than the unadjusted value. The authors discussed the reason for the unexpected decrease of the ERR and pointed to the large contribution of Berkson errors to the overall dose uncertainties whereas classical errors would increase ERR estimates. For the BelAm cohort the Bayesian Markov Chain Monte Carlo method yielded a maximum posterior ERR per unit dose of 1.2 (95% CI: 0.20, 4.3) Gy^{-1} [L15]. The central estimate is 23% lower than the unadjusted value from the same study. As the dose estimates for the BelAm cohort were based on a radioecological model of exposure pathways rather than direct measurements as for the UkrAm cohort, the dose uncertainties have a larger impact on the risk estimate.

(c) *Health outcome assessment*

427. During the period 1958–2005, Furukawa et al. [F6] identified 371 thyroid cancer cases (299 papillary carcinomas, 15 follicular carcinomas, 12 anaplastic carcinomas, 3 medullary carcinomas and 42 other carcinomas) with a first primary of size >10 mm in the cancer registry catchment area. Jacob et al. [J1] analysed 471 malignant thyroid tumours of all sizes and histologic types recorded in the LSS during the period 1958–1998.

428. To analyse the incidence of thyroid cancer in the UkrAm cohort, each listed member was screened for thyroid cancer either by a mobile team visiting the local area or at a screening centre at the Research Institute of Endocrinology and Metabolism in Kyiv, Ukraine. The procedure consisted of ultrasonography by an ultrasonographer and independent clinical examination and palpation by an

endocrinologist. Questionnaires were used to determine demographic and medical characteristics and items relevant to dose estimation such as residential history and milk consumption during the period May–June 1986. An initial assessment of any thyroid pathology was provided by the endocrinologist at the time of the screening. Cohort members with peculiar diagnosis were referred to the clinic in Kyiv for possible fine needle aspiration for nodules >5 mm in size and/or possible surgery [T11].

429. Primary risk analyses for the UkrAm cohort were performed with 45 prevalent cases from the first screening cycle [T11], 65 new cases from the second to the fourth screening cycles [B12] and 47 cases from the fifth cycle [T10]. In those studies, all histological types of papillary, follicular and medullary thyroid cancer were combined for the main risk analysis. The thyroid cancer cases among the UkrAm cohort were verified by an international panel of experts so that uncertainty from diagnosis of thyroid cancer is negligible.

430. The focus of the study by Kaiser et al. [K4] was on molecular carcinogenesis and was only concerned with the development of papillary thyroid cancer. To achieve maximal statistical power, all 115 cases of papillary thyroid cancer in the UkrAm cohort, which had undergone operation up to 2008, were included.

(d) *Study design*

431. Epidemiological studies of thyroid cancer are often influenced by screening procedures. A characteristic trait of the UkrAm cohort is an efficient screening protocol for all members of the cohort and for the whole study period up to 2015, the end of the last period of examinations. In the second to the fifth screening cycles, cases had developed within cycles of two to three years. Since the time period for cancer development is relatively short, cases from these screening cycles can be considered as incidental. Such a screening regime will produce a markedly higher number of cases compared to the general population without periodic thyroid examinations. However, due to the design of this study, the impact of a screening bias on the risk estimates is negligible.

432. The bias introduced by transfer of a risk estimate from a dedicated radioepidemiological study to the population of interest is difficult to quantify. To mitigate ambiguity, transfer procedures often apply multiplicative and additive models with different weights, where the weighting is decided by expert judgement. In addition, epidemiological studies of thyroid cancer may be burdened by a bias because of differential screening in systematically studied and general populations. For example, in the UkrAm study, the screening bias is under adequate control due to the application of the same screening protocol to all cohort members. The general Ukrainian population is not subject to periodic screening, so that the estimated radiation effects on thyroid cancer incidence in the UkrAm cohort are not fully transferable. To quantify a possible transfer bias for the special case of paediatric thyroid cancer risk after the Chernobyl accident in the Ukrainian oblast of Kyiv, Chernihiv and Zhytomir, Kaiser et al. [K2] performed a simulation study. They estimated a moderate screening bias of about 20% for the ERR from ecological risk studies of post-accident thyroid cancer. Of more importance for the present scenario is the ratio of the ERR from a hypothetical cohort study to the ERR in the population of interest, which was estimated to be 0.91 (95% CI: 0.37, 4.96) [K2]. It is noted that simulated estimates of both the ERR and the EAR in the hypothetical cohort of Kaiser et al. [K2] are close to those of Kaiser et al. for the UkrAm cohort [K4].

(e) *Confounding factors*

433. Screening conditions in the general population and the cohort are different. Thus, it is more appropriate to transfer the estimated ERR rather than the estimated EAR which is much more strongly affected by differential screening strategies [K2]. Therefore, the CER estimates from multiplicative transfer should be more consistent between different cohorts than the CER estimates from additive transfer.

434. In the LSS, confounding by screening can be estimated by comparing the baseline rates for the participants in the AHS to those for non-participants. The AHS participants were under a regime of enhanced medical surveillance from the late 1950s to the early 1970s. The AHS baseline rates were estimated to be higher by a factor of 1.7 compared to those for non-participants ([J1] table A4).

435. In November 2000, a workshop of the Ukrainian-Belarus-USA study group addressed the issue of iodine nutrition in the region and how this might have influenced the risk of thyroid tumour incidence [R7]. The study group comprised experts involved in establishing both the UkrAm and the BelAm cohort. Tronko et al. [T9] reported the results of an iodine excretion study in the UkrAm cohort where urinary iodine levels were found to be lower in rural than urban areas. They concluded that iodine status needs to be considered when evaluating the risk of thyroid cancer. Cardis et al. [C3] attempted to quantify the impact of iodine levels on the radiation risk estimates. Compared to the unadjusted estimate, self-reported intake of iodine prophylaxis was associated with a three times lower risk of radiation-related thyroid cancer (ratio of excess relative rates per unit dose of 0.34 (95% CI: 0.1, 0.9), for consumption of potassium iodide versus no consumption). Residence within iodine-deficient territories at the time of the accident was associated with a three times higher risk of radiation-related thyroid cancer (ratio of excess relative rates per unit dose of 3.2 (95% CI: 1.9, 5.5)). This result is supported by an earlier study of Shakhtarin et al. [S6]. Brenner et al. [B12] observed similar trends but emphasized that their data were not strong enough to support a modifying effect of either iodine prophylaxis or iodine deficiency. The Committee noted that “individual measurements of the iodine status at the time of the accident are not available and approximations derived ... from soil or urine 10 years after the accident, have to be considered with caution”. Nevertheless, the uncertainty from neglecting the influence of a varying iodine supply could be large. The UkrAm cohort stems partly from an iodine-deficient area; a small fraction of the cohort members took iodine prophylaxis. It is noted that the transfer of the ERR per unit dose in the LSS gives very similar results to those from the transfer from the UkrAm cohort (table 17), even though the Japanese population has an iodine-rich diet.

436. Drozd et al. [D6] observed markedly different rates of paediatric thyroid cancer incidence in the Belarussian regions of Mogilev and Brest. Whereas the estimated doses to the thyroid from ^{131}I were comparable in the two regions, nitrate contamination of drinking water trended with the rate difference. They hypothesized that high nitrate levels which range between 60–500 mg/liter in open wells could modulate the carcinogenic effect of radiation on the thyroid but did not quantify the impact on risk estimates. The Committee notes that baseline thyroid cancer incidence rates vary considerably in different regions. For example, in the Ukrainian regions of Kyiv and Chernihiv baseline incidence was found by a factor of 2.5 higher than in Zhytomir oblast [K4]. There is also considerable variation in Ukrainian and Japanese baseline rates [J1, K4]. The reasons for this variability are not fully understood, and further research is needed in this area.

(f) *Statistical methods and model uncertainties*

437. It is common practice to apply a single model of choice to estimate the risk although several similar models describe the observational data almost equally well. This has been discussed by Walsh and Kaiser [W4], who recommended the application of multi-model inference by using the averages of the risk estimates from selected models weighted by their AIC. Furukawa et al. [F7] applied a Bayesian semi-parametric approach for the same reason of avoiding a characterization of the dose response based on a single model. In the present analysis, both the EAR and ERR models from Jacob et al. [J1] and Furukawa et al. [F6] were applied for risk transfer. The risk estimates from both studies were in good agreement. Therefore, the uncertainties from the choice of an LSS risk model are considered small and do not justify an in-depth multi-model inference analysis.

438. Kaiser et al. [K4] found a descriptive model and a mechanistic model providing the same goodness-of-fit and the same risk estimates of both the EAR and the ERR. In this special situation, model uncertainty need not be considered for risk estimation. It is important to recall here that central lifetime risk estimates are reported as MLEs calculated with model parameter estimates which minimize the Poisson likelihood. Confidence intervals for the lifetime risk estimates were calculated exclusively from the Wald-based standard errors and correlations of those model parameters, which pertain to the radiation risk. In Monte Carlo simulations, multivariate normal probability distributions of 10,000 samples are generated under the constraint of conserving the covariance matrix for these parameters. From the resulting distribution of 10,000 lifetime risk estimates confidence intervals are picked as 2.5 and 97.5% quantiles.

(g) *Other sources of uncertainty*

439. The impact of uncertainties in the recorded baseline rate of the thyroid cancer incidence in the target population was tested by allowing for Poisson-distributed fluctuations in the counting for the number of cases, but these were found to be negligible in the present thyroid scenarios. However, when baseline incidence rates for the period 2001–2007 are applied in the CER predictions with multiplicative ERR models, secular trends of thyroid cancer incidence are not taken into account. Due to the enhanced medical surveillance, incidence rates are likely to increase in the future. Hence, the CER estimates, which make use of recorded baseline incidence rates, might possibly come out too low, although this effect is hard to quantify. Consequently, in the present scenario calculations, constant secular trends are implicitly assumed.

440. The transfer of effect-per-unit-dose estimates in the LSS to protracted exposure situations introduces an uncertainty additional to those considered explicitly in the risk calculations performed in the present report. In the scenario of a single uptake, the mean duration of exposure from ^{131}I can be calculated by:

$$\int_0^{\infty} t \exp\{-[t_{1/2}/\ln(2)]t\} dt / (t_{1/2}/\ln(2)) = t_{1/2}/\ln(2)$$

where $t_{1/2}$ is the effective half-life of ^{131}I in the thyroid. The biological half-life of iodine in the thyroid for children aged 1 and 10 is 15 and 58 days, respectively ([U6] annex B, table A13). When account is taken of the radioactive decay of ^{131}I , the effective half-life in the thyroid is about 5 and 7 days, respectively. For a dose to the thyroid of 500 mGy, the mean dose rate is therefore about 3 and 2 mGy/h for children exposed at ages 1 and 10, respectively. The Committee considers dose rates <6 mGy/h as low [U4]. So, the average dose rates in the scenarios are low, and there is an uncertainty in the transfer of the effect-per-unit-dose estimate in the LSS with a high dose rate, additional to those considered explicitly in the calculation of the present analysis.

441. The dose to the thyroid in the scenario (0.5 Gy) is somewhat smaller than the arithmetic mean dose 0.65 (geometric mean 0.20) Gy in the UkrAm cohort. A linear dose response was observed with a slight down-bending in the upper dose range [K4]. At 0.5 Gy the correction factor would be 0.96 but this correction has already been included in the CER estimates from the UkrAm cohort.

2. Preferred risk inference

(a) *Selection of the preferred risk inference*

442. For the thyroid scenario, the preferred risk inference was chosen in view of the following conditions. Screening has a large influence on the observed thyroid cancer incidence. The scenario was defined for contemporary screening conditions in Ukraine. These are better reflected by the product of an ERR per unit dose and the baseline incidence in Ukraine rather than by an EAR per unit dose in a population with different screening conditions. Therefore, an ERR transfer was performed. The ERR for age at exposure of 10 has considerably lower uncertainty than the ERR for age at exposure of one and is thus more informative. Basing the ERR estimate on the UkrAm cohort does not need the use of uncertain risk transfers from acute to protracted low-dose-rate exposure, or between populations with different living habits and environmental conditions (e.g. intake of stable iodine with food). Duration of follow-up was restricted to 19 years since the data on thyroid cancer incidence in the UkrAm cohort had not been published at the time of the analysis. For exposure at age 10 to a dose to the thyroid of 0.5 Gy, a follow-up until age 30, and based on the ERR per unit dose in the UkrAm cohort, the CER was estimated to be 7.7 (95% CI: 2.4, 18) chances per 10,000 persons. The estimated impact of sources of uncertainty not taken into account in the calculations is indicated in table 18 and discussed below. In the preferred risk inference, the preferred estimate of the CFR is 2.4 (table 17).

(b) *Discussion of the impact of sources of uncertainty*

443. The main sources of uncertainties associated with this risk estimate are summarized in table 18. The subsequent paragraphs give the reasons for the grading of the uncertainties (very small, small, moderate or large).

444. *Selected populations:* The cohort members of the UkrAm cohort were selected for age <19 at the time of accident under the condition that they possessed direct measurements of the dose to the thyroid over a plausible range. This condition does not question the applicability of the “preferred” estimate of risk to the general Ukrainian population aged <19. On the other hand, the cohort members resided in three northern regions of Ukraine and in Kyiv, which might not be representative for the population of the whole of Ukraine with respect to iodine intake and nitrate contamination of drinking water (see sections V.F.1(a),(e)).

445. The preferred scenario involves Ukrainian children who are exposed at age 10 to a dose to the thyroid of 500 mGy and the number of thyroid cancers is calculated up to age 30. This scenario is closely related to the actual situation with the UkrAm cohort in which the mean age at exposure was 10 and the number of thyroid cancers up to the end of the fourth screening was determined [B12]. Thus, the CER estimates for the preferred scenario possess confidence intervals with the lowest achievable range. For ages at exposure below 10, and for follow-up periods of interest longer than 20 years, the confidence interval of the risk estimate would markedly increase.

446. *Exposure assessment:* The exposure assessment, which might be prone to dose measurement errors [L14], is identical for all considered scenarios based on risk estimates from the UkrAm cohort (see sections V.F.1(a),(b)).

447. *Health outcome assessment:* The assessment of health outcome, which might suffer from case ascertainment problems [B12, T10, T11], is identical for all considered scenarios based on UkrAm cohort data (see section V.F.1(c)).

448. *Study design:* In the simulation study of Kaiser et al. [K2], the ratio of the ERR per unit dose for a hypothetical cohort study to that for the general population was estimated to be about 0.91 (95% CI: 0.37, 4.96). The central estimate of the hypothetical cohort study, which was inspired by the study design of the UkrAm cohort, closely approximates to the expected “true” value in the general target population. The range of the confidence interval is a factor of five larger than the central estimate. Such a large range was also observed in the UkrAm cohort by Tronko et al. [T11]. It reflects the “natural” statistical uncertainty introduced by the underlying Poisson distribution of case counts and does not introduce additional uncertainty for the risk transfer. Results of the simulation study suggest that the CER estimates from the preferred scenario represent the “true” value in the target population well.

449. *Confounding factors:* The potential impact of iodine deficiency on thyroid cancer risk after exposure to radioiodine has been investigated in a number of studies [B12, C3, S6, T9]. The CER estimates in the preferred risk calculation are only valid under the assumption that the average iodine-supply in contemporary Ukraine does not differ substantially from that in the UkrAm cohort. Even under this condition, there is a remaining uncertainty: In the UkrAm cohort, there was potentially an anti-correlation between dose to the thyroid (high in rural areas) and iodine supply (low in rural areas). Thus, the radiation effect per unit dose in the UkrAm cohort might have been larger than in a population without such a correlation. Therefore, there is a potential for a small systematic error resulting in too high CER values in table 17.

450. Nitrate contamination of drinking water has been identified as an additional confounder for thyroid cancer incidence in Belarus, but the impact on risk estimates could not be quantified [D6]. As in the case for stable iodine intake, the nitrate contamination of drinking water for the target cohort and the UkrAm cohort are assumed not to be markedly different. By assuming similar conditions in risk transfer for both confounders, they do not introduce additional uncertainty in the risk estimate for the preferred scenario.

451. *Statistical methods and model uncertainties:* Since the preferred thyroid scenario concentrate on the centre of the incidence data in cohort strata with many cases, plausible risk models are expected to yield similar risk estimates. In this case, the influence of model uncertainty can be neglected (see section V.F.1(f)).

452. *Other sources of uncertainty:* The use of risk estimates obtained from the UkrAm cohort study for the preferred scenario eliminates several sources of uncertainty. Corrections for the influence of dose rate effects on the CER estimate are not necessary, if risk estimates are derived for the same exposure situation. Ethnicity is excluded as a confounder with unknown impact. Additional uncertainty from extrapolation of the LSS risk estimates for time since exposure of less than 13 years (i.e. before 1958) can be avoided.

453. To integrate molecular data into their study, Kaiser et al. [K4] performed their analysis with the histological type of papillary thyroid cancer, whereas most other studies produced risk estimates for all histological types (papillary, follicular, medullary) combined. Papillary thyroid cancers constitute more than 90% of all thyroid cancers in the studies of Tronko et al. [T10, T11] and Brenner et al. [B12].

Brenner et al. published estimates of the ERR and EAR for both all histological types combined and papillary thyroid cancer alone. Central estimates of both the ERR and EAR for papillary thyroid cancer alone were found to be a factor of 0.8 smaller compared to estimates for all histological types combined.

Table 18. Characterization of the main sources of uncertainty associated with the preferred risk inference of thyroid cancer

<i>Source</i>	<i>Characterization of source</i>	<i>Judged impact^a</i>
Selected population	Selection of cohort members from the general population	Very small
Exposure assessment	Dose measurement errors	Small overestimation
Health outcome assessment	Case ascertainment	Very small
Study design	Risk transfer from the UkrAm cohort to the general population	Very small underestimation
Confounding factors	Iodine supply	No impact, since distribution of stable iodine supply in the scenario is the same as in the UkrAm cohort
Confounding factors	Nitrate contamination of drinking water	No impact, since distribution of nitrate contamination of drinking water in the scenario is the same as in the UkrAm cohort
Statistical methods and model uncertainty	Model uncertainty minimized by applying CER estimates from the centre of the data	Very small
Other sources of uncertainty	Using papillary thyroid cancer (PTC) instead of all histological subtypes	Small underestimation
Other sources of uncertainty	Development of future baseline rates	Not quantifiable, part of the scenario assumption

^a The impact of the different sources of uncertainty is classified into four categories according to the variation they are expected to induce on the reported CER: very small—less than a factor of 1.1; small—between a factor of 1.1 to 1.5; moderate—between a factor of 1.5 to 2; and large—greater than a factor of 2.

(c) Comparison with other estimates of lifetime risk and attributable fractions

454. Two independent studies were published with lifetime risk estimates of thyroid cancer after childhood exposure by the Committee [U8] and by WHO [W9]. Recently, an UNSCEAR white paper estimated the attributable fraction of thyroid cancer incidence in the period 1991–2015 in the regions affected by the Chernobyl accident [U9]. Table 19 compares the results of the present report for the preferred thyroid scenarios with the earlier estimates of lifetime risk from the studies of the Committee [U8] and of WHO [W9].

Table 19. Thyroid cancer incidence (cases per 10,000 persons) after exposure at age 10 with a thyroid dose of 500 mGy. Preferred estimates and 95% credible intervals as far as available

CBR: Cumulative baseline risk; CER: Cumulative excess risk; EAR: Excess absolute risk; ERR: Excess relative risk

Source	WHO [W9] ^a	UNSCEAR [U8] ^a	This report
Follow-up time	15 years	18 years	20 years
CBR	2.0	3.5	3.3
CER			
Preferred model	9.6	7.2 (1.3, 21) ^b	7.7 (2.4, 18) ^c
Transfer of ERR from LSS	7.1	12 ^d	7.0 (1.6, 23) ^c
Transfer of EAR from LSS	12	15 ^d	8.6 (3.1, 24) ^c

^a Incidence averaged over both sexes and CER scaled to a dose to the thyroid of 500 mGy assuming a linear dose relationship.

^b Calculations based on the BEIR VII model.

^c See text for extension of credible interval due to sources of uncertainty not taken into account.

^d Calculations took into account post-accident studies and were based on LSS data.

455. In the UNSCEAR 2012 Report, annex B [U8], simulation calculations were performed for a scenario similar to the present one: exposure of Ukrainians at age 10 to a dose to the thyroid of 200 mGy and follow-up until age 18. Based on the BEIR VII model, the sex-averaged CER was estimated to be 7.2 cases per 10,000 persons after linear scaling to 500 mGy. For a slightly shorter follow-up, the credible interval is larger by a factor 1.3. In view of the independent approaches in the UNSCEAR 2012 Report and in the present report, this agreement of the central estimates and credible intervals is likely due to the relative short follow-up period. The ERR of the BEIR VII is constant with time since exposure and will produce steadily increasing age-integrated risk estimates driven by increasing baseline incidence rates. This behaviour is likely to generate higher CER estimates for long follow-up compared to the present approach.

456. The WHO 2013 report summarized expected health effects after the Fukushima accident. Closely related to the preferred scenario are the CER estimates of thyroid cancer for Japanese children exposed at age 10 for the first 15 years after exposure (termed Cumulative Attributable Risk AR15 in WHO 2013, annexes, table 44). Risk transfer was based on both EAR and ERR models for the LSS [P11] separately and in combination with equal weight. Confidence intervals were not reported. Dose estimates were given for different villages around the Fukushima power plant for the first year ([W9], table 6). If a linear dose response is assumed, the CER estimates can be scaled to a dose of 500 mGy. The model chosen by WHO yields a sex-averaged CER of 9.6 cases in 10,000 Japanese children exposed at age 10. Taking into account the shorter follow-up period, the WHO result is about a factor of two larger than the preferred estimate in the present preferred risk estimation. In view of the wide confidence interval, this is considered to be a good agreement.

457. A recent white paper to guide the Committee's future programme of work assessed in a simplified approach the fraction of the thyroid cancer incidence during the period 1991–2015 in areas affected by the Chernobyl accident that can be attributed to radiation [U9]. Based on an average dose to the thyroid of non-evacuated children and adolescents of 170 mGy, the attributable fraction was assessed to be 25%, with a credible interval of at least 7 to 50%. A comparison with the present calculation is based on the results in table 17 for the transfer of the ERR per unit dose in the UkrAm cohort to the scenario with age at exposure of 10 and a follow-up over 30 years (i.e. up to age 40). Multiplying the CFR by a scaling factor of 170/500, which accounts for different test doses in the present scenario and in the

white paper, gives an ERR estimate for a dose to the thyroid of 170 mGy. The result is expected to be slightly larger than the estimate in the white paper, because the follow-up starts two years earlier, a period in which the attributable fraction is particularly high. Indeed, the corresponding attributable fraction is then assessed to be 30%, with a credible interval of at least 14 to 48%, which confirms the simplified approach used in the white paper [U9].

G. Conclusions

458. Estimation of lifetime radiation risks based on an effect-per-unit-dose estimate in another population involves a number of steps and each step is likely to add to the overall uncertainty. In the present scenario addressing calculations for thyroid cancer, the contribution from each source of uncertainty has been discussed and the impact estimated.

459. For the “preferred” risk estimation, most sources of uncertainty not considered in the calculations for table 17 are assessed to be small or very small. However, there is potential overestimation of the risk in the Ukrainian population after the Chernobyl accident, because the anti-correlation of dose to the thyroid and iodine supply in the UkrAm cohort probably does not apply to the general Ukrainian population. As has already been noted above, cohort members from rural areas of iodine deficiency received higher thyroid doses and iodine prophylaxis was not an important covariable in the cohort. Further, the preferred risk inference is only valid, if (a) the baseline thyroid cancer incidence rate in the Ukrainian population under consideration is comparable with that in the period 2001 to 2007; and (b) the average iodine supply in the Ukrainian population is comparable with that in the UkrAm cohort. Also, there is some suspicion that nitrate contamination of drinking water might influence thyroid cancer risk. If this is true, then also the distribution of nitrate in drinking water has to be comparable. Further research is needed on such risk factors for thyroid cancer.

460. In summary, under the conditions listed above, the CER up to age 30 after exposure at age 10 with a dose to the thyroid of 0.5 Gy is estimated to about eight with a credible interval from about 2 to 20 chances among 10,000 persons. In the thyroid scenarios considered, cancer incidence is dominated by the radiation effect as the estimated values of CFR exceed one. The CFR of 2.4 in the “preferred” risk estimation corresponds to an attributable fraction of about 70%.

461. By choosing the “preferred” risk estimation as close as possible to the Ukrainian target population, important sources of uncertainty have been neutralized. These sources include dose rate effects, and extrapolation to small times since exposure and other ethnicity, which would have occurred if the risk models from the LSS had been used.

462. Model uncertainties could be avoided to a large extent, since the preferred scenario was based on central cohort strata with large numbers of cases. In this region of the data, any credible model judged by goodness-of-fit will yield a similar risk estimate.

463. The preferred model of WHO [W9] is the mean of the results based on transfers of ERR and EAR in the LSS, while the Committee did not choose a preferred model [U8]. Table 19 summarizes the calculation result of the Committee based on the BEIR VII model and calculations taking into account post-accident studies based on LSS data. For the conditions of the preferred scenario, the CER estimate given in the UNSCEAR 2012 Report [U8], is lower than that given in WHO [W9] by a factor of about 0.7. The present preferred risk inferences give an intermediate value of the CER with a credible interval embracing the preferred estimates of the two previous studies. Compared to the BEIR VII results [N9], the credible interval in the preferred risk inference is somewhat narrower, mainly because the

uncertainty associated with transfer from an acute to a low-dose-rate exposure situation could be avoided, i.e. no DDREF was applied in the present scenario (see section I.4).

464. To conclude, risk models for thyroid cancer from the LSS provide adequate central CER estimates in risk transfer calculations for the general Ukrainian population. For the preferred scenario, however, a narrower credible interval can be achieved by using effect estimates from the UkrAm cohort.

VI. RISK OF CIRCULATORY DISEASES AFTER RADIATION EXPOSURE

A. Motivation

465. Circulatory diseases are the leading cause of death in many countries. While exposure to ionizing radiation with doses greater than a few grays is known to damage circulatory systems and consequently increase the risk of circulatory diseases, effects are less clear at lower levels of exposure (<1 Gy) [D2, W14]. In the past decade, increasing evidence of an association of circulatory diseases with moderate radiation doses has been emerging in epidemiological studies of the atomic bombing survivors and other populations exposed occupationally, environmentally or medically [K23, L13, L16]. Reports of associations between circulatory diseases and radiation exposure are much fewer in number than those on cancer and radiation exposure, and those that have been published present rather inconsistent findings. While the limited statistical power, heterogeneity in the potential confounders and uncertainty in the dose assessment play similar roles to those in the assessment of cancer risk, the relatively large effects of risk factors other than radiation, and presumably substantial errors in the diagnoses and classifications of the diseases constitute additional challenges. Nevertheless, radiation effects on circulatory diseases could be of great public health concern because the underlying rates of these diseases are so high that even small increases in relative risks could lead to considerable absolute risks in the population, and these might be of a similar order of magnitude to those of radiation-associated cancers.

B. Recapitulation of previous UNSCEAR publications

466. The UNSCEAR 2006 Report, annex B [U3] reviewed the evidence accumulated from a range of studies and concluded that given the inconsistent epidemiological data and the lack of a biologically plausible mechanism, the present scientific data were not sufficient to establish a causal relationship between ionizing radiation and cardiovascular disease at doses of less than about 1 to 2 Gy.

467. The UNSCEAR 2010 Report, section III.C [U5] briefly summarized the current status of research and recognized the emerging evidence from recent epidemiological studies indicating elevated risks of non-cancer diseases at low to moderate doses and the difficulty of estimating effects at low doses and establishing plausible mechanisms.

C. Review of recent epidemiological literature

468. A number of epidemiological studies have been conducted in the past decade on radiation-associated circulatory diseases. In this review, a literature search was performed in PubMed using the keywords “((radiation[Title/Abstract])) AND risk AND (incidence OR mortality) AND (non-cancer[Title] OR circulatory[Title] OR heart[Title] OR cerebrovascular[Title] OR stroke[Title] OR cardiovascular[Title]) AND (cohort OR case-control) AND (“2006”[Date - Publication] : “3000”[Date - Publication]).” Of the 113 papers derived from the search, this review was limited to about 40 papers that presented original epidemiological results for populations in which persons had been exposed to moderate or low doses and from which quantitative dose–risk relationships for one or more of the circulatory diseases (heart diseases and cerebrovascular diseases) had been derived.

1. Life Span Studies of the Japanese atomic bombing survivors

469. The effects of radiation exposure on circulatory diseases have been evaluated among the LSS and AHS cohorts. Using information obtained from death certificates, Shimizu et al. [S7] analysed mortality data from cardiovascular diseases among 86,611 persons (mean dose of about 0.1 Gy) in the LSS cohort in the period 1950–2003. Significant dose-dependent increases were observed in an LNT model for mortality from all circulatory diseases with an ERR per unit dose of 0.11 (95% CI: 0.05, 1.7) Gy⁻¹, from cerebrovascular disease (stroke) of 0.09 (95% CI: 0.01, 0.17) Gy⁻¹ and from heart disease of 0.14 (95% CI: 0.06, 0.23) Gy⁻¹. There was no strong evidence for non-linearity in the dose–response curves in these analyses. However, a pure quadratic model for stroke, which suggests relatively little risk at lower doses, nominally provided a better fit than the linear model. The form of the dose–response relationship was uncertain at doses less than 0.5 Gy. In analyses of subtypes of heart disease in the LSS, the mortalities from hypertensive heart disease, rheumatic heart disease and heart failure showed significant associations with radiation dose with ERRs per unit dose of 0.37 (95% CI: 0.08, 0.72) Gy⁻¹, 0.86 (95% CI: 0.25, 1.72) Gy⁻¹ and 0.22 (95% CI: 0.07, 0.39) Gy⁻¹, respectively. However, for mortality from ischaemic heart disease, the association was small and not statistically significant (ERR per unit dose of 0.02 (95% CI: –0.10, 0.15) Gy⁻¹). There was no indication of confounding by smoking, alcohol consumption, education, occupation or obesity, nor indication of variation of excess risk by sex, time since exposure, or age at exposure, although there was a slight indication of decreasing trends of the ERR with attained age.

470. With an extended follow-up in the period 1950–2008, Takahashi et al. [T2] analysed the LSS mortality data for heart disease subtypes. Significant positive associations of radiation dose with mortality from valvular heart disease, hypertensive organ damage and heart failure were observed with ERRs per unit dose of 0.45 (95% CI: 0.13, 0.85) Gy⁻¹, 0.36 (95% CI: 0.10, 0.68) Gy⁻¹ and 0.21 (95% CI: 0.07, 0.37) Gy⁻¹, respectively. No significant association was observed for other subtypes including ischaemic heart disease with an ERR per unit dose of 0.03 (95% CI: –0.08, 0.15) Gy⁻¹. Misclassification,* background incidence of disease, and accuracy of diagnosis seem to have contributed to considerable variations of the subtype-specific risk estimates. The effect on rheumatic valvular heart disease was particularly high and significant in the earliest period of follow-up (1950–1968) in contrast to that on non-rheumatic valvular heart disease, which was high and significant in the later period, in which diagnosis was more reliable.

471. Based on information obtained through biennial clinical examinations for the members of the AHS cohort, Tatsukawa et al. [T4] reported an increased incidence of cerebrovascular disease or myocardial infarction for those exposed at childhood (age <10) with an ERR per unit dose of 0.72 (95% CI: 0.24, 1.40) Gy⁻¹, while no significant increase in these diseases was observed for those exposed in utero.

472. Due to the limited statistical power, it is generally difficult to detect a departure from linearity in the dose–response relationship for circulatory diseases. As an alternative to the standard approach based on a single preferred model, Schöllnberger et al. [S2] applied a multi-model inference approach to the dose–response analysis for mortality from cardiovascular disease in the LSS cohort. A combined set of plausible models fitted equally well. With this combined set of models, they found a dose response that was about one third weaker than that with the LNT model at doses below 0.6 Gy. The dose response at higher doses was stronger. More recently, the multi-model inference approach was applied to mortality in the LSS cohort from cerebrovascular and heart disease [S3]. For cerebrovascular disease, the dose–response curve estimated by multi-model inference was below the LNT model at low to medium doses (0–1.4 Gy) while at higher doses, a higher risk was estimated compared to the LNT fit. Similarly, a sublinear dose response was found for heart disease at doses of 0 to 3 Gy. The estimated confidence bounds indicated no conclusive answer for an increased risk below 0.75 Gy for cerebrovascular disease and 2.6 Gy for heart disease.

473. While the data from the Japanese atomic bombing survivors have been providing one of the most important sources of information to evaluate the late health effects of radiation exposure, care should be taken in interpreting the LSS results for circulatory diseases and applying them to other exposed populations. In general in Japan, hypertension is considered to be the major risk factor for circulatory diseases, and thus the risk of radiation-related circulatory disease may have increased largely owing to the increased risk of the radiation-related hypertension [O7, T1]. This may not be the case in Western populations, where hypercholesterolemia or atherosclerosis is a major risk factor for these diseases.

2. Other studies

474. A number of studies following up workers employed at the Mayak Production Association in the Russian Federation have provided relatively strong evidence for radiation effects on circulatory diseases [A6, A7, A8, A9, A10, A11, A12, A13, M10, S9, S10]. Azizova and colleagues have reported radiation-associated incidence and mortality from cerebrovascular disease [A10] and ischaemic heart disease [A12] in an extended cohort of workers first employed in the period 1948–1982 with follow-up to 2008. These cohort studies contained 22,377 workers who had received prolonged external exposure to low-LET radiation (mean cumulative dose 0.54 Gy) and internal exposure to high-LET radiation (mean total absorbed alpha-particle dose to the liver of 0.23 and 0.44 Gy for males and females, respectively). Generally, the estimated risks for incidence from these analyses of the Mayak cohort were much higher than those for mortality. These results might be partly due to the increased surveillance of workers exposed to higher doses and the relatively small numbers of mortality cases. It should be also noted that incidence data were confined to workers residing in Ozyorsk, which is the dormitory town of Mayak, whereas Mayak worker mortality studies considered all members of the whole cohort since until 2004 data on causes of death were available for all Mayak workers including those who had left Ozyorsk for another place of residence. However, these data became unavailable in recent years because of new regulations on personal data protection. The ERR per unit dose associated with external exposure was estimated as 0.10 (95% CI: 0.04, 0.17) Gy⁻¹ from the incidence of ischaemic heart disease, while that from the mortality data for ischaemic heart disease was 0.06 (95% CI: <0, 0.15) Gy⁻¹. Similarly, the ERR per unit dose for the incidence of cerebrovascular disease was 0.46 (95% CI: 0.37, 0.57) Gy⁻¹, while that for the mortality from cerebrovascular disease was small and insignificant with 0.05 (95% CI: -0.03, 0.16) Gy⁻¹. All of these analyses were adjusted for smoking, alcohol consumption and internal alpha-particle exposure, and showed no indication of non-linearity in the relationship. The ERRs associated with internal alpha-particle exposure were significant for mortalities for both ischaemic heart and cerebrovascular disease. However, these results need to be interpreted cautiously, due to the dose uncertainty, e.g. related to the considerable heterogeneity of

internal exposure from plutonium, and a revised dose-response analysis based on the recently updated dosimetry system [N3] is awaited. With a subcohort restricted to those with negligible internal exposure in the Mayak cohort, Simonetto et al. [S10] conducted a detailed analysis for cerebrovascular disease. Using multi-model inference, they showed that the dose response for the incidence of cerebrovascular disease appeared to be sublinear at low doses.

475. A study of the NRRW found suggestive evidence for an increased mortality from all circulatory diseases combined, with the ERR at 1 Sv of 0.25 (95% CI: -0.01, 0.54) [M12]. An earlier study of the cohort of BNFL workers, which included the large group of workers at the Sellafield nuclear complex, and was largely subsumed into the NRRW study, had found some evidence for an association between radiation dose and circulatory disease mortality, while significant heterogeneities observed in risk estimates by employment status were suggestive of influences other than radiation [M2]. Data on potential confounders were not available for these studies. Most recently, the association between mortality from heart disease and cumulative radiation dose from external sources was studied among 174,541 persons of the NRRW cohort (with a mean 10-year lagged lifetime external dose of 23.2 mSv) followed up until the end of 2011 [Z7]. Among the subtypes of heart disease, the increasing mortalities with cumulative dose were observed for ischaemic heart disease with an ERR per unit dose of 0.32 (95% CI: 0.04, 0.61) Sv^{-1} and other heart diseases with 1.08 (95% CI: 0.03, 2.45) Sv^{-1} . For ischaemic heart disease, the increased mortality appeared at least 20 years after the first exposure (with a peak between 30 and 40 years).

476. Azizova et al. [A14] jointly analysed the mortality from circulatory diseases in the Mayak Worker Cohort (MWC, $n=22,374$) and the UK Sellafield Worker Cohort (SWC, $n=23,443$). A common methodology was used to estimate exposure from external gamma radiation and internal alpha radiation to the liver; the mean cumulative external $H_p(10)$ dose was 0.52 and 0.07 Sv for the MWC and SWC, respectively, while the mean cumulative internal dose was 0.19 and 0.01 Gy for the MWC and SWC, respectively. The dose responses for circulatory disease, ischaemic heart disease and cerebrovascular disease in relationship to internal exposure to alpha radiation did not differ significantly from zero for either the MWC, the SWC or the pooled plutonium worker cohort. The ERR per unit dose (Sv) for external exposure was significantly increased for both cohorts for circulatory disease and ischaemic heart disease (but not for cerebrovascular disease), but differed significantly between the two cohorts, the estimate for the SWC being about ten times greater than that for the MWC. In a pooled analysis of the two cohorts (for the later first-employment periods), the estimated ERRs per unit dose were 0.22 (95% CI: -0.01, 0.49) Sv^{-1} for circulatory disease, 0.22 (95% CI: -0.06, 0.57) Sv^{-1} for ischaemic heart disease and 0.24 (95% CI: -0.17, 0.80) Sv^{-1} for cerebrovascular disease. It should be noted that the significant heterogeneities mentioned in the previous paragraph would be present in the Sellafield data.

477. Studies of the emergency and recovery operation workers of the Chernobyl accident have reported significant evidence for radiation-associated circulatory diseases [I5, K6, K7]. Most recently, Kashcheev et al. [K6, K7] studied a cohort of 53,772 recovery operation workers who arrived in the zone of the Chernobyl accident within the first year after the accident (with the mean and maximum doses from external exposure of 0.161 and 1.42 Gy, respectively). During the follow-up period 1986–2012, a significant dose-response relationship was observed for the incidence of cerebrovascular disease (23,264 cases) with the ERR per unit dose of 0.45 (95% CI: 0.28, 0.62) Gy^{-1} [K6] and for the incidence of cardiovascular disease other than cerebrovascular disease (27,456 cases) with the ERR per unit dose of 0.47 (95% CI: 0.31, 0.63) Gy^{-1} [K7]. These estimates tended to vary by the duration of the workers' stay in the zone, with the highest risk observed for liquidators in the first year after arrival in the Chernobyl zone, with accumulated doses above 0.15 Gy and duration of work less than six weeks. In this study, information on factors that might cause circulatory diseases was limited other than radiation and some concomitant disease. Also, a large concern remains on the dose uncertainty and its impact on the risk estimation.

478. A cohort study of occupationally-exposed workers in 15 countries was conducted to determine whether mortality from non-cancer diseases is related to external exposure to low doses of ionizing radiation [V6]. The analyses included 275,312 workers with adequate information on socio-economic status, with an average cumulative radiation dose of 20.7 mSv. With 11,255 deaths from non-cancer diseases, the ERR per unit dose was 0.24 (95% CI: -0.23, 0.78) Sv^{-1} for mortality from all non-cancer diseases and 0.09 (95% CI: -0.43, 0.70) Sv^{-1} for circulatory diseases. Increased risks were observed among the younger workers (attained age <50) for all groupings of non-cancer causes of death. However, there are problems with the Canadian worker data used in this study due to inconsistencies in dose information in early periods, which suggests that little reliance can be placed on results including these data [A5, Z5].

479. The INWORKS followed up a part of the 15-country occupationally-exposed worker study [V6] with about 310,000 workers from France, the United Kingdom and the United States who were exposed to low-dose radiation accumulated at low dose rates (average cumulative external photon dose of 25.2 mSv). Gillies et al. [G7] reported statistically significant associations between radiation dose and mortalities from circulatory disease (ERR per unit dose=0.22 (90% CI: 0.08, 0.37) Gy^{-1}), cerebrovascular disease (ERR per unit dose=0.50 (90% CI: 0.12, 0.94) Gy^{-1}), and ischaemic heart disease (ERR per unit dose=0.18 (90% CI: 0.004, 0.36) Gy^{-1}). No significant departure from linearity in the dose response was observed for mortalities from circulatory diseases and ischaemic heart disease. However, the dose response for cerebrovascular disease mortality was better described by a linear-exponential model ($p=0.02$), with increased risks at lower doses and a flattening of risk at doses above 200 mSv. The authors also noted heterogeneities in the risk estimates that precluded firm conclusions to be drawn.

480. The association between prolonged external exposure to low doses of ionizing radiation and mortality was studied in a cohort of workers (22,393 persons with a median age of 48 at the end of follow-up) at EDF and followed up to 2003 [L4]. Based on a total of 874 deaths, no significant association between cause of death and dose was found, except for cerebrovascular diseases ($p=0.01$). However, this study was based on only 22 cases. The cohort is still relatively young and further follow-up would be necessary to confirm the findings. The EDF cohort is a part of the INWORKS [G7] and the 15-country study [V6].

481. The Wismut cohort of 58,982 uranium miners has been periodically studied for evidence of an association between exposure to external gamma radiation (mean cumulative dose of 47 mSv with a maximum of 909 mSv) and death from cardiovascular diseases [K20, K21, K22], but no statistically significant results have been found. Most recently, during the follow-up period 1946–2008, the ERR per unit dose was estimated to be -0.13 (95% CI: -0.38, 0.12) Gy^{-1} for all cardiovascular diseases (9,039 deaths), -0.03 (95% CI: -0.38, 0.32) Gy^{-1} for ischaemic heart disease (4,613 deaths) and 0.44 (95% CI: -0.16, 1.04) Gy^{-1} for cerebrovascular disease (2,073 deaths) [K22].

482. A Canadian cohort of 337,397 persons occupationally exposed to ionizing radiation and included in the National Dose Registry has been studied to assess the risk of cardiovascular disease mortality [Z8]. The cohort consisted of nuclear workers as well as medical, dental and industrial workers (mean whole-body doses of 8.6 and 1.2 mSv for males and females, respectively). During the study period 1951–1995, a significant and strong dose response was observed based on 3,533 deaths from cardiovascular disease, with the ERR per unit dose of 1.22 (95% CI: 0.47, 2.10) Gy^{-1} for males and 7.37 (95% CI: 0.95, 18.1) Gy^{-1} for females. However, the potential bias introduced by dosimetric uncertainties, possible record linkage errors and lack of adjustment for non-radiation risk factors are of concern, so that the results cannot be considered reliable.

483. A cohort of 17,660 Eldorado uranium workers was studied to assess the dose response of exposure to radon decay products and gamma-ray doses and mortality from circulatory diseases [L3].

The cohort consisted of workers first employed during the period 1932–1980 and followed up to 1999. No association was observed between exposures to radon decay products and gamma-ray doses and ischaemic heart disease, stroke or other cardiovascular diseases.

484. The cohort of French uranium miners (5,086 persons) was studied to determine whether any association existed between exposure to high-LET radiation due to radon decay products and mortality from various cancers and non-cancer diseases during a follow-up from 1946 to 2007 [R1]. An association between cumulative exposure to radon decay products and cerebrovascular risk with an ERR at 100 WLM of 0.41 (95% CI: 0.04, 1.03) was one of a number of significant associations found.

