Implications of Recent Epidemiologic Studies for the Linear Nonthreshold Model and Radiation Protection

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Preface

The National Council on Radiation Protection and Measurements (NCRP) has a long history of issuing guidance on operational radiation safety including radiation exposure limits for radiation workers and the public. Effective dose limits are based on the linear nonthreshold (LNT) dose effects model, which is based almost entirely on the human epidemiology data. This Commentary provides a review of recent epidemiologic studies and an evaluation of whether the new observations are strong enough to support or modify the LNT model as used in radiation protection today. This Report represents an update of the guidance provided in NCRP Report No.136, *Evaluation of the Linear-Nonthreshold Dose-Response Model for Ionizing Radiation* (NCRP, 2001).

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President

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1. Executive Summary

1.1 Introduction

Historically, epidemiologic studies have assessed the health effects of ionizing radiation exposure from multiple sources: occupational, accidental, environmental, military and medical. The several national and international reviews of the status of health risks associated with exposure to low levels of ionizing radiation that have been completed in the last few decades generally agreed that the expectations for health effects in humans, such as cancer induction or cardiac damage, observed at acute doses of 100 mGy and above are more reliable than those observed at <100 mGy, the low-dose region (NCRP, 2015). For the purpose of this Commentary, for low linear-energy transfer (LET) radiation, a low absorbed dose is <100 mGy delivered acutely, and a low absorbed-dose rate is <5 mGy h^{-1} for any accumulated dose. See NCRP Commentary No. 24 (NCRP, 2015) Section 1.1 for additional discussion of low doses and low dose rates.

Our understanding of the shape of the dose-response relationship and the level of risk from low-LET types of radiation at low doses and low dose rates remains uncertain because of the intrinsic uncertainties in results from the epidemiologic and radiobiological studies of low doses of radiation. This uncertainty can impact actions taken regarding radiation protection guidance, medical practice, compensation programs, environmental contamination issues, technological advances, and communication with members of the public (NCRP, 2015). For over 40 y the linear nonthreshold (LNT) dose-response model has been commonly utilized for low-LET radiation when developing practical and prudent guidance on ways to protect workers and the public from the potential for harmful effects from radiation while balancing the beneficial, justified, and optimized uses of radiation in our society. Indeed, in developing its basic recommendations, as currently given in NCRP Report No. 116 (NCRP, 1993a), the Council reiterated its acceptance of the LNT model for the purposes of radiation protection.

The purpose of this Commentary is to provide a review of recent data from studies with low dose rates and from the Life Span Study of atomic-bomb survivors to determine whether these epidemiologic studies broadly support the LNT model of carcinogenic risk or, on the contrary, whether there is sufficient evidence that the LNT model is inappropriate for the purposes of radiation protection. The strength of epidemiologic support for the LNT model is evaluated for solid cancer incidence or mortality and secondarily for low dose-rate studies of leukemia. Briefer consideration is also given to low dose studies of thyroid cancer and breast cancer. The focus of this commentary is on low doses and low dose rates.

1.2 Study Reviews

The primary approach was a critical review of each major study. The critique included an assessment of the quality of the epidemiology, dosimetry, and statistics of each study. The epidemiologic evaluation included a characterization of the study design and study population, quality of the data available, data collection methodology, the degree to which potential confounding variables or biases were assessed, and the quantitative results. Analysis of the dosimetry helped evaluate the robustness of the study in supporting the shape of the dose response curve at low doses and low dose rates. A statistical evaluation considered whether the analytic methods were appropriate, whether the study considered statistical alternatives to a linear dose-response trend, and whether sensitivity analyses or other clarifying analyses were undertaken. Based on those considerations, the contribution the study makes to the LNT model and to radiation protection is characterized. Several key studies about solid cancer mortality or incidence are briefly summarized below.

1.2.1 *Life Span Study*

Although this report focuses on studies with low doses and low dose rates, the Life Span Study (LSS) was included as a benchmark comparison study. The LSS cohort of atomic-bomb survivors (Section 4.1) has provided important data because it is a large cohort (~86,000 survivors of all ages) with relatively accurate dosimetry, a wide dose range (0 to 4 Gy colon dose, including ~68,000 with doses <100 mGy), over 50 y of high-quality follow-up for mortality and cancer incidence, and over 1,000 excess cancer cases associated with radiation exposure. These features provide relatively high statistical power and precision of risk estimates, resulting in a statistically significant dose response for all incident solid cancer over the dose range 0 to 100 mGy (Grant *et al*., 2017). Formal dose-threshold analyses for both solid cancer incidence and mortality are compatible with no dose threshold, and a pure quadratic model provided a significantly poorer fit than a linear dose-response model (Grant *et al*., 2017; Ozasa *et al*., 2012).

