SOURCES, EFFECTS AND RISKS OF IONIZING RADIATION

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Effects of Atomic Radiation

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NOTE

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ANNEX A

ATTRIBUTING HEALTH EFFECTS TO IONIZING RADIATION EXPOSURE AND INFERRING RISKS

CONTENTS

I.   INTRODUCTION

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

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

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

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

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

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

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

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[1] Technical terms are explained in a detailed glossary, and are marked with an asterisk (*) the first time that they appear.
[2] *Official Records of the General Assembly, Sixty-first Session, Supplement No. 46* (A/61/46).
[3] This annex does not rule out the possibility that at low and very low doses, radiation exposure may have some beneficial health effects that could lead to a decrease in the frequency of stochastic effects [U7].

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

   (a) Summarizing the fundamentals of scientific rationale, and the scientific knowledge base as it relates to the attributability of health effects to radiation exposure;

   (b) Clarifying the differences between attributing manifest health effects to radiation exposure and inferring risks of future health effects from radiation exposure for both individuals and populations;

   (c) Addressing whether observed health effects can be attributed to exposures, or risks of health effects can be inferred from exposures, when there are competing causes, limited data with large uncertainties, and biologically plausible* but unproven hypotheses for their development (which is particularly the case for low-level exposure).

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

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

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

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

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

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

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

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

II. BASIC ASPECTS

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

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

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

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

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

III.   ATTRIBUTING HEALTH EFFECTS TO RADIATION EXPOSURE

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

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

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

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

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

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

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

IV. INFERRING RISKS AFTER RADIATION EXPOSURE

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

18.   For acute exposure* to high doses above the relevant thresholds, there is sufficient evidence, knowledge and scientific consensus regarding causal relationships to be able to predict relatively accurately whether or not there will be a deterministic effect in an exposed individual and, if so, the likely severity of that health effect. For exposures at moderate or high doses (or more strictly, at doses at which an increased frequency of occurrence of certain health effects in a population can be confidently attributed to radiation exposure), there is also sufficient evidence, knowledge and scientific consensus on causal relationships to be able to predict with some confidence an increased risk of stochastic effects in an exposed population similar to that for which evidence exists. These predictions would fall within the group of well-founded predictions, as defined in paragraph 10, and the results are essentially the same irrespective of the method of inference.
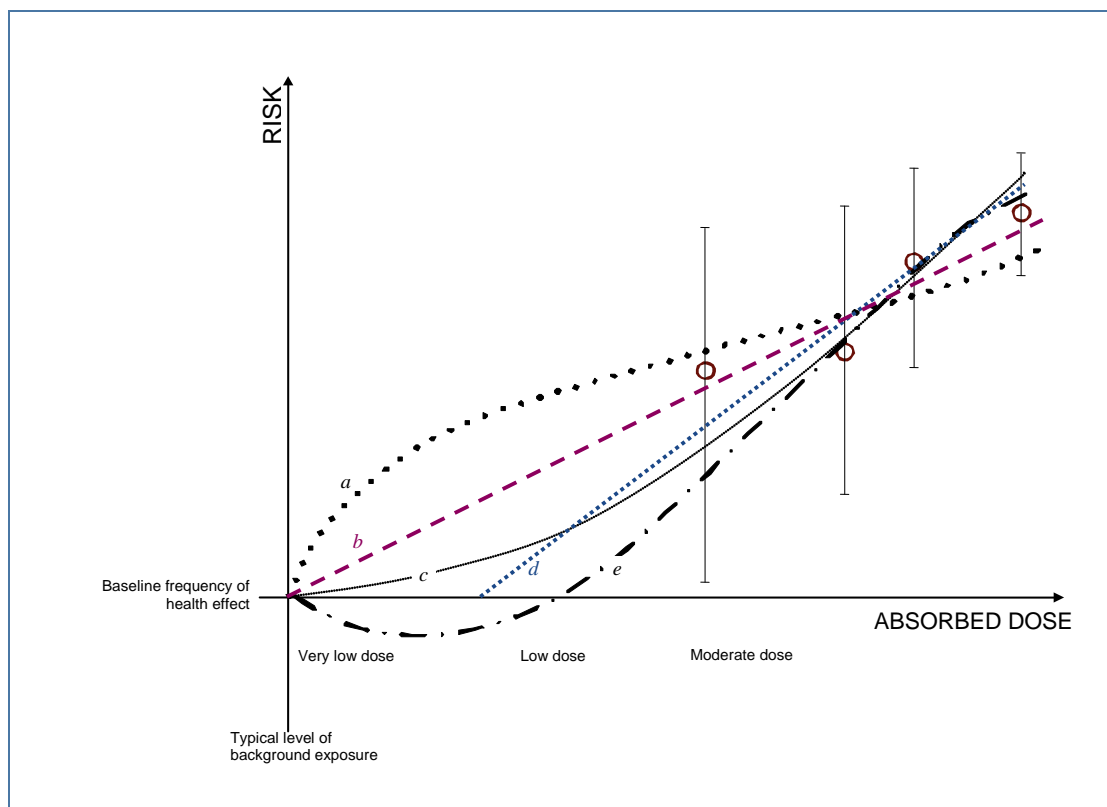
19.   There are various obstacles to precisely quantifying risks of stochastic effects after exposure. These include extrapolating from studies of populations exposed at moderate and high doses, often delivered at high dose rates, to estimating risks for other populations with different age and sex compositions and with different baseline rates* of cancer, exposed to low or very low doses of radiation of different quality, at low dose rates (see annex B). For such situations, Bayesian inference may provide additional insights.