485. The Newfoundland fluorspar miners cohort ($n=2,070$) in Canada was studied for the relationship between cumulative exposure to radon decay products and circulatory disease mortality [V3]. While the radon daughter exposure levels in this cohort were relatively high (the mean cumulative exposure of 348 WLM, and about one quarter of the miners had average annual exposures that exceeded 60 WLM in a year), no significant association was observed between exposure to radon decay products and the risk of death from coronary heart disease. This finding did not change after adjusting for the lifetime smoking status (available for about half of the cohort). Similarly, the cumulative radon daughter exposure was found to be unrelated to deaths of the circulatory system, acute myocardial infarction and cerebrovascular disease.

486. Another Canadian cohort of Ontario uranium miners ($n=28,546$ male miners with a mean cumulative radon daughter exposure of 21.0 WLM) was studied for non-cancer mortality including ischaemic heart disease and cerebrovascular disease [N4]. No increased risk from cumulative exposure to radon decay products was suggested for any of non-cancer diseases in the follow-up period 1954–2007.

487. A follow-up study over the period 1950–2003 of the Techa River cohort included about 30,000 persons who had been subjected to prolonged exposure due to radioactive discharges into the Techa River from Mayak Production Association. This study has provided some evidence for radiation-associated increases of mortality from all circulatory disease (ERR per unit dose of 0.36 (95% CI: 0.02, 0.75) Gy^{-1}) and ischaemic heart disease (ERR per unit dose of 0.56 (95% CI: 0.01, 1.19) Gy^{-1}) with a 15-year lag [K19]. The total cohort-average absorbed dose to muscle due to external and internal exposure was 35 mGy, with the maximum dose of 510 mGy.

488. A study of the cohort of Kazakhstan residents exposed to fallout from the nuclear weapons tests at the Semipalatinsk nuclear test site (with a follow-up for the period 1960–1999) reported highly significant dose-related increases in the incidence of cardiovascular disease (ERR per unit dose of 3.15 (95% CI: 2.48, 3.81) Gy^{-1}), heart disease (ERR per unit dose of 3.22 (95% CI: 2.33, 4.10) Gy^{-1}) and cerebrovascular disease (ERR per unit dose of 2.96 (95% CI: 1.77, 4.14) Gy^{-1}) with the cohort including unexposed residents [G9]. However, when account was taken of the difference in baseline rates between the exposed and unexposed groups, no statistically significant dose–response relationship was observed for any of the end points.

489. The effects of high natural background radiation on mortality were evaluated with a cohort of 31,604 males and females aged 30–74 years living in Guangdong Province, China, with a follow-up for the period 1979–1998 [T3]. The cumulative external radiation dose was estimated for each person based on hamlet-specific indoor and outdoor doses, and sex- and age-specific house occupancy factors. Mean cumulative radiation doses from radiation in the high natural background and control areas were 84.8 and 21.6 mGy, respectively. The mortality due to any non-cancer diseases was not significantly related to exposure in the high background area, with the ERR per unit dose of 0.54 (95% CI: –2.65, 6.13) Gy^{-1} for ischaemic heart disease (221 deaths) and 0.44 (95% CI: –0.88, 2.08) Gy^{-1} for cerebrovascular disease (1,302 deaths).

490. The possible association of mortality from circulatory disease with medical diagnostic exposure has been studied in cohort studies of tuberculosis patients who had received fluoroscopic procedures in Canada [Z6] and in Massachusetts [L16]. In the Canadian study (63,707 persons), with absorbed doses to the lung from fluoroscopy that were individually determined (mean cumulative person-year weighted lung dose of 0.79 Gy, maximum dose of 11.6 Gy, and median dose fractionation of 0.36 Gy per year), the ERR per unit dose was estimated to be 0.176 (95% CI: 0.011, 0.393) Gy^{-1} for ischaemic heart disease mortality with a significant dose-rate effect (a higher ERR per unit dose was found for those with the fewer fluoroscopic procedures in a year, $p=0.02$) [Z6]. In the Massachusetts study (13,568 persons), there was no evidence for such an inverse dose-fractionation pattern or significant excess risk, but there were some indications of excess deaths from circulatory disease at doses below 0.5 Gy [L16]. By pooling these two cohorts, Tran et al. [T8] observed radiation-associated increases in the risk under 0.5 Gy for all circulatory diseases ($n=10,209$; ERR per unit dose of 0.246 (95% CI: 0.036, 0.469) Gy^{-1}) and for ischaemic heart disease ($n=6,410$; ERR per unit dose of 0.267 (95% CI: 0.003, 0.552) Gy^{-1}). These risks tended to reduce with increasing time since exposure ($p<0.005$). Over the entire dose range, however, negative trends between dose and mortality from all circulatory disease ($p=0.014$) and from ischaemic heart disease ($p=0.003$) were found, possibly due to competing causes of death. Because the data on the well-known lifestyle and medical risk factors for circulatory disease were limited, potential confounding of the dose trend could not be excluded.

3. Synthesis of studies

491. A meta-analysis of 11 epidemiological studies (including those of the LSS and cohorts of occupationally and environmentally exposed populations) with moderate to low doses (whole-body doses less than 0.5 Sv) gave estimated ERRs per unit dose of 0.10 (95% CI: 0.05, 0.15) Sv^{-1} for ischaemic heart disease, 0.12 (95% CI: -0.01, 0.15) Sv^{-1} for heart disease apart from ischaemic heart disease and 0.20 (95% CI: 0.14, 0.25) Sv^{-1} for cerebrovascular disease [L12]. The results also suggested that the ERRs per unit dose do not exhibit a heterogeneity among the studies for various types of circulatory disease. For ischaemic heart disease and non-ischaemic heart disease, there was no significant heterogeneity in risks between the various studies; however, this was not the case for cerebrovascular disease and other circulatory diseases. These combined risk estimates were largely influenced by a few studies of large, significant effects. In particular, exclusion of Mayak data decreased the ERR estimates by 30% for ischaemic heart disease and by 40% for cerebrovascular disease.

492. While an increasing number of reports have been recently published on the radiation-associated circulatory diseases, there is a considerable inconsistency in the estimated associations. Aside from the common issues such as the limited statistical power, potential confounders and dose uncertainty, relatively large effects of risk factors other than radiation, and presumably substantial errors in the diagnoses and classifications of the diseases would constitute additional challenges in the circulatory disease risk assessment.

D. Definition of scenario

1. Exposure scenario

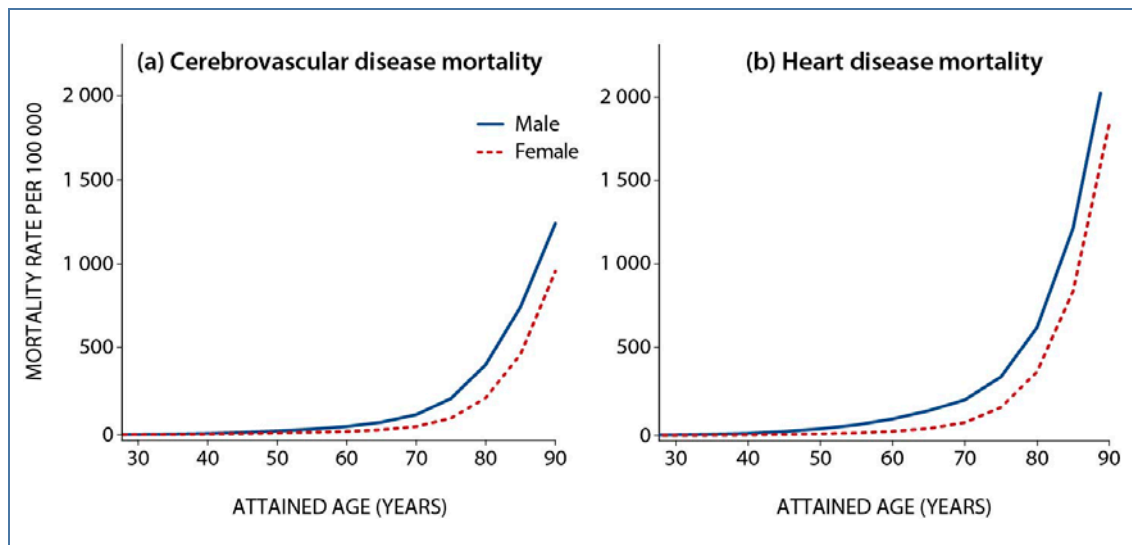
493. Circulatory diseases are multifactorial with the underlying rates varying considerably with lifestyles, socio-economic status and other personal factors, while their associations with radiation exposure are expected to be smaller than those for cancers. Consequently, assessment of the circulatory disease risk and determination of the dose–response relationship would be more challenging than that of the radiation-associated cancers. Additional concerns that are more relevant to non-cancer diseases than to cancers include potential sources of bias related to diagnostic misclassifications, with the degree of accuracy varying over the period, and the selection of the exposed populations (the impact of the healthy worker or healthy survivor effect is difficult to avoid in the selection) [P10, U3]. These issues are likely to contribute to the inconsistency in the assessed risks, and complicate comparison and transfer of the risks between populations of fairly different characteristics that might be associated with different exposure–disease mechanisms.

494. To provide a basis for the assessment of the risk of circulatory disease from radiation exposure, the risk estimated from the LSS was considered for application to the calculation of the lifetime risk for a general population in Japan, rather than transferring it to another population with different characteristics. The exposure scenario was for a population of equal numbers of males and females who received an acute exposure to a dose of 1.5 Gy at age 30 (which is roughly the mean age at exposure in the LSS cohort) to be followed up to age 60 or 90. Because the existence of effects at low doses is less clear for circulatory diseases than for solid cancers, the effect of an exposure to a relatively high dose was evaluated. In view of the fact that uncertainty about the shape of the dose response has less impact on the risk estimates for doses ranging from 1 to 2 Gy, compared to those for low to moderate doses, the effect of exposure at a dose of 1.5 Gy was evaluated.

2. Reference data

495. For the use of the life-table method, the cause-specific mortality rates in 2014, which were available from the Statistics and Information Department of the Japanese Ministry of Health, Labour and Welfare [M8], were used to calculate the baseline risks of circulatory diseases and the survival function, which were age and sex specific. Figure XI presents these sex-specific baseline mortality rates of (a) cerebrovascular disease and (b) heart disease for age 30–90.

Figure XI. Baseline mortality rate of (a) cerebrovascular disease and (b) heart disease in Japan in 2014 [M8]



3. Risk models

496. The models for the current risk evaluation were derived from the LSS follow-ups for stroke mortality (ICD-9 codes 430–438) during the period 1950–2003 [S7] and for heart disease mortality (ICD-9 codes 393–429) during the period 1950–2008 [T2]. Because of concern about diagnostic accuracy [O7, T2], rheumatic valvular heart disease (242 cases) was excluded from the heart disease.

497. The data set consisted of numbers of cases and person–years cross-classified by city, sex, radiation dose, follow-up period, attained age and age at exposure. The dose categories were defined in terms of the estimated weighted absorbed dose to the colon based on DS02 dosimetry with 22 cut points at 0, 0.005, 0.02, 0.04, 0.06, 0.08, 0.1, 0.125, 0.15, 0.175, 0.2, 0.25, 0.3, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.5 and 3 Gy. As for many other analyses of the LSS, the data were analysed using Poisson rate regression with the mortality rate of each end point modelled as $\lambda_0(s,a,c,b)\{1+\text{ERR}(d)\}$, where λ_0 describes the baseline mortality rate as a function of sex (s), city (c), attained age (a) and birth-year (b), and the ERR describes the radiation-associated excess relative risk. Conventionally, the ERR is modelled by a simple parametric form, such as the linear, linear–quadratic or pure quadratic function of dose (d), which may be multiplied by a function to allow for the variation of the dose effects by effect modifiers such as sex, attained age and/or age at exposure.

498. When the risk is associated with substantial uncertainty, as is usually the case for circulatory diseases, greater emphasis needs to be given to the determination of the uncertainty. While most of the actual, unknown dose–response relationships are expected to be simple in nature, parametric estimators generally produce much tighter confidence bands owing to the additional structure imposed by the parametric model, but if the assumptions behind the parametric structure are incorrect, the results—including their precision—are likely to be misleading [F7]. As an alternative to the standard parametric approach, a Bayesian semiparametric model has been applied to determining the dose response. With no particular assumption about the dose–response shape, this model can produce smooth and flexible dose–response curves while reasonably handling the uncertainty in the risk at low doses and elsewhere [F7]. Here, this model was applied to the dose–response estimation for circulatory diseases from the observations of the LSS.

499. The Bayesian semiparametric dose–response model consists of a connected piecewise linear function defined over a set of $C+1$ dose cut points $\{\delta_0=0, \delta_1, \dots, \delta_C\}$,

$$\rho(d) = \sum_{k=1}^C \beta_k h_k(d), \quad h_k(d) = \{\min(d, \delta_k) - \delta_{k-1}\} I(d > \delta_{k-1}), \quad k = 1, \dots, C$$

where $I(\cdot)$ is the indicator function such that $I(A)=1$ if A is true and 0 otherwise. For the LSS data, the cut points may be those used for the person–year table categorization. The slope of each dose category $\{\beta_k, k=1, \dots, C\}$ is assumed to be random* and conditionally specified by

$$[\beta_j | \beta_{j-1}] \sim N(\beta_{j-1}, \sigma^2), \quad j = 2, \dots, C$$

which can be regarded as prior distributions under the Bayesian framework (with a non-informative prior on β_1). The parameter, σ , controls the degree of smoothness of the dose–response curve and may be estimated from the data (the fitted curve converges to a straight line as $\sigma \rightarrow 0$, while a more complicated shape can be described with a sufficiently large σ). With non-informative priors on the other unknown parameters, inference for the dose–response curve (and other parameters) can be derived from the posterior distribution, which can be obtained iteratively through the Markov Chain Monte Carlo algorithm.

500. There is great uncertainty about how the radiation effect on circulatory diseases can vary with other factors. While none of the current analyses observed any statistically significant effect modification, the inclusion of effect modifiers was considered to determine how they might affect the risk evaluations. Three models for effect modification were considered: (a) constant (no effect modification); (b) sex; and (c) sex and attained age, for the ERR with a linear dose–response function.

4. Risk-transfer methods

501. The life-table method was used to estimate the radiation-associated CER (i.e. the REID) of mortality from each of the outcomes of interest (cerebrovascular and heart disease) under the defined scenario. A multiplicative risk transfer of the ERR estimated from the observations of the LSS was applied to the baseline mortality of the general Japanese population for the periods since exposure at age 30 up to the 60th and 90th birthdays under an additional assumption of a five-year latency period. The five-year latency was used because the LSS risks were estimated based on the data followed up for five years after the exposure. Alternatively, a longer latency of 10 years was considered to check the impact of this assumption.

502. While the radiation-associated circulatory disease risks may be estimated in terms of the EAR, additive risk transfer with an EAR model was not considered for the current evaluation. The EAR model fits were consistently worse than the ERR counterparts, and larger uncertainties were associated with the parameter estimates, in particular, of effect modifiers, which could lead to fairly extreme and unreasonable estimates of the lifetime risk.

E. Results

503. The fitted ERR dose–response curves of selected models are presented in figure XII for (a) cerebrovascular disease and (b) heart disease (excluding rheumatic valvular heart diseases). The solid curves represent the central estimates and the dashed curves their associated 95% confidence or

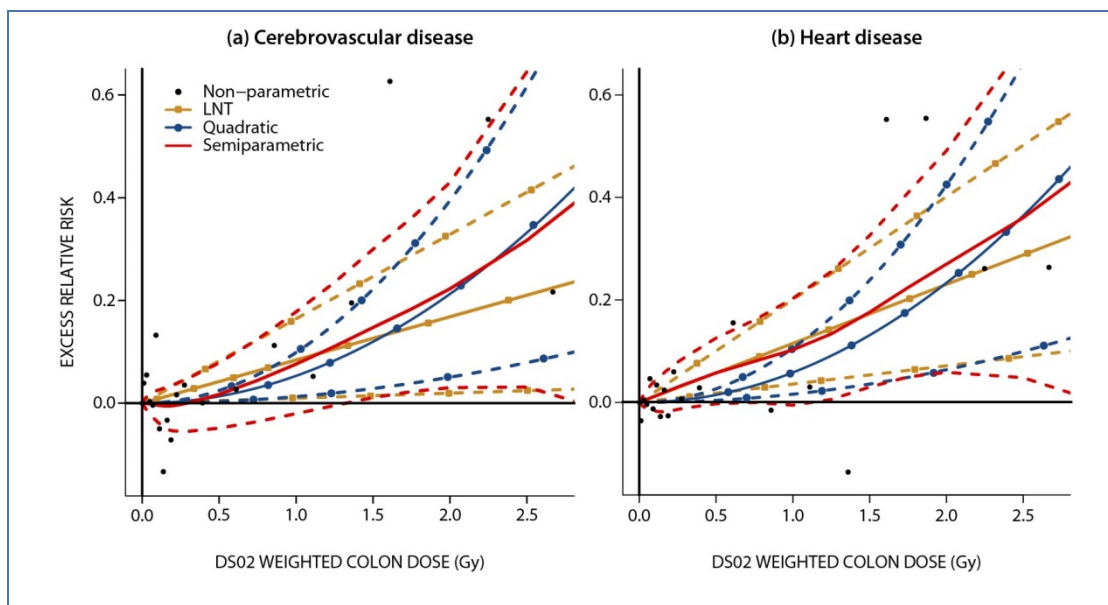
credible interval for the linear model (yellow), the quadratic model (blue) and the semiparametric model (red). All of these curves were based on the fitted models with no effect modification:

(a) For cerebrovascular disease, the quadratic ERR model was the best in AIC (−2 compared with the linear ERR model) among the considered parametric models with an ERR at 1.5 Gy of 0.12 (95% CI: 0.04, 0.24). A slight indication of decreasing trends of the ERR with attained age was found ($p=0.08$), but the ERR did not differ by sex ($p>0.5$). The estimated linear model fit was similar to the quadratic fit at 1.5 Gy with ERR=0.13 (95% CI: 0.01, 0.25) but consistently higher than the other model fits at doses lower than 1 Gy. Overall, the curve fitted by the semiparametric model was comparable to the quadratic fit with ERR at 1.5 Gy of 0.15, but with a wider uncertainty interval (95% CI: 0.01, 0.30) such that the risk was not significant in the dose range up to about 1.3 Gy;

(b) For heart disease, the AIC values of the linear and quadratic ERR models were fairly similar within a difference of one. Under the linear model, the ERR at 1.5 Gy was estimated to be 0.17 (95% CI: 0.05, 0.30) with no significant indication of departure from linearity ($p=0.20$ in the likelihood ratio test versus the linear–quadratic model). Neither of the effect modifications (by sex or by sex and age) was statistically significant ($p>0.1$). Under the semiparametric model, the ERR at 1.5 Gy was estimated to be 0.18 (95% CI: 0.03, 0.33), with the minimum dose for which the risk was significant being about 1.2 Gy. At doses below 1 Gy, the semiparametric and linear models were fairly comparable at the central estimates, but the linear model fit had a narrower confidence interval indicating a significant risk even at the lowest doses which may be misleading.

Figure XII. Excess relative risk for (a) cerebrovascular disease mortality and (b) heart disease (excluding rheumatic valvular heart disease) mortality from the LSS, in relation to radiation exposure estimated according to several models (legend) at doses of 0–2.5 Gy

Dashed curves represent the estimated 95% confidence or credible intervals. The closed circles represent the estimated ERR for each of the individual dose categories



504. The cumulative baseline mortalities calculated from the reference data for the Japanese population are presented for cerebrovascular disease mortality in table 20 and for heart disease mortality in table 21. The cumulative all-cause mortality for those who were alive at age 30 and followed up to age 60 was 569 per 10,000 persons, and that for those who were followed up to age 90 was 6,691 per 10,000 persons. The

cumulative baseline risks of death from cerebrovascular disease were 40 per 10,000 persons at age 60, and 557 per 10,000 persons at age 90. Those of heart disease death were 64 per 10,000 persons at age 60, and 934 per 10,000 persons at age 90.

505. Table 20 presents the CERs associated with the exposure scenario for cerebrovascular disease. The estimated risks were relatively consistent with the time-constant ERR models with no effect modification by age. Among them, the semiparametric model gave an estimated CER of 5.8 (95% CI: 0.4, 12) per 10,000 persons to age 60 and 80 (95% CI: 5.9, 162) per 10,000 persons to age 90. These interval estimates were slightly wider than those of the other parametric models. The cumulative fractional ratios were estimated to be 12–15% with the time-constant ERR models. The ERR model with effect modification by age yielded larger CERs at age 60 and smaller CERs at age 90 compared to those estimated with the time-constant ERR models. This difference is due to a decreasing trend in the relative risk estimate with attained age, which tended to increase the risk at earlier ages and decrease at older ages. Also, the difference between the baseline in the LSS in the last century and the baseline nowadays in Japan may have partly contributed to the variation.

506. Table 21 presents the CERs associated with the exposure scenario for heart disease. The estimated CERs were comparable among the considered ERR models. The semiparametric model gave an estimated CER of 11 (95% CI: 1.9, 21) per 10,000 persons to age 60 and 160 (95% CI: 28, 294) per 10,000 persons to age 90. Inclusion of effect modification by age and/or sex did not have much impact on the CER. Overall, the CERs of heart disease deaths at age 90 varied from 13 to 17% of the baseline cumulative risk among the considered models. The issue regarding the difference in the baseline risk in the current Japanese population and that in the LSS would also apply to the heart disease risk, but the impact was not as much as for the cerebrovascular disease.

Table 20. Cumulative risk of cerebrovascular disease mortality for a scenario of a person in a general Japanese population exposed to 1.5 Gy at age 30

CBR: Cumulative baseline risk; CER: Cumulative excess risk, estimated using the REID methodology;

CFR: Cumulative fractional ratio; CI: Confidence interval; LSS: Life Span Study

Model (effect modification) estimated with the LSS data [57]		CBR		Cumulative risk associated with the exposure scenario		
		All-cause mortality per 10 000 persons	Cerebrovascular disease mortality per 10 000 persons	CER per 10 000 persons (95% CI)	CFR (%)	
CUMULATIVE RISK UP TO AGE 60						
Semiparametric	(none)	569	40	5.8	(0.4, 12)	0.147
Quadratic	(none)			4.6	(1.8, 7.5)	0.116
Linear	(none)			4.9	(1.5, 8.4)	0.124
	(sex)			5.3	(0.3, 10)	0.134
	(sex, age)			11	(−4.5, 23)	0.273
CUMULATIVE RISK UP TO AGE 90						
Semiparametric	(none)	6 691	557	80	(5.9, 162)	0.143
Quadratic	(none)			65	(28.4, 102)	0.117
Linear	(none)			68	(22.7, 114)	0.122
	(sex)			70	(5.4, 135)	0.126
	(sex, age)			43	(−5.3, 90)	0.076

Table 21. Cumulative risk of mortality of heart disease (excluding rheumatic valvular heart disease) for a person in a general Japanese population exposed to 1.5 Gy at age 30

CBR: Cumulative baseline risk; CER: Cumulative excess risk, estimated using the REID methodology; CFR: Cumulative fractional ratio; CI: Confidence interval; LSS: Life Span Study

Model (effect modification) estimated with the LSS data [T2]		CBR		Cumulative risk associated with the exposure scenario		
		All-cause mortality per 10 000 persons	Heart disease mortality per 10 000 persons	CER per 10 000 persons (95% CI)	CFR (%)	
CUMULATIVE RISK UP TO AGE 60						
Semiparametric	(none)	569	64	11	(1.9, 21)	0.175
Quadratic	(none)			8.1	(3.0, 13)	0.127
Linear	(none)			11	(4.3, 17)	0.167
	(sex)			7.0	(−1.6, 16)	0.110
	(sex, age)	8.7	(−2.1, 28)	0.137		
CUMULATIVE RISK UP TO AGE 90						
Semiparametric	(none)	6 691	934	160	(28, 294)	0.171
Quadratic	(none)			120	(54, 183)	0.128
Linear	(none)			157	(78, 234)	0.168
	(sex)			145	(31, 256)	0.155
	(sex, age)	150	(28, 280)	0.160		

F. Discussion of scenario calculations

1. Sources of uncertainties

(a) Selected populations

507. In the current risk evaluation, the estimated risks of radiation-associated circulatory disease in the Japanese atomic bombing survivors were transferred to a population with the baseline cause-specific mortality rate given in the latest statistics for Japan. While this is expected to be less problematic than transfer to another population of fairly different characteristics regarding circulatory disease pathogenesis, there is also likely to be an intrinsic difference in the lifestyle and other characteristics that could affect the baseline circulatory disease rate between the LSS cohort and the target population. In particular, due to the extended lifespan of the Japanese population in recent decades, the baseline mortality rates now are lower than they were in the LSS cohort at relatively younger ages (<75) and then much higher at older ages after age 75.

508. In addition to radiation, some aspects of the atomic bombing survivors, such as having suffered from bomb-related injuries and malnutrition during and right after the war, might have affected their circulatory disease development in later life. Also, the construction of the LSS cohort five years after the bombings may have led to an inherent bias in the composition of the cohort members (the healthy survivor effect). This effect appeared to have a larger impact on the risk assessment of non-cancer diseases than on that of cancers, especially in the earlier years of the follow-up [P10]. This would introduce additional uncertainty even in the application of the risk obtained from the LSS data to a population of similar characteristics.

(b) Exposure assessment

509. As in the other evaluations in this chapter, the risk estimates were derived from the data from the LSS with the estimated individual doses being those using the DS02 dosimetry system. The issues regarding the uncertainty in the DS02 doses are described elsewhere (see section II.F.1.(b)). It is unlikely that the recent revision of the individual doses for the LSS (DS02R1) [C10] would have a remarkable impact on the current risk evaluation.

510. While the risks of circulatory diseases were conventionally estimated using the dose to the colon as a surrogate for the dose to the whole body, it is a matter of debate as to whether this organ is most appropriate for the assessment of the risk of radiation-associated circulatory diseases. Clarification of the underlying disease mechanism and the target tissue for radiation-associated circulatory disease would be required in order to make an appropriate choice of organ. Other possible organs include the lung, stomach and heart, although it is unlikely that replacing the colon with any of these would have a major impact on the current risk evaluation.

(c) Health outcome assessment

511. The lack of precision in the information on non-cancer diseases compared to that on cancer has frequently been noted. While misclassification of causes of death could increase the bias in the risk evaluation, it is usually not formally incorporated into the analysis. In the LSS mortality follow-up for circulatory diseases, there were major changes in disease coding in Japan owing to the introduction of ICD-10 in the mid-1990s, after which, heart failure was much less frequently diagnosed while diagnoses of ischaemic heart disease and cerebral infarction increased [O7, O8].

512. In the current risk evaluation of heart disease, rheumatic valvular heart disease was excluded due to concerns over the diagnostic accuracy and an unusually high radiation-associated risk estimate despite the small number of cases [T2]. It should also be noted that rheumatic heart disease is related to infection in childhood. This exclusion resulted in a slight decrease in the ERR estimates but little change in the cumulative risk estimates.

513. Heart failure is included in the current evaluation. The number of heart failure cases is about a third of the overall number of heart disease cases (9,303), and exclusion of heart failure would have had a non-negligible impact on the risk projection; if heart failure had been excluded, the risk estimate would have been much smaller (the ERR per unit dose = 0.07 Gy^{-1} without heart failure, compared to 0.12 Gy^{-1} with heart failure).

(d) *Study design*

514. The LSS is a cohort study with a reasonably complete follow-up of about 86,000 persons exposed at the time of the bombings. Because the proximal survivors (typically defined to be those exposed within 3 km of the hypocentre) and distal survivors differ considerably with respect to socio-economic status, lifestyle and other risk factors related to circulatory diseases, especially in the earlier periods of the follow-up, selection of the control group in the risk evaluation is known to affect the shape of the dose response for non-cancer diseases which may vary with the period, tending to negligible as the follow-up proceeded [P10].

(e) *Confounding factors*

515. In the LSS, the effects of some non-radiation factors that are closely related to the distance from the hypocentre, such as the severity of bomb-related injuries, lifestyle and socio-economic status, are often considered to be potential confounders in the determination of radiation-associated health effects. This fact, along with the healthy survivor effect, could complicate the risk evaluation. Caution is therefore required in the use of the mortality data over the period of observation in estimating the change in risk with dose.

516. The current risk evaluation did not account for lifestyle factors that are often considered to affect the risk of circulatory disease, although there has been a substantial change in the Japanese lifestyle over recent decades. In the evaluations of the risk of circulatory disease from the data obtained in the LSS, there has been no clear evidence of statistically significant confounding by smoking, alcohol consumption, education, occupation or obesity [S7, T2].

(f) *Statistical methods and model uncertainties*

517. In addition to statistical uncertainty in the estimates of the risk parameters, uncertainty in the model selection was accounted for by using a semiparametric model that assumed no specific form of the dose–response function as an alternative to the conventional parametric models. The central ERR estimates at 1.5 Gy were comparable between the semiparametric model and the linear model and the resulting cumulative risks of the two approaches agreed well. However, the semiparametric method did not support a significant effect on cerebrovascular disease at 1 Gy, and gave a borderline significant effect for heart diseases, indicating that the uncertainty intervals derived with the help of specific models, like the linear or the quadratic model, might be over-optimistic (figure XII). These results are supported by multi-model inference [S3]. Thus, the LSS data only give limited evidence for circulatory diseases being caused by a radiation dose of 1 Gy.

518. Models of different effect modifiers were considered in order to determine the impact of the uncertainty surrounding the risk modification on the lifetime risk evaluation. Neither of the effect modifying factors was statistically significant and the impact of inclusion of a modifying factor did not have a large impact among the considered models under the multiplicative transfer.

519. Aside from the model uncertainty, the current risk evaluation was likely to be associated with other sources of uncertainty from unverifiable assumptions on the risk transfer. While some assumptions, such as the latency period, may not have a large impact, others, such as the choice of transfer method (additive or multiplicative transfer along with effect modifiers), might considerably affect longer-term risk evaluations. Mainly due to the statistical power issue, which did not allow for estimation with sufficient precision of effect modifiers in the EAR models, a rigorous investigation of

the potential impact due to uncertainty involved in the risk transfer approach was not possible in the current evaluation.

(g) Other sources of uncertainty

520. The age- and sex-specific baseline mortality rates of the target population were fixed with no assumed uncertainty in the current risk evaluation, which is likely to have a marginal impact on the estimated risks.

521. While combined groups of disease were desirable for risk evaluations in order to improve the statistical power, radiation-associated circulatory diseases in the LSS appeared to vary among the different subtypes. This suggests heterogeneity in radiation-induced pathogenesis. Thus, the risk estimates for broader categories of diseases (such as overall heart disease) need to be interpreted with caution.

2. Preferred risk inference

(a) Selection of the preferred risk inference

522. For both cerebrovascular disease and heart disease (excluding rheumatic valvular heart disease), the risk at a dose of 1–1.5 Gy is more evident than that at lower doses for circulatory diseases, but uncertainty in the dose–response shape might not be adequately accounted for by the linear dose–response model fit. Also, the uncertainty associated with risk modifications (neither of which was statistically significant) might be a concern in risk projection over a longer period. These considerations lead to giving a greater weight to the results based on the ERR transfer of the risk estimate from the semiparametric model, applied for the follow-up to age 60. Thus, it was concluded that these results would be most reliable for both cerebrovascular disease and heart disease.

523. The preferred risk inferences are summarized below:

(a) The radiation-induced mortality of cerebrovascular disease cumulated up to age 60 after acute exposure to dose of 1.5 Gy to Japanese citizens at age 30: the estimate based on the LSS mortality risk estimate is 5.8 (95% CI: 0.4, 12) cases per 10,000 persons;

(b) The radiation-induced mortality of heart disease (excluding rheumatic valvular heart disease) cumulated up to age 60 after acute exposure to a dose of 1.5 Gy to Japanese citizens at age 30: an estimate based on the LSS mortality risk estimate is 11 (95% CI: 1.9, 21) cases per 10,000 persons.

(b) Discussion of the impact of sources of uncertainty

524. The main sources of uncertainties associated with this risk estimate are summarized in table 22. The subsequent paragraphs give the reasons for the grading of the uncertainties (very small, small, moderate or large).

525. *Selected populations:* The impact of population selection is likely to be small since the LSS risk was transferred to the target population with baseline rates that are relatively similar to those of the LSS. The difference in the baseline rates between the current Japanese statistics and the estimates for the youngest cohort of the LSS cohort is relatively small before age of about 75, while the increase of the current population rate is much more rapid than the LSS at older ages (>75), which suggests larger uncertainties in the risk evaluations at age 90.

526. *Exposure assessment*: The uncertainty associated with exposure has been well accounted for in the LSS doses, and its impact on the risk evaluation should be very small.

527. *Health outcome assessment*: The uncertainty in diagnostic accuracy with change in disease coding is a concern. Although it is difficult to quantitatively assess the impact of such uncertainty in outcome assessment, the uncertainty would be larger for heart disease, which received a greater impact from the coding change, than for cerebrovascular disease.

528. *Study design*: While there are concerns on the study design issues of the LSS, the potential impact of uncertainty in the study design on the estimated risk is considered to be small.

529. *Confounding factors*: None of the potential confounders examined was influential on the assessment of risk of circulatory disease in the LSS, but other unaccounted factors (e.g. severity of bomb-related injuries, lifestyle and socio-economic status) cannot be ruled out as confounders that might have non-negligible impact on the current risk evaluations.

530. *Statistical methods and model uncertainties*: The impact of choice on latency period was small if the latency was extended from 5 to 10 years. The current risk evaluation using models with different forms of effect modification indicated that uncertainties linked to the choice of effect modification might have moderate impacts, although neither of the effect modifiers considered was statistically significant.

531. *Other sources of uncertainty*: The impact of the assumption of the fixed baseline risk would be minor unless there was a significant change in the baseline risk. Use of combined groups of diseases of fairly different characteristics may not have a large impact unless the target population has a fairly different distribution in subtypes of circulatory disease from that of the LSS. The distributions of types of disease varied over time in Japan, which might have some impact if risks differ between these types.

Table 22. Characterization of the main sources of uncertainty associated with the preferred risk inference of circulatory diseases

Source	Characterization of source	Judged impact ^a
Selected populations	Difference in the baseline between the LSS and the targeted Japanese populations	Small
Exposure assessment	Dose errors and use of dose to the colon	Very small
Health outcome assessment	Diagnostic accuracy	Moderate for heart disease Small for cerebrovascular disease
Study design	Selection of control group, healthy survivor bias	Small
Confounding factors	Unaccounted potential confounders (severity of bomb-related injuries, lifestyle and socio-economic status)	Moderate
Statistical methods and model uncertainty	Latency (5 years or 10 years) Risk modification	Small Moderate
Other sources of uncertainty	The fixed baseline mortality Use of combined groups of diseases of fairly different characteristics	Small Small

^a The impact of the different sources of uncertainty is classified into four categories according to the variation they are expected to induce on the reported CER: very small—less than a factor of 1.1; small—between a factor of 1.1 to 1.5; moderate—between a factor of 1.5 to 2; and large—greater than a factor of 2.

G. Conclusions

532. Based on the excess risk derived from the study of the Japanese atomic bombing survivors, the lifetime risk of radiation-induced circulatory disease was evaluated for the entire population of Japan in the year 2014. The results indicated that the best estimate of the cumulative excess deaths due to exposure to a dose of 1.5 Gy at age 30, and followed up to age 60 might be about six deaths with a confidence interval of about 0.4 to 12 per 10,000 people from cerebrovascular disease and about 11 with a confidence interval of about 2 to 20 per 10,000 persons from heart disease excluding rheumatic valvular heart disease. These estimates were based on the multiplicative transfer of the dose–effect relationship estimated by the semiparametric dose–response model with no effect modification.

533. In the meta-analysis of Little et al. [L12], the estimated dose–effect relationship was transferred to populations of various countries to estimate the lifetime risk. For Japan, the CER per 10,000 persons per unit dose was estimated to be 219 (95% CI: 24, 414) Sv^{-1} for cerebrovascular disease, 57 (95% CI: 25, 88) Sv^{-1} for ischaemic heart disease and 80 (95% CI: –125, 285) Sv^{-1} for non-ischaemic heart disease. The high risk estimated for cerebrovascular disease seems to have reflected the fairly high pooled ERR per unit dose of 0.20 Sv^{-1} compared to the risk estimated from the LSS (ERR per unit dose of 0.08 Gy^{-1} under the linear dose–response model). The high value for the ERR per unit dose in the meta-analysis is related to the inclusion of the high estimate of 0.44 Gy^{-1} in the incidence data, and the exclusion of the low estimate of 0.03 Gy^{-1} in the mortality data for the Mayak workers.

534. Much of the uncertainty that has been only roughly accounted for in the current risk evaluation seems to be related to diagnostic accuracy, potential confounding and uncertainty in the age–risk pattern. To reduce these limitations, further studies are anticipated to accumulate evidence to allow an improved assessment on the nature of the risk and to clarify the underlying mechanism for radiation-associated circulatory disease, which are likely to be different among the disease subtypes and also between low and high exposures. It is widely accepted that high doses cause circulatory tissue damage that leads to an increased risk of cardiovascular diseases, so the findings of increased risks following high doses (including after radiotherapy) are not unexpected. However, at low doses, cell killing is not expected to be a major phenomenon, so if there is any effect at low doses then it presumably occurs via a different mechanism. Unless it is assumed that radiation-induced cardiovascular diseases are a stochastic process (even at high doses), the finding at high doses is unlikely to be generalized for low doses.

VII. RESEARCH NEEDS

535. Radiation epidemiology has considerably improved in the past decade mainly due to improved health registries, longer follow-up periods and increased international collaborations. Recent studies of cancer risk due to CT examinations during early childhood, occupational exposure and exposure to ^{131}I during childhood allow a more reliable assessment of radiation risk. Recommendations to reduce specific limitations associated with these studies are proposed in the conclusions of each respective section. Routes of potential improvement for the future also include collection of information on other risk factors in addition to radiation (e.g. other sources of exposure) and use of morbidity data in addition to mortality.

536. Epidemiological studies of patients exposed to CT-scans during childhood or of workers exposed to radiation involve rather young cohorts. These cohorts should continue to be followed up, as they are expected to provide more information on the risk of leukaemia, all solid cancers and selected individual

cancer types. Especially, extension should improve the assessment of the modifying effect of age at exposure and attained age on the dose–risk relationship. Further epidemiological follow-up and updated risk information are expected from LSS studies. Both incidence and mortality epidemiological data are useful and used for describing and understanding health effects of exposure to radiation.

537. To improve the predictions of risk of leukaemia and all solid cancers in workers exposed to low doses of radiation, epidemiological studies of workers (e.g. INWORKS) should be continued by (a) extending the follow-up of the cohort until the end of lifetime of the cohort; (b) better assessing and accounting for radiation doses from medical procedures received by workers; (c) better assessing and accounting for radiation doses (including missing and unrecorded doses) from all sources of occupational exposures (doses from employment at other facilities, neutrons, internal emitters); (d) better assessing and accounting for the effect of possible non-radiation confounding factors (e.g. smoking, alcohol, exposure to other chemicals); and (e) considering to include other workforces (e.g. other United States nuclear sites) in INWORKS.

538. The impact of uncertainties in exposure assessment on estimation of radiation effects in epidemiological studies remains challenging but needs to be further quantified. Various approaches are being developed and applied. These range from the relatively simple regression calibration to account for unshared stochastic errors to Bayesian methods based on multiple realizations of individual dose estimates aiming at capturing the effects of shared and unshared errors. There is a need to further develop these methods and tools that allow an application of these methods to more epidemiological studies.

539. In general, studies of radiation epidemiology include humans with a range of ages at exposure, doses, ages under follow-up and other parameters. A number of studies demonstrated that the estimates of health effects in the upper range of the dose distribution and in the centre of the other parameters are relatively independent of the approach used to analyse the data. However, risk estimates at lower doses, and for more peripheral values of other parameters may depend strongly on the approach. Methods are being developed to deal with this model uncertainty, among them multi-model inference, semiparametric approaches and Bayesian model averaging. These approaches need to be further developed and made available to the broader community.

540. In the optimal setting, assessments of health risks from radiation exposures are based on epidemiological studies and on an understanding of how the biological effects of radiation affect the biological processes of the genesis of the disease and of the radiation action on its genesis. The development of cancer and of circulatory diseases is a complex and multifactorial process. In the past decade, it has the complexity of the biological processes of carcinogenesis and induction of circulatory diseases become increasingly obvious and the understanding of the radiation action could not keep up with this increasing complexity. It is of utmost importance to improve the knowledge of radiobiological processes contributing to radiation-induced carcinogenesis and induction of circulatory diseases and integrate them in a modelling of effects in radiation epidemiology and risk inference.

541. Major uncertainties are linked to the transfer of risk from one population to another. Replication of epidemiological studies in different populations, with as similar as possible design, would enhance the understanding of the interactions between radiation and other risk factors. It should help consolidating the choice of the weighting scheme between the EAR and ERR transfer models, and finally improve the determination of the transfer of risk between populations. As outlined in the previous paragraph, it is only through deeper knowledge of biological mechanisms that reliable inferences of interactions between radiation and other factors can be gained, thus answering the question how to transfer risk from one population to another properly.

542. Many sources of uncertainty challenge the reliability and precision of the estimates of radiation-related health risks. While for very specific scenarios that are closely related to recent large epidemiological studies the impact of uncertainties may be considered as small, for other exposure and follow-up conditions, their impact could be much larger. Methods to better assess the impact of uncertainties on the CER need to be developed. One approach could be to develop better methodology for deriving estimates (and their uncertainties) from pooled analyses which account for both sampling and non-sampling errors.

543. As long as mortality rather than incidence data are available there is a source of uncertainty in treatment success, which could be large in some instances. More effort should be devoted to cancer registration data to avoid this source of uncertainty. It is very likely that different cancers have different dose responses, modifying factors, etc., and it would be valuable to assess particular solid cancers, such as breast cancer and colon cancer when sufficient data become available rather than combine all solid cancers. Finally, it is important to continue to gather high quality data for epidemiological studies, and that large studies remain feasible through appropriate data linkage availability.

VIII. GENERAL CONCLUSIONS

544. The objective of this work was to perform quantitative risk evaluations of radiation effects on cancer in specific exposure situations with low to moderate doses and on circulatory diseases in situations with higher doses. For each of the five scenarios (leukaemia during childhood, leukaemia during adulthood, all solid cancers, thyroid cancer and circulatory diseases) calculations of cumulative excess risk were performed using risk models derived from a study based on a population with similar characteristics as that considered in the scenario. Parallel calculations of cumulative excess risk were performed using risk models derived from the LSS, to allow comparison to be made of the results (again with the exception of circulatory diseases, where only LSS risk models were used). An important goal was to go beyond purely statistical uncertainties and to consider, as far as possible, other sources of uncertainty, e.g. exposure assessment, outcome assessment, confounding factors and study design.

545. In the present analysis, it was considered that the preferred risk inference was the one that fits best the characteristics of the considered scenario, based on an expert judgement on the magnitude of the uncertainties associated with it.

A. Health effects

546. In recent years, new results have been published from studies of leukaemia incidence among people exposed to radiation during childhood and adolescence. These studies consolidated the knowledge about leukaemia risk related to low dose exposure and confirmed the fact that, for the same dose, the strength of the effect is higher if dose is received during childhood than during adulthood. Among these studies, those on children undergoing CT scan diagnostic examinations are the most powerful.

547. Regarding leukaemia incidence and mortality associated with exposure to external radiation during adulthood, several studies have been published in recent years which complement to the LSS study. The results are mostly coherent in demonstrating a dose–effect relationship for leukaemia after exposure during adulthood, with a lower slope than estimated in studies considering exposure during

childhood. Among these, the most powerful study was the INWORKS combined analysis of occupationally-exposed workers, which provided an estimate of the ERR per unit dose for leukaemia mortality with a small confidence interval.

