Executive Summary

This Report considers the types and magnitude of the several uncertainties that are a component of the risk assessment process for cancer, heritable and noncancer effects following radiation exposure. These uncertainties can result from the nature of the input data as well as from the specific analysis and models used for developing the risk estimates. The Report is timely because new data have recently become available for cancer incidence, noncancer occurrence (particularly for cataracts and cardiovascular disease), and heritable effects. The National Council on Radiation Protection and Measurements (NCRP) was charged with conducting an analysis of the major aspects of uncertainty in relating mean absorbed dose to specific organs and tissues (organ dose) to the risk of disease including cancer, noncancer health effects, and severe heritable disorders. NCRP was charged further with preparing an analysis of the sources of uncertainty involved in making conversions from organ doses to estimates of health risk in exposed populations and in calculating the probability of disease causation (assigned share) for an individual who developed a cancer after exposure to radiation.

The Report builds upon the analyses in other NCRP reports [Report No. 158, *Uncertainties in the Measurement and Dosimetry of External Radiation* (NCRP, 2007) and Report No. 164, *Uncertainties in Internal Radiation Dose Assessment* (NCRP, 2009a)] of the sources and magnitude of uncertainties in the estimation of organ doses from exposure to external and internal sources of radiation. Topics addressed in this Report include:

- uncertainties associated with extrapolation of dose-response relationships observed in primary epidemiological studies [such as the Life Span Study (LSS) cohort of Japanese atomic-bomb survivors] to estimate the risk per unit dose (*i.e.*, organ dose or whole-body dose) in the U.S. population and other exposed populations;
- applications of meta-analyses or pooled analyses to increase the statistical power in evaluating uncertainties in dose-response relationships for exposed human populations;
- uncertainties associated with extrapolation of dose-response relationships observed for populations exposed to acute doses

of high-energy gamma rays to estimate the risk per unit dose in populations exposed to fractionated or low-dose rate chronic exposures;
- uncertainties associated with extrapolation of the dose-response relationships observed for populations exposed to high-energy gamma rays to estimate the risk per unit dose in populations exposed to low-energy photons, low-energy electrons, alpha particles, and neutrons with various energies;
- comparison of uncertainties associated with risk estimated for individual tissue or organ sites with the uncertainties associated with estimating risk of all tumors combined due to whole-body exposure;
- evaluation of opportunities for using additional epidemiological and laboratory-based biological information to modify estimates of uncertainty in risk estimation for cancer, noncancer effects, and severe heritable disorders;
- procedures for accounting for dose uncertainty in epidemiological dose-response analyses; and
- evaluation of the combined effect of uncertainty in dose estimation with the uncertainty in estimation of risk per unit dose in estimating the overall risk.

This Report also provides a comprehensive analysis of these uncertainties on the estimation of probability of radiation-induced disease, including:

- application of organ doses and associated uncertainties in estimation of probability of disease causation [including a review and analysis of the National Institute of Occupational Safety and Health (NIOSH) and National Cancer Institute (NCI) versions of the Interactive Radio-Epidemiological Program tables used to calculate probability of causation];
- evaluation of inherent uncertainties in calculating the probability of disease causation (in an individual), or assigned share of excess relative risk (ERR) for various types of cancer attributable to radiation exposure; and
- methods of improving existing procedures for estimating disease probability based on input organ doses and their uncertainties.

The estimates of radiation risk currently used by international and national bodies such as the U.S. Environmental Protection Agency (EPA), the International Commission on Radiological Protection (ICRP), the National Academies/National Research Council (NA/NRC), NCRP, and the United Nations Scientific Committee on