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

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

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

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

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

(a) The currently observed response in the moderate-dose range can be extrapolated linearly down to zero incremental dose above that from normal natural background radiation (this would be a linear non-threshold (LNT) relationship);

(b) The risk at low and very low doses is substantially higher than expected from an LNT relationship (e.g. this would be a supralinear relationship);

(c) The risk at low and very low doses is substantially lower than expected from an LNT relationship (e.g. this would be a threshold or hormetic relationship).

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

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

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

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

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

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

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

V. RESEARCH NEEDS

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

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

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

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

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

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

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

VI. SUMMARY AND CONCLUSIONS

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

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

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

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

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

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

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

ACKNOWLEDGEMENTS

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

I. INTRODUCTION

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

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

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

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

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

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

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

A. Scientific method

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

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

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

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

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

1.   Establishing causal relationships

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

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

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

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

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[5] According to critical rationalism as advanced by Popper and dominating the empirical sciences, only hypotheses that can be falsified with a severe empirical test belong to the field of science proper [P4]. Note that falsifiable is used here with the meaning of "being able to be shown/proved to be false"; it does not mean "alter information so as to mislead".
[6] Note while the concept of absolute proof exists in the abstract and can apply in mathematical theorems, in the real world, hypotheses can only be "deemed" proven, i.e. there is a very high degree of confidence generally in their validity.

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

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

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

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

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

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

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

2.   Epidemiological studies

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Table A1. Bradford Hill guidelines

A checklist for assessing evidence of causality [H6]

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

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

A25.   If the evidence is sufficiently compelling, and consensus among the scientific community so high that all reasonable challenges are successfully addressed, then the causal relationship may be deemed proven[7] as an established scientific fact (such as the link between smoking and increased frequency of occurrence of lung cancer). After successful counterfactual analysis, an increased frequency[8] of disease occurrence may thus be attributed to the cause, even if an individual instance of the disease cannot be attributed to the cause.

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[7] As mentioned earlier, hypotheses and causal relationships can only be "deemed" proven, i.e. the scientific community at large has a very high degree of confidence in them. It cannot be ruled out that, over time, with new information, confidence may fall, and there may be a need to change the explaining hypothesis and causal relationship.
[8] These studies often quote results in terms of risk (e.g. excess relative risk) but in this annex risk is used in a prospective sense (see glossary), and observations are expressed in terms of frequency or rates (e.g. excess relative rates).

B. Science-based inference

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

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

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

   (a) The health effects are very difficult to measure for technical reasons;

   (b) The health effects occur infrequently and thus the number of health effects in an exposed population is so small (and, correspondingly, the study group would have to be extremely large) in order to obtain a valid result; a serious problem for an extremely large study is that it is difficult, if not impossible, to control for bias and confounding factors) [L1, L2];

   (c) The study design would be unethical (e.g. deliberately exposing people to the noxious agent without any benefit to them);

   (d) The studies would take too long (i.e. many years or even several decades).

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

   (a) Excluding untestable hypotheses from consideration;

   (b) Making conditional predictions for risk estimation;

   (c) Incorporating non-scientific concerns.

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

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

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

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

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

   (a) Prioritizing hypotheses: Although it may not be feasible to test a hypothesis, knowledge of mechanisms, models, and inferences may make one hypothesis more plausible than another;

   (b) Assuming a consequence: A health effect can be assumed to be a consequence of exposure to a noxious agent when a defined set of criteria are satisfied;