548. A large number of epidemiological studies dealing with solid cancer incidence and mortality from exposure to low-LET radiation have been published in the last decade, including studies of the LSS cohort and of occupationally-exposed workers from nine countries (i.e. nuclear power plant workers, uranium processing workers, X-ray technicians, emergency workers and other occupationally-exposed workers). For all worker cohorts, more than 50% of the members received doses less than 100 mGy, with most cohorts having the majority of their members being exposed to doses lower than 100 mGy (i.e. ~90% or more). In most studies, the best estimate of the ERR at 100 mGy (or mSv) was greater than zero, but not all dose responses were statistically significant, especially for studies which involved small cohorts or a short follow-up and which did not have sufficient statistical power (at the present) to detect radiogenic risk. Worker studies provide dose responses relevant for long-term, prolonged exposures of adults that can be applied for prospective and retrospective risk analyses of other workers exposed to radiation. Among the occupational studies, the recent INWORKS is outstanding, because of the long observation time (more than 8 million person-years), the large number of solid cancer deaths analysed (nearly 18,000) and the high quality of data.

549. Estimates for radiation-induced thyroid cancer after exposure during childhood or adolescence have been derived in the UkrAm cohort study with a well-defined screening regime in combination with individual dose estimates. The LSS provides estimated doses to the thyroid of similar quality, but the screening conditions were not fully controlled for the whole cohort. The large cohort of about 300,000 persons who were residents under age 18 in 2011 in the Fukushima Prefecture benefited from screening conditions similar to the UkrAm cohort (although with more modern equipment), but doses to the thyroid were considerably lower and not known on an individual basis. Compared to the Fukushima cohort, the UkrAm cohort fulfils important quality criteria and thus provides a sound basis for the assessment of thyroid cancer risk after radiation exposure.

550. While an increasing number of epidemiological results have been reported on radiation-associated circulatory diseases in the past decade, the evidence on potential effects is largely inconsistent and inconclusive, in particular at low to moderate doses. The estimated radiation effects on circulatory diseases in the LSS were mostly smaller than those observed for cancers, and the biological mechanisms behind such effects are unclear, which makes it difficult to evaluate the dose-response relationship and its variation with age and other factors (effect modification). Issues specifically relevant to the assessment of circulatory disease risk, such as potentially large effects of the non-radiation risk factors and errors in diagnoses and classifications, complicate the comparison of the reported effects between the studies of different populations at different periods.

B. Risk assessments

1. Risk assessment with statistical uncertainties

551. The Committee assessed the risks of leukaemia, all solid cancer and thyroid cancer in scenarios of exposure to ionizing radiation based on recent large epidemiological studies and on effect-per-unit-dose estimates in the LSS. The best estimates of the two approaches (recent large study and the LSS estimate) agreed well for conditions that corresponded closely to those of the recent studies (table 23). For these specific scenarios, the recent studies provided a more reliable risk estimate than a transfer of

effects from the LSS to the scenario. The latter approach is burdened by major sources of uncertainty due to the transfer from moderate/high dose to low dose conditions, from acute high-dose-rate exposure to protracted low-dose-rate exposure conditions, between populations with different background rates, and from catastrophic after-war living conditions for the survivors of the atomic bombings to a normal contemporary population. It should be noted that the Committee did not apply any corrections to the effect-per-unit-dose estimates from the LSS to the scenarios involving low dose rates or low dose. The good agreement of the two approaches, when applied to the conditions of the recent study, gives some confidence that the LSS-based risk estimates can be used for ages at exposure or follow-up periods other than those in the specific scenarios.

552. The Committee also assessed the mortality risks due to circulatory diseases in a scenario of a Japanese population exposed to ionizing radiation. There are considerable differences in the frequency of the various types of circulatory diseases and their risk factors between the population in the LSS and a modern Japanese population, and between Japanese and Western populations. The pathogenesis of radiation-related circulatory diseases at low or moderate dose is not well understood. Even after an acute exposure to a dose as high as 1 Gy, there are large uncertainties in the risk estimates. A modern statistical approach was applied to assess these uncertainties for heart and for cerebrovascular diseases (table 23).

Table 23. Cumulative cancer and circulatory disease risks due to radiation exposure in specific scenarios. Preferred estimates and statistical 95% confidence intervals

Additional information for each scenario (minimum latent period, description of source data for risk models, baseline rates, etc.) are in sections II to VI. CER: Cumulative excess risk; LSS: Life Span Study

<i>Exposure scenario</i>	<i>Cumulative dose</i>	<i>Follow-up</i>	<i>CER (per 10 000 persons) based on ERR transfer</i>	
			<i>Current study corresponding to the specific scenario</i>	<i>LSS</i>
Four CT scans at age 1	20 mGy to the RBM	Leukaemia incidence up to age 30	5.3 (0.6, 18.3)	5.1 (−0.8, 30)
Occupational protracted external exposure, age 30–45	200 mGy to the RBM	Leukaemia ^a , males mortality up to age 60	4.6 (1.5, 9.6)	2.8 (−0.1, 5.6)
	100 mGy to the colon	All solid cancer, males mortality up to age 60	11 (3.1, 19.3)	6.4 (4.0, 9.8)
¹³¹ I-internal exposure at age 10	500 mGy to the thyroid	Thyroid cancer incidence up to age 30	7.7 (2.4, 18)	7.0 (1.6, 23)
Acute external exposure at age 30	1.5 Gy to the colon	Cerebrovascular disease mortality up to age 60		5.8 (0.4, 12)
		Heart disease ^b mortality up to age 60		11 (1.9, 21)

^a Excluding chronic lymphoid leukaemia.

^b Excluding rheumatic valvular heart diseases.

553. Using ERR models derived from the UK CT-scan study or from the LSS, consistent results were obtained for leukaemia incidence up to age 30 after CT scans at age 1 with a total dose to the RBM of 20 mGy. Among 10,000 persons with an assumed cumulative baseline incidence of 9 cases, a cumulative excess incidence of about 5 cases was estimated. Even though the statistical confidence intervals were large, the interval obtained using the model from the UK CT-scan study was half of that obtained using the LSS model.

554. The INWORKS provides a pertinent risk model to assess leukaemia mortality risk among male workers with a dose to the RBM of 200 mGy in the age range from 30 to 45 with a follow-up until age 60. Among 10,000 persons with an assumed cumulative baseline mortality of 10 leukaemia deaths, a cumulative excess mortality of about five leukaemia deaths was estimated, with an uncertainty range from about 1 to about 10. For this scenario, the use of the ERR per unit dose derived from the INWORKS cohort requires no extrapolation or transfer, whereas the use of risk models derived from the atomic bombing survivors relies on uncertain assumptions related to the situations of exposure being different, higher doses and different dose rates.

555. The cumulative risk of all solid cancer mortality in a population of workers subject to prolonged exposure to low-LET radiation was estimated based on risk models from the INWORKS and from the most recent studies of the LSS cohort. The specific scenario assumed exposures of United States male workers between ages of 30 and 45, to a total whole-body dose of 100 mGy. The preferred risk inference for the considered exposure scenario was the CER up to attained age 60, obtained using the ERR risk model from the INWORKS. The CER estimated based on the INWORKS risk model for all solid cancers and the full dose range is 11 (95% CI: 3.1, 19.3) cases in 10,000 persons when cumulated up to age 60 (table 23). These excess cases represent fewer than 5% of the total number of solid cancer deaths (about 230 cases) expected to occur in the absence of exposure to radiation, for the same age range. The range of the confidence interval is about a factor of 1.5 larger than the central estimate. While epidemiological studies of adult workers are an excellent source of data regarding radiation risks from prolonged or fractionated exposures, the reported risk models often do not include modifiers for age at exposure or attained age. Thus, extrapolation of risk to attained ages greater than the average age at the end of follow-up needs to be interpreted carefully. For such cases, estimates of risk obtained using models from the LSS cohort are still more reliable, although they need to account for differences in baseline rates between LSS and the populations for which the risk is assessed.

556. For the preferred thyroid scenario with age at exposure 10, the sex-averaged CER estimates based on the ERR models derived from the UkrAm cohort and the LSS cohort, agree very well. It is noted, however, that at very young age, the ERR estimates for the UkrAm cohort are markedly higher than those for the LSS cohort. However, this difference does not influence the CER estimates, because at young age, baseline incidence of thyroid cancer is very low.

557. Based on estimates of radiation-related effects per unit dose derived from the LSS analysis, the lifetime risk of radiation-induced circulatory disease was evaluated for the general population in Japan. The results indicated that the best estimate of the cumulative excess deaths due to exposure to 1.5 Gy at age 30, and followed up to age 60 might be 5.8 (95% CI: 0.4, 12) and 11 (95% CI: 1.9, 21) deaths per 10,000 from cerebrovascular disease and heart disease, respectively. These values were based on the transfer of the ERR estimated by the semiparametric dose–response model.

558. Inferences* of risk values for age at exposure, dose and follow-up periods other than those described in the preceding paragraphs are burdened by additional uncertainties related to a transfer of the risk quantities from the centre of the data in the new epidemiological studies to other conditions. Most of these are currently not possible to be quantified reliably. However, the good agreement of the two approaches in the preferred risk (i.e. the risk models derived from the LSS for a cohort

corresponding to the scenario) reassures the methodology for the estimation of risks based on effects observations in the LSS. This confirms that the LSS remains a major source of information for such risk estimations scenarios as are considered here, but possibly also for other scenarios and health outcomes. An important question remains: what is the best risk quantity to be used in the risk transfer? In principle, this question could be addressed by an understanding of the interaction of the radiation exposure with other factors causing the genesis and development of the disease. However, present knowledge on this interaction is limited. In view of this, the choice of approach on how to transfer radiation risk models from the LSS remains a major source of uncertainty in the assessment of health risks in other exposure conditions and populations.

2. Risk assessment considering additional sources of uncertainty

559. The risk estimates for the specific scenarios based on recent large epidemiological studies were preferred, because any major additional stochastic sources of uncertainties apart from the statistical uncertainties relating to the exposure and follow-up conditions are small. The credible intervals of the risk estimates were assessed using the approach described in appendix A, considering all known sources of uncertainties. The credible intervals presented in table 24 are thought to reflect both the statistical uncertainty (reflected by the 95% confidence intervals in table 23) and the potential impact of additional sources of uncertainty discussed above (listed in the sections F.2(b) in the chapters II to VI of the single scenarios). In the scenarios for cancer risks, the additional stochastic sources of uncertainty are very small or small, and most are considered to be multiplicative, but an additive component has been considered as well. It was assumed that the impact of the additional sources of uncertainty may be approximated by the maximal value of a moderate uncertainty (factor of less than two) and up to a potentially large impact for age at exposure in the CT-scan scenario (factor potentially higher than two). A Monte Carlo approach of propagating uncertainties was applied (see appendix A).

Table 24. Rounded values of cumulative cancer risk due to radiation exposures in the preferred risk inferences

The credible intervals are based on expert judgement, considering known sources of uncertainty

Exposure scenario	Cumulative dose	Follow-up	Cumulative excess risk (per 10 000 persons)	
			Preferred risk inference	95% credible interval
Four CT scans at age 1	20 mGy to the RBM	Leukaemia incidence up to age 30	5	0 to 20
Occupational external exposure, age 30–45	200 mGy to the RBM	Leukaemia mortality up to age 60 excluding CLL	5	1 to 10
	100 mGy to the colon	All solid cancer mortality up to age 60	11	2 to 20
¹³¹ I-internal exposure at age 10	500 mGy to the thyroid	Thyroid cancer incidence up to age 30	8	2 to 20

560. The sources of uncertainties associated with the preferred risk inference for leukaemia after exposure during early childhood and follow-up until young adulthood are considered to be very small (less than a factor of 1.1), small (less than a factor of 1.5), moderate for the inclusion of MDS (less than

a factor of two) and even potentially large for age at exposure (higher than a factor of two). Nevertheless, the sources of uncertainties listed above are considered to essentially compensate each other (upwards for the inclusion of MDS in the risk model and the inclusion of patients with previous cancer, and downwards for the age at exposure) so that the preferred estimate value of the ERR per unit dose was not modified. The credible interval, however, is affected by these sources of uncertainty and is considered to range from 0 to 20 leukaemia cases among 10,000 persons exposed, meaning that based on the credible interval the preferred risk inference is not significant.

561. The additional sources of uncertainties associated with the preferred risk inference for leukaemia after exposure during adulthood and follow-up until age 60 are considered to be very small (less than a factor of 1.1) or small (less than a factor of 1.5). Using this estimate of a small impact, the credible interval (table 24) is therefore only enlarged by about 11% compared to the 95% confidence interval (table 23).

562. For the exposure scenario focusing on the risk of all solid cancers combined, the largest source of uncertainty in the preferred risk inference is the statistical uncertainty in the ERR per unit dose from the INWORKS-effect model. Other sources of uncertainty are expected to have a lower contribution to the uncertainty in the preferred estimate of cumulated risk of all solid tumours combined. The 95% credible interval is judged to range from 2 to 20 cancer mortalities among 10,000 persons exposed.

563. Credible intervals (table 24) for the thyroid scenario were inferred to be close to those for the preferred scenario (table 23), although there is some evidence for a possible confounding by intake of stable iodine or nitrate in drinking water. In order to be able to assign a credible interval regardless of these sources of uncertainty, the scenario was defined by assuming a similar amount of stable iodine and nitrate in the drinking water as in the UkrAm cohort. In the thyroid scenario, cancer incidence is dominated by the radiation effect. The CER in the preferred risk inference corresponds to an attributable fraction of 70%. By preferring the risk estimate closely related to the Ukrainian target population important sources of uncertainty were avoided. Risk models for thyroid cancer from the LSS provide adequate CER estimates in risk transfer calculations for the general Ukrainian population. However, as in the other scenarios, risk estimates from a population closer to the target population provide more reliable CER estimates since some sources of uncertainty have been excluded.

564. Important to keep in mind that the preferred risk inferences in table 24 refer to specific conditions as exposure scenario, age range of follow-up, cancer specification and baseline risk in the population considered. These conditions were chosen in order to avoid major assumptions on the transfer of the effect per unit dose in an epidemiological study to the risk per unit dose in the scenario. The epidemiological studies, on which the preferred risk inferences are based, are less informative for other conditions. The more the conditions deviate from those of the preferred risk inference, the more important becomes a transfer of the effect per unit dose in the LSS, which increases uncertainties due to the assumptions needed in this transfer.

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APPENDIX A. JUDGEMENT OF CREDIBLE INTERVALS

A1. This appendix deals with unbiased and not-shared stochastic errors. Systematic errors, biases, confounding factors and shared errors are dealt with in the main text of the annex. These include:

- (a) Non-exclusion of patients with unreported previous cancer, possible overestimation of myelodysplastic syndromes (MDS) risk by the high MDS excess rate in the UK CT-scan study, and application of an average excess relative risk (ERR) per unit dose to age at exposure of one in the childhood CT-scan scenario;
- (b) Unaccounted exposure to radiation (neutron exposures, internal contamination, missed external gamma doses, job-related chest X-rays) in the scenarios based on the INWORKS study;
- (c) Surveillance (screening) of the thyroid, and the possible influence of iodine supply and nitrate in the drinking water on the excess risk in the scenario based on the UkrAm study.

A2. In the following, the cumulative excess risks (CERs) for the preferred risk inference (table 23) are given in the unit chances among 10,000 persons. The CERs have been curve-fitted using Weibull probability distribution functions (table A1) that pass through the best estimate (maximum-likelihood estimate, MLE) and through the lower and upper limits of the 95% confidence intervals.

Table A1. Cumulative excess risk (CER) of cancer in 10,000 persons

Preferred risk inference	CER (95% CI)	Parameters of Weibull ^a probability distribution function		
		Location (γ)	Scale (η)	Shape (β)
Leukaemia incidence up to age 30 after CT scans at age 1 with RBM dose of 20 mGy	0.6–18.3	–0.553	9.167	1.805
Leukaemia mortality up to age 60 after occupational exposure from age 30 to 45 with RBM dose of 200 mGy	1.5–9.6	0.415	5.243	2.350
All solid cancer mortality up to age 60 after occupational exposure from age 30 to 45 with colon dose of 100 mGy	3.1–19.3	–1.250	13.66	3.206
Thyroid cancer incidence up to age 30 after incorporation of ¹³¹ I at age 10 with thyroid dose of 500 mGy	2.4–18	0.841	9.424	2.078

^a Weibull probability distribution function shifted by the amount indicated by the location parameter.

A3. In addition to the uncertainties taken into account in the Monte Carlo calculations for estimating confidence intervals of CER (e.g. table 23), there are several sources of very small or small stochastic uncertainties (tables 4, 7, 16 and 18). The uncertainty range of CER judged based on its confidence interval and the additional sources of uncertainty is expressed by a 95% credible interval.

A4. The additional uncertainties are assumed to be mainly multiplicative, but an additive component is considered as well. The additive component is modelled by one additive uncertainty normally distributed with a 95% range from $-0.1 \cdot \text{MLE}$ to $0.1 \cdot \text{MLE}$, where MLE is the maximum-likelihood estimator of CER. The multiplicative component is modelled by one small uncertainty of maximum size (factor 1.5, i.e. 95% credible range from 2/3 to 3/2). This source of uncertainty is assumed to have a log-normal distribution with mean one and to be independent of the sources of uncertainty expressed by the confidence interval of CER.

A5. The impact of additional uncertainties on the distribution of CER is evaluated by Monte Carlo simulation based on 10,000 samples per density function. Results are presented here only for the 95% credible intervals.

A6. The results of the Monte Carlo calculations for the credible interval of CER are depicted in table A2 and figure A-I. In the final results in the main text of this annex, best estimates of CER are rounded to one-digit, lower bounds of the credible intervals to one of the digits 0, 1 and 2.

Table A2. Credible intervals and 95% confidence intervals of cumulative excess risk of cancer in 10,000 persons

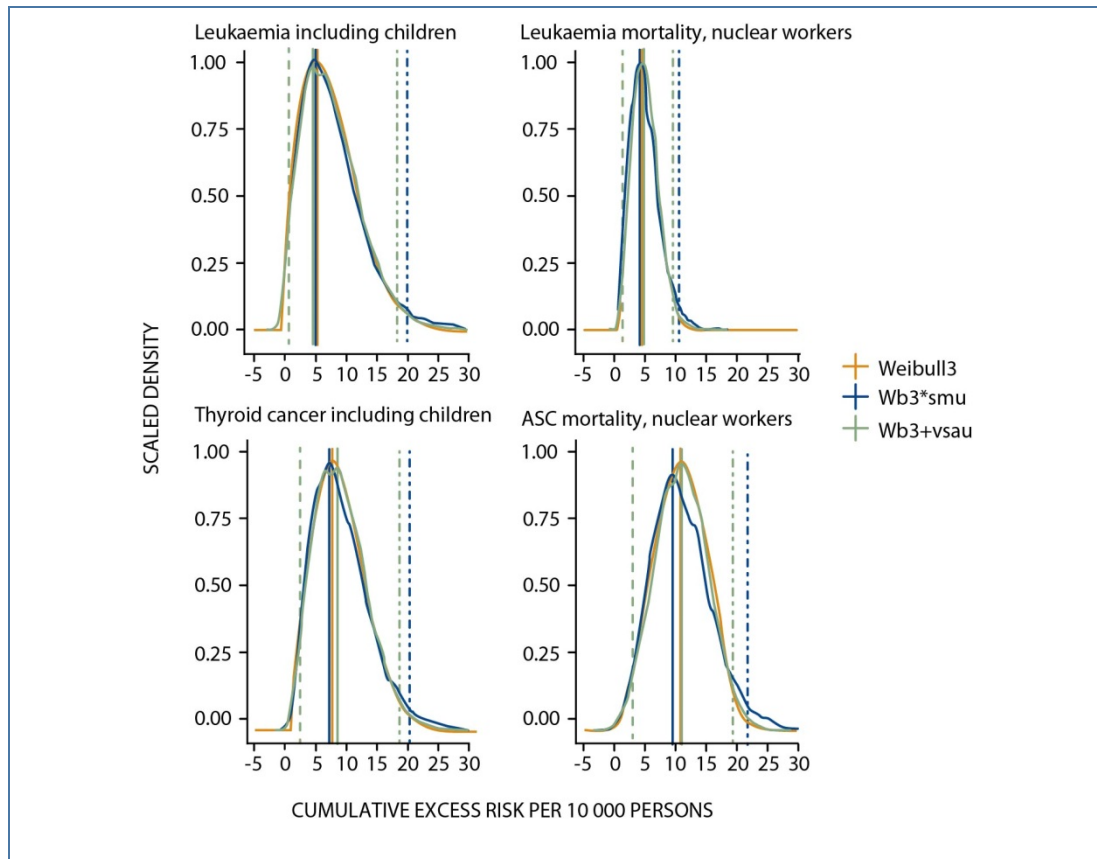
Preferred risk inference	Confidence interval (95%)	Calculated credible interval		Rounded credible interval
		Small multiplicative uncertainty	Very small additive uncertainty	
Leukaemia incidence up to age 30 after CT scans at age 1 with RBM dose of 20 mGy	0.6–18.3	0.6–19.8	0.7 ^a –18.4	0 ^b –20
Leukaemia mortality up to age 60 after occupational exposure from age 30 to 45 with RBM dose of 200 mGy	1.5–9.6	1.4–10.6	1.5–9.8	1–10
All solid cancer mortality up to age 60 after occupational exposure from age 30 to 45 with colon dose of 100 mGy	3.1–19.3	2.9–21.7	3.1–19.4	2–20
Thyroid cancer incidence up to age 30 after incorporation of ¹³¹ I at age 10 with thyroid dose of 500 mGy	2.4–18	2.3–20.3	2.4–18.6	2–20

^a The higher value of the 2.5% percentile of the credible interval compared to the confidence interval is caused by statistical fluctuations due to the limited number of Monte Carlo simulation.

^b The possibility of an overestimation of the risk coefficient (due to the inclusion of patients with previous cancer in the UK childhood CT-scan study or the inclusion of MDS cases in the risk model) has been considered in fixing the lower bound of the credible interval to zero.

Figure A-I. Three-parameter Weibull distribution of cumulative excess risk (CER) and its broadening due to a small multiplicative uncertainty (*smu) and a very small additive uncertainty (+vsau)

The density function of the undisturbed Weibull3 distribution is expressed by the exact formula, the disturbed density functions are simulated with sample size $N=10,000$; ASC=all solid cancers



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ANNEX B

LUNG CANCER FROM EXPOSURE TO RADON

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The attachment “Models of excess relative risk with modifying effects” is electronically available for download from <http://www.unscear.org/unscear/en/publications/2019.html>

I. INTRODUCTION

1. The United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) has previously considered the issue of sources and effects of exposure to radon (^{222}Rn) (including thoron (^{220}Rn)) with regard to workers and the public in two comprehensive reports in 2000 and 2006 [U3, U6]. The Committee concluded that inhaled radon and its progeny are established carcinogens for the lung (doses to other organs and tissues were at least an order of magnitude smaller than the doses to the lung). The Committee also recognized that the annual per caput dose from inhalation of radon gas and its progeny represented typically about half of the effective dose*¹ (as defined by the International Commission on Radiological Protection (ICRP) in its publication 60 [I4]) received by members of the public from all natural sources of ionizing radiation. For certain occupations, radon and its progeny also dominate occupational radiation exposure. For example, in the nuclear fuel cycle, radon inhaled following its release from uranium mines makes a substantial contribution to the workers doses.

2. There are two approaches for deriving the effective dose per unit exposure from radon and its progeny. These are hereafter referred to as “dosimetric” and “epidemiological”, the latter approach is also referred to as the dose conversion convention [I6]. The dosimetric approach derives the effective dose from a given exposure using a dosimetry model of the respiratory tract and applying radiation and tissue weighting factors. It is worth mentioning that the tissue weighting factors are determined mainly from epidemiological studies of Japanese atomic bombing survivors exposed largely to gamma radiation. The epidemiological approach compares the radiation detriment* associated with unit radon progeny exposure and unit effective dose. Thus, the lifetime risk* of lung cancer per unit exposure to radon progeny is divided by the detriment per unit effective dose. The former was determined from miner epidemiology and the latter determined mainly from epidemiological studies of Japanese atomic bombing survivors exposed largely to gamma radiation. Based on a review of available dosimetric models by an expert group of the Nuclear Energy Agency [N4], the Committee adopted in its 1982 Report an effective dose coefficient for indoor exposure of $8.7 \text{ nSv per h Bq m}^{-3}$ of equilibrium equivalent concentration (EEC)* of ^{222}Rn [U1]. This value was retained and rounded to $9 \text{ nSv per h Bq m}^{-3}$ EEC of ^{222}Rn for indoor and outdoor exposure in the UNSCEAR 1988, 2000 and 2006 Reports [U2, U3, U6]. In its UNSCEAR 2006 Report, the Committee recognized that more recent calculations with new dosimetric models resulted in higher values of the dose conversion factor. However, because of the lower value calculated with the epidemiological approach of ICRP Publication 65 [I6], the Committee concluded that the previous value of $9 \text{ nSv per h Bq m}^{-3}$ EEC of ^{222}Rn is within the range of possible dose conversion factors. Consequently, the Committee recommended that this value should continue to be used in UNSCEAR dose assessments [U6]. The value of $9 \text{ nSv per h Bq m}^{-3}$ EEC of ^{222}Rn corresponds to $1.6 \text{ mSv per MJ h m}^{-3}$ or $5.7 \text{ mSv per working level month (WLM)*}$.

3. ICRP in its Publication 115 [I10], reviewed epidemiological data of radon-induced lung cancers, focusing on low levels of exposure and exposure rates in mines [N10, T11]. As a result, for radiation protection purposes, a detriment adjusted nominal risk coefficient of $1.4 \times 10^{-4} \text{ per MJ h m}^{-3}$ equivalent to $5 \times 10^{-4} \text{ WLM}^{-1}$ was recommended for a mixed adult population of smokers and non-smokers. This is approximately twice the value given previously in ICRP Publication 65 [I6].

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

4. The Committee has not studied issues concerning exposure and effects from radon (and thoron) since its UNSCEAR 2006 Report [U6]. However, between 2006 and 2017 there have been several hundred scientific publications concerning radon exposure and lung cancer, including those related to epidemiological studies of radon-induced lung cancer in exposed populations as well as those with relevant dosimetry. The present annex, in agreement with the Committee's mandate from the General Assembly of the United Nations for estimating effects and risk from radiation exposure, aims to thoroughly assess the newly available literature.

II. DOSIMETRY

A. Introduction

5. The risk of lung cancer associated with radon arises from the inhalation of the airborne radon progeny and the resulting dose to the lung, mainly from alpha radiation. In general, lung doses from inhaling the airborne radon progeny are about two orders of magnitude higher than the corresponding lung dose from inhaled radon gas. Although lung cancers are caused by the inhaled short-lived radon progeny and not by the radon gas, it is the radon gas which is commonly measured and not its progeny. The International Commission on Radiation Units and Measurements (ICRU) in its Report 88 [I14] provided detailed information on how to measure radon, covering measurement techniques of radon in air and water. The only measurable parameters which allow the determining of lung doses are the radon and radon progeny activity concentrations and related particle size distributions. The highest doses are received by the bronchial and bronchiolar regions of the lung consistent with the observation that most of the lung carcinomas associated with radon exposure originate in the bronchi [I14, S1, U3, U6, W14].

6. Calculations of the absorbed dose* to the target tissues of the lung per unit exposure to radon progeny can be carried out with dosimetric models of the human respiratory tract. Such calculations require information on the activity size distribution of the radon progeny aerosol, the unattached fraction, the breathing rate, the fractional deposition in the airways, mucous clearance rate, transport into blood and the location of the target cells in the airways. The calculations are subject to all of the variability and uncertainty associated with the model parameter values as well as the assumptions built into the particular computational model [H3, I14, M1, M2, U3, W12, Z5]. A detailed description of dosimetric models and choice of parameter values is given in appendix A.

7. In its UNSCEAR 2000 Report [U4], the Committee reported that the dosimetric evaluation of the absorbed dose to the basal cells of the bronchial epithelium per unit exposure of EEC of ^{222}Rn were in the range of 5 to 25 nGy (h Bq m⁻³)⁻¹. A central value of 9 nGy (h Bq m⁻³)⁻¹ of EEC of ^{222}Rn was estimated for average indoor conditions. This dosimetry evaluation was reproduced in the UNSCEAR 2006 Report [U6]. By applying an apportioned tissue weighting factor of 0.08 for the bronchial (BB) and bronchiolar (bb) regions [U4] and a radiation weighting factor of 20 for alpha particles [I9], the central value in terms of effective dose per unit EEC of ^{222}Rn exposure became 15 nSv (h Bq m⁻³)⁻¹ with a range of 8–40 nSv (h Bq m⁻³)⁻¹ [U4, U6].

B. Aim and objectives

8. This section focuses on updating the UNSCEAR 2006 Report [U6] with regard to the following aspects: dosimetric models, dosimetry of radon, dose conversion factor, and uncertainties in dose conversion factors. Specific objectives are to address the following questions:

- What is the current status of the development of dosimetric models and model parameters and associated impact on the assessment of radon dose to human lung? What are the uncertainties and variations in the dosimetric assessment?
- What is the current status of dosimetric assessment for smokers and non-smokers?
- What is the current status of dosimetric assessment for different working environments/conditions?

C. Scope and literature search

9. The scope of the review includes results of primary peer-reviewed studies published in the scientific literature and publications of relevant international organizations. The focus is on dosimetric assessments of radon exposure to the lung. Additional background information about different dosimetric models and choice of parameters is found in appendix A.

10. A comprehensive literature review of scientific journal articles published since the UNSCEAR 2006 Report [U6] was conducted to identify studies providing new information on dosimetric assessment of radon exposure in homes, in indoor workplaces and in mines. Due to the physical nature of radon dosimetry, the search was performed with the database of Scopus. The literature search was conducted with query string “Search (((“lung” or “radon” [Title/Abstract]) AND “dosimetr*” [Title/Abstract])) AND (“01/01/2006-”[Date - Publication] : “31/12/2017”[Date - Publication]))).

11. In total, 98 references were identified for the radon dosimetric assessment. All articles were reviewed with respect to authors’ potential conflicts, and by using screening and quality questions. The selection criteria developed by the Committee in its UNSCEAR 2017 Report [U8] were applied for the dosimetric review.

12. Identified publications that did not meet the screening questions were excluded from the review. This included non-original publications, studies in non-human populations, and studies on measurement techniques that were not relevant to dosimetric assessment. Based on the quality questions, reviewers made the final decision on whether to include/exclude studies in the evaluation. Study item reviews, final inclusion/exclusion decisions, and reasons for the decisions were recorded, along with summaries of findings and appraisals for included studies.

13. After an initial literature search additional publications were identified that had been published since 1998 and had not been considered in the UNSCEAR 2006 Report [U6]. In total, 94 publications were reviewed in detail, 50 of them developed/assessed human lung dosimetric models or provided information on human lung dosimetry parameters. A detailed review of the results from these publications are summarized in section D.

D. Review of dosimetric assessments

1. Overview of dosimetric assessments

14. The review results of more recent dosimetric calculations of absorbed dose to regions of the lung and the corresponding dose conversion factor for unit radon progeny exposure in homes, indoor workplaces and mines are summarized in tables 1 to 3, respectively. Information on model type, breathing rates, activity size distribution of the inhaled aerosol, the unattached fraction, the assumed value for the hygroscopic growth factor (*hgf*) or the attached progeny are given whenever available in the literature. Special quantities and units that characterize the concentration and exposure of radon progeny in air, which are used in the summary tables are described in appendix A. The choice and range of model parameter values based on published experimental data are discussed in appendix A. Further, the dose conversion factor approximates the effective dose per unit exposure and is calculated as described in appendix A.

15. The dosimetric calculations have been carried out with deterministic airway generation models (DAGM) [P6, W12, Y2, Y3], stochastic airway generation models (SAGM) [H9, W13] and the ICRP human respiratory tract model (HRTM) [I7, I11]. For more details see also section II in appendix A.

16. In total, 16 assessments are summarized in table 1 for radon exposure in homes under various conditions. The assessed dose conversion factor in terms of effective doses per unit exposure of EEC of ^{222}Rn varied from 7 to 34 nSv (h Bq m⁻³)⁻¹ with an arithmetic mean of 18 nSv (h Bq m⁻³)⁻¹, and a geometric mean of 16 nSv (h Bq m⁻³)⁻¹. The corresponding doses per WLM range from 4 to 21 mSv WLM⁻¹ with an arithmetic mean of 11 mSv WLM⁻¹ and a geometric mean of 10 mSv WLM⁻¹.

17. Dose conversion factors were calculated with the HRTM for different age groups of males and females for home exposure to radon progeny [B13]. The calculated values were 20 mSv WLM⁻¹ for 3-month infants, 21 mSv WLM⁻¹ for 1 year olds, 18 mSv WLM⁻¹ for 5 year olds, 20 mSv WLM⁻¹ for 10 year olds, 18 mSv WLM⁻¹ for 15-year-old males, 16 mSv WLM⁻¹ for 15-year-old females, 18 mSv WLM⁻¹ for adult males and 17 mSv WLM⁻¹ for adult females. Calculations by Marsh et al. [M3] for different age groups with the HRTM gave lower values of 9.6 to 12.9 mSv WLM⁻¹. The reason why the dose per WLM is relatively insensitive to age is that competing effects tend to cancel each other out. For example, children have lower breathing rates, so this decreases the intakes and dose per unit exposure. However, this is partly compensated by the smaller target tissue masses, which in turn increases the dose. Children have smaller airways which increase deposition by diffusion, but this is compensated in part by smaller residence times (i.e. higher respiratory rates) that decrease deposition by diffusion [M1, N9].

18. Marsh et al. [M3] calculated effective doses per unit exposure to radon progeny for adults living in houses with and without smokers. Values for houses with smokers were calculated assuming that the subjects were in a living room in which cigarettes are smoked except while they were asleep in a smoke-free bedroom. Aerosol parameter values assumed were based on measurement data published in the literature [M2, N9, P5]. Effective dose coefficients for houses with and without smokers were 9.9 mSv WLM⁻¹ and 13 mSv WLM⁻¹, respectively. The lower value for homes with smokers was obtained because the unattached fraction was estimated to be lower and because no nucleation mode was assumed in the presence of cigarette smoke. James et al. [J3] calculated higher values of 18 and 21 mSv WLM⁻¹ for houses with and without smokers, respectively, using the HRTM. These values are higher because of the different activity size distribution and unattached fraction assumed by the authors, which were based on the measurements of Hopke et al. [H12, N10]. In contrast, for active smoking where the aerosol is dominated by cigarette smoke and the unattached fraction is negligible, Porstendörfer [P6]

calculated a dose conversion factor of 4.2 mSv WLM^{-1} using the DAGM. The value assuming no additional aerosol sources was 8.0 mSv WLM^{-1} [P6]. The DAGM developed by Zock et al. [Z5] gives correspondingly lower values for attached progeny compared with the HRTM.

19. ICRP has recently updated its Publication 66 HRTM [I7] in Publication 130 [I12]. Changes mainly relate to particle transport from the nasal passages, bronchial tree and alveolar region. However, the lung dose arising from exposure to radon progeny is not very sensitive to the bronchial clearance rates as the progeny are short-lived compared to the half-times [M1]. Therefore, lung doses calculated with the revised model are not significantly different for radon progeny. The effective dose per unit exposure to radon progeny calculated with the this model for home exposure was about 13 mSv WLM^{-1} [M5].

20. The morphometric model used to model aerosol deposition adopted by ICRP [I7] is the one suggested by James [J2]. This model is based on average airway dimensions of three models published by Weibel [W4, W5, W6], Yeh and Schum [Y1] and Phalen et al. [P2] and adjusted to a standard functional residual capacity of $3.3 \times 10^{-3} \text{ m}^3$. With a DAGM, Yu et al. [Y3] compared dosimetric calculations using the morphometric model of James [J2] with that of Yeh and Schum [Y1]. Both models were scaled to the functional residual capacity of the ICRP Reference Man [I8]. The airway generation models were used to determine the equilibrium surface activities per unit exposure in each airway (a cylindrical tube). For the dosimetry calculations, the target cell layers containing basal and/or secretory cells as defined by the HRTM [I7] were assumed. The effective doses calculated with the James model and Yeh-Schum model were respectively 12 and 8 mSv WLM^{-1} for home exposure. Thus, the HRTM predicts higher values than the Yeh-Schum model. The higher dose for the James model arises from the differences in the surface areas of the trachea-bronchial tree (T-B) between the two models [N5]. The James model has a lower surface area, which gives higher surface activities (Bq cm^{-2}) resulting in higher doses compared with the Yeh-Schum model. In other words, lower surface areas of the T-B give lower masses of the assumed target cell regions leading to higher doses. In contrast, Winkler-Heil and Hofmann [W12] also compared the morphometric models of James [J2] with that of Yeh and Schum [Y1] (normalized to the same lung volume). The two models gave similar dose conversion factors.

21. Yu et al. [Y2] carried out dose assessment for Caucasian males, Chinese males and Chinese females using the Yeh-Schum morphometric model [Y1]. Scaling factors based on functional residual capacity and mass were used to scale the airway dimensions for Caucasian males to give those for Chinese males and females. The ventilation rates for Caucasian males were also scaled to give lower values for Chinese males and females. For the dosimetry calculations, the target cell layers containing basal and/or secretory cells as defined by the HRTM [I7] were assumed. The dose conversion factors for a typical home environment for Caucasian males, Chinese males and Chinese females were 9.2, 7.4 and 6.5 mSv WLM^{-1} , respectively. Thus, lower dose conversion factors are obtained for Chinese males and females compared with that for Caucasian males.

22. Nikezic et al. [N6] carried out dose assessments following inhalation of radon progeny with the HRTM [I7] using a micro-dosimetric approach to investigate the effects of calculating cellular doses rather than the approach used by ICRP, where the absorbed doses to target cell layers are calculated. In their calculations the nuclei of basal cells were approximated as cones while those for the secretory cells as ellipsoids instead of spherical cell nuclei as assumed by Hofmann et al. [H8]. The abundance and depth of basal and secretory cells were taken from Mercer et al. [M8]. For indoor exposure, the effective dose calculated was 13 mSv WLM^{-1} with the cellular dose approach compared with 15 mSv WLM^{-1} obtained assuming target cell layers. If spherical target cells are assumed, then the effective dose is $13.5 \text{ mSv WLM}^{-1}$. The authors noted that changes in the geometry of secretory-cell nuclei have only a small effect on their absorbed doses, whereas changes from spherical to conical basal-cell nuclei reduced their absorbed doses from ~ 4 to $\sim 3 \text{ mGy WLM}^{-1}$.

23. Five studies are summarized in table 2 for radon exposure in indoor workplaces under various indoor conditions. The assessed effective doses per unit exposure of EEC of ^{222}Rn varied from 9 to 38 nSv (h Bq m⁻³)⁻¹ with an arithmetic mean of 25 nSv (h Bq m⁻³)⁻¹, and a geometric mean of 23 nSv (h Bq m⁻³)⁻¹. The corresponding doses per WLM, range from 6 to 24 mSv WLM⁻¹ with an arithmetic mean of 16 mSv WLM⁻¹ and a geometric mean of 15 mSv WLM⁻¹.

24. Tokonami et al. [T6] carried out aerosol measurements of particle size and unattached fraction in a computer room, where environmental conditions such as ventilation rate, air-conditioning and the operation of an air cleaner were varied. Using the data and the HRTM with a reference breathing rate of 1.2 m³ h⁻¹ for occupational exposure [I7], the calculated effective dose varied from 20 to 24 mSv WLM⁻¹ with changes in ventilation and air-conditioning (table 2). Lower values of 14 to 17 mSv WLM⁻¹ were calculated assuming a lower breathing rate of 0.78 m³ h⁻¹. With the air-cleaner in operation, the unattached fraction, f_p increased significantly from about 0.12 to 0.56 resulting in a higher effective dose of 56 mSv WLM⁻¹ for occupational exposure.

25. The effective doses per unit radon progeny exposure for indoor workplaces are on average higher than the corresponding values for home exposure. This is mainly because the assumed breathing rate is higher for a worker than for an adult at home. For example, with the revised HRTM of ICRP Publication 130 [I12], the effective doses per WLM are 13 and 20 mSv WLM⁻¹ for homes and indoor workplaces, respectively [I13, M5]. ICRP assumes a reference breathing rate for a standard worker of 1.2 m³ h⁻¹, where one third of the time is spent sitting and two thirds of the time is spent undertaking light exercise [I7]. For a male adult at home, the assumed breathing rate is lower: 0.78 m³ h⁻¹ (55% sleep, 15% sitting and 30% light exercise) [I7]. However, it is acknowledged that the assessed dose conversion factors for indoor workplaces and homes overlap.

26. Solomon et al. [S14] carried out activity size distribution measurements of radon progeny at the Olympic Dam underground uranium mine, Roxby Downs, South Australia in December 2013. Effective dose coefficients were calculated with the HRTM and the aerosol measurement data. For work locations with high ventilation and low levels of PAEC (i.e. at the underground workshop sites), the calculated effective dose was about 23 mSv WLM⁻¹ (6.5 mSv per mJ h m⁻³). The high fraction of the nucleation mode and the high unattached fraction accounted for the relatively high dose coefficient (table 3). For the operational areas of the mine with higher levels of potential alpha energy concentration (PAEC)*, the average effective dose was about 16 mSv WLM⁻¹ (4.5 mSv per mJ h m⁻³) (table 3). This is the most recent dose assessment to date for a mine using modern mining practices.