the Effects of Atomic Radiation (UNSCEAR) rely very heavily upon epidemiological data on cancer and noncancer from a variety of exposed populations (particularly atomic-bomb survivors, and people with occupational, medical and environmental exposures). Thus, a significant component of uncertainty associated with these risk estimates will be accounted for by aspects of these epidemiological studies. Section 2 presents a discussion of the uncertainties (both random and systematic) associated with these epidemiological studies. In general terms, the precision of epidemiological risk estimates relies, in part, upon the degree of random errors. Such errors are accounted for by the range and distribution of the relevant doses, the sample size, the duration and ages of observation, the baseline frequencies of the health endpoint of interest, the strength of the radiation-disease association (attribution), the various types of dose uncertainties, and the degree of accuracy of ascertainment of the disease of interest. In contrast, the influence of systematic errors (or bias) on epidemiologically-derived risk estimates depends on a different set of factors. These include systematic personal reporting errors, insufficient statistical adjustment for other risk factors, dose-related inequalities in disease ascertainment, errors in assigning average values for shared dosimetry factors, failure to correct for individual measurement errors, and failure to adjust for the effects of disease-related covariates. Epidemiological studies are based on observational and not experimental data and thus are susceptible to biases and confounding influences that are not often identifiable. Each study requires consideration of its own unique set of uncertainties in the analysis of risk estimates. These various random and systematic uncertainties are considered under broad subsections in Section 2 on:

- dosimetric uncertainties;
- epidemiological and methodological uncertainties;
- uncertainties from low statistical power and precision;
- uncertainties from inadequate modeling of radiation risk data; and
- transport of (or generalizing) risk estimates to different populations.

Depending on the particular study design and the available data, the magnitude of the uncertainties involved will be different.

The assignment of specific uncertainties based on study design and available data are discussed in Section 3 for selected radioepidemiological studies, considered singly or as combined studies. For this purpose, studies have been selected to illustrate specific points related to uncertainty.

The LSS of atomic-bomb survivors in Hiroshima and Nagasaki is a comprehensive study of an exposed population followed over an extended period of time (~60 y). The LSS has provided the primary data used in developing the nominal risk estimates used in radiation protection guidelines. For the present purpose, a comparison is made among the major models used for developing risk estimates based on the LSS. The study of workers at the Mayak Production Facility in the former Soviet Union (now Russia) provides an example of the uncertainties associated with chronic exposures at relatively high doses to both external and internal radiation exposures. The Mayak cohort sustained a wide range of doses from protracted exposures. The epidemiological aspects of this study are still improving, as is the dosimetry. Nevertheless, there will continue to be large uncertainties in the internal dosimetry for those who worked in plutonium areas. The analysis of uncertainty for a set of breast cancer studies (for different exposure scenarios) provides an opportunity to assess the impact on overall uncertainty from increasing the study size by combining specific studies. The Israeli study of children irradiated for *tinea capitis* (ringworm of the scalp) provides an example of potential bias due to missing dosimetry information.

The uncertainties associated with risk estimates derived from studies of populations exposed occupationally to low doses and those exposed for medical reasons, present some unique features; therefore, these studies as a whole are considered separately in this section. For example, the 15-Country Study has many strengths, but even large studies of high quality (but low statistical power) are susceptible to slight biases, undetected confounding factors, and subtle selection and analytical decisions that have the potential to distort study findings and temper the strength of the etiologic conclusions that can be drawn. There are statistical limitations that make it difficult to evaluate cancer risk in humans at doses that are <100 mGy (*e.g.*, organ doses) (NA/NRC, 2006), yet these are the levels of current scientific and societal interest. Thus, epidemiologic observations (at both high and low doses) should be combined with the latest understanding of biological plausibility to effectively model radiation worker and population risks (Dauer *et al.*, 2010; Goodhead, 2009a).

Similarly, there are unique uncertainties associated with occupational and residential exposures to radon. In Section 3.6, a separate review is conducted together with a consideration of the magnitude of the uncertainty on the risk estimates derived. Epidemiological studies of radon and radon-decay products have overwhelmingly been focused on lung cancer. Although a number of studies have examined the relationship of radon-decay products to

other diseases (*e.g.*, leukemia), no definitive links have been reported. Accordingly, this section examines uncertainties in lung cancer risk estimates arising from various studies of underground miners exposed occupationally to radon, and studies of the general population exposed to indoor radon in homes. In general, the miner studies provide stronger evidence and more precise estimates of risk due to the prevailing use of large cohorts exposed to higher levels of radon when compared to indoor radon studies. The epidemiology of radon-exposed miners and the uncertainties associated with these studies is addressed. Similarly, the epidemiological designs and uncertainties arising from indoor radon studies are considered in some detail.

As noted above, the risk estimates for cancer and noncancer diseases rely extensively on the data from radioepidemiological studies. Also, it was stated that it was very problematic to assess radiation effects for doses <100 mGy (*e.g.*, organ dose) because of the high background levels of the same diseases. One approach to estimating responses at such low doses is to use data from laboratory animal studies in a direct extrapolation approach or to use data from cellular and molecular studies to assist with the form of the extrapolation from higher dose human studies to estimate low-dose responses.