   (c) Precautionary approach: The precautionary approach can be described in the following way: "When human activities may lead to morally unacceptable harm that is scientifically plausible but uncertain, actions shall be taken to avoid or diminish that harm" [C4, E1, G2, H4, H7, H8, J4, J5, T1, W9]. In some situations, however, where it is not possible to know whether there is a positive or negative impact from exposure to a hazard, it may be important to consider the consequence of false positive as well as false negative assumptions when making decisions.
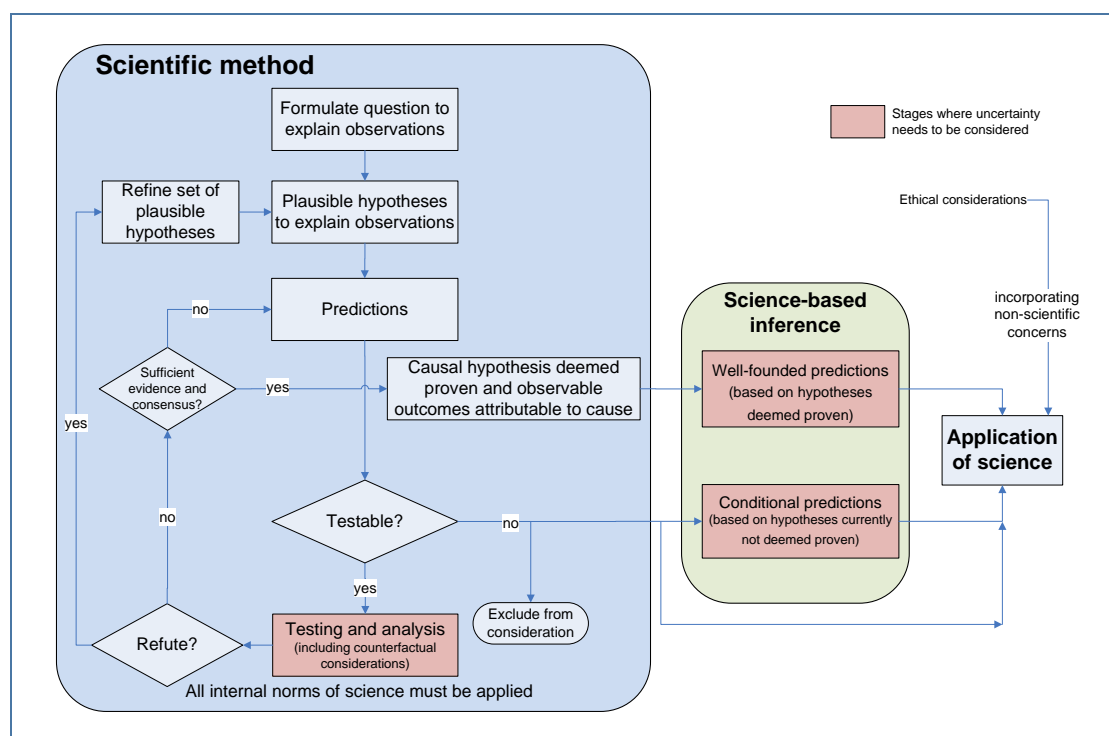
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[9] Popper defined hypotheses that were not testable or falsifiable as "non-science" [P4]. Weinberg coined the term "trans-science" to be "questions that can be asked of science, but cannot as yet be answered by science" [W4].

C. Summary of basics

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

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

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

III. ATTRIBUTING OBSERVED HEALTH EFFECTS TO RADIATION EXPOSURE

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

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

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

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

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

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

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

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

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

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

A. Deterministic effects

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

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

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

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

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

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

[c] Assuming no medical care.