Table 1. Summary of dosimetric assessments for exposure to radon progeny in homes

GSD = geometric standard deviation; hgf = hygroscopic growth factor

Model type	Aerosol source or action	Breathing rate ($\text{m}^3 \text{h}^{-1}$)	Unattached aerosol characteristics			Attached aerosol characteristics					Absorbed dose per unit exposure ^h (mGy WLM^{-1})	Dose conversion factor		Year	Reference
			f_p^a	Particle size ^b (nm)	GSD	Mode, j^d	f_{pi}^e	Particle size ^{b,f} (nm)	GSD	hgf		mSv per WLM	nSv per h Bq m^{-3} of EEC		
HRTM [I7]	Typical home environment	0.78	0.08	0.9	1.3	n, a, c	$f_{pn}=0.28$, $f_{pa}=0.7$, $f_{pc}=0.02$	50 ^f , 250 ^f , 1 500 ^f	2.0, 2.0, 1.5	1.5	BB: 8.9 bb: 9.2 AI: 0.33	15	23	2000	[M1]
DAGM [Z5]	A: no sources B: with sources (active smoking)	0.75	A: 0.05 (0.02–0.14) B: 0.005 (0.0008–0.02)	0.8	1.2	A: n, a B: a	A: $f_{pn}=0.3$, $f_{pa}=0.7$ B: $f_{pa}=1$	A: 20–40 ^f , 210 (120–350) ^f , B: 300 ^f	A: 1.7–2.2 (1.6–3.0) B: 2.0	A: 2.0 B: 1.0		A: 8.0 ^g B: 4.2 ^g	A: 13 ^g B: 7 ^g	2001	[P6]
DAGM [Y1, Y2]	Typical home environment		0.08	1.1				200 ^b				Chinese male: 7.4 Chinese female: 6.5 Caucasian male: 9.2	Chinese male: 12 Chinese female: 10 Caucasian male: 14	2001	[Y2]
Morphometry model: A: [J1]; B: [Y1]			0.08	1.1				200 ^b	2.35			A: 12 B: 8.1	A: 19 B: 13	2001	[Y3]
DAGM [W12]		0.78	0.08	0.9	1.3	n, a, c	$f_{pn}=0.28$, $f_{pa}=0.7$, $f_{pc}=0.02$	50 ^f , 250 ^f , 1 500 ^f	2.0, 2.0, 1.5	1.5	BB: 5.45 bb: 5.50	8.8	14	2002	[W12]
HRTM [I7]	A: non-smoking B: smoking	0.78	A: 0.15 B: 0.08							1	A: 8.9 ⁱ B: 7.5 ⁱ	A: 21 B: 18	A: 34 B: 28	2004	[J3]

Model type	Aerosol source or action	Breathing rate ($\text{m}^3 \text{h}^{-1}$)	Unattached aerosol characteristics			Attached aerosol characteristics					Absorbed dose per unit exposure ^h (mGy WLM^{-1})	Dose conversion factor		Year	Reference
			f_p^a	Particle size ^b (nm)	GSD	Mode, i^d	f_{pi}^e	Particle size ^{b,f} (nm)	GSD	hgf		mSv per WLM	nSv per h Bq m^{-3} of EEC		
HRTM [I7]	A: typical home without smokers B: typical home with smokers	0.75	A: 0.1 B: 0.03	0.9	1.3	A: n, a, c B: a	A: $f_{pn}=0.15$, $f_{pa}=0.83$, $f_{pc}=0.02$ B: $f_{pa}=1.0$	A: 50^f , 230^f , $2\,500^f$ B: 348^f	A: 2.0, 2.1, 1.5 B: 2.0	A: 2.0 B: 1.0		A: 13 B: 9.9	A: 20 B: 16	2005	[M3]
HRTM [I7]		0.78	0.066	0.9	1.3	n, a, c	$f_{pn}=0.28$, $f_{pa}=0.7$, $f_{pc}=0.02$	50^f , 250^f , $1\,500^f$	2.0, 2.0, 1.5	1.5	BB: 8.42 bb: 10.4	15.1	24	2006	[L5]
HRTM [I7] with cellular micro-dosimetry [N6]		0.78	0.066	0.9	1.3	n, a, c	$f_{pn}=0.28$, $f_{pa}=0.7$, $f_{pc}=0.02$	50^f , 250^f , $1\,500^f$	2.0, 2.0, 1.5	1.5	BB: 6.4 bb: 10	13	20	2006	[N6]
HRTM [I7]		0.78	0.1	1.0		n, a, c	$f_{pn}=0.15$, $f_{pa}=0.83$, $f_{pc}=0.02$	50^f , 230^f , $2\,500^f$				15	24	2011	[A2]
SAGM (IDEAL-DOSE) ^c [H9, H10]		0.78	0.1	0.8	1.3	n, a	$f_{pn}=0.2$, $f_{pa}=0.8$	40^f , 230^f	2.0, 2.1	2	BB: 4.17 bb: 2.51	5.3	8	2011	[H10]
Revised HRTM [I12]		0.78	0.1	0.9	1.3	n, a	$f_{pn}=0.2$, $f_{pa}=0.8$	40^f , 230^f	2.0, 2.0	2		13	20	2013	[M5]
HRTM [I7]		Adults A: male 0.78 B: female 0.61	0.1	1.0	1.0	n, a, c	$f_{pn}=0.14$, $f_{pa}=0.75$, $f_{pc}=0.02$	50^f , 230^f , $2\,500^f$	1.45, 2.26, 2.26	1.0		A: 18 B: 17	A: 28 B: 27	2014	[B13]

Model type	Aerosol source or action	Breathing rate ($\text{m}^3 \text{h}^{-1}$)	Unattached aerosol characteristics			Attached aerosol characteristics					Absorbed dose per unit exposure ^h (mGy WLM^{-1})	Dose conversion factor		Year	Reference
			f_p ^a	Particle size ^b (nm)	GSD	Mode, i ^d	f_{pi} ^e	Particle size ^{b,f} (nm)	GSD	hgf		mSv per WLM	nSv per h Bq m^{-3} of EEC		
SAGM (IDEAL-DOSE) ^c [H9]	Indoors	0.78	0.08	1.2	1.1	a		150 ^b	2.0		T-B ^j : 6.2 AI: 0.17	10	16	2014	[W11]
SAGM (IDEAL-DOSE) ^c [H9, H10]	Home	0.78	0.08	1.0	1.3	a		300 ^b	2.1	1.0	T-B ^j : 4.62 AI: 0.15	7.5	12	2015	[W15]
SAGM (IDEAL-DOSE) ^c [H9]	Indoors	0.54 (sitting)	0.08	1.0	1.3	a		300 ^b	2.1	1.0	BB: 5.53 bb: 2.34	6.3	10	2015	[H11]
Arithmetic mean												11	18		
Geometric mean												10	16		
Range												4 to 21	7 to 34		

^a f_p is the unattached fraction, in terms of PAEC.

^b AMTD = activity median thermodynamic diameter.

^c IDEAL-DOSE code comprises three stochastic models based on Monte Carlo methods, a stochastic particle deposition model, a stochastic bronchial clearance model, and a stochastic cellular dosimetry model [H9, W13].

^d The attached size distribution may consist of three modes, these are the nucleation mode (n), the accumulation mode (a) and the coarse mode (c).

^e f_{pi} is the fraction of the attached PAEC associated with mode i . The indices, n, a, and c represent the nucleation mode, the accumulation mode and the coarse mode, respectively.

^f AMAD = activity median aerodynamic diameter.

^g Apportionment factors of ($A_{BB}=0.80$, $A_{bb}=0.15$, $A_{AI}=0.05$) were assumed [J1].

^h The absorbed dose per WLM to regions of the lung. BB = bronchial; bb = bronchiolar; AI = alveolar interstitial.

ⁱ Absorbed dose per WLM averaged for all target cell nuclei in the lung regions (BB, bb and AI).

^j Absorbed dose per WLM averaged for all target cell nuclei in the trachea-bronchial tree (T-B).

27. Table 3 summarizes 12 dosimetric assessments for radon exposure in mines under various working conditions. Under mining conditions, the assessments were made for exposure to radon progeny in the historical units of WLM, and for the most recent assessment [S14] in units of mJ h m^{-3} . The assessed dose factors varied from 4 to 23 mSv WLM^{-1} [1.2 to 6.6 $\text{mSv per mJ h m}^{-3}$; 7 to 37 $\text{nSv (h Bq m}^{-3})^{-1}$ of EEC] with an arithmetic mean of 12 mSv WLM^{-1} [3.3 $\text{mSv per mJ h m}^{-3}$; 18 $\text{nSv (h Bq m}^{-3})^{-1}$ of EEC], and a geometric mean of 11 mSv WLM^{-1} [3.0 $\text{mSv per mJ h m}^{-3}$; 17 $\text{nSv (h Bq m}^{-3})^{-1}$ of EEC].

28. Solomon et al. [S14] also made a comparison of the measurement results of December 2013 with the measurement analysis carried out in 1992 [S15]. The 1992 measurement results were interpreted in terms of “diesel” and “non-diesel” areas of the mine and the assessed average effective doses were about 16 mSv WLM^{-1} and 27 mSv WLM^{-1} , respectively with the HRTM model. A re-evaluation of the 1992 measurement results determined sites “away from the actual working mine areas”. For these sites the effective dose was calculated as 24 mSv WLM^{-1} similar to the dose calculated for the workshops based on the 2013 measurements. Sites “close to the operating areas of the mine” with higher PAEC values were also identified from the 1992 data. Again, these gave similar doses (15 mSv WLM^{-1}) to the assessed doses based on the 2013 aerosol measurements of operational sites [S14].

29. Winkler-Heil et al. [W13] compared predicted effective doses for radon progeny inhalation obtained using the HRTM, DAGM and SAGM models. The same input parameter values were assumed for mine conditions. The three models yielded similar results: 8.3 mSv WLM^{-1} for the DAGM, 8.9 mSv WLM^{-1} for the SAGM and 11.8 mSv WLM^{-1} for the HRTM. Thus, the HRTM gives a higher value compared with the airway generation models by about 25 to 30%. The authors noted that one of the important issues affecting the comparison is the averaging procedure for the cellular doses calculated in airway generation models. For this comparison, cellular doses were averaged with equal weights over all airway generations, which is the equivalent to calculation of the arithmetic mean. It was also noted that the regional lung deposition fractions for the attached progeny were similar in the BB and bb regions for all three models. However, the HRTM predicted higher deposition fractions in the bb region for the unattached progeny.

30. Target basal and secretory cell nuclei receive a wide range of doses among human bronchial and bronchiolar airways. With the SAGM, distributions of weighted epithelial doses for each airway generation have been calculated taking account of the intra- and inter-subject variability in the morphology of the respiratory tract. These dose distributions are very wide with geometric standard deviations ranging from about 2 to 7 depending on airway generation [H9, H10]. The weighted epithelial doses were obtained by weighting the doses to the basal and secretory cells by their relative volumetric densities. Taking the median of these distributions to compute an average lung dose resulted in effective dose coefficients of 4 mSv WLM^{-1} (7 $\text{nSv per h Bq m}^{-3}$ of EEC) for mine exposure [H9, H10]. However, taking the arithmetic mean of all the cellular doses gives rise to a higher effective dose coefficient of 9 mSv WLM^{-1} for mine exposure (14 $\text{nSv per h Bq m}^{-3}$ of EEC) [W13, W15].

31. Smoking may change the morphological and physiological parameters of the lung. Lung dosimetry for inhaled radon progeny in smokers was studied by Baiaş et al. [B1, B2] using the SAGM for four different categories of smokers. These were: (a) light, short-term smokers; (b) light, long-term smokers; (c) heavy, short-term smokers; and (d) heavy, long-term smokers. Calculations were performed for a typical mine atmosphere, and for never smokers a dose conversion factor of 7.2 mSv WLM^{-1} was estimated [B2]. Dose conversion factors for light, short-term smokers hardly differed (<1%) from those for never smokers because only small changes in morphological and physiological parameters have been reported. For light, long-term smokers and heavy, short-term smokers, lung doses were reduced due to the thickening of the mucous layer. The majority of the studies reviewed by the authors indicated an average thickening of the mucous layer between 20 to 40%. Assuming a thickening of the mucous layer of 28%, reduced the dose conversion factor by about 10% compared with never smokers. For heavy, long-term smokers, the determining factors

modelled by the authors were: thicker mucous layer, impaired mucociliary clearance, higher breathing frequencies and reduced lung volume due to obstructive lung diseases. The combined effect of these factors increased the dose conversion factor by approximately a factor of two relative to a never smoker. Histological data show that heavy long-term smoking can damage and destroy cilia, and consequently the authors assumed a significant decrease in mucociliary clearance [B2] (see also section III.F, appendix A). It is noted that physiological and morphological data of the influence of smoking vary widely among different sources, so the physiological effects of smoking categorized by the authors represent only rough approximations [I14]. However, it can be concluded that the results of the dosimetric calculations alone cannot account for the large difference in risk between smokers and never smokers due to the sub-multiplicative or multiplicative interaction* between smoking and radon. For example, assuming a multiplicative interaction between smoking and radon, the absolute risk of lung cancer per unit increase in radon is about 25 times greater in current smokers (of 15–24 cigarettes d⁻¹) compared with lifelong non-smokers [D3].

Table 2. Summary of dosimetric assessments for exposure to radon progeny in indoor workplaces

GSD = geometric standard deviation; hgf = hygroscopic growth factor

Model type	Aerosol source or action	Breathing rate ($\text{m}^3 \text{h}^{-1}$)	Unattached aerosol characteristics			Attached aerosol characteristics					Absorbed dose per unit exposure ^g (mGyWLM^{-1})	Dose conversion factor		Year	Reference
			f_p^a	Particle size ^b (nm)	GSD	Mode, i^c	f_{pi}^d	Particle size ^{b,e} (nm)	GSD	hgf		mSv per WLM	nSv per h Bq m^{-3} of EEC		
DAGM [Z5]	With cigarette smoking	1.2	0.005	0.8	1.2	a	1.0	300 ^e	2.0	1.0		5.7	9	1999	[P5]
DAGM [Z5]	A: no sources B: with sources & coarse mode	1.2	A: 0.05 (0.02-0.14) B: 0.01 (0.007-0.02)	0.8	1.2	A: n, a B: n, a, c	A: 0.3, 0.7 B: 0.3, 0.6, 0.1	A: 15-40 ^e , 300 ^e (150-450) B: 15-40 ^e , 300 ^e , 5 000 ^e (3 000-8 000)	A: 1.6-2.2, 2.5 (1.8-4.0) B: 1.6-2.2, 2.5, 1.8(1.1-2.8)	A: 2.0 B: 1.0		A: 11.5 ^f B: 11.2 ^f	A: 18 ^f B: 18 ^f	2001	[P6]
HRTM [I7]	A: A/C on, Vent. off B: A/C off, Vent. off C: A/C on, Vent. On	1.2	A: 0.13 B: 0.10 C: 0.13					A: 196 B: 210 C: 193	A: 1.6 B: 1.6 C: 1.7			A: 22.3 B: 19.9 C: 24.2	A: 35 B: 31 C: 38	2003	[T6]
HRTM [I7]	Mineral treatment industry: Office building	1.2		1.0	1.3	a	1.0	470 ^e	2.2	1.0		13	20	2012	[K4]

Model type	Aerosol source or action	Breathing rate ($\text{m}^3 \text{h}^{-1}$)	Unattached aerosol characteristics			Attached aerosol characteristics					Absorbed dose per unit exposure ^g (mGyWLM^{-1})	Dose conversion factor		Year	Reference
			f_p ^a	Particle size ^b (nm)	GSD	Mode, i ^c	f_{pi} ^d	Particle size ^{b,e} (nm)	GSD	hgf		mSv per WLM	nSv per h Bq m ⁻³ of EEC		
Revised HRTM [I12]		1.2	0.08	1.0	1.3	n a	0.2 0.8	30 ^b 250 ^b	2.0 2.0	2 2	BB: 11 ^h bb: 11 ^h AI: 0.5 ^h	20	31	2017	[I13]
Arithmetic mean												16	25		
Geometric mean												15	23		
Range												6 to 24	9 to 38		

^a f_p is the unattached fraction, in terms of PAEC.

^b AMTD = activity median thermodynamic diameter.

^c The attached size distribution may consist of three modes, these are the nucleation mode (n), the accumulation mode (a) and the coarse mode (c).

^d f_{pi} is the fraction of the attached PAEC associated with mode i. The indices, n, a, and c represent the nucleation mode, the accumulation mode and the coarse mode, respectively.

^e AMAD = activity median aerodynamic diameter.

^f Apportionment factors of ($A_{BB}=0.80$, $A_{bb}=0.15$, $A_{AI}=0.05$) were assumed [J1].

^g The absorbed dose per WLM to regions of the lung. BB = bronchial; bb = bronchiolar; AI = alveolar interstitial.

^h These regional doses averaged between males and females were used to calculate effective doses per WLM for ICRP Publication 137 [I13, M7].

Table 3. Summary of dosimetric assessments for exposure to radon progeny in mines

GSD = geometric standard deviation; hgf = hygroscopic growth factor

Model type	Aerosol source or action	Breathing rate ($\text{m}^3 \text{h}^{-1}$)	Unattached aerosol characteristics			Attached aerosol characteristics					Absorbed dose per unit exposure ^k (mGyWLM^{-1})	Dose conversion factor		Year	Reference
			f_p^a	Particle size ^b (nm)	GSD	Mode, j^d	f_{pi}^e	Particle size ^{b,f} (nm)	GSD	hgf		mSv per WLM	nSv per h Bq m^{-3} of EEC		
DAGM [Z5]	A: working + diesel B: without working	A: 1.7 ^g B: 1.2	A: 0.006 B: 0.02	0.8		a		A: 200 ^f B: 350 ^f		1		A: 9.0 B: 6.7	A: 14 B: 11	1999	[P5]
HRTM [I7]		1.2	0.028							1	8.7 ^h	21	33	2004	[J3]
HRTM [I7]	Typical mine	1.2	0.01	0.8	1.3	a		250 ^b	2.4	2		12.5	20	2005	[M3]
A: HRTM [I7] B: DAGM [W12] C: SAGM (IDEAL-DOSE) ^c [W13]	Uranium mines	1.2	0.01	0.8	1.3	a		250 ^f	2.39	2		A: 11.8 B: 8.3 C: 8.9	A: 19 B: 13 C: 14	2007	[W13]
SAGM (IDEAL-DOSE) ^c [W13]	A: never-smoker B: light, short-term smoker C: light, long-term smoker ^g D: heavy, short-term smoker ^g E: heavy, long-term smoker	1.2	0.01	0.8	1.3	a		250 ^f	2.39	2		A: 7.20 B: 7.25 C: 6.4 ⁱ D: 6.4 ⁱ E: 13.34	A: 11 B: 11 C: 10 ⁱ D: 10 ⁱ E: 21	2010	[B2]

Model type	Aerosol source or action	Breathing rate (m ³ h ⁻¹)	Unattached aerosol characteristics			Attached aerosol characteristics					Absorbed dose per unit exposure ^k (mGyWLM ⁻¹)	Dose conversion factor		Year	Reference
			f _p ^a	Particle size ^b (nm)	GSD	Mode, j ^d	f _{pl} ^e	Particle size ^{b,f} (nm)	GSD	hgf		mSv per WLM	nSv per h Bq m ⁻³ of EEC		
SAGM (IDEAL-DOSE) ^c [H9]	Typical mining condition	1.2	0.01	0.8	1.3	a		250 ^b	2.39	1.5	BB: 3.18 bb: 2.25	4.3	7	2010	[H9]
SAGM (IDEAL-DOSE) ^c [H9, H10]		1.2	0.01	0.8	1.3	a		250 ^b	2.39	2	BB: 4.5 bb: 2.05	5.2	8.2	2011	[H10]
HRTM [17]	Uranium mines wet drilling + medium ventilation (no diesel)	1.2	0.01	0.8	1.3	a		250 ^f	2.2	1.5	BB: 6.7 bb: 7.0 AI: 0.4	11	18	2012	[M4]
Revised HRTM [112]	Diesel-powered mine with medium-to-good ventilation	1.2	0.01	0.9	1.3	a		250 ^b	2.0	1.0		10.6	17	2013	[M5]
SAGM (IDEAL-DOSE) ^c [H9, H10]	Uranium mine	1.2	0.01	1.0	1.3	a		500 ^b	2.4	1.0	T-B ⁴ : 5.54 AI: 0.09	8.9	14	2015	[W15]
Revised HRTM [112]	Diesel-powered mine with medium-to-good ventilation	1.2	0.01	1.0	1.3	a		250 ^b	2.0	1.0	BB: 4.6 ^l bb: 8.3 ^l AI: 0.4 ^l	11	17	2017	[I13]

Model type	Aerosol source or action	Breathing rate (m ³ h ⁻¹)	Unattached aerosol characteristics			Attached aerosol characteristics					Absorbed dose per unit exposure ^k (mGyWLM ⁻¹)	Dose conversion factor		Year	Reference
			f _p ^a	Particle size ^b (nm)	GSD	Mode, i ^d	f _{pi} ^e	Particle size ^{b,f} (nm)	GSD	hgf		mSv per WLM	nSv per h Bq m ⁻³ of EEC		
Revised HRTM [I12]	A: 420 Drill workshop	1.2	A: 0			A: n, a	A: 0.46, 0.53	A: 28 ^b , 267 ^b	A: 1.2, 1.3			A: 23	A: 36	2018	[S14]
	B: 420 Auto workshop		B: 0.28	B: 0.6	B: 1.1	B: a	B: 1.0	B: 160 ^b	B: 2.0			B: 23	B: 37		
	C: 49MB52 Exploration		C: 0			C: n, a	C: 0.1, 0.9	C: 27 ^b , 186 ^b	C: 1.2, 1.2			C: 14	C: 21		
	D: 39Blue 102, drilling site		D: 0			D: n, a	D: 0.33, 0.67	D: 42 ^b , 182 ^b	D: 1.4, 1.4	1.0		D: 17.5	D: 27		
	E:36Yellow 419, drilling site		E: 0			E: n, a	E: 0.33, 0.68	E: 38 ^b , 179 ^b	E: 1.4, 1.7			E: 17	E: 27		
	F: Whenan crusher		F: 0			F: a	F: 1.0	F: 114 ^b	F: 1.6			F: 15	F: 24		
Arithmetic mean												12	18		
Geometric mean												11	17		
Range												4 to 23	7 to 37		

^a f_p is the unattached fraction, in terms of PAEC.

^b AMTD = activity median thermodynamic diameter.

^c IDEAL-DOSE code comprises three stochastic models based on Monte Carlo methods, a stochastic particle deposition model, a stochastic bronchial clearance model, and a stochastic cellular dosimetry model [H9, W13].

^d The attached size distribution may consist of three modes, these are the nucleation mode (n), the accumulation mode (a) and the coarse mode (c).

^e f_{pi} is the fraction of the attached PAEC associated with mode i. The indices, n, a, and c represent the nucleation mode, the accumulation mode and the coarse mode, respectively.

^f AMAD = activity median aerodynamic diameter.

^g At the higher breathing rate of 1.7 $\text{m}^3 \text{h}^{-1}$, Porstendörfer and Reineking [P5] assumed the miner breathed through the mouth, whereas miners with a breathing rate of 1.2 $\text{m}^3 \text{h}^{-1}$ were assumed to be nose breathers.

^h Absorbed dose per WLM averaged for all target cell nuclei in the lung regions (BB, bb and AI).

ⁱ For light, long-term smoker and the heavy, short-term smoker it is assumed that the mucous thickness increases by 128±5%. However, some publications argued that the increase in mucous thickness is much greater (500±200%), and assuming these values would give an effective dose coefficient of 1.74 mSv WLM^{-1} (3 nSv per h Bq m^{-3} of EEC) [B2].

^j Absorbed dose per WLM averaged for all target cell nuclei in the trachea-bronchial (T-B) tree.

^k The absorbed dose per WLM to regions of the lung. BB = bronchial; bb = bronchiolar; AI = alveolar interstitial.

^l These regional doses averaged between males and females were used to calculate effective doses per WLM for ICRP Publication 137 [I13, M7].

2. Uncertainties and variations in dosimetric assessment

32. Uncertainties in the calculated doses occur due to the uncertainty and variability of model parameter values and due to uncertainties associated with the assumptions built into the particular model. Such uncertainties may arise because the structure of the model provides an over-simplification of the known processes; because the calculations cannot account for unknown processes; or because part of the model structure is based on mathematical convenience rather than the actual processes [I12].

33. Several researchers have carried out uncertainty analyses of the lung dose per unit exposure to radon progeny [B8, H3, H9, I14, M2, W12, Z5]. The main sources of uncertainty considered include:

- The activity size distribution of the radon progeny aerosol including the unattached fraction;
- The breathing rates;
- The model used to predict aerosol deposition in the respiratory tract;
- Lung clearance including mucociliary clearance and absorption into blood;
- The identification of the target cells and their location within the bronchial and the bronchiolar epithelium;
- The inter-subject variation in the morphology of the lung;
- The relative sensitivity of different cell types to radiation;
- The regional differences in the radiation sensitivity of the lung.

34. The range of variations and uncertainties associated with the model parameters were recently assessed by Harley [H3]. There are five major parameters that must be evaluated to model and calculate bronchial airway dose from inhaled radon and its progeny. These are the breathing rate, inhaled activity particle size, airway particle deposition, airway particle clearance, and target cell depth within the bronchial epithelium. Overall, the models and the parameters that define a model showed that dose factors are variable ranging 20 to 50% from a mean value [H3].

35. Marsh and Birchall [M1] performed a sensitivity analysis to identify those HRTM parameters that significantly affect the equivalent dose* to lung (H_{lung}) per WLM under typical conditions found in houses. However, the ICRP alpha radiation factor, w_R was not included in the sensitivity analysis. Using reference parameter values or “best estimate values” proposed by the authors, the effective dose was calculated to be 15 mSv WLM⁻¹. The sensitivity of H_{lung} per WLM to each of the HRTM parameters was examined by varying the values of one while keeping all other parameters equal to their reference values. The parameters most affecting H_{lung} per WLM were the unattached fraction, the unattached aerosol size, the nucleation fraction, the nucleation aerosol size, the breathing rate, the basal cell weighting factor, and the target cell layer depth and thickness of the target cell layer. Table 4 shows the sensitivity of the dose conversion factor (mSv WLM⁻¹) to these parameters, quantified by the reliability factor. The reliability factor is defined as $(B/A)^{1/2}$, where A and B are the minimum and maximum values of the dose conversion factor per WLM within the given parameter value range, respectively. Thus, all values between A and B are within the reliability factor of the geometric mean of A and B . For the unattached fraction (f_p), ranging from 0.03 to 0.15, the effective dose varies from 13 to 18 mSv WLM⁻¹, an increase of 38%. Without a nucleation mode, the effective dose would decrease from 15 to 11 mSv WLM⁻¹, a decrease of 30%.

Table 4. Sensitivity of the dose conversion factor to HRTM parameters

Best estimate values for aerosol parameters are those proposed by the authors for home conditions [M1]

Description of parameter	Best estimate or reference value	Parameter value range	Range of dose conversion factors ^a (mSv WLM ⁻¹)	Reliability factor ^b
Breathing rate	0.78 m ³ h ⁻¹	0.45–1.5 m ³ h ^{-1 c}	10–25	1.58
Nucleation aerosol size (AMAD)	50 nm	10–80 nm	12–24	1.36
Unattached fraction (f_p) ^d	0.08	0.03–0.20	13–20	1.26
Nucleation fraction ^e	0.28	0–0.4	11–16	1.21
Basal cell weighting factor ^f	0.5	0–1	12–17	1.19
Target cell layer depth and thickness factor ^g	1	0.5–1	15–21	1.18
Unattached aerosol size (AMTD)	0.9 nm	0.5–3.5 nm	13–18	1.18
Fraction breathed through nose (F_n)	1.0	0.4 ^h –1	15–19	1.13

^a The dose conversion factor was calculated as $w_{\text{lung}} \times H_{\text{lung}} = 0.12 \times H_{\text{lung}}$, which approximates the effective dose, whereas w_{lung} is the ICRP lung tissue weighting factor.

^b The reliability factor is defined as $(B/A)^{1/2}$, where A and B are the minimum and maximum values of the dose conversion factor per WLM within the given parameter value range, respectively.

^c The ICRP reference ventilation rates for sleep and light exercise are 0.45 and 1.5 m³ h⁻¹, respectively [I7].

^d Expressed as a fraction of the total PAEC.

^e Expressed as a fraction of the attached PAEC.

^f HRTM assumes that the basal and secretory cell populations in the bronchial epithelium are equally sensitive to dose [I7]. Thus $H_{\text{BB}} = 0.5H_{\text{bas}} + 0.5H_{\text{sec}}$. A basal cell weighting factor of 1.0 means that $H_{\text{BB}} = H_{\text{bas}}$, whereas a basal cell weighting factor of zero means that $H_{\text{BB}} = H_{\text{sec}}$.

^g This parameter is a multiplying factor by which the target cell layer depth and thickness of the target cell layer are multiplied.

^h ICRP Publication 66 recommends an F_n value of 0.4 for a mouth breather performing light exercise [I7].

36. The effective dose is very sensitive to particle sizes of the unattached mode (0.5 to 5 nm) and the nucleation mode (10 to 100 nm). However, it is less sensitive to particle sizes in the region of 150 to 900 nm corresponding to the accumulation mode [I13, I14, J3, P6].

37. Marsh et al. [M2] carried out a parameter uncertainty analysis with the HRTM to calculate the probability distribution of the effective dose per unit exposure to radon progeny in the home. Parameters considered included: (a) aerosol parameters; (b) subject related parameters such as breathing rate, fraction breathed through the nose, and particle transport rates; (c) target cell parameters such as depth of basal and secretory cell layer; and (d) absorption rates of attached and unattached radon progeny. The resulting distribution was approximately log-normal with a geometric mean of 14 mSv WLM⁻¹ (95% confidence interval* corresponded to 6.3–31 mSv WLM⁻¹) and a geometric standard deviation of 1.5. Birchall and James [B8] also carried out a parameter uncertainty analysis with the HRTM to calculate the distribution of effective doses per unit exposure to radon progeny in a mine and obtained similar results for the statistical parameters of the dose distribution.

38. Hofmann et al. [H9] carried out an uncertainty analysis with the SAGM to derive the frequency* distribution of bronchial doses per WLM. The inter- and intra-subject variability of the airway

dimensions, the respiratory parameters, the mucociliary clearance rates and the depth of the target cells were all considered, while aerosol parameter values were fixed for a “typical” mine atmosphere. In the model, the depth of the target cells is assumed to be related to the airway diameters. Resulting bronchial dose distributions were approximated by log-normal distributions; BB: median=3.2 mGy WLM⁻¹, $\sigma_g=2.3$; and bb: median=2.3 mGy WLM⁻¹, $\sigma_g=4$. The median values correspond to an effective dose coefficient of 4 mSv WLM⁻¹ (7 nSv per h Bq m⁻³ of EEC). The geometric standard deviations, σ_g of the bronchial dose distributions for a given airway generation ranged from about 2 to 3 in airway generations 1–9 and from 3 to 7 in airway generations 10–20. Thus, the inter-subject variations were significantly higher in the peripheral bronchial airways than in the larger bronchial airways. The results also show that a small fraction of cells in each airway generation may receive doses that are roughly an order of magnitude higher than the median doses, particularly for the peripheral airways. The parameters that most affected the dose distribution were the asymmetry and variability of the airway dimensions, the filtering efficiency of nasal passages, and the depth of the target cells. The dose distributions are much wider than the distributions obtained with the HRTM [M2, M4] indicating that inter-subject variability in the morphology of the respiratory tract is an important source of uncertainty in the dose calculations.

39. Hofmann and Winkler-Heil [H11] investigated the effects of different weighting procedures for combining target cell doses to calculate an average lung dose with the SAGM. These included equal weighting for basal and secretory cells and weighting factors based on: (a) relative frequencies of basal and secretory cells; (b) number of progenitor cells; (c) contribution of dose enhancement at airway bifurcations; and (d) promotional effect of cigarette smoking. Calculations were performed assuming aerosol parameters for indoor exposure with a breathing rate for sitting (0.54 m³ h⁻¹). Assuming the ICRP apportionment factors of ($A_{BB}=0.333$, $A_{bb}=0.333$, $A_{AI}=0.333$) [I7], the detriment-weighted absorbed dose to lung range from 2.1 to 3.4 mGy WLM⁻¹; (corresponding to dose conversion factors between 6.3 and 8.2 mSv WLM⁻¹). This represents a variation of a factor 1.6. However, assuming ($A_{BB}=0.80$, $A_{bb}=0.15$, $A_{AI}=0.05$) [J1], the variation in the lung doses is greater with dose conversion factors ranging from 6.0 to 21 mSv WLM⁻¹, which represents a variation of a factor 3.5.

E. Summary of dosimetric assessments

40. Published results of dosimetric calculations carried out with the HRTM, DAGM or SAGM models are summarized in tables 1 to 3 for radon progeny exposure in homes, indoor workplaces and mines. The absorbed doses to regions of the lung and the corresponding effective dose per unit radon exposure are given. Due to uncertainties associated with the model parameter values and with the assumptions built into particular models, the variation of the assessed effective dose coefficients is large. The mean values of effective dose coefficients calculated with dosimetric models are similar for exposure in homes and in underground mines (18 nSv per h Bq m⁻³ of EEC of ²²²Rn; tables 1 and 3). However, the assessed mean effective dose coefficient is higher for indoor workplaces (25 nSv per h Bq m⁻³ of EEC of ²²²Rn) compared with that for home exposure. This is mainly because the assumed breathing rate is higher for a worker compared with an adult at home.

41. For home exposure, the range of the assessed effective doses per unit of exposure of EEC of ²²²Rn are from 7 to 34 nSv per h Bq m⁻³ with an arithmetic mean of 18 nSv per h Bq m⁻³, and a geometric mean of 16 nSv per h Bq m⁻³. This is similar to the central value of 15 nSv per h Bq m⁻³ previously estimated by the Committee in the range of 8–40 nSv per h Bq m⁻³ of EEC of ²²²Rn for average indoor conditions based on dosimetric evaluations [U4, U6].

III. EPIDEMIOLOGY

A. Introduction

42. Radon (^{222}Rn) is widely regarded as the second leading cause of lung cancer among tobacco smokers and the leading cause among non-smokers. Already in 1988, the International Agency for Research on Cancer (IARC) classified radon as a proven human carcinogen and placed radon in the same IARC carcinogen group as tobacco smoke, asbestos and benzene [I1]. Accordingly, there is great interest in considering the exposure to radon as a public health issue and in estimating the lung cancer risk from exposure to radon in both occupational and residential settings. The World Health Organization (WHO) provided several guidelines and recommendations to the management of health risk related to radon as an indoor air pollutant [W7, W8, W9]. A recent analysis of 66 countries conducted by Gaskin et al. [G1] concluded that 16.5% of lung cancer cases were attributable to residential radon exposure.

43. The Committee has previously considered the issue of effects from radon exposure (including ^{220}Rn commonly known as thoron) with regard to workers and the public in two comprehensive reports in 2000 and 2006 [U3, U6]. The Committee also concluded that inhaled radon and its progeny are established carcinogens for the lung, however, doses to other organs and tissues were at least an order of magnitude smaller than the doses to the lung. In the UNSCEAR 2006 Report, studies of miners occupationally exposed to radon were noted to provide a direct basis for assessing their lung cancer risk [U6]. The sixth report from the United States National Research Council's Committee on Health Risks of Exposure to Radon in the study series Biological Effects of Ionizing Radiation (BEIR VI) had previously estimated an excess relative risk (ERR)* of 0.012 (95% CI: 0.002, 0.025) per WLM for miners with radon exposure below 50 WLM [N10]. The Committee reviewed in its UNSCEAR 2006 Report [U6] cohort studies of miner cohorts that had been updated since BEIR VI and found the general patterns of risk with dose and time since exposure to be consistent with the BEIR VI findings. Because of high exposure levels in the early days of the mining industry, studies of miners were identified as providing a strong basis for investigating the effects of potential modifiers of the dose-response relationship, such as age at exposure, attained age*, radon exposure rate and time since exposure.

44. Prior to the UNSCEAR 2006 Report, radon concentrations in mines were routinely extrapolated down to those typical in homes to provide an indirect basis for assessing the lung cancer risk from residential exposure to radon [U6]. However, by the time of the report, direct risk estimates were available from over 20 published epidemiological studies of residential exposure. The Committee evaluated these studies and identified the pooled analyses of European, North American, and Chinese residential case-control studies as the primary sources of synthesized residential risk estimates. Based on the available evidence, it was concluded that there was a small but detectable increased frequency of lung cancer from residential exposure that increased with increasing exposure. In particular, the Committee recommended adoption of the uncertainty-corrected excess relative risk estimate of 0.16 (95% CI: 0.05, 0.31) per 100 Bq m⁻³ from a pooled analysis of the European studies [D3]. Furthermore, smokers were inferred to account for nearly 90% of the population average risk from residential radon due to a synergistic interaction between the effects of radon exposure and inhalation of tobacco smoke.

45. Although there are major uncertainties in extrapolating lung cancer effects of radon exposure in mines to the residential setting, good agreement was observed between risk estimates derived from miner studies and those derived from residential case-control studies. Nevertheless, the Committee concluded in the UNSCEAR 2006 Report that more work is needed to better understand and account for the influence of modifying and confounding factors, especially tobacco smoking [U6].

B. Aim and objectives

46. The main aim of the present literature review is to update the UNSCEAR 2006 Report [U6] with the best and most up-to-date knowledge concerning lung cancer risk due to residential and occupational radon exposure, and uncertainties in exposure assessment. Specific objectives are to address the following research questions:

- What is the current status of evidence regarding increased frequency of lung cancer for smokers and non-smokers, for subgroups of different age and sex, due to exposure to radon?
- What is the confidence in any inferred risk estimates?

C. Scope and literature search

47. The scope of the review is primary peer-reviewed studies published in the scientific literature and publications of relevant international organizations. The focus is on epidemiological studies of lung cancer risk due to radon exposure.

48. A comprehensive literature review was conducted of scientific journal articles published since the UNSCEAR 2006 Report [U6] to identify epidemiological study results providing new information on the lung cancer risk associated with radon. The selection criteria developed by the Committee in its UNSCEAR 2017 Report [U8] were applied for the review. A literature search in PubMed, Scopus, and Web of Science was performed with the query string “Search ((((((“lung” or “pulmonary” [Title/Abstract]) AND “cancer”, “carcinoma”, or “neoplasm” [Title/Abstract])) AND (“01/01/2006-”[Date - Publication] : “31/12/2017”[Date - Publication]))) AND radon [Title/Abstract]” resulted in 261 entries. The results from the literature searches were merged, where duplicates were discarded. The articles were reviewed with respect to authors’ potential conflicts, publication type, and screening and quality questions. Screening questions were discussed and agreed prior to the review.

49. Epidemiological studies that did not meet the screening questions were excluded from the review. This included non-original publications, studies in non-human populations, and risk assessments in diseases other than lung cancer. Publications meeting the requisite screening questions were further assessed with respect to their quality. Based on the quality questions, a final decision on whether to include/exclude studies in the evaluation were made. Study item reviews, final inclusion/exclusion decisions, and reasons for the decisions were recorded in a master file, along with summaries of findings and appraisals for included studies. A selected subsample of 35 publications underwent a secondary review to identify potential differences in the application of review criteria. Differences were discussed and reconciled among the experts, and prior reviews were updated accordingly.

D. Review of epidemiological studies for occupational exposure

1. Overview of cohort studies

50. The first papers studying occupational health risks from radiation exposure among uranium miners were published in the 1960s and early 1970s [A7, L13, M10, S7, W1]. A first comprehensive study using the same methodology was published in the BEIR IV report [N8], which included cohort studies of

Colorado Plateau, Ontario, Eldorado, and Malmberget miners (table 6). The report's final model of relative risk included modifying factors of time since exposure and age. In 1999, the BEIR IV report was substantially extended to include 11 miner studies resulting in the BEIR VI report [N10] (table 5). The BEIR VI model of relative risk included modifying factors of time since exposure (5–14, 15–24, 25+ exposure windows), age (four categories), and exposure rate (six categories). Since the BEIR VI report, several studies were extended and in Germany a new study (Wismut) was established. These studies were described and evaluated in detail in the UNSCEAR 2006 Report [U6] (table 7).

Table 5. Summary information of studies included in the 1999 BEIR VI report [N10]

<i>Study</i>	<i>Period of follow-up</i>	<i>Number of cohort members^a</i>	<i>Number of person-years</i>	<i>Number of lung cancers</i>	<i>Mean cumulative exposure (WLM)</i>	<i>ERR per 100 WLM^b</i>
Beaverlodge ^c	1950–1980	6 895	67 080	56	21.2	2.33
China	1976–1987	13 649	134 842	936	286.0	0.17
Colorado	1950–1990	3 347	79 556	334	578.6	0.44
Czechoslovakia ^d	1952–1990	4 320	102 650	701	196.8	0.67
France	1948–1986	1 769	29 172	45	59.4	0.51
New Mexico	1943–1985	3 457	46 800	68	110.9	1.58
Newfoundland	1950–1984	1 751	33 795	112	388.4	0.82
Ontario	1955–1986	21 346	300 608	285	31.0	0.82
Port Radium ^e	1950–1980	1 420	30 454	39	243.0	0.24
Radium Hill	1948–1987	1 457	24 138	31	7.6	2.75
Sweden	1951–1991	1 294	32 452	79	80.6	1.04
Total ^e		60 606	888 906	2 674		0.76

^a Excluding miners with zero exposure.

^b Two-stage statistical modelling approach.

^c Subsequently included in Eldorado study.

^d The former Czechoslovak study included data of Czech and Slovak miners until 1993. Afterwards it is known as Czech study.

^e Totals adjusted for miners and lung cancers that were included in both the Colorado and New Mexico studies.

Table 6. Summary information of studies included in the 1988 BEIR IV report [N8]

<i>Study</i>	<i>Period of follow-up</i>	<i>Number of cohort members^a</i>	<i>Number of person-years</i>	<i>Number of lung cancers</i>	<i>ERR per 100 WLM (95% CI)</i>
Colorado	1951–1982	3 347	73 642	256	0.6 (0.3, 1.3)
Eldorado	1950–1980	6 847	114 170	65	2.6 (1.3, 6.0)
Malmberget	1951–1976	1 292	27 397	51	1.4 (0.3, 8.9)
Ontario	1955–1981	11 076	217 810	87	1.4 (0.6, 3.3)
Total		22 562	433 019	459	1.3 (0.8, 2.3)

^a Including miners with zero exposure.

Table 7. Summary information of studies of miners included in the UNSCEAR 2006 Report [U6]

<i>Study</i>	<i>Period of follow-up</i>	<i>Number of cohort members^a</i>	<i>Number of person-years</i>	<i>Number of lung cancer</i>	<i>Mean cumulative exposure (WLM)</i>	<i>ERR per 100 WLM (95% CI)</i>
Beaverlodge ^b	1950–1999	10 050	285 964	279	23.2	0.96 (0.56, 1.56)
China	1976–1987	13 639	135 357	936	277.4	0.16 (0.1, 0.2)
Colorado	1950–1990	3 347	75 032	327	807.2	0.42 (0.3, 0.7)
Czech Republic	1952–1999	9 941	261 428	915	70	1.6 (1.2, 2.2)
France	1946–1994	5 098	133 521	125	36.5	0.8 (0.3, 1.4)
Newfoundland	1950–2001	1 751	70 894	206	378	0.47 (0.28, 0.65)
Ontario	1955–1986	21 346	319 701	282	30.8	0.89 (0.5, 1.5)
Port Radium ^b	1950–1999	3 300	111 222	230	174.2	0.37 (0.23, 0.59)
Sweden	1951–1991	1 294	32 452	79	80.6	0.95 (0.1, 4.1)
Wismut	1946–1998	59 001	1 801 626	2 328	242	0.21 (0.18, 0.24)
Total^c		69 766	1 425 571	3 379		0.59 (0.35, 1.0)

^a Including miners with zero exposure.

^b Subsequently included in Eldorado study.

^c Totals and combined ERR estimate exclude the Wismut cohort, which was under development at the time of the report [U6].

51. Table 8 summarizes the occupational studies published in the period of 2006–2017 and reviewed in this section. Included among these are further extensions of eight existing studies and new results from the Wismut study. Recently published numbers are provided for the cohort sizes, person-years of follow-up, observed lung cancers, and estimated average excess relative risk. Overall, the extended data from the German, Czech, French, Canadian, and United States' studies represent 1,110,287 additional person-years of follow-up and 2,874 new lung cancers accumulated since the UNSCEAR 2006 Report [U6]. Descriptive summaries of the updated cohort studies are presented in this section.

(a) *Colorado Plateau uranium miners*

52. Studies of uranium miners in the Colorado Plateau area were started in 1949 by the United States Public Health Service, in cooperation with the United States Atomic Energy Commission and the state health departments of Arizona, Colorado, New Mexico and Utah. From 1950 to 1960, a cohort of 4,137 males who had worked in a uranium mine in the area for at least one month was established. The cohort was followed through 2005 and linked to national databases to ascertain vital statuses and causes of death [S5].

53. Radon exposure assessment relied on estimates from the early 1970s. Exposure information consisted of the dates on which each miner's exposure to radon progeny reached 1 of 9 cumulative exposure levels (0, 60, 120, 240, 360, 600, 840, 1,800, and 3,720 WLM). Daily exposure for each were then interpolated between the reported dates. Exposure to radon progeny from prior non-uranium mining was included as occurring on the day before uranium mining employment began. Smoking status was available for the miners from surveys conducted up until 1985.

54. In an update of the Colorado Plateau cohort covering the period of 1991–2005, Schubauer-Berigan et al. [S5] calculated a standardized mortality ratio (SMR) for lung cancer of 3.99 (95% CI: 3.43, 4.62) for white miners and 3.27 (95% CI: 2.19, 4.73) for American Indian miners. Keil et al. [K1] subsequently used G-estimation of structural nested models to adjust for healthy worker survivor bias* in estimating the time ratio (relative change in median survival time) associated with radon exposure. In their statistical analysis, the authors estimated that median lung cancer survival time decreased by a factor of 1.168 (95% CI: 1.152, 1.174) per 100 WLM.