In the past, animal models have been used to estimate human risks for cancer and other radiation-induced toxicities (NCRP, 2005), although the applications of animal systems today are not only for extrapolating risk but are also considered essential for understanding specific mechanisms that can be used to further inform risk. While human studies are a preferred source of such estimates, human exposures have been limited to high-dose accidental or incident-related exposures. Animals have been used to examine radiation consequences in a more systematic fashion under carefully controlled conditions. One of the major uncertainties associated with interpretation of results of these animal studies is the degree to which they can be used to extrapolate to the human situation; not all animal models have the same relevance to humans. For example, hematologic effects of radiation in the mouse are very different from the human response, while the onset and types of hematologic abnormalities in canines are very similar to the human experience. NCRP (2005) provides critical analyses and approaches for selecting a potentially-appropriate animal system to study a specific type of radiation-induced cancer in humans. Section 4 outlines historically some of the most important studies that contributed to risk assessments in humans and discusses more recent studies that point to mechanisms that are contributing to an understanding of risk.

The utility for risk estimation of animal studies described in Sections 4.2 and 4.3 has been influenced by a series of *in vitro* studies in cell- and tissue-culture systems. In contrast to animal studies, it is much more difficult to assess risk to humans from cellular studies. Most studies in mammalian cells have focused on the identification of mechanisms and pathways that are important in the radiation responses, and then the eventual testing of these pathways in animal systems so that their relationship to risk can be defined. An understanding of deoxyribonucleic acid (DNA) repair pathways, carcinogenesis pathways, and mechanisms of mutation induction has helped shape the field of radiation biology and has contributed to a more clear understanding of *in vivo* mechanisms. Studies of low-dose responses have been especially advanced by research in cell-culture systems. For example, mutations at low doses are extremely difficult if not impossible to assess in animals because of the large number of animals required to determine a statistically-significant number and establish that an effect is real.

One unanticipated outcome of these low-dose cellular studies was the identification of novel mechanisms that occur at low doses but not apparently at high doses. Many of these studies have identified processes that are evident at very low doses in cultured cells that may have relevance to human radiation risk. The adaptive response is an apparent beneficial effect of low-dose radiation exposure where a very low priming by radiation prior to a larger challenging dose can be protective of radiation toxicities including mutations and chromosomal damage. Recent studies of the repair of DNA double-strand breaks suggest that mechanisms for repair may be more efficient at low doses compared with high doses. Alternatively, some responses have been shown to enhance radiation effects at low dose, such as the bystander effect where cells that are not in the radiation field but are close to irradiated cells are capable of showing mutation induction, chromosomal damage, and other radiation consequences. This suggests that risk for mutation induction following exposure may be greater than predicted by dose and DNA damage alone. Other similar effects such as delayed mutation induction and genomic instability have also been found to occur at low doses. Some of these responses have also been shown to occur in whole-animal systems, but the relationship between these and human risk of radiation exposure is not readily apparent. The relationship of these cellular phenomena to disease outcomes, if any, is not yet known although it is generally considered that when risks are calculated directly from cancer data itself, such cellular phenomena will be accounted for. It is anticipated that there will be an increased reliance on cellular studies in support of risk assessments

because of an increased sophistication of such studies and a greater relevance to disease outcome for use in cross-species or *in vitro* to *in vivo* extrapolations.

Section 5 describes the quantitation of several uncertainties that are associated with the application and projection of risks. For many cancer sites, dose response and its uncertainty are highly quantified, and provide a useful basis for radiation protection and for adjudication of compensation claims for radiation-related cancer. Section 5 thus provides an assessment of the approaches to estimating cancer risks and their uncertainties for different overall purposes, in particular, radiation protection and probability of causation/assigned share (PC/AS) for compensation adjudication. The approaches are by necessity different because of the nature of the application; one being for populations, the other for individuals respectively. In part this has led to the use of different values for comparing the effectiveness of radiations of different qualities. In Section 5, relative biological effectiveness (RBE) is defined as the ratio of a dose of a low linear energy transfer (LET) reference radiation to a dose of another type of radiation that gives an identical biological effect. In radiological protection, the RBE for stochastic effects at low doses [maximum low-dose relative biological effectiveness (RBE_M)] is of particular interest. In contrast, the so-called radiation effectiveness factor (REF)[1] has been used to modify the estimate of radiogenic cancer risk when exposures occur to radiation types other than high-energy gamma radiation, and when the primary source of radiation risk coefficients is the LSS cohort of Japanese atomic-bomb survivors. This is an important distinction.