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

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

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

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

B.   Stochastic effects

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

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

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

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

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

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

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

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

Table A4. Biological indicators of radiation exposure

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

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

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

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

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

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

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

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

A55.   Although radiation exposure is an established cause of cancer, there are a number of cancer types that have not been convincingly shown to be caused by radiation exposure. These include cancers of the rectum, prostate, pancreas and uterine cervix, and Hodgkin's lymphoma and chronic lymphocytic leukaemia. This does not necessarily mean that radiation-induced transformations do not occur in those tissues. For example, latency periods* might be so long that the cancers do not become manifest during lifetime (in a sense, a practical threshold) or the frequency of radiation-induced cancers in those tissues might be too low, relative to the baseline frequencies for those cancers, to be observable.
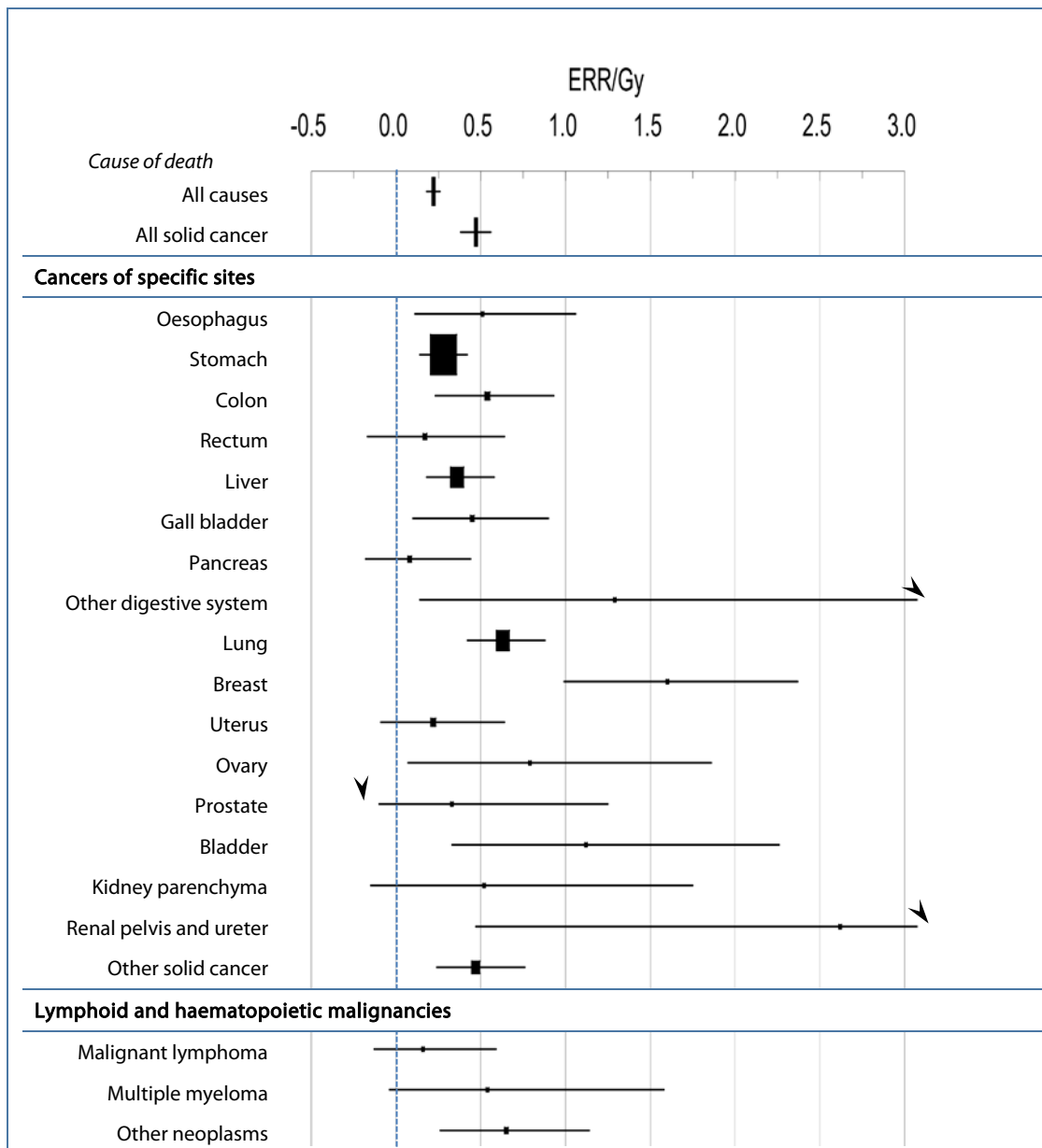
A56.   Applying counterfactual analysis to the attribution problem for a population implies consideration of the question: if a population had not been exposed to radiation, would an observed increased frequency of occurrence of disease have been observed at the same time and of the same magnitude. As mentioned earlier, there is no generally accepted theory of provability to establish causation. Nevertheless, increased frequencies of occurrence of certain stochastic health effects in a population can be attributed to exposures in the moderate- and high-dose range when the evidence is compelling and consensus among the scientific community is high, in part by use of the Bradford Hill guidelines (table A1) and more recent developments [M1]. This can nevertheless be challenging because: *(a)* latent periods for cancer development are long; and, as mentioned earlier, *(b)* the baseline frequency of cancer occurrence and the variability* of that frequency with time are relatively high, and other uncertainties in both exposure and disease frequency estimation obscure any increased frequency of occurrence of disease in a population that might be due to radiation exposure, in particular, following exposure at low and very low doses (see annex B for detailed considerations of uncertainties).

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

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

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

This graphic adapted from Ozasa et al. [O4] is used here to illustrate observed excess relative rates per unit dose and the associated aleatory uncertainties at 90% confidence intervals. The uncertainty associated with extending the excess frequency observed among a living cohort over the rest of their lives is an example of epistemic uncertainty. The values for rectum, pancreas, uterus, prostate, kidney parenchyma and malignant lymphoma, while positive, are not statistically significant. An increased frequency of mortality from cancers in these organs cannot be ruled out, but there is no compelling evidence from this study to support causation. The arrows indicate confidence intervals that are beyond the limits of the graph or not specified

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

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

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

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

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

IV. INFERRING RISK OF HEALTH EFFECTS FROM RADIATION EXPOSURE

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

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

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

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

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

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

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

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

1. Extrapolation of risks over lifetime

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

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

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

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

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

2.   Transference to another population

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

3.   Transference from one type of radiation to another

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

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

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

4.   Inferring risks from low-dose-rate exposure

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

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

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

5.   Inferring risks from low and very low doses

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

6.   Other issues related to inference

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

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

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

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

exposed to high doses[11] [U9]. Clearly, such inferences of risk cannot be unequivocally verified or refuted at the present time.