A nonparametric analysis of the most recent mortality data indicated excess risk over the range of 0 to 200 mGy that was congruent with the LNT dose response model. Nevertheless, the most recent solid cancer mortality and incidence data provide some evidence for upward curvature in the dose response consistent with a linear-quadratic model. This implies a shallower, but still positive, dose-response slope at low doses than at higher ones, though this curvilinearity appeared to be confined primarily to males. In summary, the study provides strong support for the use of a LNT model, with consideration of a low-dose effectiveness factor (LDEF), for use in radiation protection. However, unlike most other studies reviewed in this report, the LSS assesses the effects of a single, brief exposure and the associated LDEF, but it does not assess protracted or highly-fractionated doses.

1.2.2 *Worker Studies*

Radiation worker studies assess risks in worker groups exposed largely to low doses received at low dose-rates, addressing directly the validity of the LNT model for low dose-rate exposures. Further, cumulative doses can be several hundred mGy, especially for workers in early periods, so that some studies can offer reasonable statistical power.

INWORKS Study: Large studies that combine data from workers from numerous nuclear installations in a number of countries have now been conducted (Cardis *et al*., 1995; 2007). An important study is the International Nuclear Workers Study (INWORKS), which included workers from nuclear facilities in the United States, United Kingdom, and France (Leuraud *et al*., 2015; Hamra *et al*., 2016; Richardson *et al*., 2015) (reviewed in Section 4.2.2). INWORKS found an association between the cumulative external photon dose to the red bone marrow (RBM) and mortality from leukemia [excluding chronic lymphocytic leukemia (CLL) excess relative risk (ERR) Gy^{-1} of 3.0, 90 % confidence interval (CI) of 1.2 to 5.2]. External dose to the colon (used as the prototypic organ) was associated with mortality from all solid cancers combined (ERR Gy^{-1} of 0.47, 90 % CI of 0.18 to 0.78). For solid cancer there was no evidence of nonlinearity ($p = 0.44$). These risk estimates were similar to those in the LSS data. Even when the cumulative colon dose was restricted to 0 to 100 mGy, a statistically significant dose response was seen for all cancers excluding leukemia.

Mayak Study: The Russian Mayak workforce is of particular interest because of the high cumulative doses received (mainly at a low dose rate) by many workers during the early years of operations at this installation (Section 4.2.3). The investigators reported statistically significant associations between external dose and mortality from leukemia (excluding CLL) and from all solid cancers excluding lung, liver and bone (*i.e*., excluding cancers at the major sites of plutonium deposition); and adjusting for plutonium exposure; ERR Gy^{-1} of 0.12, 95 % CI: 0.03 to 0.21 (Sokolnikov *et al*., 2015). For solid cancer there was no indication of nonlinearity ($p > 0.5$) based on external dose to the colon. For leukemia, excluding the chronic lymphocytic type, the linear ERR Gy^{-1} estimate was 3.57 (90 % CI 1.55, 8.22) for cumulative external radiation dose to the red bone marrow, adjusted for plutonium exposure. The linear-quadratic model fit marginally better than the linear model ($p = 0.11$), and the pure linear and pure quadratic models fit about equally well.

Summary of Worker Studies: Overall the nuclear worker studies lend considerable support to the inference that an excess risk of cancer exists following protracted exposure to low doses received at a low dose rate, and the excess risk is compatible with a LNT model, perhaps modified by a DDREF. Although the accuracy of the risk estimates is

limited to some degree by uncertainties in dosimetry and epidemiology, the studies provide substantial support for the LNT model. The Million Worker Study is underway in the United States; when it is completed it is expected to augment appreciably the information available on worker radiation-related cancer risks and reduce the uncertainties in risk estimation after exposures at low dose rates (Boice, 2015a; 2017c; Boice *et al*., 2014; Bouville et al., 2015; Till *et al*., 2014).

1.2.3 *Environmental Exposure Studies*

Techa River Study: Between 1949 and 1956 the Russian Mayak nuclear weapons facility released radioactive waste into the Techa River and exposed approximately 30,000 residents to relatively low doses at low dose rates from gamma rays (external) and ^{137}Cs and ^{90}Sr (internal). The recent studies of the Techa River Cohort have found associations between radiation dose and incidence and mortality rates for solid cancers and leukemia (other than CLL) that they report are linear in dose response (Davis *et al*., 2015; Krestinina *et al*., 2013a; Schonfeld *et al*., 2013) (Section 4.3.1). However, inherent uncertainties in the dose reconstruction along with some limitation in the cancer ascertainment weaken inferences about the shape of the dose-response curves and the LNT model.