Quantitative uncertainty analysis is a well-accepted methodology developed in a decision-theoretic framework that has been extensively applied to nuclear reactor safety and to other issues (Gilbert *et al*., 1996; IAEA, 1989; NRC, 1975; 1990; Warren-Hicks and Moore, 1998). Quantitative uncertainty analysis involves the application of Bayesian probability methods to estimates and decision rules based on uncertain statistical and subjective information. Advantages of this approach include improved transparency

[1]Kocher *et al*. (2005) introduced a quantity called the *radiation effectiveness factor* (REF) to compare the cancer causing potential in humans of a specific type of radiation relative to some standard. According to their definition the REF is to be distinguished from measured RBE that may be used as a basis for estimating the REF, although the RBEs themselves may have been measured for a different endpoint or in a different species (EPA, 2011). The REF represents the ratio of risks that are produced at the same dose, whereas the RBE is the ratio of doses to produce the same effect.

and credibility, avoidance of worst-case assumptions, and improved decision support. Two NCRP (1996; 1997) reports delineate a quantitative uncertainty analysis-based "new paradigm" for expression of radiation-related cancer risk and for dealing with uncertain but necessary assumptions. More recent applications include a risk-based computer algorithm to assist in adjudication of compensation claims against the U.S. government for cancers associated with occupational exposure to ionizing radiation (Land *et al*., 2003a), an analysis of the implications of uncertainty for low-dose extrapolation of radiation-related cancer risk (ICRP, 2005), and the Committee on the Biological Effects of Ionizing Radiation (BEIR) report (NA/NRC, 2006) on health risks from exposure to low levels of ionizing radiation. These applications all involve expressing radiation-related cancer risk as a mathematical function of specified components. These modular components and their uncertainty structures are transparent (*i.e*., they are clearly specified, available for comment, and subject to critical review).

A major emphasis of the analysis of uncertainty is for the considerations of dose response, as this is critical for the development of risk estimates at low doses. In fact, it is necessary to adjust the modeled dose response for the presence of dose uncertainty. The other components that are related to dose-response considerations are latency period (time between exposure and diagnosis of disease, considerations of the nature of dose responses for different cancer sites, and the relative impact of single- versus pooled-data sources in the context of uncertainty). An area of considerable debate and uncertainty is the approach to be used for extrapolating from one exposed population to predict the response for another very different population (*e.g*., from the Japanese LSS population to a U.S. population). The basic approaches are described for the incorporation of baseline cancer rates, DDREFs, and REFs applied for radiations of different qualities.

Additional considerations for propagating uncertainty through dose and risk models is provided in Section 5.4. It is well known that random error in the assignment of a dose value to individual members of an epidemiological cohort can bias the central value of the dose response towards underestimation of actual risk and will understate the width of the confidence interval (CI) of the dose response (Armstrong, 1985; Carroll *et al*., 2006; Schafer and Gilbert, 2006). The effect of such uncertainty in individual dose assignment on risk estimation can be profound when uncertainties are not random, but are shared among different cohort subgroups. An example is when there are uncertain degrees of systematic bias in the estimation of the expected value of dose for members of

cohort subgroups. If the degree of shared uncertainty is different between subgroups associated with the higher and lower doses, the uncertainty may be differential with dose, and the effect on the dose-response function may be unpredictable unless the uncertainty is accounted for explicitly through the use of bias correction factors, which themselves may be uncertain (Greenland, 2005; JCGM, 2008a; 2008b; 2009; NCRP, 2009a).