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

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

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

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

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

C. Application of science-based inference

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

(a) Early indication of potential health impact and directing future scientific research (e.g. assumptions about credible risks can be used to plan epidemiological and laboratory studies to possibly confirm and quantify them);

(b) Public health resource planning (e.g. comparisons of burdens of disease from various competing causes can be used to allocate resources efficiently, or to optimize health-screening studies);

(c) Radiation protection and risk management (which influence for example, the derivation of protection criteria);

(d) Legal liability purposes (e.g. compensation payments to individuals exposed to radiation from weapons tests or in the workplace).

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

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

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

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

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

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

A96.   The Committee recognizes though that public health bodies need to allocate resources appropriately, and this may involve making estimates of numbers of health effects from low and very low doses for comparative purposes. Such conditional predictions , although based upon reasonable but unverified hypotheses, could be useful for such purposes provided that it were applied consistently, the uncertainties in the assessments were taken fully into account, and it were not inferred that the projected numbers of health effects were other than notional. For example, this has been done for the purposes of gaining insight into the appropriate age at which to commence screening for breast cancer among asymptomatic women [B9]. It has also been done to gain insight into the possible health impact on a population of the Chernobyl accident (e.g. [B1, C1]) and of the diagnostic use of radiation in medicine (e.g. [B6]). The Chernobyl Forum approached the problem of possible health impact of the Chernobyl accident by differentiating between populations with moderate doses for which the possibility of cancer induction can be predicted and those with low and very low doses for which risk can only be inferred through the use of dose–response models [W6]. For its part, the Committee has estimated the collective effective doses[12] to people outside the former Soviet Union where doses were low or very low and has made scientific statements that emphasize that any risks would be too low to be detectable. At the same time, the Committee highlights that the inability to detect any increase in the cancer frequency does not exclude the possibility of a small increase in the percentage of disease at these doses.[13]

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

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

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

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

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

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

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

V. RESEARCH NEEDS

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

(a) On epidemiological studies with complete follow-up of the exposed cohorts over the remainder of their lives (such as the Life Span Study of the survivors of the atomic bombings in Japan, studies of persons exposed to medical radiation as infants or in early childhood, and studies of workers who were occupationally exposed to radiation over a period of years), describing any increased frequency of health effects by age and sex;

(b) On improving the quality of epidemiological studies (e.g. reducing bias by publishing protocols in advance of studies, addressing incomplete follow-up and determination of outcomes, and the quality of dosimetry);

(c) How increased frequency of specific types of cancer in an exposed population vary with radiation dose; dose rate; the particular type/energy of radiation; the age at exposure and age at manifestation of health effect; the time after exposure;

(d) The latency period between exposure and manifestation of a health effect;

(e) The impact of variations in human genetic susceptibility;

(f) Interactions* with other carcinogens/factors (e.g. smoking, viruses, and diet/lifestyle factors);

(g) Rigorously quantifying uncertainty in such analyses (see annex B).

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

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

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

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

A102. *Molecular epidemiology*. Molecular epidemiology[14] has revealed molecular factors related to cancer occurring after exposure to ionizing radiation [S1]. Such studies may contribute to improving understanding of individual predisposition to radiogenic cancer and should be encouraged. One aspiration of molecular epidemiology for improving the quantification of risks from low-dose exposure is the identification of one or more early molecular markers for radiation-induced cancer. Such markers might be detectable with epidemiological studies at lower doses than a fully developed disease such as cancer.