Chernobyl Thyroid Cancer Studies: New studies of cohorts of children in Ukraine and Belarus who had thyroid measurements of ^{131}I shortly after the Chernobyl accident and systematic thyroid screening have added appreciably to our knowledge about thyroid cancer risk after protracted internal exposure (Brenner *et al*., 2011; Zablotska *et al*., 2011) (Section 4.3.2). Both cohorts showed strong linear dose-response functions with no evidence of nonlinearity, though perhaps with a somewhat lower risk per unit dose than seen in studies of children exposed to external gamma radiation. The thyroid doses are believed to be sufficiently accurate to support a LNT interpretation.

1.2.4 *High Background Radiation Areas*

Studies of residents in areas of high natural background radiation have been conducted in Kerala, India and Yangjiang, China. However, it is exceedingly difficult to conduct a geographic study of background radiation, *e.g*., it is difficult to find a suitable low exposure control group with highly similar lifestyles and natural disease rates to whom the highly exposed group may be compared. The better and larger of the two studies, the Kerala study of cancer incidence, included 70,000 individuals and over 1,300 cancers from high-background or low-background areas (Nair *et al*., 2009) (Section 4.3.3). The dosimetry was based on measurements of ambient levels within and near homes, coupled with average house-occupancy factors by age and sex. They reported an ERR Gy^{-1} of –0.13 (95 % CI –0.58, 0.46) for all cancer except leukemia, and there were too few leukemia cases to be informative. The Yangjiang study reported a positive, but nonsignificant, risk coefficient for all cancer except leukemia and liver

cancer [ERR Gy^{-1} 0.19 (95 % CI –1.9, 3.0); Tao *et al*., 2012]. These studies are nominally more supportive of little or no effect after low dose-rate exposures rather than the LNT model. However, the fact that much of the dose variation is attributable to geographic locations, which may be associated with risk factors other than radiation level, introduces ambiguity into the inference regarding radiation effects. Furthermore, the substantial uncertainties in dosimetry, the weaknesses in cancer ascertainment, and the wide confidence intervals on the risk estimates mean they need to be interpreted with caution.

1.2.5 *Childhood Radiation Studies*

Medical exposures are typically partial body and study results are subject to significant uncertainties including, but not limited to, historical exposure data, limited organ dosimetry for organs other than the target organ, and potential biases because radiologic procedures are often administered for an existing health condition. Recent epidemiologic studies have involved populations who had received computed tomography (CT) scans during childhood when risk might be greater because CT doses were relatively high and children may be more radiosensitive to cancer induction than adults (Section 4.4.2). However, information on organ doses from CT examinations in the 1980s and 1990s is sparse and individual doses have not been reconstructed. CT studies suffer from potential biases: confounding by indication (CT examinations more likely for those who have conditions that confer risk for cancer) and reverse causation (pre-existing but undetected malignancy). Because of the weak dosimetry and potential for bias, the results are considered unreliable for evaluating the LNT dose response model.

The data on postnatal diagnostic medical exposures and childhood leukemia risk are inconclusive (Wakeford, 2008). Studies of juvenile irradiation and breast cancer generally support a linear dose response. A recent pooled analysis of external thyroid irradiation in childhood and subsequent thyroid cancer in nine studies showed a significant dose response from 0 to 100 mGy and no evidence of nonlinearity (Lubin *et al*., 2017). An analysis of solid cancer incidence among the Japanese atomic-bomb survivors exposed prenatally or during childhood showed a clear dose response, but marginal upward curvature ($p = 0.09$) suggested that the dose-response slope may be shallower in the low-dose range. In general, the low dose data on children are sparse, the number of specific types of cancer is small and uncertainties are large enough that such studies do not yield definitive information on the LNT model. In the case of thyroid cancer and breast cancer, the data broadly support the LNT model.

1.2.6 *Diseases Classified as Tissue Reactions*

Most of the available data on noncancer effects have large associated uncertainties and limitations that do not yet support a quantitative estimate of a specific threshold value for effects from either acute or protracted lens

exposures. However, the preponderance of evidence suggests the possibility that effects (such as lens opacities or cardiovascular disease) could occur at lower doses than previously thought.