More recent approaches to dose reconstruction that address complex sources of uncertainty in epidemiological investigations involve two-dimensional (2D) Monte-Carlo simulation to separate uncertainty about quantities that are fixed but unknown with respect to the conditions of exposure (often called Type-B uncertainties), and true quantities that vary either at random, independently from one person to the next (often called Type A uncertainties), or that vary according to conditions explained by values for terms included in the exposure and dose model (*i.e.*, sex, age, dietary source and consumption rates, location, work, and residence history). The extent of shared uncertainty may be complex, affecting different subgroups in the cohort to different degrees. Examples of 2D Monte-Carlo approaches to dose reconstruction and additional discussion on the distinctions between Type-A and Type-B uncertainties are given in reports by the International Atomic Energy Agency (IAEA, 1989) and NCRP (1996; 2007; 2009a; 2009b).

The great majority of the effort on estimating risks has been developed for low-LET x rays and gamma rays. However, there is a parallel need to consider the risk and associated uncertainties for other radiation types, especially given their increasing use in medical applications. The relative effectiveness of different radiation types is reviewed in Section 5.3.3. The radiation types considered are neutrons, alpha particles, lower-energy photons, low-energy electrons, protons, fission fragments, and heavy ions.

A relatively large amount of data is available that can be used to estimate REFs for induction of cancer in humans and their uncertainties in cases of exposure to fission neutrons, alpha particles, and low-energy tritium beta particles relative to high-energy photons, which is the preferred reference radiation. Although data on the biological effectiveness of photons at the energies of orthovoltage (200 to 500 kV) x rays and below relative to high-energy photons also are extensive, it is doubtful that the data on RBE_M for induction of dicentric chromosome aberrations in human lymphocytes can be used to estimate radiation effectiveness factor for low doses and dose rates (REF_L) for lower-energy photons. Limited data are available for estimating REFs and their uncertainties for exposure to neutrons of energies higher or lower than the principal

energies of fission neutrons, for low-energy electrons other than tritium beta particles, for higher-energy helium nuclei, protons, and fission fragments and for heavy ions. There are no data for other radiation types of interest, including photons of energy between ~100 keV, which is a typical highest significant energy of photons in orthovoltage x rays, and ~250 keV, above which the biological effectiveness should not differ substantially from one, and intermediate-energy electrons (*e.g.*, at energies of ~15 to 60 keV). However, some gaps in data for low-LET radiations could be addressed by taking into account that the biological effectiveness of incident photons of a given energy is determined by the biological effectiveness of the secondary electrons that are produced by the first interactions of the photons with constituents of tissue.

Even when relevant data are relatively abundant, however, uncertainties in REFs are substantial and should be important to uncertainties in estimating cancer risks from actual exposures whenever the organ dose from a radiation type other than high-energy photons is significant. When data are less abundant, uncertainties in REFs generally should be larger and often would need to be estimated mainly on the basis of judgment.

A complicating factor in estimating REFs that would apply in cases of external exposure to high-LET radiations (neutrons, helium nuclei, and heavy ions) is that the types and energies of radiations at the location of an organ or tissue of interest may be significantly different from the type and energies of the radiation incident on the body surface. This complication affects the applicability of RBEs for induction of cancer in small animals by fission neutrons to induction of cancer in humans, for example, and it generally confounds the problem of estimating REFs in cases of external exposure to high-LET radiations that would apply to specific organs or tissues or to all organs and tissues. If such an REF is intended to apply to all organs and tissues, its uncertainty should be substantially greater than the uncertainty in an REF that might apply to a specific organ or tissue.

Estimates of quality factors (Q) and radiation weighting factors (w_R) developed for purposes of radiation protection, especially recommendations on the Q versus LET relationship, and more detailed track-structure analyses based on microdosimetric calculations can be used to inform judgments about REFs for different radiation types. However, it should be recognized that the problem of estimating REFs and their uncertainties for use in estimating cancer risks from actual exposures is different in important ways from the problem of estimating quantities used in radiation protection, and that using protection quantities to estimate REFs generally would

involve significant uncertainty. Furthermore, microdosimetric calculations are based on physics only and may not adequately represent the effects of biologic processes on induction of cancer. Consequently, their use in developing REFs may involve substantial, but unknown, uncertainty.