(b) *Czech uranium miners*

55. The cohort was established in 1969 using a database of approximately 100,000 Czech and Slovak uranium miners. The selected cohort included 4,364 miners first employed underground since 1948 in the former Czechoslovak uranium industry for at least four years (S subcohort). First analyses based on 244 lung cancers were reported in 1971 [S7]. By 1970, the cohort was extended by 5,625 miners firstly employed since 1969 for at least one year (N subcohort), first report on this study was in 1997. The study population of the cohort (after excluding duplicates) now consists of a total of 9,978 miners. The mean duration of exposure in the entire cohort was seven years. Information on vital status and dates of death were obtained from the Czech Population Registry at the Ministry of the Interior. Before 1982, the causes of death were obtained from local death registries, and since 1982 from the Institute of Health Information and Statistics of the Czech Republic.

56. Details of exposure estimation have been described elsewhere [S7, T9]. Briefly, exposure estimates in the S subcohort were derived from extensive measurements of radon that had already commenced in 1949. On average, there were about 200 measurements of radon gas per each shaft and year. The concentrations of radon gas were converted to concentrations of radon progeny using measurements of equilibrium factors* in mines also when ventilation was not operated for one month. Each miner's annual exposure to radon progeny was estimated, combining measurement data with registered employment details, including duration of underground work at different shafts and job category. In the N subcohort the exposure estimates were based on personal dosimetric records, based on several thousand measurements per year and shaft. Exposure of some miners in both cohorts involved work in non-uranium mines. Their exposure (substantially lower than those in uranium mines) were derived from radon measurement in non-uranium mines [S6].

57. Results from the Czech study were reported in 1971 [S7], more detailed analyses in 1988 [S8], and further summarized in 1990s publications [T9, T10]. The last report [T15] included 1,141 lung cancers observed in the cohort by 2010. The relative risk models included all modifying factors like attained age, age at exposure, time since exposure, and exposure rate. Smoking was assessed in a nested case control study within the cohort [T16]. This study resulted in an evaluation of the risks from radon and smoking based on 1,029 lung cancer cases and 2,648 controls matched by year of birth, age, and subcohort. Data on smoking in the study were collected from subjects by personal interview, from medical records, and from relatives. The combined effect from radon and smoking was analysed in terms of geometric mixture models of which the additive and multiplicative models are special cases. The resulting model is relatively close to the additive interaction (mixing parameter of 0.2).

(c) *Eldorado miners*

58. The previous analyses of the Beaverlodge mine workers were based on 10,945 male workers employed at the mine between 1948 and 1980 during 1950–1980 [H13, H15]. The cohort was updated to include 305 workers who joined the Beaverlodge mine between the cut off of the original study and the

final closure of the mine in June 1982 [L3]. Improvements in the quality and quantity of identifying data in the nominal cohort and work histories resulted in a final updated cohort of 11,788 workers.

59. The previous analysis of the Port Radium uranium mine workers included all male workers employed at the mine between 1942 and 1960 and known to be alive at the start of follow-up in 1950 and followed up for mortality during 1950–1980 [H14]. The original nominal cohort included 2,696 workers, many of whom were excluded from linkage and analysis because of missing date of birth information [H14]. After an extensive search and review of original records, the updated nominal cohort was expanded to include 4,079 workers.

60. Mortality follow-up of Beaverlodge and Port Radium cohorts was extended from 1980 to the end of 1999 and, for the first time, incidence analysis was conducted for cancers occurring during 1969–1999. For updated follow-up, these two cohorts were combined and analysed together with workers of the Port Hope radium and uranium refinery and processing facility as the Eldorado cohort study [L3]. In total, the Eldorado cohorts includes 17,660 workers. Analyses were restricted to 16,236 (91.9% of the cohort) male workers with a mean cumulative radon exposure of 100 WLM (117 WLM, weighted by person-years, among those with non-zero exposure). Lung cancer was the only cancer site with significantly elevated death (SMR=1.31; 95% CI: 1.21, 1.42) and incidence rates (SIR=1.23; 95% CI: 1.14, 1.33) compared to the general Canadian male population. The excess relative risk per 100 WLM of lung cancer mortality ($n=618$; ERR per 100 WLM=0.55; 95% CI: 0.37, 0.78; $p<0.01$) and incidence ($n=626$; ERR per 100 WLM=0.55; 95% CI: 0.37, 0.81; $p<0.001$) increased linearly with increasing radon exposure. Adjustment for effect modification by time since exposure, exposure rate and age at risk resulted in comparable estimates of risk of lung cancer. All models were adjusted for age at risk, calendar year at risk and duration of employment by stratification [L3].

61. Recently, Lane et al. [L4] assessed the risk of lung cancer mortality at low radon exposure (<100 WLM), among a joint cohort of Czech, French and Beaverlodge miners employed when quality radon exposure measurements were available (1953, 1956, and 1965, respectively) and radiation protection programmes were in place. For Beaverlodge, an ERR per 100 WLM estimate of 2.4 (95% CI: 0.9, 4.7) was obtained with a Poisson regression model for grouped survival data, with background stratification by age at risk categories. Similar to studies with smoking information [B9, H7, L7], two sensitivity analyses found that smoking was not a strong confounding factor in the joint cohort. A statistically significant decrease in risk with time since exposure was observed. Exposure rate was not an effect modifier, consistent with other studies with quality radon measurements, low exposure and low exposure rates [K6, N10, T4, T12]. The models were adjusted for age at risk [L4].

62. A separate analysis of Port Hope radium and uranium refining and processing workers with no mining experience was published after the update of the Eldorado cohort study [Z2]. This analysis was based on a slightly different cohort with more detailed exposure information, including exposure to radium and uranium, than was included in the Eldorado cohort [L3] and excluded all workers with any mining experience. This analysis also used different analytical methods than in the Eldorado cohort to analyse and compare mortality and cancer incidence in the cohort with special attention to cancers of the lung and bronchi, leukaemia and lymphoma, bone, liver and kidney cancers, as well as non-malignant respiratory, renal and cardiovascular diseases.

63. The Port Hope radium and uranium refinery and processing plant became operational in 1932 and continues to operate today as Cameco Corporation Port Hope Conversion Facility. Port Hope workers were exposed to a wide variety of chemicals and radiation types. In addition to gamma radiation and radon decay product radiation, they were exposed to relatively concentrated forms of uranium (sulphates and nitrates during the refining years and UO_2 , UO_3 and uranium fluorides more recently) through inhalation and ingestion. Workers were also exposed to radium, which tends to naturally concentrate in

the bones, potentially exposing the surrounding tissues, including bone marrow, to ionizing radiation. There were no early radon measurements taken at Port Hope at the time of the start-up in 1932. In the 1930s to 1950s, radon estimates were based on the quantities of radium present in the plant in ore and at various stages of refinement, measured radon emanation rates from various radium-bearing materials, building air volumes and estimates of air exchange rates. In the early 1970s, radon measurements were conducted in the yellowcake warehouses, but occupancy was generally low, and no exposure estimates were made. The individual annual exposure in working level months were calculated from working level (WL)* estimates for each type of workplace, the proportion of employees in each occupation and the proportion of time spent in each type of workplace by employees in each occupation. Gamma radiation was the primary type of radiation exposure at Port Hope. There were no measurements at the time of start-up. Film badges were used on some individuals in the late 1940s and were worn by most radium workers and a sampling of others from mid-1947 to early 1953. Full individual external dosimetry (100% coverage) was in place by about 1970 and individual records were kept. Individual gamma doses were calculated from the average dose rates and time on the job and expressed in millisieverts for everyone who had not been wearing a personal dosimeter. All gamma doses were whole-body effective doses.

64. The Port Hope cohort includes about 3,000 workers who were employed between the age of 15 and 75 years sometime between 1932 and 1980, had their last contact after 1940 and never worked in underground or open-pit mines [Z2]. All workers were included regardless of the duration of employment. In analyses restricted to males ($n=2,645$), the person-year weighted mean cumulative radon exposure was 15.9 WLM and the mean cumulative whole-body gamma radiation dose was 134.4 mSv. Risks of lung cancer mortality and incidence were comparable with the general Canadian male population (SMR=1.08; 95% CI: 0.88, 1.32 and SIR=1.08; 95% CI: 0.89, 1.30, respectively). Small, non-statistically significant increases in radiation risks of mortality and incidence of lung cancer due to radon exposure ($n=99$; ERR per 100 WLM=0.21; 95% CI: <-0.45, 1.59 and $n=108$; ERR per 100 WLM=0.77; 95% CI: <-0.19, 3.39, mortality and incidence, respectively), were reported, with similar risks for those exposed to radium and uranium [Z2]. All other causes of mortality and cancer incidence were not significantly associated with radon exposure or gamma radiation doses or a combination of both.

(d) *French uranium miners*

65. Vacquier et al. [V1] described the results conducted on the updated French uranium miner cohort after the extension of the follow-up until 1999. The cohort included 5,086 miners employed at least one year by the CEA-COGEA group between 1946 and 1990 and followed up during 30.1 years in average. Among the 1,411 deaths, 159 were from lung cancer. A significant excess of mortality from lung cancer was found again in the cohort (SMR=1.43; 95% CI: 1.22, 1.68) and this excess was significantly associated with cumulative radon exposure (ERR per 100 WLM=0.58; 95% CI: 0.20, 1.17, on the base of a Poisson regression model with internally defined baseline risk, or ERR per 100 WLM=0.71; 95% CI: 0.29, 1.35, on the base of a Poisson regression model with baseline risk assumed proportional to an external reference population).

66. Radon levels* in French uranium mines decreased sharply in 1956 with the setting up of the radioprotection measures and the introduction of the forced ventilation in mines; mean annual radon exposure was 21.3 WLM before 1956 and 1.7 WLM after 1956. A sensitivity analysis was conducted according to the period of exposure and showed a higher ERR per 100 WLM of 2.0 (95% CI: 0.91, 3.65) after 1956 compared to an ERR per 100 WLM of 0.20 (95% CI: NA, 0.70) before 1956.

67. The modifying effect of time-dependent factors and other non-temporal factors on the relationship between cumulative radon exposure and lung cancer risk has been studied among French uranium miners [V2]. The method of windows of cumulative exposure defined according to the modifying factors was used

and the ERR assessment was based on internal Poisson regression. Period of exposure appeared as a major modifying factor with an ERR per WLM ten times higher for exposure received after 1956 compared to those received before 1956 (ERR per 100 WLM=2.09 (standard error 0.68) and ERR per 100 WLM=0.21 (standard error 0.22)). The ERR per WLM decreased significantly with the time since exposure. A possible inverse exposure rate effect was suggested due to a decrease in the ERR per WLM especially for exposure rate greater than 1 WL per year. Mine type and physical activity appeared to be also strong modifying factors: ERR per WLM was significantly higher for underground miners (compared to open pit miners) and for miners with high physical activity (compared to low/intermediate activity).

68. The systematic measurements of the exposure to radon, long-lived radionuclides, and external gamma radiation began in 1956 in the French uranium mines. The influence of these multiple ionizing radiation exposure was analysed among the 3,377 French uranium miners hired after 1955 in the post-55 subcohort by Vacquier et al. [V3]. A significant excess of mortality from lung cancer was still observed ($n=66$; SMR=1.30 [1.01–1.65]). The ERR for lung cancer death was significantly associated with cumulative radon exposure (ERR per 100 WLM=2.12; 95% CI: 0.53, 5.28), and also with the other exposure. But methodological limits due to the strong correlation between exposure and a lack of statistical power did not allow to take into account multicollinearity and the estimated effect of each separate ionizing radiation exposure.

69. The absorbed dose to lung has been calculated in the French post-55 subcohort by Rage et al. [M4, R2]. The lung dose results from the chronic exposure* to alpha particle emitters, i.e. radon gas, radon short-lived progenies, and long-lived radionuclides, and to low-linear energy transfer radiations, i.e. gamma radiation. Radon short-lived progenies contributed to 97% of the absorbed lung dose caused by alpha particle emitters, which are the main contributor with 58% of the absorbed lung dose. Consequently, the dose-risk relationship was driven primarily by radon short-lived progenies exposure. When considering the value of relative biological effectiveness (RBE)*=20 for alpha particles, generally accepted for alpha emitters, the ERR per Sv associated with the total dose was equal to 0.22 (95% CI: 0.06, 0.53) and with the radon short-lived progenies was equal to 0.23 (95% CI: 0.07, 0.56).

70. The effect of chest X-ray screening examinations on the exposure-risk relationship was studied by Laborde-Castérot et al. [L1]. Chest X-ray exposure received by French uranium miners during their occupational medical surveillance was assessed from different scenarios based on the type of procedure, period, frequency, and the lung dose delivered. No evidence of a confounding effect of X-ray exposure was observed. However, X-ray exposure was not associated with lung cancer mortality and did not confound the dose-risk relation between radon exposure and lung cancer mortality.

71. In the last update of the French cohort, an additional eight years have been added [R3]. At the end of 2007, the duration of follow-up was 35.1 years in average and a total of 1,935 deaths were counted including 211 from lung cancer. Mortality analysis confirmed the significant increased risk for lung cancer death with a SMR=1.34; 95% CI: 1.16, 1.53. Among the post-55 subcohort, the excess of mortality from lung cancer remained borderline (SMR=1.18; 95% CI: 0.96, 1.45). Excess relative risk remained significantly associated with cumulative radon exposure both in the French cohort and the post-55 subcohort (ERR per 100 WLM=0.71; 95% CI: 0.31, 1.30 and ERR per 100 WLM=2.42; 95% CI: 0.90, 5.14, respectively).

(e) *New Mexico uranium miners and millers*

72. The cohort of New Mexico uranium miners has been previously presented in the BEIR VI and UNSCEAR 2006 Reports [N10, U6]. It included 3,457 underground uranium miners with at least one year of mining experience [S2]. Another retrospective cohort study consisted of 2,745 workers engaged

in uranium mining and milling activities near Grants, New Mexico, during 1955–1990. Some of the Grants underground miners were likely included in the previous cohort of miners in New Mexico published by Samet et al. [S2]. Assignment of exposure potential to uranium ore or processing was based on job titles. Workers vital status and causes of death were determined from various linkages with national databases. Smoking histories were not known. Boice et al. [B10] reported disease-specific mortality for the 63,395 person-years of follow-up accumulated during 1979–2005. Overall, statistically significant increased numbers of deaths were found for lung cancer (SMR=1.65; 95% CI: 1.36, 1.97; $n=117$). In stratified analyses, an excess number of lung cancer deaths was observed for workers with underground mining experience (SMR=2.17; 95% CI: 1.75, 2.65; $n=95$) but not for those without such experience (SMR=0.85; 95% CI: 0.52, 1.29; $n=21$). No statistically significant elevation in any cause of death was seen among the 904 non-miners employed at the Grants uranium mill.

(f) *Newfoundland fluorspar miners*

73. The Newfoundland fluorspar cohort was updated in 2007 with an 11-years extension of follow-up to 2001 [V10]. The cohort included 1,742 underground miners with a mean exposure of 378 WLM and 328 unexposed surface miners. Underground miners were exposed to radon from water running through the mine, which eliminated the possibility of confounding from gamma radiation or thoron. The SMR for lung cancer in the underground miners was 3.09 (95% CI: 2.66, 3.56) based on 191 lung cancer deaths. The ERR per 100 WLM among underground miners adjusted for age and calendar period with a 5-year lag was 0.43 (95% CI: 0.23, 0.62). The ERR per WLM decreased with attained age and time since last exposure and an inverse dose-rate effect was also observed. Smoking history was available for 53% of the full cohort. The ERR per WLM for ever smokers did not differ significantly from never smokers but did increase with cigarettes smoked per day.

(g) *Ontario uranium miners*

74. The Ontario uranium miners' cohort was updated with 21 additional years of mortality follow-up (through 2007), as well as cancer incidence follow-up through 2005 [N1]. The cohort was also expanded through broader inclusion criteria and by identifying additional previous miners through Canada's National Dose Registry, which was also used to improve the assessment of radon exposure. The cohort now includes 28,959 miners who worked for at least one week between 1954 and 1996, when mining operations ceased. Analyses were restricted to 28,546 male miners with a mean cumulative radon exposure of 21.0 WLM and increased lung cancer mortality (SMR=1.34; 95% CI: 1.27, 1.42). Based on 1,230 lung cancer deaths, the ERR per 100 WLM was 0.66 (95% CI: 0.44, 0.87). Results were similar for lung cancer incidence. All models were adjusted for the calendar period and attained age. A subsequent paper assessed uncertainty in radon exposure assessment due to natural variations in radon concentration, estimation of working time, precision of the radon measurement method, unintended errors during sampling, and record keeping and transcription of exposure data using the root sum square method [N2]. Exposure uncertainty was found to be 53 to 67% prior to 1968 and 31 to 39% for the period 1968 to 1996 with natural variations being the most important source of uncertainty.

(h) *Swedish iron miners*

75. The Swedish cohort among iron underground miners exposed to radon is one of the oldest studies [A8, D1, E1, J5, R1, S13]. The cohort participated in joint studies of BEIR IV and BEIR VI. The iron ore mine was established in 1890. In the early 1900s, this mine was mainly open cast but by 1920 about 80%

of mining took place underground. Originally the mine only had natural ventilation, forced ventilation was gradually introduced during 1950s and 1960s. Radon measurements began in 1969 and were improved in 1972–1973. The exposure matrix was specified over time for different ore bodies being constant from 1974 until 1998. Data from 1969–1972 were considered as representative of earlier periods; the level in 1910 was set to 380 Bq m^{-3} followed by linear increase from 1910 until 1925.

76. Jonsson et al. [J4] focused on a cohort of surface and underground workers who had worked at the mine between 1923 and 1996. Employment data were collected from manual work records in years 1923–1981 and from computerized register since 1982. Follow-up relied on the Swedish personal registry. Combining the two sources resulted in a cohort of 5,588 males. Mortality data in the period 1952–2000 were obtained by record linkage to the national cause of death register and the national population register. After excluding males not found in the registries, the cohort consisted of 5,486 males. Since lung cancer morbidity was available only for years 1958–2000, the cohort was further restricted to 5,449 miners alive at 1958. Data on smoking were available for 2,310 workers from health examinations.

77. By the end of employment, the mean cumulative exposure in the cohort was 65 WLM, with a maximum of 665 WLM [J4]. The overall excess relative risk per WLM was 0.022, and an excess lung cancer risk was found for small cell and squamous cell but not for adenocarcinoma histological types. Risk from radon was also evaluated in relation to cumulative quartz exposure. When radon excess relative risk was adjusted for cumulative quartz, the estimate decreased from 0.022 to 0.015 per WLM [J4].

78. Another study among iron ore miners was conducted in the combined Malmberget and Kiruna cohort [B7]. Because of the lower radon exposure levels than in the Malmberget study, the lung cancer risk was evaluated only in relation to quartz and diesel exhaust exposure. The main implication of the results is for interpretation of the dose-response curve for radon and lung cancer in underground iron ore miners. Since exposure to radon and quartz is often correlated, quartz exposure can be a confounder.

(i) *German Wismut uranium miners*

79. The German Wismut cohort includes approximately 59,000 miners employed for at least six months between 1946 and 1989 at the Wismut uranium mining company in Eastern Germany. Grosche et al. [G3] described the first results covering the follow-up period 1946–1998. The cohort included 59,001 former employees, with a mean duration of follow-up of 30.5 years, 1,801,630 person-years at risk and 2,388 lung cancer deaths. The average ERR per 100 WLM was 0.21 (95% CI: 0.18, 0.24). Time since exposure, attained age and exposure rate were strong modifiers of the ERR per WLM based on the BEIR VI exposure-age-concentration model.

80. The Wismut uranium mining company operated from 1946 to 1989. The early period of mining (1946–1955) was characterized by high radon exposure due to natural ventilation. In 1955, ambient air measurements of radon gas were initiated in the different mines, and between 1955 and 1958 the radon concentrations sharply decreased due to introduction of several ventilation measures in the different mines. A comprehensive job-exposure matrix was used for the cohort to retrospectively estimate the exposure to radon progeny in WLM for each calendar year, place of work (surface, underground, milling, open pit), mining facility/mine shaft and job type. For the period 1946–1954, radon concentrations were estimated by an expert rating based on measurements from 1955, considering, for example the ventilation rate, vein space and uranium content. The mean cumulative radon level among exposed cohort members was 280 WLM, with a maximum of 3,224 WLM [G3, K7].

81. Lung cancer risk was doubled in the cohort compared to external exposure rates (SMR=2.03; 95% CI: 1.96, 2.10) based on 3,016 lung cancer deaths with end of follow-up 2008 [W3]. Application of an

internal parametric Poisson regression model with exponential effect modifiers, demonstrated that time since exposure, age at exposure and exposure rate were strong effect modifiers of the ERR per WLM. Adjustment for potential confounders such as external gamma radiation, long-lived radionuclides or silica dust did not lead to major changes in ERR per WLM, indicating little confounding.

82. Kreuzer et al. found an average ERR per 100 WLM of 0.19 (95% CI: 0.17, 0.22) based on the extended follow-up period (1946–2013) with 3,942 lung cancer deaths and 2,332,008 person-years at risk [K7]. The ERR per WLM significantly decreased with increasing time since exposure, age at exposure and exposure rate. The ERR per 100 WLM was 0.75 (95% CI: 0.59, 0.98) for age at median exposure of 30 years, time since median exposure of 20 years and a mean exposure rate of 3 WL. The method for determining radon exposure did not have an important influence on risk estimation, indicating no major differences in the quality of exposure assessment in the early or later years (i.e. before 1955 and from 1955 onwards).

83. In order to determine specifically the risk at low exposure or exposure rates within the Wismut cohort and to investigate as far as possible effect modification by time and age, several strategies were used. Person-years at risk were restricted to <0.5 WLM, <50 WLM, <100 WLM [K7] and two subcohorts with low exposure and exposure rates were considered. The 1960+ subcohort with miners first hired in 1960 or later with low-radon concentrations all based on measurements (average exposure rate 0.2 WL) [K6, K7] and the subgroup of millers [K5].

84. The miller subcohort consists of 4,054 males of the Wismut cohort study, who worked between 1946 and 1989 in milling facilities, but never underground or in open pit mines [K5]. Mortality follow-up was from 1946 to 2008, accumulating 158,383 person-years at risk and 159 lung cancer deaths. Mean radon exposure was very low with 8 WLM and a maximum of 127 WLM. An increased, however, imprecise, radon-related lung cancer risk was found (ERR per 100 WLM=3.39; 95% CI: -0.01, 6.78).

85. The 1960+ subcohort included 26,677 miners and 334 or 495 lung cancer deaths in the follow-up period from 1960 to 2008 [K6] or to 2013 [K7], respectively. Mean radon exposure among exposed miners was 17 WLM. There was a clear exposure-response-relationship (ERR per 100 WLM=1.1; 95% CI: 0.6, 1.7). Smoking information was available for 56% cohort members. Most of the miners had been smokers and smoking turned out to be no major confounder of the ERR per WLM. No statistically significant effect modification of the ERR per WLM by age or time since exposure was observed. However, the cohort members were relatively young and only 19% were deceased [K7].

86. Restricting the full Wismut cohort to person-years at risk with low exposure (<50 WLM or <100 WLM) or exposure rates (<0.5 WL) showed a clearly increased radon-related risk of lung cancer (ERR per 100 WLM=0.6) that is modified by time since exposure and to some extent by age at exposure [K7]. In the cohort with restriction to <100 WLM, the ERR per 100 WLM was 1.6 (95% CI: 0.8, 2.8) at an age at exposure of 30 years and time since exposure of 20 years.

Table 8. Summary of occupational radon studies of miners published since the UNSCEAR 2006 Report [U6]

<i>Study</i>	<i>Period of follow-up</i>	<i>Number of cohort members</i>	<i>Number of person-years</i>	<i>Number of lung cancers</i>	<i>Mean cumulative exposure (WLM)</i>	<i>ERR per 100 WLM (95% CI)</i>	<i>Reference</i>
Colorado	1950–2005	4 137	120 437	612	794	NA	[S5]
Czech	1952–2010	9 978	308 910	1 141	73	0.97 (0.74, 1.27) ^a	[T15]
Czech and French	1946–1995	10 100	248 782	574	46.8	1.6 (1.0, 2.4)	[T12]
Eldorado	1950–1999	17 660	508 673	618	100.2	0.55 (0.37, 0.81)	[L3]
Beaverlodge	1950–1999	10 050	285 846	279	84.8	0.96 (0.56, 1.56)	[L3]
	1965–1999	NA	134 113	123	32.3	2.4 (0.9, 4.7)	[L4]
Port Hope	1950–1999	2 645	82 999	99	15.9	0.21 (–0.45, 1.59)	[Z2]
Port Radium	1950–1999	3 300	111 297	230	180.1	0.37 (0.23, 0.59)	[L3]
French	1956–1999	3 377	89 405	66	17.8	0.22/Sv ^b (0.06, 0.53)	[R2]
	1946–2007	5 086	179 995	211	36.6	0.71 (0.31, 1.30)	[R3]
	1946–1999	5 086	153 063	159	36.6	0.58 (0.20, 1.17)	[V1]
	1946–1999	5 086	153 063	159	36.6	0.58 (0.18, 0.98)	[V2]
	1956–1999	3 377	89 405	66	17.8	2.12 (0.53, 5.28)	[V3]
	1946–1999	5 086	153 063	159	36.6	0.53 ^c (0.19, 1.07)	[L1]
New Mexico	1979–2005	2 745	63 395	117	NA	NA	[B10]
Newfoundland	1950–2001	1 742	59 797	191	378	0.43 (0.23, 0.62)	[V10]
Ontario	1954–2007	28 546	805 650	1 230	21.0	0.64 (0.43, 0.85)	[N1]
Swedish	1958–2000	5 486	170 204	122	65	2.20 (0.73, 3.77)	[J4]

<i>Study</i>	<i>Period of follow-up</i>	<i>Number of cohort members</i>	<i>Number of person-years</i>	<i>Number of lung cancers</i>	<i>Mean cumulative exposure (WLM)</i>	<i>ERR per 100 WLM (95% CI)</i>	<i>Reference</i>
Wismut	1946–1998	59 001	1 801 630	2 388	241	0.21 (0.18, 0.24)	[G3]
	1960–2008	26 766	846 809	334	17	1.30 (0.7, 2.1)	[K6]
	1946–2008	4 054	158 383	159	8	3.39 (–0.01, 6.78)	[K5]
	1946–2003	58 987	1 996 880	3 016	218	0.19 (0.16, 0.22)	[W2, W3]
	1946–2013	58 974	2 332 008	3 942	241	0.19 (0.17, 0.22)	[K7]
			1 620 190	1 254	18.4	0.6 (0.3, 1.0) ^d	
			956 776	495	16.8	1.1 (0.6, 1.7) ^e	

^a 90% CI.

^b Related to equivalent lung dose from radon gas and short-lived progenies, long-lived radionuclides and gamma radiation.

^c In a scenario that was based on chest X-rays using the lowest doses (~0.1 mGy) that were theoretically achievable during occupational medical surveillance.

^d Analysis restricted to <100 WLM person-years at risk.

^e Analysis restricted to 1960+ cohort.

2. Overall evaluation of miner studies

87. In order to compare the most current updates of occupational radon studies in miners with results reported in the previous UNSCEAR 2006 Report [U6], only those studies (unadjusted for modifying factors and covering the whole cohort) are considered as listed in table 9. Based on a random effects meta-analysis model with inverse-variance weighting* [D6], the combined ERR estimate from the entire cohorts of recently published studies is 0.60 (95% CI: 0.34, 0.87) per 100 WLM. This new estimate is in close agreement with the previous combined estimate of 0.59 (95% CI: 0.35, 1.0) per 100 WLM. Also summarized in the table are risk estimates for recent periods of work were provided, or for low exposure to radon otherwise. These include estimates for miners in the Czech study who began working during 1968–1974 (mean 7.5 WLM), cumulative exposure below 100 WLM in the Eldorado study (mean 32.3 WLM), workers hired after 1955 (mean 17.8 WLM) in the French study, Newfoundland miners hired in 1960 or later, miners in the Ontario study with exposure rates below 5 WLM per year, the cohort of the Swedish iron ore miners which had relatively low rates of radon exposure (mean 65 WLM), and Wismut workers hired in 1960 or later (mean 17 WLM). Altogether, the combined ERR for low radon exposure was estimated as 1.53 (95% CI: 1.11, 1.94) per 100 WLM.

Table 9. Estimates of ERR per 100 WLM in studies of miners published since the UNSCEAR 2006 Report [U6]

Study	Entire cohort		Recent work periods/low radon exposure	
	ERR per 100 WLM (95% CI)	Reference	ERR per 100 WLM (95% CI)	Reference
Czech	0.97 (0.74, 1.27) ^a	[T15]	2.0 (0.1, 5.3) ^a	[T15]
Eldorado	0.55 (0.37, 0.81)	[L3]	2.4 (0.90, 4.7)	[L4]
French	0.71 (0.31, 1.30)	[R2]	2.42 (0.90, 5.14)	[R3]
Newfoundland	0.43 (0.23, 0.62)	[V10]	2.85 (–2.58, 8.27)	[V10]
Ontario	0.64 (0.43, 0.85)	[N1]	3.08 (0.56, 5.60) ^b	[C23]
			1.81 (0.88, 2.73) ^b	
Swedish	2.20 (0.73, 3.77)	[J4]	2.20 (0.73, 3.77)	[J4]
Wismut	0.19 (0.17, 0.22)	[K7]	1.1 (0.6, 1.7)	[K7]
Combined^c	0.60 (0.34, 0.87)		1.53 (1.11, 1.94)	

^a 90% CI.

^b Estimates for separate low-exposure rate categories of <2 and 2 to <5 WLM per year, respectively.

^c Combined estimate from a random-effects meta-analysis model with inverse-variance weighting.

3. Modifying factors in relative risk models

88. The first studies of miners reported the risk in terms of risk coefficients (ERR per WLM or EAR per 10⁴ PY WLM) for different subgroups defined by attained age, age at first exposure and time since first exposure. Later results included risk coefficients for low cumulated exposure (<100 WLM). Models of BEIR IV [N8] were developed using Poisson regression, where the regression coefficient represented

ERR per WLM. The model included the modifying effect of time since exposure (in two “time since exposure” windows: 5–14, ≥ 15 years) and attained age (in three categories: ≤ 54 , 55–64, ≥ 65 years).

$$RR = 1 + (b_{5-14} W_{5-14} + b_{15+} W_{15+}) a(j) \quad j: \leq 54, 55-64, \geq 65$$

where cumulative radon exposure W is partitioned into temporal exposure windows, with W_{5-14} and W_{15+} denoting exposure incurred 5–14 and ≥ 15 years prior to the current age; b_{5-14} and b_{15+} represent the relative contributions to risk from the corresponding exposure; and $a(j)$ is the modifying effect of attained age.

89. Models reported in BEIR VI [N10] were extended to three time since exposure windows (5–14, 15–24, ≥ 25) and four attained age categories (≤ 54 , 55–64, 65–74, ≥ 75). The main difference to earlier results was the inclusion of exposure rate modifying factor (<0.5 WL, 0.5–1 WL, 1–3 WL, 3–5 WL, 5–15 WL, ≥ 15 WL for the exposure-age-concentration model).

$$RR = 1 + (b_{5-14} W_{5-14} + b_{15-24} W_{15-24} + b_{25+} W_{25+}) a(j) c(k)$$

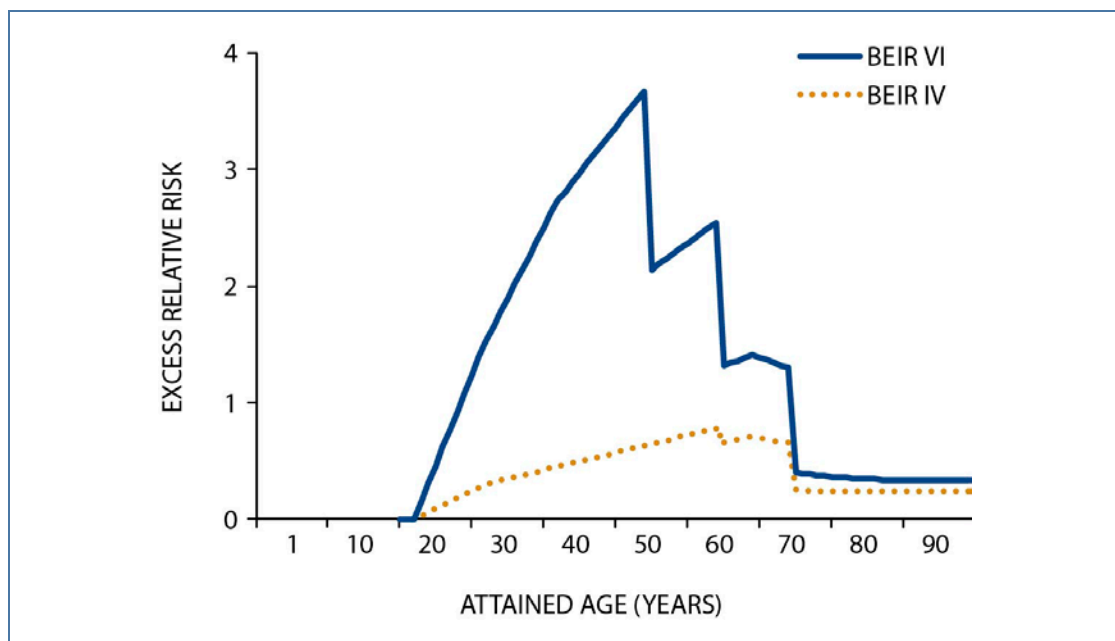
(attained age categories) $j = \leq 54, 55-64, 65-74, \geq 75$

(exposure rate categories) $k = <0.5, 0.5-1, 1-3, 3-5, 5-15, \geq 15$ WL

where the W and $a(j)$ model terms are defined as before; $c(k)$ is an additional modifying effect of exposure rate; and WL stands for exposure rate levels defined as the ratio of cumulated WLM exposure to cumulated duration of exposure in months (170 hours).

90. The modifying effect of time since exposure and attained age was similar to the risk model of BEIR IV. The exposure rate modifying effect, however, substantially influenced the predicted risk (figure I). The difference between the first and last categories of exposure rate was approximately a factor of nine. The predicted risks in radiation protection reflect present levels in mines (mostly below 0.5 WL).

Figure I. Predicted excess relative risks (ERR) from annual exposure of 2 WLM at age 18–64 years according to BEIR IV and BEIR VI models



91. The strong exposure rate effect has several possible explanations:

- Random or systematic errors in estimates of annual exposure;
- Non-linearity between exposure and dose to target cells at high exposure rates;
- Cell killing at high exposure rates [S8];
- Genuine inverse dose-rate effect at cellular level [C5];
- Effect due to the multistage nature of carcinogenesis [B12, T1].

92. As noted in the NIOSH-NIEHS Joint Monograph No. 1 [L13], proportionally more measurements were made in areas of mines that experienced high radon levels which tended to yield radon-progeny values greater than would have been obtained by sampling all work areas with equal frequency. As demonstrated in risk models with an exposure rate modifying factor, the exposure assessment is the most important issue in occupational epidemiological studies. The approach used in BEIR VI which is based on average exposure rate, however, is sometimes misleading because the mean exposure rate for a long exposure duration combines different levels of exposure rates. Considering the hypothetical example given in table 10 of a 15-year total exposure of 80 WLM, the exposure would be wholly classified as a mean exposure rate of less than 0.5 WL, a 50 WLM (1961–1963), however, the majority is at a higher exposure rate category of 1–2 WL and only a 30 WLM minority belongs to the below 0.5 WL category.

Table 10. Example of cumulative exposure and exposure rates for a hypothetical 15-year period in which the rate is relatively low overall (0.48 WL) but high (1.52 WL) over the first three years where the majority of cumulative exposure occurs

<i>Year/Period</i>	<i>Period-specific cumulative exposure (WLM)</i>	<i>Period-specific mean exposure rate (WL)</i>
1961	20	1.82
1962	15	1.36
1963	15	1.36
1964	4	0.36
1965	4	0.36
1966	4	0.36
1967	3	0.27
1968	3	0.27
1969	3	0.27
1970	2	0.18
1971	2	0.18
1972	2	0.18
1973	1	0.09
1974	1	0.09
1975	1	0.09
1961–1975	80	0.48
1961–1963	50	1.52
1964–1975	30	0.23

93. Because of the above differences in the assessment of exposure rate, another approach was used in analyses from a French and Czech combined study [T11]. In addition to the aforementioned reason, cumulated exposures were separated according to the background of annual estimates (measured versus estimated). In this approach, the cumulated exposure was considered in two exposure windows (measured and estimated). In addition to estimated levels in non-uranium Czech mines, the French study made the clear distinction between exposure before and after 1956 in their assessment. Indeed, the risk coefficient related to pre-1956 exposure was substantially lower (even if adjusted for age and time since exposure). A similar approach in the risk models was applied in analyses of three European studies within the Alpha-Risk project [T14]. The estimated ERR per WLM in the joint study were virtually equal when related to exposure after 1953, 1956 and 1964 in the Czech, French and German studies, respectively.

94. A recent paper on the Czech uranium miners [T15] found no differences in exposure rate categories below 7 WL. The ERR per 100 WLM adjusted for time since exposure was 3.6 (95% CI: 2.6, 5.1) below 7 WL and 1.0 (95% CI: 0.3, 2.0) above 7 WL. The risk related to higher exposure rates probably reflects reasons other than systematic errors in estimates of annual exposure. It should be noted that extensive measurements of radon levels were conducted since the first years of mining.

95. The results on exposure rate effect point out the importance to report on the reliability of exposure estimates. This is not always addressed in scientific reports. It is crucial to report numbers of measurements of radon and its progeny. Often, radon levels were estimated or extrapolated in early years of mining, resulting in uncertainty and over estimation. As the number and quality of radon exposure increased and radiation protection was in place, radon exposure measurements became more reliable. For these reasons, models should take account of this issue.

96. The results published in 2006–2017 in nine epidemiological studies (table 8) are mostly given in terms of a simple linear excess relative risk model for lung cancer and other cancers, with the exception of the Colorado and New Mexico studies that only reported SMRs in different categories of exposure. In some studies, this model was also fitted for gamma radiation (France, Ontario, Wismut and Eldorado) and long-lived alpha exposure (France, Germany). Effects of other exposure (silica, quartz) were investigated in the German and Swedish studies. Modifying effects of single factors (age, time since exposure, age at exposure) were investigated in the Newfoundland study. Only four studies (Czech-French, Wismut, Czech and Eldorado) reported the combined effect of all modifying factors (age, time since exposure, exposure rate) using the same or similar model as in the BEIR VI report.

97. The same model as BEIR VI was fitted in the Eldorado, Wismut, and Czech studies. Age-specific estimates for the Eldorado study were similar to the BEIR VI studies. In the Wismut study, the parameters of modifying factors were very close to those of BEIR VI, but the age-specific ERR estimates were substantially lower giving about a third of the risk (table 11 and figure II). In the Czech study, the BEIR VI model was evaluated in a slightly different way using exposure windows of time since exposure, age at exposure and exposure rate. Exposure rate and age were the most influential modifying effects in the risk models. Risk decreased 6–9 times for exposure rates 15+ versus <0.5 WL and 3–11 times for ages 75+ versus <55. In the Czech study the inverse exposure rate effect was not observed, suggesting that exposure rate reflects the overestimation of exposure in early periods of mining. This effect is studied in categories of exposure rate defined as mean exposure rate for the entire exposure history. For this reason, mean exposure rates over 3 WL were not observed. However, the annual variability in exposure rates within each category of exposure rate is quite large. For this reason, a new model of exposure rate effect is suggested and discussed in the electronic attachment of this annex. The modifying effect of time since exposure in all four studies is similar. The modifying effect of attained age is generally similar. Statistical comparisons of the Eldorado, Wismut, and Czech age and time since exposure-specific rates were only significantly different for age <55 ($p=0.014$).

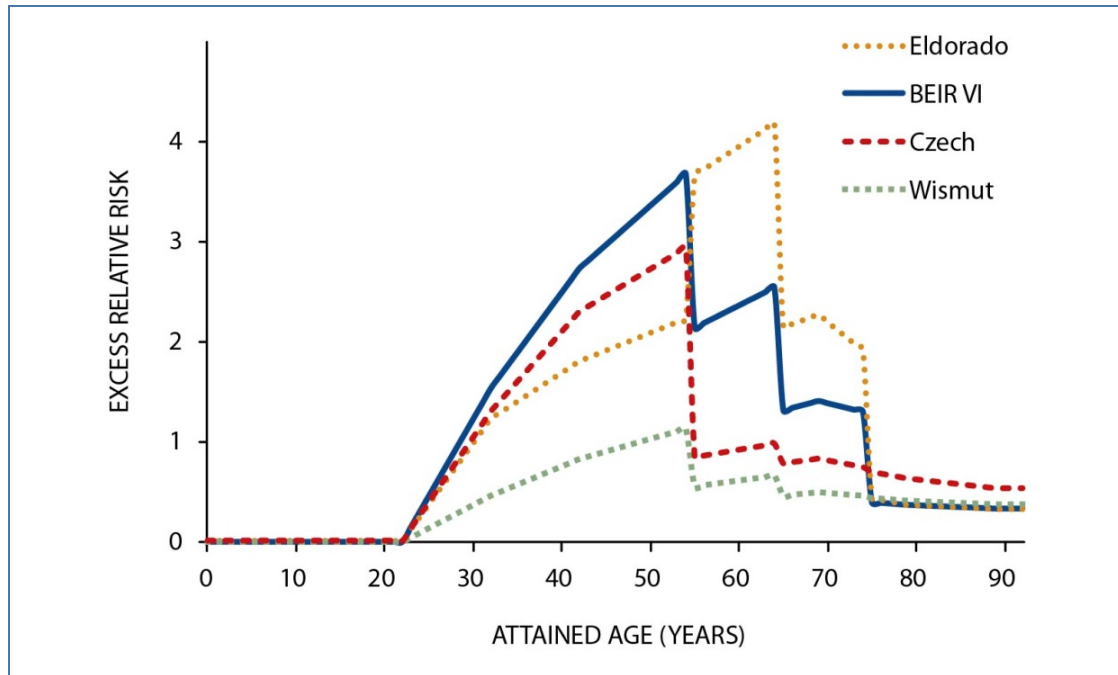
Table 11. Estimates of ERR per 100 WLM from exposure-age-concentration model employed in the BEIR VI report and individually applied to the Eldorado and Wismut and Czech studies

Age (years) ^a	ERR per 100 WLM (standard error)				p-value ^b
	BEIR VI	Eldorado	Wismut	Czech	
<55	7.68	6.11 (3.11)	2.31 (0.71)	6.47 (1.31)	0.014
55–64	4.38	9.90 (5.55)	1.11 (0.36)	1.81 (0.37)	0.125
65–74	2.23	5.01 (3.04)	0.76 (0.26)	1.42 (0.47)	0.191
75+	0.69	1.16 (4.92)	0.74 (0.28)	1.36 (1.06)	0.850
Time since exposure (years)					
5–14 (reference)	1	1	1	1	
15–24	0.78	0.47 (0.54)	0.79 (0.21)	0.77 (0.12)	0.855
25+	0.51	0.29 (0.59)	0.54 (0.14)	0.41 (0.07)	0.687
Exposure rate (WL)					
<0.5 (reference)	1	1	1	1	
0.5–1	0.49	1.05 (0.55)	0.61 (0.17)	0.63 (0.20)	
1–3	0.37	0.47 (0.23)	0.44 (0.10)	1.29 (0.27)	
3–5	0.32	0.34 (0.19)	0.39 (0.09)		
5–15	0.17	0.31 (0.15)	0.34 (0.08)		
15+	0.11	0.16 (0.08)	0.16 (0.06)		

^a Estimates adjusted to 5–14 years since exposure and exposure rate <0.5 WL.

^b Difference between Eldorado, Wismut and Czech study estimates.