There is growing epidemiologic evidence to suggest a raised risk of cardiovascular disease (CVD) at lower levels of exposure to radiation than previously thought, implying that poorly understood radiobiological mechanisms associated with low-to-moderate doses and/or low dose rates may produce an increased risk of CVD (Section 5.1). Studies of nuclear workers and other exposed groups provide a mixed picture as to CVD risk, and most of them lack information on important confounding factors associated with lifestyle and concurrent conditions (*e.g.*, diabetes, obesity). Therefore, the evidence is too weak and inconsistent to support a LNT model for CVD at this time.

Studies of cataracts in the atomic-bomb survivors and following Chernobyl exposures have revealed the development of minor lenticular opacities at doses lower than previously considered to be cataractogenic. Ophthalmologically detectable opacities are reported at doses of 0.5 to 2 Gy with large uncertainties below about 0.5 Gy. So, at this time, the NCRP recommends use of a threshold model for cataracts (NCRP, 2016).

1.3 Results of Study Evaluations

Support by studies for any model requires adequacy of the study components, which for epidemiologic studies can be classified broadly as adequacy of epidemiologic methods, dosimetry, and statistics. For each component of the major studies, this commentary has critiqued both the methods used and the adequacy of the results of those methods (Section 7). The Committee evaluated these components for 26 principal studies or groups of studies of cancer risk. As a minimal criterion of study adequacy, 18 of the studies had no component on which they were scored as weak. Thirteen of the studies were scored moderate to strong on all three components of evaluation.

The Committee also rated each study or group of studies on their strength of support for the LNT model, as shown in Table 1.1. Twenty-one studies (80 %) provided some support for the LNT model, including five studies (19 %) providing strong support and seven providing moderate support.. Five of the studies (19 %) provided essentially no or inconclusive support for the LNT model. A rating of moderate versus strong support for LNT sometimes hinged upon the size of the study or other limitation and not on indications of nonlinearity. most of the larger,

Table 1.1—*Ratings of the degree of support for the LNT model by the cancer studies reviewed.*

Study (or groups of studies) a	Support for LNT Model
Life Span Study (LSS), Japan atomic bomb (Grant *et al*., 2017)[b]	Strong
INWORKS (U.K., U.S., French combined cohorts) (Richardson *et al*., 2015)	Strong
Tuberculosis fluoroscopic examinations and breast cancer (Little and Boice, 2003)	Strong
Childhood atomic-bomb exposure (Preston *et al*., 2008)	Strong
Childhood thyroid cancer studies (Lubin *et al*., 2017)	Strong
Mayak nuclear facility (Sokolnikov *et al*., 2015)	Moderate
Techa River, nearby residents Davis *et al*., 2015)	Moderate
Chernobyl fallout, Ukraine and Belarus thyroid cancer (Brenner *et al*., 2011)	Moderate
Breast cancer studies, after childhood exposure (Eidemüller *et al*., 2015)	Moderate
In utero atomic-bomb exposure (Preston *et al*., 2008)	Moderate
In utero exposures, medical (Wakeford, 2008)	Moderate
Canadian worker study (Zablotska *et al*., 2013b)	Moderate
Japanese worker study (Akiba and Mizuno, 2012)	Weak to moderate
Chernobyl cleanup workers, Russia (Kashcheev *et al*., 2015)	Weak to moderate
U.S. radiologic technologists (Liu *et al*., 2014; Preston *et al*., 2016)	Weak-to-moderate
Mound facility (Boice *et al*., 2014)	Weak-to-moderate
Rocketdyne facility (Boice *et al*., 2011)	Weak-to-moderate
Medical x-ray workers, China (Sun *et al*., 2016)	Weak-to-moderate
Background radiation levels and childhood leukemia (Kendall *et al*., 2013)	Weak-to-moderate
Taiwan radiocontaminated buildings, residents (Hwang *et al*., 2008)	Weak-to-moderate[c]
Pediatric CT examinations (Pearce *et al*., 2012)	Weak-to-moderate[c]
Childhood leukemia studies (Wakeford and Little, 2003)	Weak-to-moderate
In utero exposures, Mayak and Techa (Akleyev *et al*., 2016)	Weak-to-moderate
Hanford ^{131}I fallout study (Davis *et al*., 2004)	None
Kerala, India, high natural background radiation area (Nair *et al*., 2009)	None
Yangjiang, China, high natural background radiation area (Tao *et al*., 2012)	Inconclusive[c]
U.S. atomic veterans (Beck *et al*., 2017)	Inconclusive
Fallout studies (aggregate of eight studies) (Lyon *et al*., 2006)	Inconclusive[c]

[a]A number of studies were excluded for various reasons described in the text, these include but are not limited to: ecological studies of residents around nuclear power plant facilities, studies of hereditary effects, studies of tissue reaction (or "deterministic") effects, and the 15-country study

[b]A representative recent publication is listed for each study or study group.