Section 6 presents a review of the uncertainties associated with the estimation of risks of noncancer effects from all types of exposure. New information from studies on the Japanese atomic-bomb survivors reveals an increased mortality and occurrence of hypertension, and cardiovascular diseases and cataracts at doses lower than previously reported. UNSCEAR published an extensive review of cancer and noncancer effects (UNSCEAR, 2008). They reviewed data on noncancer disease from 47 different studies through 2006, which were characterized as positive, inverse, not significant, or without supportive published data. Effects included all noncancer diseases (as a categorized class), and specific studies reporting cardiac, circulatory, infectious, respiratory, digestive, genitourinary, and other diseases including cataracts. The present Report builds on the UNSCEAR (2008) report. The estimated noncancer and cancer mortality from current analyses of atomic-bomb survivor studies reveals an approximately threefold difference between the number of deaths attributed to cancer (625 deaths) versus noncancer (210 deaths) (Shimizu *et al*., 2010). A major issue that remains is whether there is credible evidence for a threshold for all noncancer effects, and if so its magnitude for specific diseases. Increased incidence of cataracts is well established in the Japanese atomic-bomb survivors. There is evidence for a threshold in the range of 0 to 0.8 Gy (lens of the eye dose) (Shore *et al*., 2010). However, newer data are beginning to indicate that a minimal threshold or indeed no apparent threshold is quite possible (ICRP, 2012). These observations are sufficiently well established to merit consideration of changes in radiation protection guidance for cataracts as recently proposed by ICRP (2012). Weaker evidence has been presented for the magnitude of the threshold for other noncancer disease involving cardiovascular and cerebrovascular effects and behavioral effects (*e.g*., ICRP, 2012; Shimizu *et al*., 2010).

Clearly, there are opportunities to expand the use of these particular case studies or to include additional studies for both cancer and noncancer effects. However, for illustrative purposes for this Report, it was considered that these need to be covered in an abbreviated form to be exemplary rather than to be comprehensive.

The third class of risks to humans from exposure to ionizing radiation is that of heritable effects. In general terms, heritable effects are those that are induced in germ cells and transmitted to

offspring resulting in a disease phenotype. Such phenotypes can be expressed at birth as congenital defects or later in life as chronic multifactorial diseases. Because human studies have failed to reveal statistically-significant evidence of transgenerational effects, estimates of risk rely on animal data. The estimation of heritable risk was significantly modified for UNSCEAR (2001) to be based on the rates of radiation-induced germ-line mutations in mice and on human data for background mutations in the population. The current process itself is somewhat more complex than previous ones because allowance has been made for the proportion of potentially heritable effects that are indeed the result of genetic alterations and the probability of recovering mutant phenotypes in live-born offspring. For considering the uncertainties associated with the measurement or estimation of these values, Section 7 is divided into the components of the risk assessment process, namely:

- baseline incidence;
- doubling dose (*DD*);
- mutation component (*MC*); and
- potential recoverability correction factor (*PRCF*).

There are other uncertainties that influence the assessment of heritable risk: dose and dose-rate effectiveness factor (DDREF) and differential radiosensitivity within the population. These are considered in the context of relative sensitivity and the attendant uncertainty in estimating magnitude of response.

A strong rationale for this Report's review of uncertainties in the estimation of radiation risks is to present updated information within the context of radiation protection. To this end, Section 8 discusses how estimates of risks of stochastic health effects (cancers and severe hereditary effects) from exposure to ionizing radiation and uncertainties in estimated risks are used in radiation protection. Discussions focus primarily on the use of estimates of risk and their uncertainty by ICRP and NCRP for the purpose of developing recommendations on:

- dose limits for occupational exposure and exposure of members of the public;
- criteria to limit exposures of workers and members of the public to radon and its short-lived decay products; and
- the dosimetric quantity (effective dose) used in radiation protection.

The primary concern of radiation protection generally has been to "provide an appropriate standard of protection for man without unduly limiting the beneficial practices giving rise to radiation exposure" (ICRP, 1991; Lindell *et al.*, 1998). This concern has not

changed even though scientific information that could be used to evaluate risks from exposure to ionizing radiation and the many judgments, both scientific and societal, involved in defining acceptable levels of health risk from radiation exposure and in balancing risks and benefits, have changed greatly since radiation protection standards were first developed in the 1930s. Concerns about limiting risks of stochastic health effects were paramount even before efforts to develop quantitative estimates of risk began in the 1950s. Once estimates of risk were developed from epidemiologic studies, those estimates and their periodic revisions have played an important role in radiation protection.