Figure II. Projection of the risk in the BEIR VI, Eldorado, Czech and Wismut cohorts from annual exposure of 2 WLM at age 18–64 years



4. Lifetime risk calculation

98. The concept of lifetime risk is generally used in ICRP recommendations [I4, I5, I6, I9]. The idea is to extrapolate risk from cohorts with incomplete follow-up to complete lifespan. The risk models for cohorts in this extrapolation should therefore include temporal and age modifying factors that enable risk predictions over follow-up periods.

99. The approach for estimating lifetime risk related to occupational radon exposure was introduced in ICRP Publication 65 [I6]. The ICRP excess relative risk model was based on a meta-analysis of seven cohort studies: Colorado, New Mexico, Ontario, Beaverlodge, Czech, French and Swedish. The risk projection model involved modifying effects of time since exposure and age at exposure (estimated from the Czech cohort), but not exposure rate. The background lung cancer rate was taken as the average of five countries: China, Japan, Puerto Rico, United Kingdom and United States. Calculations were based on combined male and female rates, assuming that the ERR model is not different between male and female populations. This assumption, however, was not appropriate because the ERR per Sv in females is about three times higher than in males as estimated from the life span study [I9]. The lifetime risk, i.e. the probability of death from a specific cause at age a (during remaining life) is calculated as follows:

$$LR(a) = \sum_{t \geq a} r(t) S(t|a)$$

where $r(t)$ is the cause specific mortality at age t , $S(t|a)$ is the probability of survival from age a to t

$$S(t|a) = \prod_{a \leq u \leq t} (1 - q(u))$$

and $q(u)$ is the annual mortality from all causes at age u . The probabilities of survival can be obtained from life tables routinely published by statistical offices.

100. The lifetime risks were calculated for ages $a=18$ to $t=95$ using background age specific lung cancer rates $r_0(t)$ in a “non-exposed” population and with rates $r_E(t)$ for an exposed population. The lung cancer mortality rates for exposed and non-exposed populations are related as follows:

$$r_E(t) = r_0(t) RR(t, E)$$

where $RR(t, E)$ is the relative risk at exposure E and age t according to the projection model.

101. Lifetime excess absolute risk (LEAR) is calculated from a background rate and from a radon risk model with modifying effects of attained age, time since exposure and exposure rate. The calculation makes use of the lung cancer mortality in age categories and all causes mortality in the whole lifespan from ages 18 to 95 years. Therefore, the risk is projected to the lifetime of adult populations.

102. As indicated in the UNSCEAR 2006 Report [U5], the lifetime risk estimates are sensitive to variations in underlying rates. Issues of uncertainty in lifetime risk estimates are discussed in more detail in NCRP Report No. 126 [N3] and in the BEIR VII report [N11].

103. For a constant exposure scenario of 2 WLM per year from 18 to 64 years of age, the LEAR was calculated for the ICRP Asia and Euro-American male population [I9] from age 18 up to 95 years of age. For comparison with ICRP 65 [I6], lifetime risks were calculated for combined male and female populations. Calculations were performed using the BEIR VI exposure-age-concentration model [N10]. The model was applied individually to the Czech, Wismut and Eldorado cohort miner studies as well as to the joint analysis of the 11 cohort studies from the BEIR VI report. Results are given in table 12. The LEAR per WLM estimates were 2.4×10^{-4} for the newly published large Wismut study, 3.9×10^{-4} for the updated Czech study and 7.5×10^{-4} for the updated Eldorado study. For the BEIR VI studies, the LEAR per WLM was 5.5×10^{-4} . LEARs were also calculated for male populations only (table 12).

Table 12. Lifetime excess absolute risks according to the BEIR VI exposure-age-concentration model for a constant exposure scenario of 2 WLM per year from 18 to 64 years of age

Cohort	BEIR VI (combined 11 studies)	Czech	Wismut	Eldorado
ICRP male and female rates LEAR per 10^4 persons per WLM (standard error)	5.5 (1.3)	3.9 (1.0)	2.4 (0.6)	7.5 (3.0)
ICRP male rates LEAR per 10^4 persons per WLM (standard error)	7.0 (1.6)	5.0 (1.3)	3.0 (0.7)	9.6 (3.8)

5. Smoking-radon interaction in occupational studies

104. The earlier analyses of smoking-radon interaction in occupational studies were given in the BEIR VI report [N10]. Smoking data were available from six cohorts (China, Colorado, Newfoundland, Sweden, New Mexico and Radium Hill). The estimates of ERR per 100 WLM in never smokers (1.02; 95% CI: 0.15, 7.18; 64 cases) were higher in comparison to ever-smokers (0.48; 95% CI: 0.18, 1.27;

1,292 cases). In addition to these analyses, BEIR VI suggested analyses based on fitting the so-called geometric mixture models of additive and multiplicative interactions:

$$RR = ((1 + c S) (1 + b W))^{\theta} (1 + c S + b W)^{1-\theta} \quad (\text{Model G1})$$

where S is smoking indicator (never-, ex-, and current-smoker), W is cumulated exposure to radon and c and b are estimated risk coefficients. The mixture model has as special cases models with multiplicative ($\theta=1$) and additive ($\theta=0$) effects of smoking, as well as models that are intermediate ($0 < \theta < 1$), sub-additive ($\theta < 0$), sub-multiplicative ($\theta < 1$), and super-multiplicative ($\theta > 1$). Lower mixing parameters are in favour of additive interaction. BEIR VI reported estimates of θ obtained with maximum likelihood methods applied to data from each of the cohort studies. Estimates ranged from -0.3 to 0.7 with a mean value of 0.5 .

105. Smoking-radon interaction in the period 2006–2017 was investigated in three European studies as well as the Colorado, Newfoundland, and Wismut studies. The numbers of cases were similar to the numbers in original cohorts. The design of European studies was based on case-control studies nested within cohorts. The analyses in these studies depended mostly on numbers of non-smoking cases. Basic information is given in table 13. In studies, where numbers of non-smoking cases are large, the risk coefficients in never-smokers are substantially higher than in ever-smokers. The geometric mixture models resulted in sub-multiplicative interaction with mixing parameters ranging from 0.5 in the three European studies (BEIR VI) to 0.2 in the Czech study.

Table 13. Summary information on smoking and radon in underground miner studies

Study	Number of lung cancers	ERR per 100 WLM (95% CI)			Reference
		Overall	Non-smokers	Smokers	
BEIR VI	1 356	0.53 (0.20, 1.38)	1.02 (64) (0.15, 7.18)	0.48 (1 292) (0.18, 1.27)	[N10]
Colorado	612		3.0 (76) ^a	0.3 (536) ^a	[S5]
Czech	1 028	1.4 (0.9, 2.3)	4.9 (80) (1.0, 17.9)	1.0 (948) (0.6, 1.7)	[T16]
French	62	0.98 (0.18, 3.08)			[L6]
Wismut	421	0.23 (0.11, 0.46)			[S4]
	246		2.0 (28) ^b (−1.6, 5.7)	1.2 (218) ^b (0.4, 2.1)	[K7]
Three European studies	1 046	0.8 (0.4, 1.4)	1.2 (197) ^c (0.5, 2.6)	0.7 (849) ^c (0.3, 1.3)	[L7]
	1 046	0.8 (0.4, 1.4)	1.1 (64) ^d (0.3, 4.0)	0.8 (982) ^d (0.3, 1.3)	[H17]
Newfoundland	140	0.47 (0.28, 0.65)	0.42 (8) (<0, 0.85)	0.48 (132) (0.29, 0.67)	[V10]

^a Calculated from the SMR in Schubauer-Berigan et al. [S5].

^b Smokers defined as persons who ever smoked in the last 20 years.

^c Smokers defined as current or ex-smokers who had quit within 10 years.

^d Smokers defined as current smokers and non-smokers as ex- or never-smokers.

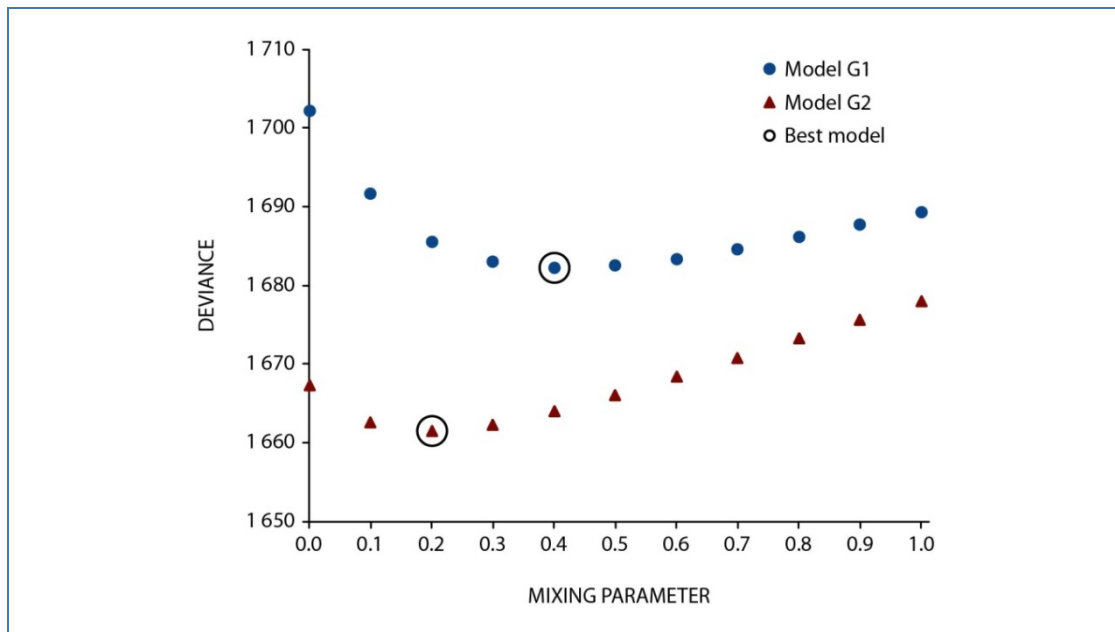
106. In the 1960+ German subcohort, the ERR per WLM for the group of non/light smokers (ERR per 100 WLM=2.0; 95% CI: -1.6, 5.7 based on 28 lung cancer deaths) was slightly higher compared to that of moderate/heavy smokers (ERR per 100 WLM=1.2; 95% CI: 0.4, 2.1; $n=218$) pointing to a sub-multiplicative interaction between smoking and radon. Also, geometric mixture models were fitted to investigate the nature of interaction between smoking and radon. They indicated a supra-multiplicative interaction. Due to small numbers of deaths in the respective smoking categories and thus low statistical power, the findings are consistent with both a supra-multiplicative and a sub-multiplicative interaction.

107. The geometric mixture model was fitted in the Czech nested case-control study using model G1 and further with the following model:

$$RR = ((1 + c S) (1 + b_1 W_1 + b_2 W_2))^{\theta} (1 + c S + b_1 W_1 + b_2 W_2)^{1-\theta} \quad (\text{Model G2})$$

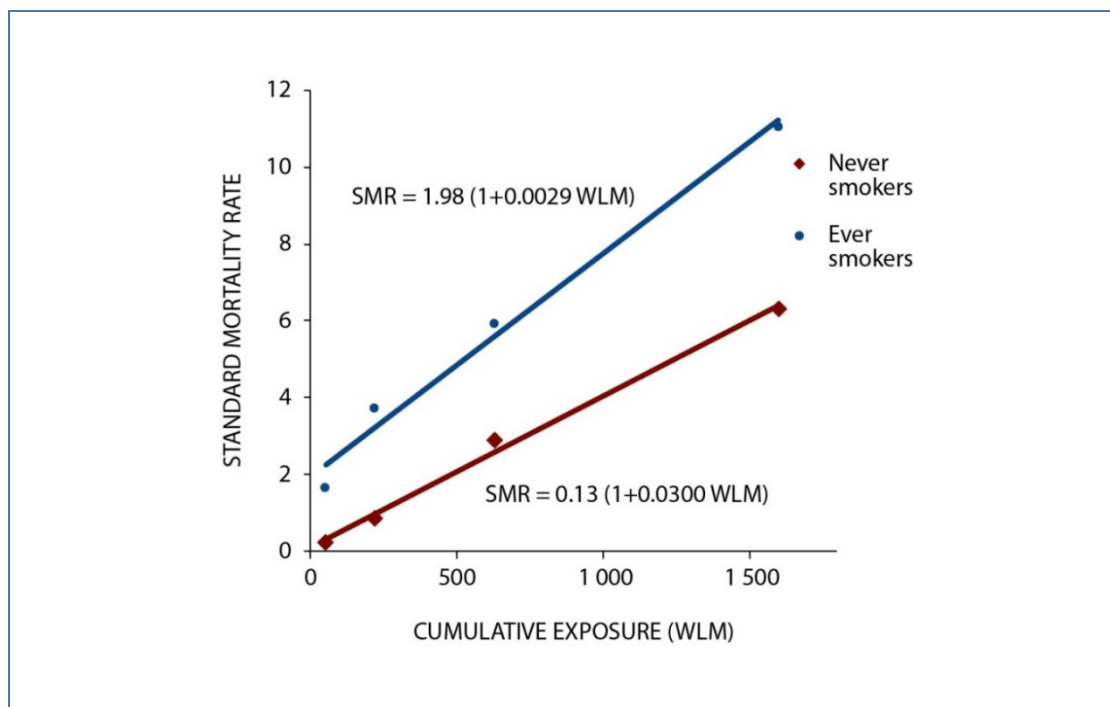
where W_1 and W_2 are cumulated exposures in time since exposure windows (5–19, 20+). As indicated by the lower model deviances shown in figure III, the best fitting model was G2 with a mixing parameter close to additive interaction. In statistical comparisons, model G2 was found to provide a significantly better fit to the data than model G1 ($p<0.001$).

Figure III. Model fit deviances over ranges of mixing parameter values for geometric mixture models G1 (cumulated exposure) and G2 (time since exposure) fit in the Czech study [T16]



108. Smoking was recently investigated in the Colorado study [S5]. Results were given in terms of SMR classified by smoking categories and cumulated exposure. The dependence of risks (SMR) on smoking and radon exposure is shown graphically in figure IV. From the fitted lines, it can be derived that ERR per 100 WLM=3.0 in never-smokers and 0.3 in ever-smokers. The relative risk of smoking at zero exposure is $RR=15.2$. Effects of radon by smoking status were also estimated in a joint analysis of three European nested case-control studies of uranium miners. As reported by Leuraud et al. [L7], ERR per 100 WLM was found to be 1.2 (95% CI: 0.5, 2.6) in never- and long-term ex-smokers and 0.7 (95% CI: 0.3, 1.3) in short-term ex- and current smokers. Hunter et al. [H17] considered other classifications of smoking status for this study and reported ERR of 1.0 (95% CI: 0.3, 4.0) for never-smokers, 1.2 (95% CI: 0.5, 3.4) for long-term ex-smokers, and 0.7 (95% CI: 0.3, 1.3) for current smokers.

Figure IV. Lung cancer risk (SMR) in dependence on cumulated exposure (WLM) and smoking in the Colorado study (adapted from [55])



6. Summary of occupational studies

109. Reviewed occupational evidence of lung cancer risk due to radon included published extensions of eight pre-existing studies (Colorado, Czech Republic, Eldorado, France, New Mexico, Newfoundland, Ontario, Sweden) and new results from the Wismut study. Substantial variability in overall ERR estimates was observed, with values ranging from 0.19 to 3.4 per 100 WLM. Likewise, mean cumulative exposure to underground radon ranged from 17 WLM in low-exposed Wismut miners to 794 WLM in Colorado miners. A combined ERR estimate of 0.60 (95% CI: 0.34, 0.87) per 100 WLM was calculated based on results for the entire cohorts in each study. A higher combined ERR estimate of 1.53 (95% CI: 1.11, 1.94) was calculated when considering subcohort results for more recent work periods and lower exposure.

110. Growing evidence of the modifying effects of exposure rates, age, and times since exposure raised doubts about the appropriateness of a combined estimate of unadjusted risk from studies that are heterogeneous with respect to exposure. The BEIR VI risk model was summarized for its role in past risk estimation approaches to account for the modifying effects of exposure rate as well as time since exposure and attained age. The BEIR VI model estimates were calculated with current data available from the Czech, Eldorado, and Wismut studies. Resulting central estimates at 5–14 years since exposure, attained age <55, and exposure rate <0.5 WL ranged from 2.31–6.47 ERR per 100 WLM as compared to the BEIR VI published estimate of 7.68. Exposure rate level and attained age were found to be strong modifying factors with risks decreased by 6–9 times at rates of 15+ versus <0.5 WL and by 3–11 times for ages 75+ versus <55 years. Modifying effects of time since exposure decreased by factors of 2–3 for ages 25+ versus 5–14 years. The BEIR VI approach is based on average exposure rate which combines different levels of exposure rates.

111. Smoking-radon interaction tended to be sub-multiplicative in the three European studies, as well as in Colorado and in Newfoundland studies. Excess relative risk per unit exposure estimates were higher among non-smokers in all, apart from the Newfoundland study, where the confidence intervals were wide due to relatively small numbers of lung cancer cases.

112. Since the previous pooled study of 11 underground miner cohorts in BEIR VI, the cohorts have been extended, their follow-up has been updated and new cohorts have been set up. Miners working in more recent periods have been exposed to lower levels of radon and the assessment of their exposure estimates were more accurate. As a result, the increased statistical power reached with this hindsight allows for improved risk estimation of cancer and non-cancer diseases, in particular at low levels of radon exposure. The collaborative Pooled Uranium Miners Analysis (PUMA) is an ongoing international initiative set up to gather the most informative cohorts of uranium miners and to conduct statistical analyses with a greater ability to study the risks associated with radon exposure. The PUMA cohort includes seven cohorts of uranium miners: three European cohorts (Czech, French and Wismut), two Canadian cohorts (Eldorado and Ontario) and two American cohorts (Colorado Plateau and New Mexico). This combined cohort includes a total of 124,507 uranium miners (twice the size of the BEIR VI cohort) among which there are 7,825 cases of death from lung cancer (three times more than in the BEIR VI cohort). Specific objectives dealing with radon-related lung cancer risk are focused on low exposure and low exposure rate effects, on the time-dependent modifying factor effects, on the risk among non-smokers and on the impact of the other radiological exposure present in the atmosphere of uranium mines. Future findings from the PUMA study should strengthen our understanding of radon and radon progeny-related lung cancer risks.

E. Review of epidemiological studies for residential exposure

113. The UNSCEAR 2006 Report [U6] identified the main studies of residential radon to be the pooled analyses of European [D2, D3], North American [K8, K10] and Chinese [L10] residential case-control studies. Summarized in table 14 are the lung cancer risk estimates from the three studies.

Table 14. Summary of lung cancer excess relative risk estimates per 100 Bq m⁻³ (95% CI) from major residential studies included in the UNSCEAR 2006 Report [U6]

<i>Study</i>	<i>Primary analysis</i>	<i>Restricted analysis</i>	<i>Exposure adjusted for uncertainty</i>
European [D2, D3]	0.084 (0.03, 0.158)	0.094 ^a (0.034, 0.175)	0.16 ^b (0.05, 0.31)
North American [K8, K10]	0.11 (0.00, 0.28)	0.18 ^a (0.02, 0.43)	
Chinese [L10]	0.133 (0.01, 0.36)	0.319 ^c (0.07, 0.91)	
Combined	0.093 (0.04, 0.15)	0.11 (0.05, 0.19)	

^a Restricted to individuals who had lived in at most two residences during the previous 30 years.

^b Statistical correction for measurement error uncertainty.

^c Restricted to individual who had lived in only one residence with complete radon coverage.

114. The UNSCEAR 2006 Report concluded that these study results indicate a significant association between residential radon exposure and lung cancer risk. Moreover, the studies were noted to have found no significant heterogeneity in relative risk estimates from radon for individuals with different smoking habits. Based on the evidence available at the time, the Committee deemed it reasonable to adopt the

uncertainty adjusted estimate from the European study of 0.16 (95% CI: 0.05, 0.31) per 100 Bq m⁻³ excess relative risk from residential radon. A review of the literature was conducted for the present report to identify new evidence concerning the lung cancer risk posed by radon [U6]. Review findings are presented here for residential studies with direct measurements of radon exposure, indirect measurements, and studies combined in meta-analyses.

1. Studies with direct radon measurements

(a) *North American pooling*

115. Two case-control studies (*a*) New Jersey, United States and (*b*) Connecticut, Utah and Southern Idaho, United States included in the Northern American pooling had their main findings published after the UNSCEAR 2006 Report. Since the main findings from these studies were not available for the previous report, their study designs and results are briefly summarized here.

116. The New Jersey study involved 651 and 740 sex, race, age, and smoking-matched cases and controls enrolled during 1989–1992 [W10]. Cases had primary, histologically confirmed lung cancer. Radon concentrations were measured with alpha-track detectors placed in the living areas of homes for one-year periods. An attempt was made to measure homes previously lived in for a minimum of two years over an exposure time window of 5–30 years prior to study enrolment. Radon exposure was calculated as a time-weighted average over the exposure time window with equal weights given to all years and as a BEIR VI weighted average with decreasing weights of 1.0, 0.8, and 0.3 for exposure time window years 5–14, 15–24, and 25+, respectively. Subjects were 46.7% males. Cases and controls were 6.1 and 16% never smokers and had mean time/BEIR VI weighted average radon exposures of 46.0/36.2 and 46.4/36.4 Bq m⁻³. Multivariable regression was used to estimate ERR due to radon while adjusting for sex, age, smoking, number of residences and years of radon monitoring. Overall, the ERR was estimated to be 0.05 (95% CI: –0.14, 0.56) per 100 Bq m⁻³ for time weighted exposures. In subset analysis, estimates were –0.13 (95% CI: –0.30, 0.44) for males and 0.29 (95% CI: –0.12, 1.70) for females. Risk estimates were also computed separately by age and smoking categories but not found to be significantly different.

117. The Connecticut, Utah and Southern Idaho study enrolled 1,474 and 1,811 eligible cases and controls between 1989–1993 [S3]. Random recruitment was employed to maximize the proportion of non-smoking cases and to select a control group that was similar with respect to age, sex and smoking. Eligible subjects were 40–79 years of age, residents of their respective states, and residents of Utah and Southern Idaho for at least 50% of the time from age 25 to five years prior to enrolment or residents their entire adult lives (after age 25) in Connecticut. In addition, cases had a pathologically confirmed primary lung cancer. Radon concentrations were measured with 12-month alpha-track detectors placed on multiple levels of current and past homes occupied by study participants. Radon exposure was calculated as the average of concentrations on each level of the homes lived in five to 25 years prior to enrolment, weighted by the proportion of time spent in each location. Subjects were 57.1% males. Cases and controls were 8.7 and 14.1% never smokers and had mean estimated radon exposures of 40.3 and 44.8 Bq m⁻³. Multivariable regression was used to estimate ERR due to radon while adjusting for state, age, sex, study phase, altitude, population density, smoking, residential stability, working hours, and education level. Overall, the ERR was estimated to be 0.002 (95% CI: –0.21, 0.21) per 100 Bq m⁻³. In subset analyses, estimates were 0.134 (95% CI: –0.23, 0.50) for Connecticut; –0.112 (95% CI: –0.34, 0.11) for Utah and Southern Idaho; –0.006 (95% CI: –0.29, 0.27) for males; 0.061 (95% CI: –0.30, 0.43) for females; and 0.141 (95% CI: –0.47, 0.75) for non-smokers.

(b) *Massachusetts, United States*

118. Thompson et al. [T2] conducted a case-control study of residential radon exposure and lung cancer in Worcester County, Massachusetts. The study was carried out between 1990–1999 with 200 cases and 397 age and sex-matched controls all enrolled from the same health maintenance organization. Subjects were eligible to participate if they were at least 40 years of age, had the permission of their primary care physician, had lived in a radon-testable residence for at least 10 years, and were not cigar or pipe smokers. In addition, cases had histologically or cytologically confirmed primary lung cancers. Radon concentrations were measured with Radtrack etch-track detectors (Tech/Ops Landauer, Inc.) placed for a period of one year in the living area most often used, the present bedroom, any former bedroom, and any other level of the house that had been used on average for one or more hours per week. Exposure rate was calculated as a weighted average of detector measurements and time spent in the locations in which they were placed. Subjects were 58% males and had a mean age of 67.3 years and home residency of 30 years. Cases and controls were 7.5 and 40.8% never smokers and had mean estimated radon exposures of 67.5 and 66.3 Bq m⁻³. Multivariable regression techniques were used to estimate the lung cancer risk associated with radon. Covariates were included to adjust for potential confounding effects of smoking, residency, job exposure, income and education. Based on a linear model, excess lung cancer odds were estimated to be 0.04 (95% CI: -0.20, 0.35) per 100 Bq m⁻³. Conditional logistic regression analysis produced estimated odds ratios* of 1.00 (reference), 0.53 (95% CI: 0.24, 1.13), 0.31 (95% CI: 0.13, 0.73), 0.47 (95% CI: 0.20, 1.10), 0.22 (95% CI: 0.04, 1.13), and 2.50 (95% CI: 0.47, 13.46) for radon categorized as <25, 25–49, 50–74, 75–149, 150–249, and ≥250 Bq m⁻³, respectively. Risk estimates stratified by age, sex, or smoking were not provided for this study.

(c) *Galicia, Spain*

119. Barros-Dios et al. [B6] reported on the findings from a hospital-based case-control study of residential radon exposure and lung cancer in Galicia, Spain. The study was conducted between 2004 and 2008 with 349 cases and 513 sex-matched controls from two hospitals. Subjects were eligible to participate if at least 30 years of age and resided in their radon-measured home for at least five years. Cases had a pathologically confirmed lung cancer; whereas, controls were hospital patients receiving non-tobacco-related surgeries. Radon measurements were obtained with alpha-track detectors (Radosys Inc.) placed away from doors, windows, and electric devices for a period of three to six months. Measurements were seasonally adjusted. Subjects were 87% males and had lived in their homes for a median of 30 years. They were distributed 9, 57, and 34% across age categories <50, 51–70 and >70 years; and 32, 35, 16 and 17% across radon exposure categories <50, 50–100, 101–147 and >147 Bq m⁻³. Cases and controls were 15.3 and 45.5% never smokers. Lung cancer risk was estimated with multivariable logistic regression adjusted for age, sex and tobacco consumption. Estimates of linear excess risk were not provided. Rather, odds ratios were reported as 1.00 (reference), 1.87 (95% CI: 1.21, 2.88), 2.25 (95% CI: 1.32, 3.84) and 2.21 (95% CI: 1.33, 3.69) for the four radon exposure categories. Statistical evidence of an interaction between radon and smoking indicated an additive (*p*-value<0.001) and not a multiplicative (*p*-value=0.19) effect. Risk estimates stratified by smoking categories were also obtained as shown in table 15. Estimates of linear excess risk were not provided.

Table 15. Risk estimates stratified by smoking categories [B6]

Radon exposure (Bq m ⁻³)	Odds ratios by tobacco consumption (pack-years ^a)			
	Never smokers	1–33	34–66	>66
0–50 (reference)	1.00	1.00	1.00	1.00
51–100	0.89	3.92	2.22	1.66
101–147	1.39	4.12	5.15	1.05
>147	1.16	6.09	1.85	2.57

^a Packs of (20) cigarettes smoked per day multiplied by the number of years smoked.

120. Torres-Durán et al. [T18] conducted another hospital-based case-control study in the Northwest of Spain (Galicia and Asturias) in which 521 never smokers (192 cases and 329 controls) were enrolled between 2011–2013. Subjects were eligible to participate if they were over 30 years of age. Cases had pathologically confirmed lung cancer. Controls were selected from ambulatory individuals undergoing minor, non-oncological surgery and frequency matched to cases according to age and sex. Radon measurements were obtained with alpha-track detectors placed in participants' bedrooms for a minimum period of three months. Measurements were seasonally adjusted. Subjects were 21% males and had a median age of 70 years. The median number of years lived in measured homes was 30 years for cases and 36 years for controls. Radon exposures were distributed 24, 19, 20 and 37% across defined categories of ≤ 100 , 101–147, 148–199 and ≥ 200 Bq m⁻³. Multivariable logistic regression was used to estimate lung cancer risk for radon as a categorical effect and included adjustment variables for age, sex and environmental tobacco smoke exposure. When compared to the reference exposure of ≤ 100 Bq m⁻³, odds ratios were 0.80 (95% CI: 0.43, 1.50) for 101–147 Bq m⁻³, 1.16 (95% CI: 0.64, 2.11) for 148–199 Bq m⁻³ and 2.42 (95% CI: 1.45, 4.06) for ≥ 200 Bq m⁻³. Statistical significance was observed for the highest exposure category, as indicated by the confidence interval. Odds ratios were additionally estimated in a sub-analysis of female participants to be 0.87 (95% CI: 0.43, 1.75), 1.00 (95% CI: 0.52, 1.95) and 2.84 (95% CI: 1.58, 5.09). Estimates of linear excess risk were not provided.

121. In a secondary analysis of 216 and 329 never-smoking cases and controls from the aforementioned study, Torres-Durán et al. [T19] estimated lung cancer odds ratios for radon exposure (≥ 200 versus < 200 Bq m⁻³) by histological types to be 2.14 (95% CI: 1.45, 3.17), 2.39 (95% CI: 0.89, 6.42), 2.19 (95% CI: 1.44, 3.33) and 2.05 (95% CI: 0.85, 4.95) for all histologies, squamous, adenocarcinoma and other types. Estimates were adjusted for age, sex and environmental tobacco smoke. Risk from radon was not significantly different across histological types (p -value=0.16). Radon risk was also assessed by age at diagnosis and found to be non-significantly higher among younger cases (p -value=0.28).

122. In a study by Barbosa-Lorenzo et al. [B5], a cohort of 2,127 disease-free participants were enrolled between 2002–2009 from the Galician radon map study and one of the prior case-control studies. Twenty-four lung cancers were observed during the follow-up period ending 31 December 2012. Radon was measured with alpha-track detectors placed for a period of three to six months in the rooms in which participants spent the majority of their time. Measurements were seasonally adjusted. Subjects were 57.4% males, 50% aged 51 or older at the time of enrolment, 54% never smokers, and 53.1% residents of their current home for over 25 years. Radon was categorized as < 50 and ≥ 50 Bq m⁻³ for risk analysis with 64% of all subjects falling in the higher category. Relative risk for the high versus low radon categories was estimated with multivariable Cox regression models adjusted for sex, age, and tobacco use to be 1.2 (95% CI: 0.5, 2.8) overall and 1.4 (95% CI: 0.5, 3.6) for males. Excess relative risk estimates were not provided, nor were smoking-specific risks.

(d) *Czech study*

123. A nested case-control study of residential radon and lung cancer was conducted in the Czech study [T16]. Controls were matched to cases on birth, age, sex and cohort. Subjects were selected from two cohorts. The first was a Mid-Bohemia Pluton cohort study designed in 1989 that contributed 289 cases and 1,156 controls to the present study. The second was a hospital-based case-control study (Bulovka) in Prague and adjacent regions in Central Bohemia that contributed 81 cases and 243 controls. Subjects were included if they had resided in their current home for at least 30 years. Radon progeny was measured with passive track detectors placed for a period of one year in the two most occupied rooms of each home. Risk estimates were reported in terms of radon gas derived from radon progeny measurements and simultaneous placement of electrets and CR-39 detectors. Mean radon exposures were 87, 423 and 361 Bq m⁻³ among the Bulovka, Pluton and combined study subjects, respectively. ERR was estimated with conditional logistic regression models. In the primary analysis, smoking was included in the models as a multiplicative effect. An ERR estimate of 0.14 (90% CI: 0.03, 0.39) per 100 Bq m⁻³ was obtained in the analysis of all subjects combined. In subset analyses of never and ever smokers, the ERRs were 0.73 (90% CI: 0.02, 1.90) and 0.14 (90% CI: 0.02, 0.30), respectively. A geometric mixture model, which is a weighted combination of multiplicative and additive models for smoking, was additionally fitted and placed more weight (60% versus 30%) on the additive model. Risk estimates stratified by age or sex were not provided.

2. Studies with modelled radon exposure estimates

(a) *Danish study*

124. Bräuner et al. [B11] assessed long-term association between radon and lung cancer risk in a prospective cohort of 57,053 Denmark residents recruited during 1993–1997. Subjects had to be between 50 and 64 years old and cancer-free at the time of enrolment and were followed for occurrence of any cancer up to 27 June 2006 at which time 589 primary lung cancers were observed. Thirty-five years of home address information from 1971–2006 was obtained for each participant. Radon was not measured directly in this study. Instead, radon concentrations for each address were predicted from a validated regression model that used nine explanatory variables for geographic location, soil type and dwelling characteristics. Time-weighted average radon concentrations were then calculated for cohort member's addresses occupied during the study follow-up period. Subjects were 47.5% males and 63.7% non-smokers with a median radon exposure of 39.5 Bq m⁻³. Multivariable Cox proportional hazards regression was used to estimate incidence rate ratios with radon exposure included as a time-dependent variable and covariate adjustment for age, sex, body mass index, length of school attendance, socio-economic status, smoking status, environmental tobacco smoke, fruit intake, alcohol, residence type, employment in an industry or job associated with higher risk for lung cancer, and traffic-related NO_x exposure. Reported estimates of incidence rate ratios (95% CI) per 100 Bq m⁻³ increase in exposure for the entire cohort as well as for subgroups as summarized in table 16. Incidence rates in this study are noted to have been estimated as exponential, and not linear functions, of radon exposure.

Table 16. Estimates of incidence rate ratios (95% CI) per 100 Bq m⁻³ increase in exposure for the entire cohort, non-smokers and smokers [B11]

Sex	Smoking status		
	All	Non-smokers	Smokers
Males	1.01 (0.62, 1.64)	1.35 (0.44, 4.11)	0.95 (0.55, 1.63)
Females	1.06 (0.64, 1.77)	2.02 (0.70, 5.76)	0.89 (0.49, 1.61)
Both sexes	1.04 (0.69, 1.56)	1.67 (0.69, 4.04)	0.92 (0.58, 1.46)

(b) American Cancer Society study

125. Turner et al. [T21] examined the association between residential radon exposure and lung cancer mortality in a cohort of 811,961 participants enrolled into the American Cancer Society Cancer Prevention Study-II in 1982. At the time of enrolment, participants were at least 30 years of age and had at least one family member aged 45 or older. Since cigarette smoking information was only collected at enrolment, follow-up for the present study was restricted to the first 6 years of the study, at the end of which 3,493 lung cancer deaths were observed. Indirect estimates of radon exposure were obtained by linking participant addresses to county-level radon concentrations derived from non-random, screening measurement obtained by the University of Pittsburgh [P3], and other state-level sources. Participants were 44.7% males and 46.2% never smokers, with the mean radon concentration being 53.5 Bq m⁻³. Multivariable Cox regression was used to estimate the risk due to radon while adjusting for education; marital status; body mass index; cigarette smoking; vegetable, fruit, fibre, and fat intakes; occupational exposure to asbestos, formaldehyde, coal or stone dusts, coal tar/pitch/asphalt, and diesel engine exhaust; and other occupational pollutants. An estimated 0.15 (95% CI: 0.01, 0.31) increased lung cancer risk was reported per 100 Bq m⁻³ increase in radon.

(c) Irish longitudinal study

126. The relationship between radon and lung cancer prevalence was examined using 5,590 subjects enrolled during 2009–2011 into the Irish longitudinal study on aging [D4]. Study participants were 50 years or older and had to have lived in their homes for at least five years to be included in the analysis. During the study follow-up, 35 lung cancers were observed. Indirect estimates of radon exposure were obtained by linking participant addresses to a radon risk map of Ireland published by the Irish Environmental Protection Agency. The map provides the percentage of homes in each 10 km grid square predicted to have radon concentrations above the national reference level of 200 Bq m⁻³ based on results of the Irish National Radon Survey conducted between 1992–1999. Participants were 45.7% males and 45.7% never smokers with an average age of 63.1 years. The distribution across radon risk categories of <1, 1–5, 5–10, 10–20 and >20% of households above 200 Bq m⁻³ was 25.9, 27.4, 21.0, 12.9 and 12.9%. Risk was estimated with multivariable logistic regression and adjusted for smoking, age, sex, education and population density. Resulting odds ratio estimates for the upper four radon categories relative to <1% were 1.12, 0.87, 2.85 and 0.65, respectively. The *p*-values for tests of these odds ratios did not achieve statistical significance at the 5% level.

(d) *Canada National Enhanced Cancer Surveillance System*

127. Hystad et al. [H18] linked ecologic radon exposure to subjects from a case-control study of 2,390 lung cancer cases and 3,507 controls enrolled between 1994–1997 from eight Canadian provinces. Cancer cases were drawn from provincial cancer registries to which population controls were sex and age matched. Complete 20-year geocoded residential histories were required for participants to be included in the analysis. Two radon risk maps were created from: (a) a residential radon survey of three-month radon concentration measurements from approximately 14,000 households; and (b) a radon risk map grouped into three zones (guarded, moderate or high) of equal landmass according to geology, soil uranium geochemistry and aerial gamma spectrometry. Subjects were 51.3% males with a mean age of 60.8 years. Cases and controls were 6% and 38% never smokers and had average health region radon concentrations of 81.3 and 78.6 Bq m⁻³. Mixed effects multivariable logistic regression was used to estimate the lung cancer odds associated with radon. Included in the models were random effects for census divisions and covariate adjustments for age, sex, study province, smoking exposure, education, income, dietary intake, occupational exposure and geographic covariates. Odds ratios were estimated to increase by 0.14 (95% CI: -0.12, 0.46) for every 100 Bq m⁻³ increase in regional radon concentrations and by 0.11 (95% CI: 0.01, 0.23) for every 10 years lived in a high radon potential geological region.

3. Meta-analyses

128. Zhang et al. [Z4] performed a meta-analysis of published residential radon studies. Studies were eligible for inclusion if they met the following criteria: (a) case-control study design; (b) residential radon as the primary exposure, measured with alpha-track detectors, and expressed as a time-weighted mean; (c) lung cancer incidence as the primary outcome; and (d) odds ratios reported or calculable from reported data. Twenty-two primary studies published between 1990–2008 were identified from a literature review to be included in the meta-analysis. By region, there were 11 European, 8 North American, 2 Chinese and 1 Japanese study. The total numbers of cases and controls were 13,380 and 21,102. A dose-response analysis was performed with studies reporting three or more exposure levels and providing the data for categories of median exposure levels, numbers of cases and controls, and adjusted logarithm of the OR with its standard error. Five of the 22 studies were excluded for not having reported all data needed for this analysis. With the remaining 17 studies, the ERR was estimated to be 0.07 (95% CI: 0.04, 0.10) per 100 Bq m⁻³. This result is not statistically different from those of the three pooled analyses reported in table 14.

129. An unconventional Bayesian meta-analysis of case-control, cohort and ecological studies of lung cancer risk associated with residential radon exposure was conducted by Dobrzyński et al. [D7]. Studies had to meet the following criteria for inclusion: cases and controls were subject to well-defined criteria; residential histories were given for all periods considered; periods of measurements were provided along with clear indicators of smoking habits, sex and mean age, and information about the methods of group selection. Adjusted relative risks or odds ratios and their 95% CIs were obtained from each study. Thirty-two independent studies published between 1990–2014 were identified and covered approximately 22,000 cases and 900,000 controls. Most of the controls, about 812,000, as well as 3,500 cases come from the cohort study of Turner et al. [T21] which used ecological indicators of residential radon. The meta-analysis combined estimates of lung cancer incidence as well as mortality. Linear effects of radon on OR/RR were estimated over four ranges of annual equivalent (mSv per year) radon doses to lungs. The ranges in terms of radon concentrations were 0–84, 0–168, 0–391 and 0–838 Bq m⁻³ with corresponding linear slope estimates of 0.09 (95% CI: -0.39, 0.57), 0.07 (95% CI: -0.04, 0.18), 0.07 (95% CI: 0.04, 0.11) and 0.00 (95% CI: -0.02, 0.02) per 100 Bq m⁻³. The authors assessed the relative fits of models with constant and quadratic effects for radon, and ultimately concluded that the constant

model with no dose-response effect of radon was most consistent statistically with the meta-analysis data. The results of these meta-analyses are quite different from the results of the three pooled analyses reported in table 14 and from the previously described meta-analysis conducted by Zhang et al. [Z4].

4. Summary of residential studies

130. Table 17 summarizes the main findings of reviewed residential studies in which risk estimates were reported for radon exposure individually linked to lung cancer outcomes. Information is provided on the study region, design, number of cases, numbers of controls for case-control (C-C) studies and total number of subjects for cohort studies, type of risk measure reported and corresponding risk estimates. Of the three United States' studies, the Connecticut, Utah and Southern Idaho study, and the New Jersey study were included in the 2006 North American pooling and published individually afterwards; whereas, the Massachusetts study represents a new independent finding. Likewise, the three Spanish and one Czech study represent new independent findings. The two meta-analyses provide an aggregate synthesis of case-control studies published since 1990. Of the new studies, quantitative excess relative risks of 0.04 (95% CI: -0.20, 0.35) and 0.14 (95% CI: 0.03, 0.39) per 100 Bq m⁻³ are provided by the Massachusetts and Czech studies, respectively. The Spanish studies provide categorized risk estimates. In particular, categories whose midpoints are ~100 Bq m⁻³ larger than the references provide overall odds and hazard ratio* estimates of 2.25 (95% CI: 1.32, 3.84) for 101–147 versus <50 Bq m⁻³ and 1.2 (95% CI: 0.5, 2.8) for ≥50 versus <50. Risk estimates are provided for different smoking habits (never and ever-smokers) in the Spanish and Czech studies. The former reported reduced risk for never smokers, whereas the latter reported increased risk. However, the confidence intervals were wide and no statistically significant evidence of differential risk by smoking was noted in the reviewed studies. To a greater extent, currently reviewed and past epidemiological studies have not been able to assess exposure in childhood and adolescence. Thus, the impact of radon exposure at young ages on the induction of lung cancer is unclear.

Table 17. Summary of main study findings from epidemiological studies of residential radon published since the UNSCEAR 2006 Report [U6]

Region	Design/subset	Cases	Controls/ cohort	Risk ^a		Reference					
				Measure	Estimate (95% CI)						
United States	Connecticut and Utah	Case-control	1 474	1 811	ERR	0.002 (−0.21, 0.21)	[S3]				
		Males	846	1 029	ERR	−0.006 (−0.29, 0.27)					
		Females	628	782	ERR	0.061 (−0.30, 0.43)					
		Never smokers	128	255	ERR	0.141 (−0.47, 0.75)					
	New Jersey	Case-control	651	740	ERR	0.05 (−0.14, 0.56)	[W10]				
		Males	302	348	ERR	−0.13 (−0.30, 0.44)					
		Females	349	392	ERR	0.29 (−0.12, 1.70)					
	Massachusetts	Case-control	200	397	ERR	0.04 (−0.20, 0.35)	[T2]				
	Spain	Case-control	349	513	OR	<50: 1.00 (reference) 50–100: 1.87 (1.21, 2.88) 101–147: 2.25 (1.32, 3.84) >147: 2.21 (1.33, 3.69)	[B6]				
						Case-control Never smokers		192	329	OR	≤100: 1.00 (reference) 101–147: 0.80 (0.43, 1.50) 148–199: 1.16 (0.64, 2.11) ≥200: 2.42 (1.45, 4.06)
Females											153
Cohort						24		2 127	HR	<50: 1.0 (reference) ≥50: 1.2 (0.5, 2.8)	[B5]
		Males	20	1 220	HR		<50: 1.0 (reference) ≥50: 1.4 (0.5, 3.6)				

Region	Design/subset	Cases	Controls/ cohort	Risk ^a		Reference
				Measure	Estimate (95% CI)	
Czech Republic	Nested case-control	370	1 399	ERR	0.14 (0.03, 0.39) ^b	[T16]
	Never smokers	58	670	ERR	0.73 (0.02, 1.90) ^b	
	Ever smokers	312	NA	ERR	0.14 (0.02, 0.30) ^b	
Meta-analyses	Case-control	13 380	21 102	ERR	0.07 (0.04, 0.10)	[Z4]
	Mixed (case-control, cohort, ecological)	22 000	900 000	Stratified ERR	0–84: 0.09 (–0.39, 0.57) 0–168: 0.07 (–0.04, 0.18) 0–391: 0.07 (0.04, 0.11) 0–838: 0.00 (–0.02, 0.02)	[D7]

^a Excess relative risk (ERR) estimates are for an increase in radon concentrations of 100 Bq m^{–3}; odds ratio (OR) and hazard ratio (HR) estimates are for the indicated categories of Bq m^{–3} concentrations.