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

A104. In addition, the Committee considers that research should continue: *(a)* into better characterizing tissue reactions that occur in the longer term after protracted exposures (such as cataracts and circulatory diseases); *(b)* into developing and applying methods to integrate and synthesize the results of many studies (e.g. using Bayesian inference) to better make quantitative and qualitative statements on the confidence that can be placed in causal relationships, hypotheses and predictions.
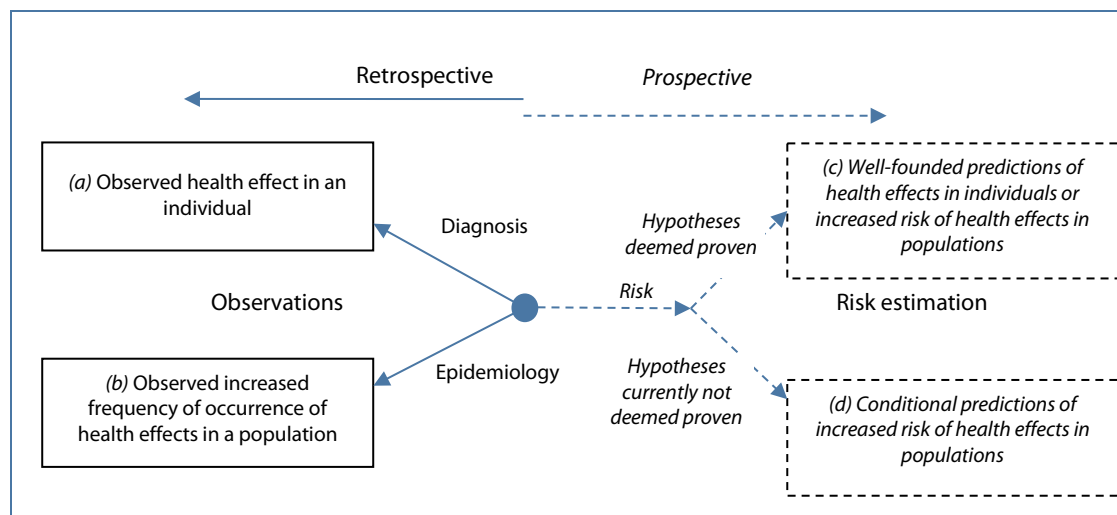
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[14] Molecular epidemiology is a branch of medical science that focuses on the contribution of potential genetic and environmental risk factors, identified at the molecular level, to the aetiology, distribution and prevention of disease within families and across populations [I4].

VI. SUMMARY

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

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

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

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

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

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

Table A5. Attribution of observed health effects to radiation exposure

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

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

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

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

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

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

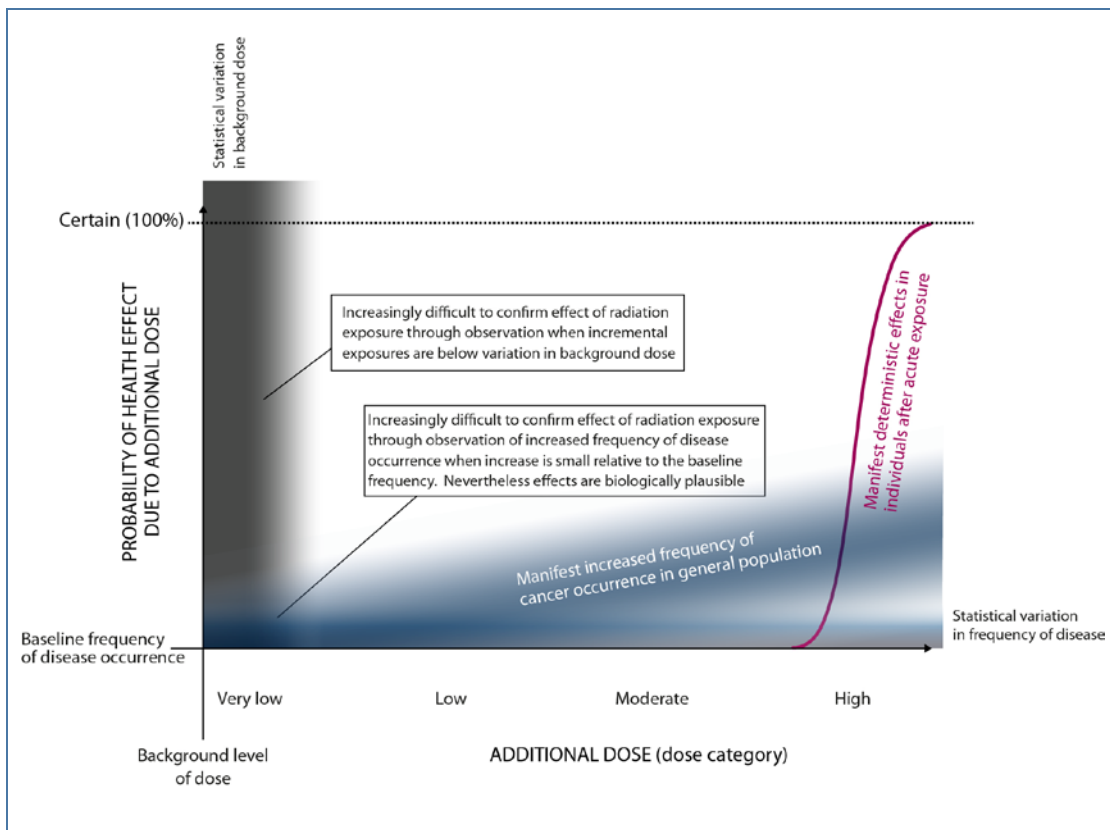### Table A6. Inference of risk of health effects from radiation exposure