[c]Considered "weak" support or "inconclusive" primarily because of epidemiologic method or dosimetric weaknesses. The other studies in these categories were reasonable methodologically but provided little or no support for the LNT model because their risk coefficients were essentially zero or negative.

stronger studies broadly supported a LNT model. The studies that provided no support for the LNT model either had a totally null dose response or had excessively unreliable data. It should be noted that all the studies being considered, except for the Life Span Study of atomic-bomb survivors, had exposures at low dose rates or multiple small exposures. Furthermore, the preponderance of study subjects had cumulative doses under 100 mGy. Thus these studies are very relevant for contemporary radiation protection concerns.

1.4 Future Improvements

To stimulate radiation epidemiology efforts to address the LNT model and low- dose risks, the Committee suggested a number of profitable areas of focus for future research (report Section 8), and a few are mentioned here.

Atomic-Bomb Survivors: The low-dose data need to be examined in more detail, using additional covariables, statistical methods and analytic strategies, not only for solid cancer and leukemia, but also to evaluate specific cancers or cancer groups, cardiovascular diseases, and various clinical health endpoints. An examination is needed of whether the dose-response LNT model applies to tumors of various organs or organ systems, insofar as statistical limitations permit, which will provide evidence regarding the generality of the LNT model across tumor sites. The large bank of blood and tissue samples should be studied more robustly by the biomedical community to identify bioindicators of drivers of adverse outcome pathways that mediate between radiation and disease development.

Worker Studies: Much of the statistical power of these studies derives from those workers who have accumulated moderate doses of several hundred milligray over many years, most of whom started work in earlier years. Continuing follow-up of worker cohorts is desirable, as much of the cancer incidence and mortality is yet to occur. Doses in the early years tended to be highest but also had the greatest uncertainties because most dose recording technologies and dose record keeping practices were less advanced. Therefore, scrutiny of dose records is necessary to identify any deficiencies in recorded doses. Issues of neutron exposures, internal exposures and missing doses need to be addressed further. Valid risk estimates depend, inter alia, upon reliable dose estimates, so this area should be pursued vigorously.

Environmental Radiation Studies: All the environmental study groups should consider measures to reduce individual dose uncertainties. The Kerala and Yangjiang studies should increase efforts to improve cancer ascertainment and diagnosis, and to closely examine sociodemographic and geographic factors that may affect the

adequacy of cancer ascertainment. Further validation of reconstructed doses by personal dosimetry measurements would also be valuable. The Techa River studies should continue to improve dosimetry, enhance their follow-up and outcome ascertainment and further address the medical exposures received.

Other Future Directions: Uncertainties should be provided with the dose estimates and used to adjust risk coefficients and confidence intervals (Stram *et al*., 2015; UNSCEAR, 2015). For radiation-induced adverse health outcomes, a clear need is to identify bioindicators that define the pathway from normal to malignant cells that can be used for developing biologically based dose-response models. Analyzing epidemiologic data in conjunction with relevant radiobiological concepts and data has the potential to provide insights about low-dose risk that augment knowledge gained from the empirical epidemiologic data in isolation (NCRP, 2015).

1.5 Summary

Quantitative solid cancer risk estimates, based on estimated individual doses, of cancer mortality or incidence have been reported for nearly one million individuals with low dose rates and mostly low doses from studies of radiation workers or those exposed to elevated environmental radiation levels (Shore *et al*., 2017). The completion of the million person study will considerably augment the available information (Boice, 2012a). The more robust studies have many strengths, with relatively good quality dosimetry, high rates of cohort mortality/morbidity ascertainment, attention to potential confounding variables, and proper analysis. Nevertheless, it is recognized that all studies have limitations, ranging from minor to serious, in their contribution to the quantitative evaluation of the LNT model. The individual low- dose studies intrinsically have limited statistical power and precision in risk estimation. These studies complement the LSS study of atomic-bomb survivors with its high dose rate and high dose range.