^b 90% CI.

F. Uncertainties in epidemiological studies

131. Measurement error* in assessment of residential radon exposure stems from several sources, but the fundamental issue is the need to cover long-term residential history, with dwellings at least during the period 5–20 years preceding the diagnosis, practically always with retrospective assessment. Further, none of the residential studies have evaluated radon exposure outside the home. For the miner studies, major uncertainty is related to the early period, typically before the 1960s, with few or no radon measurements [P7]. Also, during the later periods, the measurements did not cover all sites within the mining area and additional uncertainty stems from inaccurate data on working locations. During the past decades, personal dosimetry has strongly reduced these uncertainties.

132. As outlined in the UNSCEAR 2012 Report [U7], uncertainties in epidemiological studies include those related to outcome data (health effect information), and those concerning exposure assessment. Dosimetric models are always used for estimating radiation dose from radon from measured activity concentrations. Parameter values used in the models always involve uncertainties. Such uncertainties can affect the dose response (shape and steepness of the gradient) and the precision (confidence interval width). The bias from shared or differential errors in dosimetry can introduce major bias in risk estimates. Non-differential unshared errors tend to attenuate any real effect, and assignment (Berkson-type) error would not bias the result but only decrease precision [H5]. In addition, overly simplified models ignoring important influences can involve conceptual uncertainty besides uncertainty from imprecise parameter values.

133. The key components of uncertainty in exposure assessment for residential studies arise from the variability in exposure, which is difficult to cover completely, i.e. to construct complete and accurate cumulative exposure estimates over time from concurrent measurements of radon concentrations. First, the alpha track detectors used for measuring radon concentrations have a relatively small level of uncertainty. More importantly, radon concentrations vary within a building at a given time between rooms (spatial variation within the home), and over time. This includes short-term variation depending on changes in heating and ventilation, seasonal differences and possible structural changes that affect in- and outflow of air including insulation (particularly of windows), renovation or remodelling and radon remediation measures [K9]. Studies with repeated measurements in the same dwellings have also shown yearly variation reflecting influence of behavioural factors and weather [H2, S16]. Exposure estimation also relies on assumptions concerning time spent in the dwelling (occupancy), which is often presumed to be similar for a group of subjects. Nearly all studies of lung cancer risk from residential radon have been case-control studies, in which exposure assessment is always retrospective. Using concurrent radon concentration as a proxy indicator of past radon level adds to uncertainty. If the behaviours that affect the radon levels are not similar for the current residents of the dwelling and the study subjects, additional error results. Radon exposures outside the home, e.g. workplace and any secondary residence have not been covered in epidemiological studies. Radon measurements involve additional uncertainty related to the fact that only radon gas and not its progeny (or thoron) is measured, and the assumption that activity concentration is a valid indicator of the radiation dose to the lung.

134. Empirical studies of radon risk nearly always have missing data, and imputation* of missing values with credible estimates adds to uncertainty (it should be noted that ignoring the missing data can increase uncertainty even more). Reconstruction of complete residential history with valid measurements in all dwellings during the aetiologically relevant period is very challenging and some studies have focused on persons with stable residence. Often, 20–30% of the intended residential period has not been covered by radon measurements. Measurements after the residential period may be distorted by behavioural factors such as ventilation and heating habits, as well as any structural changes that can influence radon levels.

Some additional uncertainty may stem from imperfect accounting for different effects of exposures incurred during various time periods, including time since exposure and age at exposure (i.e. not being able to incorporate correct weighting for exposures during different time windows prior to cancer occurrence). Residential radon exposure starts in childhood, unlike occupational exposure in mining setting. The role of radon exposure in childhood on lung cancer risk has not been examined.

135. Several analyses of lung cancer risk from residential radon have employed statistical techniques to account for both classical and Berkson type measurement error in exposure assessment [F1, H4, H5, R5]. Uncertainties in exposure assessment tend to attenuate the dose response (bias the results toward the null) if non-differential, but the effect can be difficult to predict across exposure categories [D8]. In the large European pooled analysis of residential studies, the risk estimate per unit exposure was doubled after correction for uncertainties in radon measurements [D2].

136. Due to the highly complex combination of factors (related to both building and soil characteristics) strongly influencing radon levels in a dwelling, it has been exceedingly difficult to create prediction models that could provide accurate estimates without performing radon measurements. Therefore, studies without empirical exposure estimates were not included in this annex.

137. Thoron is present everywhere together with radon. Therefore, both radon and thoron can be detected in varying concentrations. In some epidemiological studies, no distinction is made between exposure to radon and its progeny and exposure to thoron and its progeny [U6]. Since thoron and its progeny can be an important component of the total exposure in some situations (workplaces or dwellings), it can thus be a source of error in radon studies that do not distinguish radon and thoron contributions to the total exposure [C20, S10, T3, T5, T7]. More details on thoron interference with radon measurements and risk assessment are given in section III.H.

138. In occupational studies, uncertainty in exposure assessment was highest during the early periods with the highest exposure levels with substantial improvement over time. Especially for older time periods, radon measurements were not comprehensive in terms of all mining locations, and also performed infrequently. Data on the workers' locations within the mines also have inaccuracies. Assigning exposure levels for workers in various parts of the mines at different times from a very limited set of measurements involves substantial uncertainty. Therefore, misclassification of exposure is likely to impact on risk estimates from miner studies even more than residential studies. Dosimetric models also incorporate assumptions regarding equilibrium factors for radon and its progeny, unattached fraction, and breathing rate. Regression calibration, Bayesian methods and other approaches have been used to deal with the effects of measurement error [A5, A6, H7, S19]. The impact of the correction for uncertainty in dosimetry has ranged from negligible to 50–60% of the effect size, and it tends to amplify the dose response (as is expected when classical measurement error diluting an effect is involved). Yet, the error correction methods also involve assumptions or priors, and the results may depend on methodological approaches applied.

139. In addition to uncertainty from exposure assessment, epidemiological studies assessing the health risk of exposure to radon also involve systematic errors such as selection bias, information bias* and confounding. In the residential case-control studies, selection bias could arise from differential participation of controls recruited for the studies. In particular, participation proportions among controls is a concern, as commonly 20–50% of the invited controls have refused. If for instance highly educated people are more likely to participate as is often the case [C24, R9], radon exposure in the population free of lung cancer is likely overestimated (as a high level of education is associated with residence in houses that have higher radon levels than flats), which would result in underestimation of risks. In occupational studies such as underground miners, healthy worker bias may result in underestimation of risk or distorted dose responses if an employed cohort is compared with the general population (standardized mortality

ratios). Information bias could occur if better radon exposure data are available for controls than cases (the former are likely to be alive and hence similar ventilation behaviour could be expected than for cases likely to have succumbed to their disease).

140. Smoking is a major potential confounder in indoor radon studies and as socio-economic factors are associated with both smoking habits and type of dwelling (houses have higher radon potential than flats), substantial negative confounding has been reported in studies of indoor radon (i.e. lack of adequate adjustment tends to decrease or mask the true effect of radon). In case-control studies, information bias may occur, as smoking history has to be obtained from proxy respondent for deceased cases, with more complete and precise data for controls with fewer deceased subjects. Matching for vital status has been employed in some studies to minimize this potential bias. To fully account for the effect of smoking, information should be obtained for intensity and duration of smoking, age at start and time since quitting, as well as types of tobacco products and exposure to environmental tobacco smoke. Any imprecision in the confounder data will reduce the effectiveness of control of confounding and result in residual confounding despite efforts to adjust for such effects. In the European pooled study of residential radon, smoking masked the effect of radon nearly completely in the preliminary analysis without adjustment for the effect of smoking [D2]. In miner studies, confounding by smoking does not appear to be very strong [H17, L6, L7, R8, S4, T13].

141. Besides being a confounder, smoking also modifies the effect of radon on lung cancer risk. In residential studies, the relative risk per unit exposure has been similar among smokers and non-smokers (no modification in the context of the multiplicative model, suggesting the findings are consistent with a multiplicative joint effect or combined effect) [D3]. In miner studies, on the other hand, a sub-multiplicative (but supra-additive) interaction has been reported [L7, S5, T13], although some results are also consistent with an additive interaction. A sub-multiplicative joint effect implies larger risks per unit exposure for non-smokers (on the multiplicative scale). A possible explanation for the discrepancy is the lack of sufficient power in residential studies with substantially lower exposure levels and effect sizes for radon than in miner studies. Converting relative risks into absolute risks, in both cases (i.e. in residential and miner studies) the absolute lung cancer risk from radon exposure would be much higher for a smoker than for a non-smoker, due to the much higher lung cancer risk from smoking.

142. Other known risk factors for lung cancer are also potential confounders, including exposure to asbestos, chromium, nickel, silica dust and diesel exhaust gas [I2, I3]. Of these, silica dust and diesel exhaust gas occur also in mining environment and may correlate with radon exposure. In such cases, positive confounding can occur, with incomplete control of other exposures exaggerating the effect of radon. The possible role of uranium dust in miner studies has not been examined, though its contribution to lung dose is smaller than that from external gamma radiation and from inhaled radon progeny [M4, R2]. Other risk factors for lung cancer that should ideally be also evaluated in both residential and miner studies cancer include benign lung disease and dietary factors [D5, V9].

G. Alternative models for lung cancer risk from radon exposure

143. Lung cancer risk after occupational radon exposure depends in a complicated way on the temporal modifiers attained age, age at exposure and time since exposure, and on exposure rate. Furthermore, the temporal modifiers are interrelated and cannot be easily separated. Therefore, alternative models to the BEIR VI model have been developed and applied to various cohorts. The parametric ERR models are structurally similar to the BEIR VI model but use continuous functions for the temporal modifiers. The biologically-based models of carcinogenesis try to quantify the effects of radon exposure on lung cancer development and to infer risk from these processes.

1. Parametric ERR models

144. Parametric ERR models were developed based on the observation that the relative risk consistently decreases with increasing attained age (or increasing age at exposure), increasing time since exposure and increasing exposure rate. Whereas the relative risk in the BEIR VI model is given for each modifier by categories, and each category by a separate parameter, parametric models usually assume an exponential dependence of the excess relative risk with the modifiers, with one parameter for each modifier. These models therefore have a smaller number of parameters related to radiation than used for description of the BEIR VI categories and avoid discontinuous changes of risk at the category limits. The smaller number of parameters should have better statistical support from the data and might be more robust among different cohorts.

145. Tomášek et al. [T12] applied an ERR model with exponential modifying terms on time since exposure and age at exposure. In both cohorts, the French and Czech uranium miners, similar decreasing modifying effects of time since exposure and age at exposure were found, and the relative effects were significantly different in the joint study.

146. The Wismut miners were analysed both with parametric ERR models and the BEIR VI model by Walsh et al. [W3]. Among various tested parametric models, two alternative formulations were found to describe best the data. The first model is linear in radon exposure with exponential effect modifiers that depend on age at median exposure, time since median exposure, and radon exposure rate. The second model is similar to the first one but includes attained age as covariable instead of the age at median exposure. Since age at median exposure, time since median exposure and attained age are linearly related, the two different formulations are identical in terms of quality of fit.

2. Mechanistic models of carcinogenesis

147. Biologically-based mechanistic models of carcinogenesis describe the development from early cellular changes towards malignant cells. In an effective way, the complex process is reduced to a few time-limiting steps. Essential elements of the model include mutational processes between different stages, clonal expansion of pre-malignant cells, and the transition from pre-malignant to malignant cells. Malignant cells turn into a detectable cancer after a certain lag period. In principle, radiation can act on any stage in the carcinogenic process. More details on this class of models and its applications to radio-epidemiological cohorts can be found in Rühm et al. [R11]. Several studies applied these models to miners exposed by radon and analysed the effect of radon on the different stages and the consequences for radiation risk. Most often the two-stage clonal expansion model was used that includes two stages from healthy stem cells towards malignant cells. The end point of all studies was lung cancer mortality.

148. The two-stage clonal expansion model was applied to the Colorado miners by Luebeck et al. [L12]. The effect of radon on clonal expansion was highly significant. An additional effect on the initiation step was observed but was not significant. It was shown that the inverse dose rate effect* is a consequence of radon exposure acting on clonal expansion. Smoking information was available, and the risk of smoking and radiation was between additive and multiplicative. This analysis was later extended to three stages by Little et al. [L9].

149. European miners from the Czech Republic, France and Germany were analysed with the two-stage clonal expansion model by Heidenreich et al. [H6]. Different possible actions of radon on the model parameters were tested. All three cohorts indicated a highly significant action of radon exposure on clonal expansion with a linear-levelling form. An additional action on initiation was only minor and not

significant in all cohorts, and an action on transformation was not found to be significant. The analysis included a correction for radon measurement errors.

150. The Eldorado cohort was analysed by Eidemüller et al. [E2] with the two-stage clonal expansion model. Again, the action of radiation on the clonal expansion rate was highly significant. The clonal expansion rate increased in a non-linear way, with a steep increase until exposure rates of about 20 WLM per year, and a smaller increase above. The authors mentioned that such an exposure response might be related to a bystander effect. In addition, the data were analysed by a parametric ERR model and the BEIR VI model, and the risk predictions from the different models were compared.

151. The Wismut workers were analysed by van Dillen et al. [V4] with a two-mutation carcinogenesis model that is structurally similar to the two-stage clonal expansion model and includes two stages and a net clonal expansion of intermediate cells. Assuming that radiation could only affect initiation or transformation, but not the net clonal expansion rate, the authors found a significant cell killing contribution in the second mutation rate and a large value of the lag time of 13–14 years from a malignant cell to an observable tumour. They further consider that there is low biological plausibility of a strong dose-dependent net-clonal expansion rate.

152. An updated data set of the Wismut workers with a longer follow-up and more workers and lung cancer deaths was studied by Zaballa and Eidemüller [Z1] with the two-stage clonal expansion model. Among a variety of models, the best model describing the data included an exposure-dependent clonal expansion rate. At lower exposure rates, it increased linearly with annual exposure. At rates around 100 WLM per year, the exposure response saturated. No indication for an additional radiation effect on the initiation rate or on the transformation rate was found. Applying the model for typical domestic exposure with a total of 11 WLM during 25 years of exposure, the model predicted a decrease in ERR per dose with attained age of about 25% per decade.

153. The mechanistic studies of lung cancer after radon exposure indicate a very consistent exposure response. All studies in which a radiation action on clonal expansion was tested showed a strong preference for radiation modifying clonal expansion. A possible additional effect of radon on initiation was minor and not observed in all studies, and almost no effect on transformation was found. Furthermore, the clonal expansion rate increased with exposure rate in a non-linear way, with a steeper increase at lower exposure rates, and a smaller increase or saturation at higher exposure rates. Noteworthy, such an exposure response is different to low-LET studies, where radiation usually acts either on initiation or on clonal expansion in a linear way [R11]. In the mechanistic model framework, the distinctive dependence of risk on the temporal modifiers as well as the inverse exposure rate effect results from the specific non-linear dependence of the clonal expansion on exposure rate. With a given model, risk predictions for different exposure scenarios are obtained from the annual exposure rates without explicit parametrization of the temporal modifiers.

154. The mechanistic studies were all applied to miner cohorts including also higher levels of radon exposure and exposure rate. Therefore, the suggested mechanisms from these studies are strongly influenced by the high exposure part of the cohorts. It is unknown whether the inferred mechanisms are similar to those operating at low levels of exposure and exposure rate. A better understanding of the biological mechanisms of radon carcinogenesis at different exposure levels, together with improved mechanistic description, can help to improve future risk inference* at lower exposure levels.

3. Discussion of alternative models

155. Since the temporal modifiers are interrelated, it is possible to obtain a similar description of the radio-epidemiological cohorts with different sets of modifiers, e.g. by using attained age and time since exposure, or by using age at exposure and time since exposure. Due to the complex model structure with many correlated parameters, the transfer of risk to other populations with different exposures involves a substantial uncertainty that relates to the type of selected model. A risk comparison of the BEIR VI model, the parametric ERR model and the two-stage clonal expansion model was conducted by Eidemüller et al. [E2] for different exposure scenarios with 50 and 500 WLM, and for 2 and 5 years of exposure duration. The resulting uncertainty from the choice of model was found to be larger than the statistical uncertainty.

156. Compared to the BEIR VI model, the parametric ERR model assumes a specific functional form of the temporal modifiers with a smaller number of parameters. The mechanistic model structure is fundamentally different and based on the long-term cancer development. The model parameter values can change during radiation exposure depending on the annual exposure rate. Similar predictions from different types of models for specific exposure scenarios, as well as consistent parameter values for a particular model type across various cohorts, can strengthen the confidence in the risk estimates. Better understanding of the underlying mechanisms can help to guide the risk transfer to other populations.

H. Thoron interference with radon measurements and risk assessment

157. Thoron (^{220}Rn) is an isotope of radon (^{222}Rn), and therefore also an inert noble gas, which arises from the decay chain of thorium-232 (^{232}Th). Thorium is a common element in the earth's crust and therefore, like radon, thoron is found in air at varying concentrations.

158. In the past, exposures to thoron and its progeny were often ignored due to usually low concentration of thoron and its progeny in indoor environments. Since thoron ($t_{1/2}=55\text{ s}$) has a much shorter half-life than radon ($t_{1/2}=3.83\text{ days}$), the distance it can travel before undergoing radioactive decay is very much shorter than the distance radon can travel in the same medium. Thoron in the soil gas beneath a building cannot survive long enough, in most situations, to enter a building and thereby accumulate to a significant level in indoor air. Indoor thoron is generally due to the exhalation of thoron from thorium that may be present in the materials of the internal surfaces of the building. Because of its short half-life, thoron gas migration from the source is generally considered to be very limited in the indoor environment as well. This is true when the ventilation rate is low or poor [C11].

159. In most epidemiological studies, no distinction is made between exposure to radon and its progeny and exposure to thoron and its progeny [U6]. However, it has become increasingly clear that exposure to thoron and its progeny cannot be ignored in some specific environments (both workplaces and homes) as it contributes to the risks otherwise assigned solely to exposure to radon and its progeny.

160. A number of authors reported that the contribution of thoron and its progeny can be a significant component of the total exposure (radon and thoron). For example, Evans and Goodman [E3] measured the thoron content in the air of workplaces and found that some locations in a thorium mantle plant had thoron gas concentrations ranging from 8,510 to 148,000 Bq m^{-3} (230 to 4,000 pCi/L) which were greater than the average radon gas concentration measured in the Schneeberg and Jachymov mines. Data for two Elliot Lake mines showed thoron decay product levels ranging from 0.1 to 0.3 WL, with parallel radon decay product levels ranging from 0.2 to 0.5 WL [C4]. Radon and thoron levels were investigated in old

uranium mines in Dolina Bialego, Tatra Mountains, Poland [K3], where the average ratio of thoron to radon concentration was 0.017. Stegnar et al. [S17] assessed radiation exposure at selected former uranium mining and processing sites in the Central Asian countries of Kazakhstan, Kyrgyzstan, Uzbekistan and Tajikistan. While radon measurements were performed at all sites, thoron measurements were limited. The available results showed that outdoor radon and thoron concentrations varied from 16 to 1,500 Bq m⁻³ and from 8 to 500 Bq m⁻³ in Digmai; while indoor radon and thoron concentrations varied from 43 to 470 Bq m⁻³ and from 5 to 810 Bq m⁻³ in Kadji-Sai, respectively.

161. Since thoron is present everywhere together with radon, both radon and thoron can be detected in residential homes in varying concentration. The ratios of thoron to radon gas concentration varied from 0.023 to 0.29 with an average of 0.11 in 3,215 Canadian homes [C10], 0.82 to 3.1 with an average of 1.7 in high background radiation areas in 747 Indian homes [M9], and 1.6 to 11 with an average of 4.5 in Chinese traditional residential dwellings constructed with loam bricks or soil walls ($n=164$) [S9]. Average ratios between thoron and radon gas concentrations were also determined as 0.51 in the Balkan region ($n=300$) [S18], 0.65 in South Korea ($n=1,550$) [K2], 0.8 in the high background radiation areas of India ($n=200$) [C22] and 2.1 in Sokobanja municipality of Serbia ($n=40$) [Z7].

162. Simultaneous long-term measurements of thoron and its progeny were carried out in 248 Canadian homes [C7, C9]. While thoron gas was not detectable in 54% of the homes, thoron progeny was measured in all homes tested. This means that one of thoron's progeny, ²¹²Pb with a relatively long half-life of 10.6 hours can migrate away from its source and enter the immediate environment of human beings before undergoing radioactive decay. The results showed that thoron progeny may have enough time to escape from the point, where it is formed and migrate a considerable distance in an indoor environment while thoron gas concentration may fall off rapidly with distance from its source, especially with poor ventilation.

163. Measurements of radon and radon progeny together with thoron and thoron progeny were carried out in 141 dwellings in a thorium abundant beach environment of south west India [V11]. The average radon gas concentration was 24 Bq m⁻³ while the average thoron gas concentration was 37 Bq m⁻³. The average equilibrium equivalent progeny concentrations were found to be 11 Bq m⁻³ and 1.6 Bq m⁻³ for radon and thoron, respectively. On average, thoron progeny concentration was much lower than radon progeny concentration while thoron gas concentration was higher than radon gas concentration. Based on progeny concentrations, it was estimated that thoron contributes 35% to the total inhalation dose from exposure to radon and thoron.

164. A large-scale study on radon gas concentrations and thoron progeny concentrations (EETC) in 2,500 dwellings was conducted in the Netherlands [S12] leading to an overall average radon gas concentration of 15.6 Bq m⁻³ and an average thoron-progeny concentration of 0.64 Bq m⁻³. Applying an equilibrium factor of 0.4 for radon and a dose conversion factor of 9 nSv (h Bq m⁻³)⁻¹ EEC for radon and a 40 nSv (h Bq m⁻³)⁻¹ EETC for thoron, the thoron progeny in Dutch dwellings contribution is about 30% of the total effective dose due to radon and thoron and their progeny.

165. Since thoron and its progeny can be a significant component of the total exposure in some specific situations (workplaces or dwellings), it can thus be a source of error in radon studies that do not distinguish radon and thoron contributions to the total exposure [C20, T3, T5]. For example, with radon/thoron discriminative alpha-track detectors, Shang et al. [S10] measured radon and thoron gas concentrations in Gansu, China, where a radon study with a popular radon gas detector (Radtrak) was conducted jointly by the US National Cancer Institute and the China Ministry of Health. The average radon and thoron gas concentrations were 120±61 Bq m⁻³ and 430±210 Bq m⁻³, respectively. Based on the re-investigation results, the actual level of indoor radon gas was about 3 times lower than that reported by Lubin et al. [L11] which was heavily affected by high concentrations of thoron gas.

166. A study conducted by Tokonami et al. [T7] in 202 cave dwellings in Shanxi and Shaanxi provinces of China found that indoor radon gas concentrations ranged from 19 to 195 Bq m⁻³ with a geometric mean of 57 Bq m⁻³ while indoor thoron gas concentrations ranged from 10 to 865 Bq m⁻³ with a geometric mean of 153 Bq m⁻³. The study revealed that thoron is not negligible for accurate radon measurements and thus that special attention should be paid to thoron and its progeny for dose assessment in such specific environment.

167. Lung cancer risk due to residential radon has been revised based on more recent epidemiological data analyses in Europe [D2, D3] and North America [K8, K10]. In these large-scale surveys, passive radon gas detectors were used for exposure assessment. Although these kinds of detector are well designed so as to detect radon effectively, it is however also true that, in general, thoron (²²⁰Rn) can also be detected. Some popular passive radon detectors were tested for their thoron sensitivity [C6, T8]. The relative sensitivity (RS) between thoron and radon was very low for some detectors, such as RS=0.05 for NRPB/SSI detectors used in radon studies in the United Kingdom, Ireland and Sweden and RS=0.02 for detectors used in the Winnipeg case-control study. However, for some detectors, the thoron and radon sensitivities were comparable, such as RS=0.68 for the Radtrak detector used in radon studies in the United States and RS=0.78 for the KfK detector used in radon studies in Germany [U9].

168. Five types of radon gas detectors commonly available to Canadian home owners were tested for their thoron sensitivity [C8]; the thoron sensitivity varied widely from 0.012 to 0.741. For example, a linear fitting of the average reported radon concentrations and the actual thoron concentrations at three different levels revealed a thoron sensitivity of 7.5% for radon gas detectors used by Health Canada's National Radon Laboratory. This means that a thoron gas concentration of 100 Bq m⁻³ could be reported as a false radon gas concentration of 7.5 Bq m⁻³ added to the true radon indoor concentration.

169. When a radon gas detector has a sensitivity to thoron, the reported radon result will always be the sum of the "true" radon concentration and a portion of the thoron concentration. The latter will be falsely treated as additional radon concentration, i.e. it will give a "false" radon concentration. If radon and thoron had the same potential alpha energy, this false reading would not be a big issue. In this case, the radon measurement from a detector equally sensitive to radon and thoron could then serve as an indicator of radiation dose to the lung. However, as indicated in the Committee's reports [U3, U6], at the same gas concentration, the annual effective dose of radon is 4.5 times the annual effective dose of thoron. This means the thoron gas concentration must be 4.5 times higher than the radon gas concentration in order to deliver the same amount of radiation dose to the lung. In other words, at a given concentration, thoron could be 4.5 times less effective than radon in producing damage to the lung.

170. Radon case-control studies have been performed to estimate the risk of radon-induced lung cancer. Radon gas detectors highly sensitive to thoron gas were used in some such studies. This suggests that in some studies radon exposure could have been overestimated, i.e. radon measurements may have been contaminated by the presence of thoron. Thoron contamination in radon measurements could have a significant impact on the assessment of lung cancer risk following radon exposure, because the risk associated with the radon exposure could, in fact, be underestimated. For observed lung cancer incidents, an overestimation in radon exposure will result in an underestimation in the risk. For more details see also appendix B.

I. Summary of epidemiological studies reviews

171. New epidemiological information on the lung cancer risk due to radon and radon progeny was found in the form of updated occupational studies, new results from the Wismut study, and new residential studies conducted in Massachusetts, United States, Spain and Czech Republic. Combined risk estimates from the updated underground miner studies were derived from published results reported for the entire cohorts as well as for recent periods of work and/or low radon progeny exposure. The combined ERR estimate of 0.60 (95% CI: 0.34, 0.87) per 100 WLM for the entire cohorts was similar to the UNSCEAR 2006 Report's estimate 0.59 (95% CI: 0.35, 1.0) [U6]. A higher combined ERR estimate of 1.53 (95% CI: 1.11, 1.94) was obtained when considering more recent work periods and lower exposure. Risk estimates from the Spanish residential studies were higher than the 0.16 (95% CI: 0.05, 0.31) ERR per 100 Bq m⁻³ adopted in the previous UNSCEAR 2006 Report [U6]. However, the Spanish study is much smaller (349 cases and 512 controls compared to 7,148 cases and 14,208 controls for the European pooled study), and the Spanish study did not provide estimates of linear excess relative risk. Estimates from the other residential studies reviewed were closer to and had wider confidence intervals that included the adopted ERR. There still exists a degree of variability in residential risk estimates, for example with regard to smoking habits and sex and uncertainty of exposure in dependence of duration of measurements.

172. Residential and occupational risk estimates can be compared by converting a residential radon concentration into a cumulative exposure. To do so, assumptions must be made about home occupancy, the equilibrium of radon with its progeny, and time-period of exposure. Applying 7,000 hours indoor occupancy in a year an equilibrium factor of 0.4 and the European pooling exposure period of 30 years [D2], the relationship between radon concentration and cumulative radon progeny exposure is that 100 Bq m⁻³=13.2 WLM [I6]. Accordingly, the UNSCEAR 2006 Report [U6] residential ERR estimate can be expressed as 1.21 (95% CI: 0.38, 2.35) per 100 WLM, which is between the occupational estimates for entire cohorts and subcohorts of more recent work periods, closer to the occupational estimate of 1.53 (95% CI: 1.11, 1.94) per 100 WLM at low exposure.

IV. FUTURE RESEARCH NEEDS

173. Even though extensive research has been conducted on dosimetric and epidemiological evaluations related to lung cancer from exposure to radon and progeny, large uncertainties were reported. The main uncertainties in the assessment of dose by using the dosimetric approach are primarily due to the uncertainty and variability of model parameter values and uncertainties associated with the assumptions built into the particular model, including over-simplification of the underlying processes. The current literature review has highlighted several areas, where future research is required in order to improve estimates for dose conversion factor. Estimates of dose conversion factors still vary widely irrespective of the chosen approach and future research should aim at reducing the uncertainties inherent in both dosimetric and epidemiological studies where possible.

174. Further research studying the influence of smoking versus non-smoking on incidence of lung cancer attributable to radon exposure is necessary for subgroups of different age and sex as well as for different working environments/conditions. Limitations in evaluation of differences in risk across subgroups of the population include low precision due to small numbers of lung cancer cases among non-smokers, women, younger age groups as well as the lack of studies conducted on radon exposure during childhood. Besides the risk of lung cancer, further studies need to be conducted on risks of cancer other than lung and non-cancer diseases. Ongoing projects, such as the PUMA study would be able to provide important new information to improve knowledge on radon risks.

175. For existing residential studies, further combined analyses should be conducted in order to take modifying factors, such as age and sex, into consideration, while for studies of uranium miners, further analyses are needed to address exposure rate effect. Exposure estimates should also be described in more detail, including exposure uncertainties, method of measurements (radon gas or radon progeny measurement), and number of radon measurements in calendar periods.

176. In workplaces, other possible confounding factors such as asbestos, crystalline silica, diesel engine exhaust, nickel, chromium, lead and other ionizing radiations such as external gamma radiation or long-lived radionuclides also merit further research to study the extent to which they can alter or enhance the effects of exposure to radon.

177. Further research studying effect modifiers such as childhood exposure, exposure rate, time since exposure and attained age is also important, as well as more research detailing uncertainty analyses when calculating dose conversion factors.

178. In addition, further research is needed to assess the impact of low dose and low dose-rate exposures to radon. In order to reduce the impact of misclassification of exposure, this research should focus on studies, or time periods within studies, with the best exposure assessment available.

179. The current literature review has also highlighted the need for further research investigating the effects of thoron. Since thoron and its progeny can be a significant component of the total exposure in some specific situations (workplaces or dwellings), it can be an additional source of error in radon studies that do not distinguish radon and thoron contributions to the total exposure. Thoron contamination in radon measurements could have an impact on the assessment of lung cancer risk following radon exposure. In a similar manner, further research regarding the possible influence of external radiation on risk assessment for lung cancer is also identified as a future research need.

V. GENERAL CONCLUSIONS

180. The Committee has previously considered the issue of sources and effects of exposure to radon (^{222}Rn) and thoron (^{220}Rn) and their progeny with regard to workers and the public in several evaluations. The Committee confirmed that inhalation of radon and its progeny is an established carcinogen for the lung. Since its last evaluation in the UNSCEAR 2006 Report [U6], many new articles have been published concerning radon exposure and lung cancer, including epidemiological studies, as well as relevant information on radon dosimetry. The present work, in agreement with the Committee's mandate from the United Nations General Assembly for estimating effects and risk from radiation exposure, has thoroughly assessed the newly available literature, and presents the Committee's conclusions here.

181. The Committee reviewed 33 dosimetric assessments in homes, indoor workplaces and mines. For home exposures, the range of the assessed effective doses per unit of exposure of EEC of ^{222}Rn are from 7 to 34 nSv per h Bq m⁻³ with an arithmetic mean of 18 nSv per h Bq m⁻³, and a geometric mean of 16 nSv per h Bq m⁻³. These values are consistent with the central value of 15 nSv per h Bq m⁻³ with a range of 8–40 nSv per h Bq m⁻³ of EEC of ^{222}Rn previously estimated by the Committee for average indoor conditions based on dosimetric evaluations.

182. The Committee identified 26 articles reporting on epidemiological studies (five residential and 21 occupational) of lung cancer risk from radon exposure published since 2006. Among these new studies, the ERR estimates from residential studies varied from -0.13 to 0.73 per 100 Bq m⁻³ for exposure to radon gas concentration, with the mean ERR of 0.13 per 100 Bq m⁻³. It is noted that no new pooled

analysis has been carried out after the three major pooled residential radon studies reported in the UNSCEAR 2006 Report [U6]. However, a recent analysis of radon exposures for 66 countries concluded that 16.5% of lung cancer cases were attributable to residential radon in 2012 [G1]. Currently reviewed epidemiological studies did not assess exposure in childhood or adolescence. Thus, the impact of radon exposure at young ages on the induction of lung cancer remains unclear.

183. Occupational studies of miners published since the UNSCEAR 2006 Report [U6] were based on extended follow-up of earlier cohort studies and the new Wismut study. Substantial variability in ERR estimates was observed in updated occupational studies, with values ranging from 0.19 to 3.4 per 100 WLM without adjustment for modifying factors. Based on a random-effects meta-analysis with inverse-variance weighting, the combined ERR estimated from the entire study cohorts is 0.60 (95% CI: 0.34, 0.87) per 100 WLM, in close agreement with the previous combined estimate of 0.59 (95% CI: 0.35, 1.0) per 100 WLM [U6]. A higher combined ERR estimate of 1.53 (95% CI: 1.11, 1.94) per 100 WLM was obtained when restricting the analysis to more recent work periods and lower exposure. Preference is given to the latter estimate due to improved radon exposure assessments in more recent periods and to these radon exposures being more reflective of current mining conditions. However, this estimate is less precise due to smaller sample sizes.

184. Residential and occupational risk estimates can be compared by converting a residential radon concentration into a cumulative radon progeny exposure with 7,000 hours indoor occupancy in a year, using an equilibrium factor of 0.4 and cumulative exposure period of 30 years. The residential ERR estimate of 0.16 per 100 Bq m⁻³, adjusted for exposure uncertainty, can thus be expressed as 1.21 (95% CI: 0.38, 2.35) per 100 WLM, which is between the occupational combined risk estimate of 0.60 for the combined entire miner cohorts and 1.53 for combined subcohorts for more recent work periods. Although similar, residential and miner risks are not expected to be the same due to the different conditions under which the two populations are exposed.

185. A notable limitation of the combined estimates is that they ignore the modifying effect of exposure rate and attained age across studies, which reduces the comparability of individual results. In studies that did report on effect modifiers, risk was observed to decrease with increasing attained age, with increasing time since exposure, and with increasing exposure rate, albeit only for cumulative exposure above 50 to 100 WLM. Modifying effects of sex could not be investigated by the occupational studies. It is concluded that models including effect modifiers are preferred for better comparability across studies and improved risk transfer to specific combinations of modifying factors.

186. Lifetime risk up to age 95 from constant exposure to 2 WLM per year from age 18 to 65 years was estimated by applying the BEIR VI exposure-age-concentration model to the Czech, Wismut and Eldorado miner studies and the combined 11 studies used in the BEIR VI report. The estimates of lifetime excess absolute risk were 2.4 per 10,000 persons WLM⁻¹ for the newly published large Wismut study, 3.9 for the updated Czech study and 7.5 for the updated Eldorado study. For the BEIR VI studies, the estimated lifetime risk was 5.5 per 10,000 persons WLM⁻¹. The totality of this evidence is compatible with previous UNSCEAR assessments of lung cancer risk due to radon.

187. The joint effect of smoking and radon exposure was assessed in several epidemiological studies. Smoking-radon interaction was studied occupationally in a combined analysis of three European case-control studies as well as individually in each of the Colorado, Newfoundland and Wismut cohort studies. Evidence of sub-multiplicative interaction was found in the combined analysis, whereas sub- to supra-multiplicative interaction was indicated by the Wismut analysis. Reported risk estimates per unit exposure were higher among non-smokers in all but the Newfoundland study, although confidence intervals in general were wide due to relatively small numbers of lung cancer cases among non-smokers. In residential studies, no obvious deviation from a multiplicative effect has been consistently observed,

although point estimates have been reported as higher for non-smokers than for smokers in both European and North American pooled analyses. The difference in results may be due to lower statistical power in residential studies, a reflection of substantially lower exposure levels and smaller risks attributable to radon. However, as in the occupational analyses, large uncertainties in the estimates were reflected by wide confidence intervals and lack of statistically significant differences across smoking status.

188. Neither the new nor the previous residential studies show a significant difference in risk per unit exposure from radon for smokers and non-smokers. Analyses of miner studies show largely sub-multiplicative joint effect of radon and smoking. Assuming a synergistic effect of smoking and radon means that the lifetime absolute risk from radon depends on the prevalence of smoking in the population—when the prevalence decreases, the risk decreases.

189. Even though extensive research has been conducted on dosimetric and epidemiological evaluations, uncertainties remain large. The main uncertainties in the assessment of dose arise from dosimetric considerations, which are primarily due to the uncertainty and variability of model parameter values and uncertainties associated with the assumptions built into the particular model including over-simplification of the underlying processes. Both the miner studies and the residential studies of lung cancer risk from radon are subject to limitations arising mainly from uncertainties in estimates of radon exposure, particularly in early mining periods, and confounding by other exposures such as smoking. Limitations in evaluation of differences in risk across subgroups of the population include low precision due to small numbers of cases among non-smokers, women and younger age groups. As outlined in the UNSCEAR 2012 Report [U7] on uncertainties in risk estimates for radiation-induced cancer, uncertainties are likely to underestimate ERR estimates in studies of residential radon by 50–100%. Since thoron and its progeny can be a significant component of the total exposure in some specific situations (workplaces or dwellings), it can be an additional source of error in radon studies that do not distinguish radon and thoron contributions to the total exposure. Thoron contamination in radon measurements could have an impact on the assessment of lung cancer risk following radon exposure.

190. Given that the uncertainties from both dosimetric and epidemiological aspects of studies give rise to a broad range of risk estimates, and that values from the current dosimetric and epidemiological reviews are consistent with those used in previous UNSCEAR reports, the Committee further recommends, when estimating the impact of radon exposure levels in a population, the use of the general dose conversion factor of $9 \text{ nSv (h Bq m}^{-3}\text{)}^{-1}$ EEC of ^{222}Rn , which corresponds to $1.6 \text{ mSv (mJ h m}^{-3}\text{)}^{-1}$ (5.7 mSv WLM^{-1}). Applying the Committee's default equilibrium factors for the indoor and outdoor environment of 0.4 and 0.6 results in a dose conversion factor in terms of ^{222}Rn gas exposure of $3.6 \text{ nSv (h Bq m}^{-3}\text{)}^{-1}$ indoors and $5.4 \text{ nSv (h Bq m}^{-3}\text{)}^{-1}$ outdoors.

191. The evidence reviewed by the Committee is compatible with the previous UNSCEAR assessment of lung cancer risk due to radon. Therefore, the Committee concluded that there is no reason to change the established dose conversion factor for its assessments. The Committee continues with its general review of population exposure to radon, with a focus on the consequent risk of lung cancer.

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APPENDIX A. RADON DOSIMETRY

A1. This appendix describes the special quantities and units used to characterize the concentration of the radon and radon progeny in air, and the resulting inhalation exposure. Further, dosimetric models of the human respiratory tract are used for calculations of the absorbed dose to the target tissues of the lung per unit exposure to radon progeny. These models together with various influencing parameters are described in this appendix.

I. SPECIAL QUANTITIES AND UNITS

A2. The radon activity concentration is the activity per unit volume of the gas, expressed in units of Bq m^{-3} . The dose to the lung mainly arises from the inhalation of airborne radon progeny and the alpha particles emitted during their decay and that of their short-lived progeny. Consequently, the quantity “potential alpha energy concentration (PAEC)” of the radon progeny mixture was historically used as a measure of concentration that was an indicator of dose and risk. The PAEC is the total alpha energy ultimately emitted by the decay of the short-lived progeny in unit volume of air. The historical unit of PAEC was the working level (WL), where a concentration of 1 WL is defined as any combination of the short-lived radon progeny in 1 m^3 of air that will result in the emission of $1.300 \times 10^8 \text{ MeV}$ of alpha energy [I6, I13, U1]:

$$\begin{aligned} 1 \text{ MeV} &= 1.602 \times 10^{-13} \text{ J} \\ 1 \text{ WL} &= 1.300 \times 10^8 \text{ MeV m}^{-3} \text{ or } 2.08 \times 10^{-5} \text{ J m}^{-3} \end{aligned}$$

A3. The equilibrium equivalent concentration (EEC) is defined as the activity concentration of radon gas in equilibrium with its short-lived progeny which would have the same potential alpha energy concentration as the existing non-equilibrium mixture. One WL equals approximately $3,750 \text{ Bq m}^{-3}$ of EEC of ^{222}Rn (radon gas) or approximately 275 Bq m^{-3} of EEC of ^{220}Rn (thoron gas) [I13]. The EEC is therefore a measure of the radon progeny concentration or more precisely the PAEC. The EEC (in Bq m^{-3}) can be converted to the PAEC by the relationships [U6]:

$$\begin{aligned} 1 \text{ Bq m}^{-3} &= 5.56 \times 10^{-9} \text{ J m}^{-3} = 2.67 \times 10^{-4} \text{ WL } (^{222}\text{Rn}) \\ 1 \text{ Bq m}^{-3} &= 7.56 \times 10^{-8} \text{ J m}^{-3} = 3.64 \times 10^{-3} \text{ WL } (^{220}\text{Rn}) \end{aligned}$$

A4. The equilibrium factor, F , is defined as the ratio of the EEC to the radon gas concentration (C_{Rn}). In other words, it is the ratio of the PAEC for the actual mixture of radon progeny to that which would apply at radioactive equilibrium:

$$\text{EEC} = F \times C_{\text{Rn}}$$

A5. Exposure is the time integral of the concentration. The potential alpha energy (PAE) exposure is the time integral of the PAEC in air and has the historical unit of the working level month (WLM).

The WLM is defined as the cumulative exposure from breathing an atmosphere at a concentration of 1 WL for a working month of 170 hours. The relationship between the historical and SI units is:

$$1 \text{ WLM} = 3.54 \text{ mJ h m}^{-3}$$

$$1 \text{ mJ h m}^{-3} = 0.282 \text{ WLM}$$

A6. The exposure in terms of EEC (in h Bq m^{-3}) can be converted to the PAE exposure by the relationships:

$$1 \text{ h Bq m}^{-3} = 5.56 \times 10^{-6} \text{ mJ h m}^{-3} = 1.57 \times 10^{-6} \text{ WLM } (^{222}\text{Rn})$$

$$1 \text{ h Bq m}^{-3} = 7.56 \times 10^{-5} \text{ mJ h m}^{-3} = 2.14 \times 10^{-5} \text{ WLM } (^{220}\text{Rn})$$

For ^{222}Rn , if the exposure is expressed in terms of the radon gas concentration then the two units are related via the equilibrium factor: $1 \text{ WLM} = (6.38 \times 10^5/F) \text{ h Bq m}^{-3}$.

II. DOSIMETRIC MODELS

A7. Calculations of the absorbed dose to the target tissues of the lung per unit exposure to radon progeny can be carried out with dosimetric models of the human respiratory tract. A dosimetric model for the respiratory tract needs to describe the morphometry, the respiratory physiology, the deposition of the inhaled material, clearance from the respiratory tract and the dosimetry including the location of target tissues and cells at risk.