Section 8.2 presents a summary of the various uses of estimates of risk of stochastic effects and their uncertainty in the development of current ICRP and NCRP recommendations on radiation protection standards. This summary is based on a review in Appendix A of the development of ICRP and NCRP recommendations beginning in the 1930s. A historical perspective is important in understanding how estimates of risk and their uncertainty are used in radiation protection at the present time. Section 8.3 considers how estimates of stochastic risk and their uncertainty could be used more directly in setting radiation protection standards. These considerations are based on discussions in ICRP and NCRP reports and an established approach to health protection in the United States that is not based on ICRP and NCRP recommendations.

A detailed discussion of the major radioepidemiological studies used in the development of cancer risk estimates and their associated uncertainties is provided in this Report. However, it is clear that there are limitations for each of these studies and gaps in needed information when these studies are considered collectively. Section 9 discusses the types of study that could fill these gaps together with information on ongoing studies that have been designed to address issues of uncertainty in the current risk estimates. There are several areas for which new epidemiologic data could help reduce the uncertainty in radiation risk estimates (Boice, 2011). Uncertainty is used here in a broad context and not limited to statistical or dosimetric uncertainties but rather to include unresolved or inadequately studied topics such as:

- tissue sensitivities for cancer induction;
- low dose-rate effects;
- risks from intakes of radionuclides;
- individual variations in cancer risk (*e.g.*, genetic susceptibility);
- risks for noncancer diseases and hereditary effects; and
- risks to the embryo or fetus at low doses.

Tissue susceptibility is fundamental to understanding radiation effects. Should all cancers be considered inducible by radiation and for those that are, what are the modifying effects of age-at-exposure, age-at-observation, time-since-exposure, sex and perhaps other demographic, lifestyle, environmental, and genetic factors (UNSCEAR, 2008)? A critically-important unanswered question that radiation epidemiology can address is the potential risk associated with chronic low dose and low dose-rate exposures experienced over long periods of time (Brooks *et al*., 2009; NCRP, 1980; 1993a; Shore, 2009). Low doses might be considered as below ~100 to 200 mGy (*e.g*., organ dose) and low dose rates might be considered as below ~5 to 10 mGy h^{-1} (Wakeford and Tawn, 2010). In principle, epidemiologic data on protracted and fractionated exposures, such as those from environmental, occupational, and some medical circumstances, should be directly informative on low dose risk. Statistical uncertainties and the inability to adequately control for confounding factors, however, hinder the direct estimation of risk below ~100 to 200 mGy (*e.g*., organ dose) (Boice, 2010a; Gilbert, 2001; ICRP, 2005; 2007; Kellerer, 2000; Land, 1980; UNSCEAR, 2008) so there is a need for studies covering a broad dose range as well as a better integration of epidemiologic data with biological principles in the estimation of risk; and not totally relying upon statistical modelling of observational data.

Fruitful avenues for investigation might include new or continued studies of cancer survivors, patients receiving frequent diagnostic-imaging procedures, early radiation workers in the United States and other countries, pooled or meta analyses of early radiation worker studies, nuclear weapons test participants, prenatal studies of cancer patients who are pregnant when treated, and communities living in areas of high background radiation (Boice *et al*., 2010).

The possible interaction between radiation and genetic susceptibility is emerging as an important area of research. There should be a renewed emphasis on evaluating specific organs and tissues (*e.g*., breast, lung, stomach, colon, thyroid and leukemia), and a move away from lumping or combining all cancers together (which includes cancers with uncertain associations at low doses) and then applying a DDREF to estimate risks at low doses and low dose rates from such a heterogeneous grouping of malignancies with different etiologies and radiation sensitivities. Pooled analyses of site-specific organs, such as was done for the breast and thyroid (Preston *et al*., 2002; Ron *et al*., 1995) should be encouraged for organs with uncertain estimates of risk. Thus, Section 9 addresses new or updated epidemiologic studies that might contribute to

reducing the uncertainty in radiation risk estimates and increasing knowledge of radiation associations.

The issue of uncertainty in estimation of radiation-induced risks of cancer, noncancer diseases, and heritable genetic effects analyzed in this Report is of great importance in evaluating the effects of ionizing radiation on human health, in decisions involving the safe use of ionizing radiation and in addressing public controversy. Uncertainty analyses should become increasingly important in the future as the sophisticated methodologies continue to develop and become more available.