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

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

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

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

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

APPENDIX B. CASE STUDIES

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

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

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

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

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

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

I.   SKIN BURN AFTER INTERVENTIONAL CARDIOLOGY PROCEDURE

A.   Scenario

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

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

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

B. Analysis

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

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

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

B12.   The fourth point is that the absorbed dose to the chest wall or skin almost certainly exceeded 15–20 Gy, a level of dose that is known to result in the observed temporal course and appearance of the lesion. The patient's records indicated that the dose–area product (DAP) was 1,631 $Gy\,cm^2$ compared to an average of 83 $Gy\,cm^2$ for similar procedures [V1] (in order to compensate for attenuation by the patient's body mass and still get an acceptable image, the radiation dose may have needed to be 4–6 times higher than that for a normal patient). The literature also indicates that patients usually get skin changes when the DAP exceeds 1,000 $Gy\,cm^2$ and that the average number of cine images for a coronary angioplasty is about 1,000; in this case there were more than 6,000.

C. Conclusion

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

II. PREGNANCY WITH MENTALLY RETARDED INFANT

A. Scenario

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

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

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

B. Analysis

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

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

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

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

C. Conclusion

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

III. THYROID CANCER AFTER THE CHERNOBYL ACCIDENT

A. Scenario

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

B. Analysis

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

B23.   Various epidemiological studies have shown that the thyroid gland is highly susceptible to the carcinogenic consequences of external radiation exposure during childhood ([U10] annex A). These include studies of the survivors of the atomic bombings in Japan and those exposed in childhood for various medical reasons (e.g. treatment of tinea capitis). A combined analysis of these studies [R1] showed a marked influence of the age at exposure with little apparent increase in frequency of disease after age 20 years; it also showed that the increased frequency began to decline about 30 years after the first exposure. A pooled analysis* of five epidemiological studies of children exposed to external radiation showed an average excess relative rate of 7.7 (95% CI: 2.1, 28.7) at 1 Gy. (Further discussion on the uncertainty of the risk estimates is provided in annex B.)
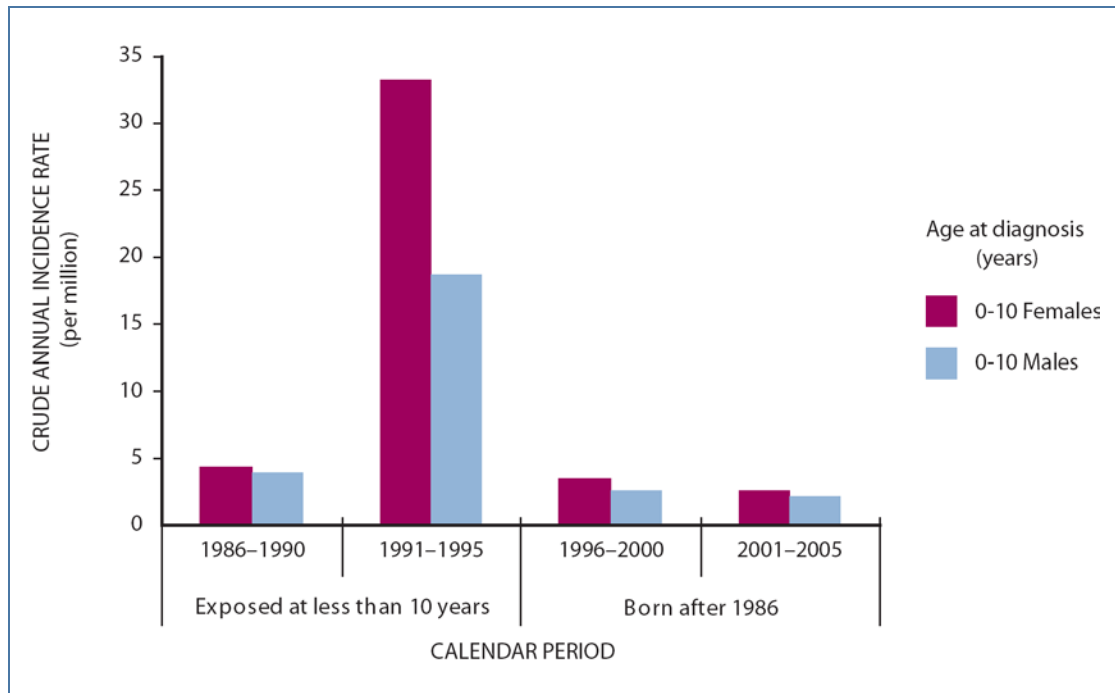
B24.   The average dose to the thyroid of those who were evacuated was estimated to have been about 500 mGy (with individual values ranging from less than 50 mGy to more than 5,000 mGy). For the more than six million residents of the contaminated areas of the former Soviet Union who were not evacuated, the average dose to the thyroid was about 100 mGy, while for about 0.7% of them, the doses to the thyroid were more than 1,000 mGy ([U14] annex D).