A8. The human respiratory tract is composed of three functional regions: (a) the extrathoracic region, consisting of the anterior nose, posterior nasal passages, larynx, pharynx and mouth, acting primarily as a filter to protect the lungs; (b) the tracheobronchial region, consisting of bronchial and bronchiolar airways, whose primary task is to conduct air to the gas-exchange region; and (c) the alveolar interstitial (pulmonary) region, where the gas exchange between lung and blood takes place via the alveoli. Clearance of deposited material is a competitive process between absorption into blood and particle transport to the alimentary tract and lymph nodes. The tracheobronchial and alveolar regions differ in their particle transport mechanisms, with relatively fast mucociliary clearance in the bronchial and bronchiolar airways and relatively slow macrophage-mediated transport in the alveolar region.

A9. There are currently three different type of modelling approaches used to calculate doses to the lung from inhaled radon progeny:

- *Deterministic airway generation models (DAGM)*. These are anatomical or biological models in which the absorbed dose to the sensitive target cells for each airway generation of the tracheobronchial tree is calculated. Such models include those developed by Winkler-Heil et al. [W12, W13]; Harley et al. [H1] and Zock et al. [Z5]. To calculate an average lung dose, a weighting procedure for combining the target cell doses needs to be applied.
- *Stochastic airway generation models (SAGM)*. These are also anatomical or biological models but here the inherent asymmetry and variability of the human airways system is described in terms of probability density functions of airway parameters [H9, H10]. Monte Carlo methods are applied to obtain a distribution of absorbed doses to the sensitive target cells for each airway generation reflecting inter- and intra-subject variability in the morphology of the lung.

- *Semi-empirical compartment models.* Such as the ICRP human respiratory tract model (HRTM) [I7]. In comparison with the airway generation models, these models simplify the anatomical representation of the respiratory tract by combining airway generations into compartments.

A10. In comparison with airway generation models, the overall structure of the HRTM has been simplified for the purposes of dosimetry. For example, the lung is divided into three regions: the bronchial region (BB), the bronchiolar region (bb) and the alveolar interstitial (AI) region. Target cell layers within the BB and bb regions are identified. For the BB region, two layers are defined; one that contains basal cells and the other that contains secretory cells, which lie at different depths. The HRTM defines the absorbed dose to the BB region as the average dose of two layers, giving equal weighting to the basal and secretory layers: $D_{BB}=0.5D_{bas}+0.5D_{sec}$. The absorbed dose to the bb region is given by the average dose to the target cell layer in that region, which are Clara cells (a type of secretory cell). It is the dose to the target cells in the BB and bb regions of the lung that are of importance for radon progeny. In comparison, the dose to the alveolar region is significantly lower [M1, U1].

A11. In the DAGM, the tracheobronchial tree consists of about 15 airway generations with all airways in a given generation being identical in terms of length, diameter and branching angle. The SAGM consists of a variable number (12 to 20) of asymmetric airway generations with airways in a given generation having variable dimensions. Basal and secretory cells are considered to be the target cells for bronchial carcinomas located at different depths in the epithelium. Cellular doses in each airway are calculated and the depth distribution of the targets cells is assumed to be a function of airway diameter, whereas in the HRTM a constant depth for the target cell layer is assumed for each anatomical region [W12, W13]. Hofmann and Winkler-Heil weigh the doses to basal and secretory cells in the bronchial region by their volumetric densities in the epithelium [H10]. This results in a higher weight to the basal cells compared with the secretory cells in the bronchi (e.g. 0.83:0.17 in generations 0–4) [W12]. Mucociliary clearance flow rates are also assumed to be proportional to airway diameter [H9, H10].

A12. The equivalent dose to an organ and the effective dose are ICRP quantities used for radiation protection purposes. The HRTM calculates the equivalent dose to the lung as follows: $H_{lung}=w_R \times (A_{BB} D_{BB} + A_{bb} D_{bb} + A_{AI} D_{AI})$, where D_{BB} , D_{bb} and D_{AI} are the absorbed doses to the bronchial (BB), bronchiolar (bb) and alveolar interstitial (AI) regions. The apportionment factors, A_i represent the regional's estimate sensitivity relative to that of the lung and the assumed values are: $A_{BB}=1/3$, $A_{bb}=1/3$, $A_{AI}=1/3$ [I11]. The ICRP radiation-weighting factor, w_R , for alpha particles is 20 [I9]. As H_{lung} contributes most of the effective dose following inhalation of radon progeny, the effective dose can be approximated by multiplying H_{lung} by the lung tissue weighting factor, w_{lung} , of 0.12.

III. DOSIMETRIC PARAMETERS

A13. Equivalent doses to the lung depend mainly on the potential alpha exposure (i.e. radon progeny concentration in air and the duration of exposure), the breathing rate and the aerosols' properties, including the activity size distribution of the radon progeny aerosol and the unattached fraction. If the exposure is characterized by radon gas measurements, a value for the equilibrium factor, F , is required to estimate the concentration of radon progeny in air, or more precisely the EEC. When using dosimetric models to calculate doses to the lung, additional information on various parameters is required, such as the fractional deposition in the airways, mucous clearance rate, absorption into blood, and the location of the target cells in the airways. The ICRU Report 88 [I14] and ICRP Publication 137 [I13] give a detail discussion of model parameter values. A discussion of aerosols parameter values for homes, indoor

workplaces and mines is given in this appendix. Target cell depth in bronchial epithelium, airway dimensions of the bronchial region and the effects of cigarette smoke on the lung mucociliary clearance are also discussed.

A. Aerosol parameters

A14. Radon (^{222}Rn) gas decays into a series of short-lived radionuclides creating an aerosol of solid particles suspended in air. As described in the ICRU Report 88 [I14], the aerosol is created in two steps: after decay of the radon gas, the freshly formed radionuclides react rapidly (<1 s) with trace gases and vapours and grow by cluster formation to form particles around 0.5 to 5 nm in size. Within 100 s after formation, this unattached progeny may also attach to existing aerosol particles in the atmosphere. The attached progeny may have a trimodal activity size distribution, which can be approximated by a combination of three log-normal distributions [P6]. These consist of the nucleation mode with activity median diameters (AMD) between 10 and 100 nm, the accumulation mode with AMD values of 100–450 nm and a coarse mode with an AMD > 1 μm . Generally, the greatest fraction of PAEC is in the accumulation mode.

A15. Measurements carried out by several researchers of the size distribution of the unattached progeny were found to be unimodal with AMD in the range 0.5 to 1.7 nm and geometric standard deviations (σ_g) between 1.2 and 1.4 [I13, M6]. However, Porstendörfer measured a trimodal distribution with AMDs of 0.6, 0.85, and 1.3 nm with σ_g of approximately 1.2 [P6]. The largest mode (1.3 nm) was not measured in places with high radon concentrations. For the purposes of dose calculation and for simplicity, a unimodal distribution is assumed for the unattached progeny with AMD values between 0.8 to 1.2 nm and a σ_g of 1.3 for all exposure scenarios (tables 1–3 of the annex).

B. Homes and indoor workplaces

A16. Typically, nucleation and coarse modes are introduced when there is a specific source such as small aerosols released in cooking or large aerosols from dispersion activities. However, inter-comparison measurements performed in a house in Germany, without additional aerosols (i.e. for an aged aerosol), showed nucleation and accumulation modes with the fraction of the attached PAEC in the nucleation mode, f_{pn} , being about 0.2 [R7]. The AMD of the nucleation mode was about 50 nm. Measurements of the activity size distribution of the attached progeny in a dwelling in Japan also showed a nucleation mode with an activity fraction of 0.14 and an AMD between 15 and 40 nm [K4]. This is in contrast to measurements carried out in France, where the attached size distribution consisted only of the accumulation mode for an aged aerosol [H16].

A17. Porstendörfer [P6] summarized the measurement results of the activity size distribution of the attached radon progeny for dwellings and reported values of $f_{\text{pn}}=0.3$ (0–0.4) and AMD=20–40 nm for the nucleation mode and AMD=210 nm (120–350) for the accumulation mode. It was noted that in low ventilated rooms without additional aerosol sources, the coarse mode is insignificant because of the greater plate-out rate of large aerosol particles on room surfaces. The AMD for the accumulation mode is consistent with results from other studies, which range from 100 to 350 nm for dwellings [I13, I14].

A18. As described in the ICRU Report 88 [I14], only a few activity size measurements have been carried out in indoor workplaces. Reichelt et al. [R6] carried out activity size measurements of radon (^{222}Rn) progeny in offices, workshops, factories, kitchens, agricultural facilities and public buildings, such as schools, hospitals and art galleries. Porstendörfer [P6] summarized their results and suggested dividing workplaces into three categories regarding activity size distribution and particle concentration:

- Workplaces in rooms without coarse particles;
- Workplaces with coarse particles generated by human activities and dispersion processes;
- Workplaces with one dominant aerosol source such as combustion aerosols, resulting in a uni-modal distribution for the attached progeny.

A19. For the first two categories, the nucleation mode represents about 0.3 of the attached PAEC, with a range of $f_{\text{pn}}=0.2$ to 0.5. AMD values for the nucleation mode range from 15 to 40 nm [P6]. Coarse particles produced by re-suspension may occur when ventilation conditions vary considerably and when the ventilation rate is above 0.5 h^{-1} [R6].

A20. The magnitude of the unattached fraction, f_p , depends mainly on ambient particle concentration, which depends on local conditions. Measurements of f_p in homes and indoor workplaces have shown a wide range of values typically between 0.03 and 0.15 with some values greater than 0.2. In working places with additional aerosol sources due to technical processes, combustion and human activities, the particle concentration can be high resulting in low f_p values of about 0.01 or less. However, f_p is greater than 0.10 for poorly ventilated rooms (ventilation rate $<0.5 \text{ h}^{-1}$) without additional aerosol sources, rooms with an operating air cleaner, and poorly ventilated underground caves [I14, P6].

A21. Because radon progeny in the air can be removed by plate-out (i.e. by deposition on surfaces), the activity concentrations of the short-lived radon progeny in the air are less than that of the radon gas. This is quantified by the equilibrium factor (F), which is a measure of the degree of disequilibrium between the radon gas and its progeny. The equilibrium factor (F) is decreased further (i.e. there is greater disequilibrium) as a result of ventilation because as the ventilation rate increases, there is less time for the radon progeny to grow-in. If the exposure is characterized by radon gas measurements, then a value for the equilibrium factor (F) is required to estimate the radon progeny concentration in air for the calculation of doses to the lung.

A22. The UNSCEAR 1988 Report adopted a value of 0.4 as the average F value for dwellings and this value was retained in the UNSCEAR 2006 Report [U2, U6]. The Committee noted that while indoor measurements carried out in the United States and in India show a range from 0.1 to 0.9, most were within 30% of the typical value of 0.4 [H12, R4]. The ICRP recommended an F value of 0.4 for indoor workplaces and homes [I13]. A recent review of more than 14,500 measurements in 20 countries showed that measured F values vary widely, from as low as 0.1 to as high as 0.8, with a mean of 0.41 and a standard deviation of 0.11 [C12]. The F values are significantly higher in poorly ventilated houses and in homes, where smokers abide. The wide range of F values suggests that location specific values are more appropriate than a worldwide average value when calculating lung bronchial doses based on radon gas measurements.

A23. For indoor air, where the ventilation rate is not too high, F is negatively correlated with f_p [I13, I14, U2]. Consequently, it has been shown that for indoor air, the radon gas concentration is a better index of dose than the PAEC or EEC under a range of aerosol conditions normally encountered [V5, V6]. Based on their 430 measurements of f_p and F , Vargas et al. derived a log-power equation between f_p and F [V6]. Using this equation with the HRTM it can be shown that as F varies between 0.2 and 0.7, the effective dose rate per radon gas concentration only varies from 7–13 nSv per h Bq m^{-3} (i.e. within 30% of the

mean) [M1]. However, if the correlation is not considered then the effective dose rate would vary from 5–19 nSv per h Bq m⁻³ (i.e. within 60% of the mean). Thus, if location specific values of F are used when calculating doses from radon gas measurements, an appropriate value of f_p should also be used.

A24. Some of the ambient aerosols, to which radon progeny are attached, are hygroscopic and are assumed to grow rapidly on inhalation. Typically, this is modelled by assuming the AMD increases instantaneously by the hygroscopic growth factor (hgf) as the particle enters the nose or the mouth. It is generally assumed that hgf have values between 1 and 2 for attached progeny [I13, I14]. The size of the unattached progeny is assumed to remain constant in the lung.

A25. Sinclair et al. [S11] carried out growth measurements of atmospheric particles, originating from an industrial area close to the sea, and found that the diameters increased by a factor of two when the relative humidity (RH) increased from zero to 98%. The authors expected the ambient aerosol to consist of a mixture of NaCl and (NH₄)₂SO₄ salts with a mixture of acids (HNO₃, H₂SO₄ and HCl). The data also showed that the particle diameters would increase by factors of 1.5 and 1.8 as the humidity increases from the relative humidity of indoor air (~30–50%) to 99% relative humidity in the respiratory tract. Measurements of growth factors of a background continental aerosol had two modes with values of 1.5 for the low hygroscopic mode and 2.9 for the more hygroscopic mode [P1]. Li and Hopke measured hgf of indoor combustion aerosols including cigarette smoke, incense smoke, candle flame, natural gas flame and propane fuel flame [L8]. The average hgf values ranged from 1.5 to 1.9, which represents maximum growth as these measurements were made starting with a dried aerosol and increasing the humidity to 99% relative humidity. In contrast, radon progeny attached to aerosols produced from cooking oil are hydrophobic [D9]. Based on these data, it could be assumed an hgf value of 1.5–2.0 for attached progeny following indoor exposure (tables 1–3 of the annex).

C. Underground mines

A26. The activity size distribution of the radon progeny in underground mines depends on the different types of mining conditions and activities such as use of diesel- or electric-powered equipment, different ventilation rates, and use of propane heaters, blasting, drilling and ore carrying equipment. Results from activity size measurements carried out in mines have been summarized by the ICRU [I14] and by the ICRP [I13]. For example, in mines, where the aerosol is dominated by diesel particles, the size distribution of the attached progeny is unimodal with an AMD of about 250 nm [I13].

A27. Tu et al. [T20] carried out measurements in the winter of 1995 to characterize the aerosol in a wet underground uranium mine (Eagle Point mine) in northern Saskatchewan, Canada. The mine uses diesel-powered equipment, propane heaters, and is ventilated at a high rate (~one air change per 3 minutes) [C1]. Measurements carried out at a stope and a drilling area, where miners were working, showed predominately a two-modal distribution for the attached progeny. The fractions of the attached PAEC associated with the “nucleation” and accumulation modes were approximately 65 and 35%, with mean AMDs of ~60 and ~330 nm, respectively. For the unattached progeny, the AMD was about 0.6 nm and f_p was 0.01. Measurements were also carried out at a bolt-storage bay next to a major mine exhaust, which gives an estimate of the “average” mine atmosphere. Most of these measurements showed that the attached progeny consisted of the nucleation mode containing approximately 97% of the attached PAEC, on average, with AMD values between 55 and 75 nm. The coarse mode accounted for the remaining 3% of attached PAEC with AMAD between 2 and 8 µm. For the unattached progeny, the measured AMD at the bolt-storage bay was mainly about 1 nm (0.6–3 nm) with f_p less than 0.02. The authors concluded that a combination of diesel particles and combustion particles from burning

propane gas caused a modal diameter shift to a smaller size range, 50–85 nm compared with the previous reported values (100–200 nm). Calculations with the HRTM for a mine atmosphere show that a shift from an AMD of 200 to 65 nm would increase the effective dose coefficient by a factor of two [I13]. The authors also noted that there was no nuclei mode in the range of 2–30 nm.

A28. Aerosol measurements were also carried out during the summer time of 1996 at the same Canadian mine (Eagle Point mine) in northern Saskatchewan [C1, C2, C3]. During the summer months propane heaters are not used. Throughout the mine, the measured AMD values ranged from 50 to 120 nm with a mean value of 85 nm and σ_g of approximately 2.0. The average value of f_p was approximately 6%, whereas the expected value based on particle concentration was 0.3%. This unexpectedly high f_p value was theoretically shown to occur under conditions of high ventilation, where the radon progeny is far from equilibrium [C1]. The average value of the equilibrium factor F was 0.08.

A29. In 2013, activity size distribution measurements of radon progeny were carried out at the Olympic Dam underground uranium mine, Roxby Downs, South Australia [S14]. Measurements were made with a multiscreen continuous diffusion battery at six locations representing a range of working atmospheres. Two were at underground workshops, characterized by high ventilation rates, low PAEC and low F values. The activity size distribution at these sites were mainly bimodal, one with unattached and accumulation modes and the other with nucleation and accumulation modes (table 3 of the annex). The other four sites were in locations within the operational areas of the mine with higher levels of PAEC. Three of these sites had bimodal distributions consisting of nucleation modes with mean AMDs of ~30 to 40 nm and accumulation modes with mean AMDs of ~180 nm. The fraction of the nucleation mode varied from 0.1 to 0.3 across these three sites. The fourth site near an ore crusher showed a single accumulation mode with a mean AMD of 114 nm. These measurements are important as they show the presence of the nucleation mode and because there is very little data on aerosol characteristics in modern mines (table 3 of the annex).

D. Target cell depth in bronchial and bronchiolar epithelium

A30. Measurements of the basal and secretory cell depths in human bronchial epithelium have been made mainly for radon progeny bronchial dose models [B3, B4, G2, M8, R10]. Robbins et al. [R10] obtained human bronchial specimens removed for various pathologies from 115 persons and dissected airway generations 3 to 6 from non-involved areas of the lungs. The cell depth was measured from the midpoint of the nucleus to the free epithelial surface. The arithmetic mean basal and secretory cell depths averaged over airway generations 3 to 6 were 27 and 19 μm , respectively [I14]. The average cell depths were approximately the same for male and female smokers, non-smokers and ex-smokers. Generation 3 also had a small percentage of samples having basal cell depths ranging from 40 to 70 μm .

A31. Baldwin et al. [B3] obtained tissue from 29 patients undergoing lobectomy for lung carcinoma and non-specific inflammatory changes. Measurements of the basal cell depth (epithelial surface to basal cell nucleus) gave similar results as reported by Robbins et al. [R10]. However, the airways in the Baldwin study [B3] were characterized by diameter, which does not permit exact identification of airway generation as a range of diameters exist for each generation [I14].

A32. Mercer et al. [M8] obtained three lung lobes from surgical resections that were used for study of the airway epithelium of the human lung. The lobes were from non-smokers who had normal pulmonary function tests and chest radiographs. The lobes were used to measure the distribution of nuclear cell depth for different cell types in the bronchi and bronchioles. In large and small bronchi, the basal cell depths

averaged for the three lungs ranged mainly from 36 to 48 μm with most cells at 48 μm . For the secretory cells, the nuclei depths ranged mainly from 12 to 36 μm in the large bronchi and from 24 to 48 μm in the small bronchi. In the bronchioles, basal cells were absent, and the secretory cell depths ranged mainly from 4 to 8 μm . The nuclei depths were measured from the epithelial surface to the cell nucleus (excluding cilia).

A33. The histological measurements of Mercer et al. [M8] are the basis of the model of the target cell depth distribution (basal and secretory cells) of the HRTM [I7], the DAGM and SAGM models of Zock et al. [Z5], Winkler-Heil et al. [W12, W13] and Hofmann et al. [H9, H10]. In contrast, based on the data of Robbins et al. [R10], the DAGM of the bronchial region developed by Harley et al. [H1] assumes smaller target cell depths, particularly for the basal cell nuclei. Thus, the target cell depth distribution is a source of uncertainty. Harley [H3] estimated that the bronchial dose can change by $\pm 20\%$ due to the different target cell assumptions selected by various models. With the HRTM, Marsh and Birchall [M1] estimated that the dose conversion factor increases from 15 to 21 mSv WLM^{-1} , if the target cell depth and thickness is decreased by a factor of 2 (table 4 of the annex).

E. Airway dimensions

A34. Available morphometric models of the human tracheobronchial tree are based on measurements of a small number of individual measurements from a few laboratories. To determine the degree of variability of the bronchial tree, Nikiforov and Schlesinger performed an analysis of airway lengths, diameters and branching angles using solid casts of the upper bronchial tree from eight human right lungs [N7]. The casts were made from the level of the main bronchus (generation 1) through the eighth branching level beyond the trachea (generation 8). The results showed that there is considerable variability in the lengths, diameters and branching angles within the same generation. The intersubject differences in dimensions generally increased with increasing generation number. For example, the coefficient of variation for diameters by generation for the eight casts varied linearly from 13% for generation 1 to 40% for generation 8. The intersubject variation of the airway dimension affect deposition of inhaled radon progeny and consequently the bronchial doses [H9].

A35. The morphometric models published by Weibel [W4] and by Yeh and Schum [Y1] were compared with the airway dimension data of Nikiforov and Schlesinger [N7]. The length and diameter mean of the Weibel model were in good agreement with the corresponding means of the measured data of Nikiforov and Schlesinger (within 20%). The length and the angle mean of the Yeh and Schum model were also in similar agreement with the means of the measured data but the mean diameters of the Yeh and Schum model were considerably larger. However, comparisons should take account of relative inflation of the fixed lungs of the cast. Yeh and Schum [Y1] acknowledged their preparation of the casts resulted in enlargement of the airways, probably to the total lung capacity. Thus, they recommended that the airway dimensions should be scaled down to functional residual capacity. Before evaluating the effect of different morphometric models on lung dose, Yu et al. [Y3] scaled the morphometric models to the functional residual capacity of ICRP Reference Man [I8].

F. Lung clearance of smokers and non-smokers

A36. Studies of the effects of cigarette smoke on the lung mucociliary clearance have shown conflicting results [I7, I14]. Based on studies with inhaled radioactive labelled particles, Albert et al. [A3] showed that the 90% clearance time (i.e. the time after which 90% of the inhaled particles were cleared from the lungs) was the same for both smokers and non-smokers. In comparison, Aldas et al. [A4] observed an overall faster clearance in smokers probably because of more central deposition. However, the authors stated that the clearance rate in the large proximal airways was slower than in non-smokers ($T_{1/2}=2.3$ hours in smokers; $T_{1/2}=42$ minutes in non-smokers), but faster in the more peripheral airways. Generally, slower clearance in the trachea or the large proximal airways is observed for chronic smokers compared with non-smokers [A1, C21, T17]. Vastag et al. [V7, V8] found that the lung mucociliary clearance (overall and inner zone) was less for smokers compared with non-smokers and decreased with cigarette consumption. The decrease was more pronounced in the central than the peripheral airways.

IV. PARTITION OF DETRIMENT AMONG THORACIC REGIONS

A37. Considering differences in radiation sensitivity between different regions of the lung apportionment factors, A_i are applied in the calculation of equivalent dose to the lung as follows: $H_{\text{lung}}=A_{\text{BB}} H_{\text{BB}}+A_{\text{bb}} H_{\text{bb}}+A_{\text{AI}} H_{\text{AI}}$, where H_{BB} , H_{bb} and H_{AI} are the equivalent dose to the bronchial (BB), bronchiolar (bb) and alveolar interstitial (AI) regions. The apportionment factors, A_i represent the regional's estimated sensitivity relative to that of the lung. Thus, A_i represents the fraction of the total lung detriment assigned to region i of the lung following uniform exposure of the lung. In deriving values for the apportionment factors, ICRP considered applying the relative risk concept, in which it is assumed that the induction of cancer by radiation exposure is proportional to the background cancer rates in tissue [I7].

A38. In the development of the HRTM, values of the apportionment factors, A_i were initially derived on the basis of regional distribution of background lung cancer rates in the general population [J1]. Initial estimates were: 0.8 for the BB region, 0.15 for the bb region and 0.05 for the AI region. These estimates were reviewed and values of 0.6 for the BB region, 0.3 for bb region and 0.1 for the AI region were obtained for a population of non-smokers and smokers [I7]. ICRP reviewed data from studies of underground miners exposed to radon, Japanese atomic bombing survivors and from experiments with laboratory animals [I7, L2, M11, Z6]. Following this review, ICRP noted that uniform irradiation of the thorax is more likely to lead to the induction of cancer in the BB region than in the AI region and probably also in the bb region. However, it was concluded that there is no basis for deriving factors, with any acceptable degree of confidence, to represent regional differences in radiation sensitivity among the three regions of the lung: BB, bb and AI. Consequently, equal weighting was assigned to each of the regions ($A_{\text{BB}}=0.333$, $A_{\text{bb}}=0.333$, $A_{\text{AI}}=0.333$).

A39. Saccomanno et al. [S1] measured the distribution of tumours in the bronchial tree for a cohort of 467 miners and 311 non-miners. Ninety-five per cent of the miners were cigarette smokers. The position and type of tumour in the miners were compared with those of non-miners of the same age, all with positive smoking histories, who developed lung cancer in the same calendar year as the miner. All the subjects were male. Three anatomical zones were considered: central (0–8 airway generations), middle (9–18 airway generations) and peripheral. These regions approximately correspond to the bronchial (BB), bronchiolar (bb) and alveolar interstitial (AI) regions of the HRTM. The results gave the following distributions of tumours in the BB:bb:AI regions as (0.68:0.15:0.16) for miners and (0.59:0.18:0.23) for non-miners. The majority of the tumours originated in the BB, mainly within the first few airway generations (1 to 3). The number of small cell carcinomas among the miners was a factor of 4 higher

compared with the non-miners, and these mainly occurred in the BB region (~90%). The number of squamous cell carcinomas originating in the BB region was only 20% higher for the miners compared with non-miners. The adenocarcinomas in the bb and AI regions were twice as high for the miners compared with non-miners. To conclude, the data indicates that for smokers, the inhalation of radon progeny preferentially induces small cell carcinomas in the BB region, although an increase was also observed in the bb region. Similar data for non-smokers would be useful information to determine the region's radiation sensitivity relatively to that of the whole lung.

A40. Winkler-Heil et al. [W14] tested the current assumption of equal apportionment factors by comparing different radon and thoron exposures, which produce different regional dose distributions, with pathological observed regional cancer distributions. Exposure conditions considered were (a) radon progeny inhalation; (b) thoron progeny inhalation; (c) thoron and thoron progeny exhalation (thorotrast patients); and (d) radon progeny inhalation in rats. Regional lung deposition of cigarette smoke particles was also calculated. Following inhalation of radon progeny or thoron progeny, the calculated regional dose factors were similar for the BB and bb regions, whereas the AI dose was only a few per cent of the average lung dose. The similarity of the BB and bb doses is inconsistent with pathological data that showed more tumours in the bronchial region compared with the bronchiolar region [S1]. This indicates higher radiation sensitivity for the BB region compared with the bb region. In addition, a lower sensitivity for the AI region compared with central airways was inferred from the thorotrast patient data. This was concluded as there were no excess cancers observed among the thorotrast patients despite the relatively high dose to the AI region compared with the bronchial and bronchiolar regions at levels, where lung cancer induction was expected. Taking account of dose enhancement at bronchial bifurcations during inhalation, which increases BB doses relative to bb doses, the authors concluded that apportionment factors of $\sim(A_{BB}=0.65, A_{bb}=0.30, A_{AI}=0.05)$ may represent a realistic estimate.

A41. Calculations with the HRTM [M1] and calculations performed by Winkler-Heil et al. using the SAGM gives similar doses to BB and bb regions of the lung [W14]. In contrast, other publications by the same group gave higher doses to BB compared with bb by 60:40 or more using their SAGM [H9, H10, H11]. Hofmann and Winkler-Heil noted that the average bronchial doses are higher than the average bronchiolar doses by a factor of ~2–3 [H11]. The reason for this discrepancy is due to different averaging procedures of doses among different airway generations. Due to the stochastic asymmetry of the airways, all airway generations between ~12–20 can contain both bronchioles and respiratory bronchioles with varying degree of probability. The respiratory bronchioles (bronchioles with some alveoli apposed) are defined as part of the AI region. Higher doses in BB region relative to bb region are obtained if the average bronchiolar dose is calculated by weighting the doses in a given airway generation by the relative frequency of bronchiolar airways in that generation. If the dose to BB region is higher than bb region this may partly explain the pathological data that showed more tumours in the BB region compared with the bb region [S1]. Similar doses to BB and bb regions were obtained when the average bronchiolar dose was calculated without considering the fraction of the bronchiolar and alveolated airways in a given generation [W15]. The revised HRTM [I12] gives similar doses to BB and bb regions of the lung for indoor workplace exposure (table 2 of the annex) whereas for mine exposure, the dose to BB is lower than to bb (table 3 of the annex) assuming ICRP reference aerosol parameter values [I13].

A42. The equivalent dose to the lung is sensitive to the assumed values of the apportionment factors; higher doses are obtained if more weight is given to the BB and bb regions compared with the AI region [H11, I14, M1]. Assuming apportionment factors ($A_{BB}:A_{bb}:A_{AI}$) of $\sim(0.65:0.30:0.05)$ [W14], $(0.6:0.3:0.1)$ [I7], $(0.6:0.2:0.2)$ [S1] and $(0.333:0.333:0.333)$ [I7] gives effective doses calculated with the HRTM for home exposures of 21, 20, 17, 15 mSv WLM⁻¹, respectively [M1].

APPENDIX B. THORON EPIDEMIOLOGY

B1. In recent decades, it has become increasingly clear that exposure to thoron and its progeny cannot be ignored as it contributes to the risks otherwise assigned solely to exposure to radon and its progeny [U6]. Although only a limited number of measurements of thoron are available, levels of thoron in workplaces and residential dwellings of various types were reviewed and summarized in previous UNSCEAR reports [U3, U6].

B2. Up to now, there is no epidemiological study specifically designed to assess lung cancer risk due to thoron exposure in addition to exposure to radon. However, some radon epidemiological studies (both occupational and residential) evaluated the impact or the effect of thoron exposure on the assessment of radon risk [U6].

I. OCCUPATIONAL STUDIES

B3. For studies in workplaces, two studies mentioned thoron [U6]. In the studies of Ontario uranium miners [K11], the Canadian investigators recognized that estimates of radon decay product concentrations involved some uncertainty, especially for the early years of mining, and that thoron progeny contribute an appreciable radiological exposure in the Elliot Lake mines. However, the reconstruction of early underground uranium mining environments undertaken in 1985 confirmed that the exposure values used for the early years did not overestimate the working exposure at that time [U6].

B4. In the studies of French uranium miners [Z3], workplace area monitors were replaced by personal alpha and gamma dosimeters after 1983. Those personal dosimeters record energy depositions of short-lived progeny of radon and thoron, long-lived alpha emitters contained in ore dust as well as gamma radiation. However, there was no mention of either thoron levels recorded or associated effects [U6].

B5. In a subgroup of 592 males who worked for at least one year in selected jobs that had the highest exposure to thorium dust (mean alpha-particle emission per minute per cubic metre of air was 426) and thoron (mean concentration of 32.6 kBq m⁻³) that was followed up more intensively, the standardized mortality ratio (SMR) for lung cancer was 1.68 (95% CL: 0.81, 3.09), while that for respiratory diseases was 1.20 (95% CL: 0.52, 2.37). The SMRs were assessed as a combined effect from exposure to thorium dust and thoron gas. Information on smoking habits in a sample of survivors suggested that smoking could have explained at least part of the excess mortality from lung cancer and from diseases of the respiratory system.

B6. Solli et al. [S13] investigated the incidence of cancer among 318 male employees of a niobium mining company which was operated between 1951 and 1965. Many of the workers, especially underground miners, were exposed to the daughters of radon and thoron and also to thorium dust. The mean radon daughter concentration was 1.0 WL (ranging from 0.5 to 2.2 WL) and 0.2 WL (ranging from 0.1 to 0.2 WL) for thoron daughters. However, the measurement technique was considered rather crude. The dust concentration in the air was very high at the time of the measurements. The accumulated doses to the workers from short-lived radon and thoron daughters in the mine atmosphere were assessed to be

relatively low; up to 300 WLM. For the radon and thoron daughter exposure, about 50 excess cases per million person-years at risk per WLM were observed. The authors considered thoron daughter exposure to the workers in the mine to be relatively low, and that thoron seemed to have contributed relatively little to the radiation hazard among the workers.

B7. The Bayan Obo Rare-earth Iron Mine is an open pit mine, and has been operated since 1958. Its ore contains not only iron, rare-earth elements and silica dioxide but also thorium (ThO_2) at a concentration of 0.04%; uranium (U_3O_8) at a concentration of 0.0001%; SiO_2 is found at a concentration of 10%. Chen and his colleagues have conducted follow-up studies on thorium lung burdens of thorium dust exposed miners for more than two decades [C13, C14, C15, C16, C17, C18, C19]. Air concentrations of dust containing thorium in the crushing workshop were extremely high; the average thorium concentration was 189 mg m^{-3} (ranging from $9\text{--}875 \text{ mg m}^{-3}$) and the average thoron progeny concentration was $1.08 \times 10^4 \text{ MeV L}^{-1}$ (ranging from 4.20×10^2 to $6.77 \times 10^4 \text{ MeV L}^{-1}$), which was a factor of 10 higher than radon progeny concentration in the same area [C13]. The average value of the thorium lung burden from 1,270 measurements among 751 dust exposed miners was 1.6 Bq. About 23% of the 1,270 measurements reached the investigation level of 2.2 Bq for thorium lung burden [C19].

B8. For the total person-years of observation of the 62,712 dust exposed miners and the 34,672 unexposed miners during the 22 years follow-up period, the study showed that the lung cancer mortality of the dust exposed miners was significantly ($p < 0.005$) higher than that of the non-exposed group [C16]. Significant increase of incidences of respiratory symptoms, lung function disorders and pneumoconiosis stage 0+ and stage 1 were reported too. They estimated aetiological attribution of risk factors, among the 27 cases of lung cancer deaths in the dust exposed miners, 1 case was induced by inhaled thorium, 2 cases by the inhaled short-lived thoron progeny, 12 cases with cigarette smoking, and the remaining 12 cases to SiO_2 . In their latest report [C18], it was concluded that long-term exposure to thorium-containing dusts (carcinogens are ThO_2 and SiO_2) and to thoron progeny induced an excess of lung cancers. However, the high rate of smoking among the Bayan Obo miners (80%) and the high gamma radiation exposure in the mining workshops might have enhanced the carcinogenic effects of the inhaled thorium-containing dust and thoron progeny in inducing the excess lung cancers.

B9. In summary, nine publications were identified in the literature review that assess the exposure to thorium dust and/or thoron progeny in workplaces. In addition to thorium dust, exposure to thoron decay product also contributes to increased risk of developing lung cancer among exposed workers. However, no detailed assessment of thoron induced lung cancer is available to date.

II. RESIDENTIAL STUDIES

B10. In the UNSCEAR 2006 Report [U6], it was recognized that the results of radon epidemiological studies conducted in the Loess Plateau region of China were affected by the presence of thoron and its progeny, and reassessment of risks due to radon exposure may be needed to take the presence of thoron into account. However, for this evaluation, there were a few studies on health effects of residents who lived in cave dwellings in northwestern rural areas of China, where radon and thoron levels are relatively high, no industrial pollution exists and where there has been very little migration before the 1980s [G4].

B11. In order to explore the feasibility of an epidemiological study on lung cancer in areas with elevated indoor radon and thoron exposures, 202 residences including loess caves, brick caves, stone caves, and ordinary houses in 20 villages were selected from Yan'an and Luliang areas in the Chinese Loess Plateau [S20, S21]. Indoor levels of thoron and its progeny as well as radon were determined with passive radon-

thoron discriminative detectors and thoron progeny deposition rate devices. The exposure period covered from August 2001 through August 2002. The indoor radon concentration in loess caves ranged from 17 to 179 Bq m⁻³, with geometric means of 73 and 71 Bq m⁻³ in Luliang and Yan'an, respectively. Thoron levels varied substantially depending on the distance between the device and the wall, ranged from 10 to 760 Bq m⁻³, with geometric means of 145 and 185 Bq m⁻³ in Luliang and Yan'an, respectively. Geometric mean of EEC of ²²⁰Rn (thoron) were estimated to be 1.6 Bq m⁻³ in Luliang and 2.2 Bq m⁻³ in Yan'an. The study revealed that the indoor air pollution, indexed by cooking fuel source, in Yan'an was low compared with that in Luliang. Migration levels before the 1980s were very low, 86% of the subjects had no history of migration in Yan'an. Ninety per cent of the cave-dwellings, where the subjects once lived, were available for measurements when the survey was conducted. The results showed the investigated cave-dwelling area with low levels of industrial pollution was suitable for conducting epidemiological study on residential thoron and radon exposure and lung cancer. Later on, a pilot case-control study on radon and thoron induced lung cancer was conducted there. However, the results are not yet available at the time of this evaluation.

B12. In summary, like in workplaces, evidence has shown that thoron exposure in residential homes contributes to the total radiation dose to the lung and increases the risk of developing lung cancer. However, no quantitative result of epidemiological studies on thoron induced lung cancer is yet available at the present time.

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GLOSSARY

Note: The glossary is based on the glossary included in the UNSCEAR 2012 Report to ensure consistency of terms and definitions [U3]

Absorbed dose, D : The fundamental dose quantity given by

$$D = \frac{d\bar{\epsilon}}{dm}$$

where $d\bar{\epsilon}$ 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 “Protracted exposure” or “Chronic exposure”.

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.

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”.

Attained age: Age at observation or during the follow-up, usually refers to age as time-dependent characteristic in a cohort study.

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.

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.

Case-control study: An epidemiological study type, where cases with the health outcome of interest are selected from the population and compared in terms of exposure with control free of the outcome, who represent the exposure distribution in the population. The effect of exposure on the outcome in a case-control study is expressed as an odds ratio.

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”.

Cohort study: An epidemiological study type, where people free of the health outcome of interest are selected and subdivided into groups based on exposure of interest. The occurrence of the health outcome (typically incidence or mortality) is recorded for the entire study population and the effect of exposure on the risk of the outcome is expressed as a rate ratio, risk ratio or hazard ratio. Follow-up for development of disease cases since start of study period can be prospective or retrospective (collection of information of the cases that have already occurred).

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 exposure (e.g. radiation exposure or dose) and the 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.

Credible interval: This term originates from Bayesian inference and refers 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].

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.

Effective dose, E : The sum over all tissues and organs of the equivalent doses weighted by the tissue weighting factor w_T , which represents the contribution of that organ or tissue to the total detriment resulting from uniform irradiation of the whole body. Effective dose has the unit joule per kilogram, which is given the name Sievert (Sv). The recommended values of w_T are given in the ICRP Publication 103 [I1].

Equilibrium equivalent concentration, EEC : The concentration of radon in air, in equilibrium with its short-lived decay products, which would have the same potential alpha energy concentration as the existing non-equilibrium mixture. The SI unit for equilibrium equivalent concentration is joule per cubic metre ($J\ m^{-3}$) and the special unit is Becquerel per cubic metre ($Bq\ m^{-3}$). $1\ Bq\ m^{-3} = 5.56 \times 10^{-9}\ J\ m^{-3}$.

Equilibrium factor, F : The ratio of the equilibrium equivalent concentration to the actual radon gas concentration.

Equivalent dose, H_T : The averaged absorbed dose in tissue or organ T , modified by the radiation weighting factor, w_R . The unit of equivalent dose is joule per kilogram, which is given the name Sievert (Sv). The recommended values of w_R are given in the ICRP Publication 103 [I1].

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.

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.

Hazard: In epidemiology and statistics, a measure of occurrence obtained as time integral of risk and interpreted as risk intensity. With respect to aspect of health and safety, the term “hazard” refers to any source of potential damage, harm or adverse health effects.

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.

Hazard ratio: A measure of association used in prospective studies describing an instantaneous risk over the study time period, or some subset thereof. It is the ratio of *two* hazard rates (functions) corresponding to the conditions described by *two* levels of a variable. Using a defined end point, hazard ratio differs from relative risk and odds ratio as it is not cumulative over the entire study time and can indicate risks that happen before the end point.

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.

Healthy worker (survivor) bias: A form of selection bias due to health requirements for employment; resulting from comparison of an employed group with the entire population comprising also those unable to work due to health reasons. Healthy worker bias tends to underestimate effects of occupational exposures and can be avoided by selection of an appropriate reference group (or use of internal comparisons within a cohort).

Imputation: A statistical technique for generating a plausible value to replace a missing value.

Inference: The process of drawing conclusions from scientific observations, evidence and reasoning in the presence of uncertainty. While this report is focused on prospectively inferring risk, note that estimating an assigned share (or probability of causation) is also inference, but retrospective.

Information bias: Distortion of research results due to differences in quality or completeness of information between groups being compared such as cases and controls, or across exposure levels in a cohort study.

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”).

Inverse dose (or exposure) rate effect: A form of effect modification, where the risk per unit cumulative dose is increased under circumstance of lower exposure intensity (dose rate).

Inverse-variance weighting: A statistical technique used in meta-analysis to place more emphasis on results from studies providing more information.

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.

$$L = \frac{dE}{dl}$$

The unit of L is J/m, often given in keV/ μm .

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 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 lifetime attributable risk (LAR), which is defined as

$$\int_{t_0}^{\infty} [h_c(u, D) - h_c(u, 0)] S(u, 0) du$$

or the excess lifetime risk (ELR) 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: Doses below 100 mGy are called low doses [U3], though the threshold value is necessarily arbitrary.

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, U2].

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.

Misclassification: Measurement error for discrete variables (sex, ethnicity etc.), where individuals are wrongly classified into a group to which they do not belong. If the classification error depends on the value of other variables (e.g. it differs by exposure group), it is called differential misclassification. If it is independent of the value of other variables, the term non-differential misclassification is used. The latter generally introduces a bias towards the null value, but there are exceptions.

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.

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.

Odds ratio: the effect measure used in case-control studies. Its interpretation is similar to that of a risk ratio or rate ratio, but its numerical value is more extreme (further from the null), particularly when the studied disease is common. An odds ratio is obtained as the ratio of the number of exposed cases to non-exposed cases relative to the ratio of exposed controls to non-exposed controls. It can also be computed from studies using other designs, with slightly different interpretation. For ubiquitous exposures such as indoor radon or natural background radiation, a lower level is used as reference instead of no exposure.

Point estimate: The most supported single value of the property estimated from the observed data, e.g. rate ratio or odds ratio in an epidemiological study. The results of a study are, however, best interpreted as consistent with a range of values, e.g. that in the confidence interval or supported range, though the data generally lend more support to the central values within that range.

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*”.)

Potential alpha energy concentration (PAEC): The concentration of short-lived radon progeny in air in terms of the alpha energy released during complete decay through polonium-214. The SI unit for PAEC is joule per cubic metre (J m^{-3}) and the historical unit is the working level. See also “Working level”.

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.

Protracted exposure: Exposure received over a long time period (compare with “Acute exposure” and “Chronic exposure”).

Radon levels: Radon concentration in air. The unit for radon level is Becquerel per cubic metre (Bq m^{-3}).

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. An estimate is considered precise if there is little random error.

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”, “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.

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 ^{60}Co) 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.

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).

Reverse causation: Cause and effect have been misidentified, meaning that the effect actually is the cause.

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.

Selection bias: This bias occurs when the group of persons under study differs from the intended target group, and this difference affects (biases) the study results. An example is selective enrolment of volunteers into a study, which will lead to biased results.

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.

Statistical power: The expected probability of being able to detect an effect of a specified magnitude, estimated before the start of a study. It depends on study size, baseline risk and effect size. Statistical power reflects only random error in outcome occurrence, while ignoring measurement error and typically assumes no bias in the study.

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.

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.

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.

Working level (WL): Any combination of the short-lived decay products of radon in one litre of air that will result in the emission of 1.3×10^5 MeV of potential alpha energy. See also “Potential alpha energy concentration”.

Working level month (WLM): The cumulative exposure from breathing an atmosphere at a concentration of 1 WL for a working month of 170 hours ($1 \text{ WLM} = 3.54 \times 10^{-3} \text{ J h m}^{-3} = 6.38 \times 10^5 \text{ h Bq m}^{-3} \text{ EEC}$).

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This publication contains:

REPORT OF THE UNITED NATIONS SCIENTIFIC COMMITTEE ON THE EFFECTS
OF ATOMIC RADIATION TO THE GENERAL ASSEMBLY

Scientific Annexes

Annex A: Evaluation of selected health effects and inference of risk due
to radiation exposure

Annex B: Lung cancer from exposure to radon



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.