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

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

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

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

C. Conclusion

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

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

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

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

IV. LUNG CANCER FROM EXPOSURE TO RADON

A. Scenario

B31.   The arithmetic and geometric mean radon concentrations in 117 randomly selected homes in Winnipeg, Canada, were found in a survey to be 148 and 112 Bq/m^3, respectively [C2]. The geometric standard deviation was 2.07 with 20% of homes exceeding a radon concentration of 200 Bq/m^3. The measured radon concentrations ranged from 20 to 483 Bq/m^3. The question is whether it would be reasonable to predict an increased risk of lung cancer among the population and whether in any future epidemiological study an increased frequency of lung cancer would be discernible.

B. Analysis

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

B33.   Now, however, there are more than 20 case–control studies of lung cancer and radon exposure in homes. While individual studies have limited power, pooled analyses of European [D1, D2], North American [K5, K6] and Chinese [L6] studies provide a clear demonstration that an increased frequency of lung cancer is significantly associated with radon exposure. Taken together with application of the Bradford Hill guidelines (in particular, strength, plausibility, consistency, specificity, temporality, and biological gradient, see [H6], there is good evidence that an increased frequency of lung cancer can be attributed to radon exposure in dwellings when concentrations are significantly higher than average. In one study [D1], the dose–response relationship appeared to be linear without threshold and the excess relative rate at a concentration of 100 Bq/m^3 was statistically significant at the 95% confidence level (annex E of UNSCEAR 2006 Report [U11]). Thus, it could be concluded that an increased risk of lung cancer in a population exposed to a concentration of radon of 100 Bq/m^3 could be predicted under certain conditions.

B34.   On the basis of the results from these studies, the Committee inferred an excess relative risk of 0.16 (95% CI: 0.05, 0.31) per 100 Bq/m^3 as an appropriate, if possibly conservative, estimate of the lifetime risk from exposure to radon in homes.

B35.   Inferences of the lifetime risk of lung cancer for given exposures to radon based on this analysis of the epidemiological information and the assumption that the exposure conditions are maintained over 30 years are given in Table B1. Thus, for a population exposed to an average radon concentration of about 150 Bq/m^3, as in the Winnipeg study, an increased risk of 24% above the baseline for each sex and smoking category can reasonably be predicted (i.e. can be regarded as well-founded). The actual number of additional cases of lung cancer due to exposure to radon would be dominated by those who smoke, but is unlikely to be observable in the population in the homes that were surveyed here (number of homes, 117, which implies a population of around 500 on the basis of an average of four individuals in each home). In fact, one case-control study of radon and lung cancer in 1,438 persons in Winnipeg showed no increase in lung cancer for any histologic type [L4]. However, if the results of the survey were truly representative of the levels of exposure of the population of Winnipeg as a whole (say 700,000 people), then an increased frequency of lung cancer ought to be observable in that population.

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

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

^{222}Rn concentration (Bq/m^3)	Increased risk	Inferred lifetime risk of lung cancer[a] (%)			
		Men who smoke	Men who don't smoke	Women who smoke	Women who don't smoke
Baseline[b]	0%	12	0. 9	6.8	0.6
100	16%	14	1.0	7.9	0.7
150	24%	15	1.1	8.4	0.7
300	48%	18	1.3	10	0.9
400	64%	20	1.5	11	1.0

[a] *The value used in calculation 0.16 (95% CI: 0.05, 0.31) for exposure to 100 Bq/m^3 [D1].*

[b] *Baseline rate from [N6].*

C. Conclusion

B37.   An increased frequency of lung cancer among miners had been attributed to exposure to radon in mines. On the basis of the pooling of results from large epidemiological studies, an increased frequency of lung cancer in the general population can now be attributed to exposure to radon in homes at elevated levels, specifically at concentrations greater than about 100 Bq/m^3. Consequently, the lifetime risk of lung cancer in a population exposed to such elevated levels of radon (which is the case in the Winnipeg study), can be predicted provided that the exposure conditions remain constant for extended periods. The predicted increased frequency of lung cancer is unlikely to be observable among the people living in the Winnipeg homes sampled because of the small numbers involved; however, if the size of the population exposed at the same levels were large enough, then the predicted increased frequency is potentially observable (i.e. the prediction is, in principle, testable).

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

V.   ESTIMATED RISK FROM COMPUTED TOMOGRAPHY SCANS

A. Scenario

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

B.   Analysis

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

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

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

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

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

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

C. Conclusion

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

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

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

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

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