Strengths of some of the large epidemiologic studies such as INWORKS and the LSS lie in the long follow-up and large numbers of cancers and person-years at risk. The length of follow-up of epidemiologic studies is particularly relevant since a large fraction of both spontaneous and radiation-related cancers occur at 60 y of age and beyond. Although an historic weakness of many worker and environmental radiation studies was inadequate dosimetry, in recent years investigators have been focusing more on improving the quality and accuracy of the dosimetry. However, most studies considered in this report did not consider the effects of shared vs unshared uncertainty and classical as opposed to Berkson error (UNSCEAR, 2015), and then adjust for the effects of dose uncertainty on the risk estimates. Nearly all studies have adjusted for potential confounding by sex, attained age and sometimes age at exposure. However, few studies have analyzed radiation risks with control for possible confounding by lifestyle (*e.g*., smoking), other disease risk factors or other sources of radiation exposure; these

factors may diminish the consistency of findings. Nevertheless, it should be emphasized that lifestyle or other disease risk factors will cause confounding only if their frequency (or intensity) varies appreciably according to dose. The most prominent lifestyle risk factor is smoking. Adjustment for socioeconomic status is used in several studies as an indirect approach for controlling for smoking and other lifestyle factors. Indirect approaches to examine the impact of smoking in several major studies have not found that smoking introduced substantial bias (Akiba, 2013; Davis *et al*., 2015; Hunter *et al*., 2013; Richardson *et al*., 2015). For a few studies, concomitant medical radiation exposures have been examined; for the Techa River study diagnostic medical exposures at the official clinic were included in the doses (Schonfeld *et al*., 2013). Other factors, such as losses to follow-up or incomplete disease ascertainment, would cause bias in the risk estimates only if they occur differentially according to dose levels. Few studies currently have biological samples to evaluate genetic or phenotypic biological factors that might cause effect modification of radiation risks.

Because individual studies with low doses (less than 100 mGy) almost inevitably have relatively low statistical power, the findings for radiation and solid cancer are often not statistically significant. Furthermore, studies may have sampling variation or confounding by other exposures (*e.g*., smoking or other lifestyle factors) which can diminish the consistency or validity of findings. Nevertheless, most large and high quality low- dose studies show positive risk coefficients (Shore *et al*., 2017), suggesting there may be cancer effects at low doses, which is consistent with, though not necessarily proving, the applicability of the LNT model for radiation protection. However, it should be recognized that, the risk of cancer at low doses is small.

The data regarding noncancer effects at low doses—cardiovascular diseases, cataracts, thyroid dysfunction, central nervous system effects—are mixed or null, suggesting at this time that an LNT assumption for radiation protection purposes for noncancer effects is not appropriate.

1.6 Overall Conclusions on the Use of the LNT Model

While the ongoing development of science requires a constant reassessment of prior and emerging evidence to assure that the approach to radiation protection is optimal, though not necessarily perfect, NCRP concludes that, based on current epidemiologic data, the LNT model (perhaps modified by a DDREF) should continue to be utilized for radiation protection purposes. This is in accord with judgment by other national and international scientific committees, based on somewhat older data than in the present report (ICRP, 2007; NA/NRC, 2006; UNSCEAR, 2008), that no alternative dose-response relationship appears more pragmatic or prudent for radiation protection purposes than the LNT model.

2. Introduction

2.1 Background

For over 40 y the linear nonthreshold (LNT) dose-response model has been used to develop practical and prudent guidance on ways to protect workers and the general public from the potential harmful effects of radiation while, at the same time, balancing the beneficial, justified, and optimized uses of radiation in our society. Indeed, in developing its basic radiation protection recommendations, as currently given in NCRP Report No. 116 (NCRP, 1993a), the Council reiterated its acceptance of the LNT for the dose-risk relationship. Specifically, "based on the hypothesis that genetic effects and some cancers may result from damage to a single cell, the Council assumes that, for radiation-protection purposes, the risk of stochastic effects is proportional to dose without threshold, throughout the range of dose and dose rates of importance in routine radiation protection. Furthermore, the probability of response (risk) is assumed, for radiation protection purposes, to increase linearly with dose. At higher doses, received acutely, such as in accidents, more complex (nonlinear) dose/risk relationships may apply" (NCRP, 1993a).

NCRP later reassessed the weight of scientific evidence for and against the LNT model without reference to associated policy implications in Report No. 136 (NCRP, 2001). As in previous reviews by the NCRP (1980; 1993c; 1997) the Council concluded that there was no conclusive evidence on which to reject the assumption of a LNT dose-response relationship for many of the risks attributable to low-level ionizing radiation (although it was acknowledged that additional data were needed) (NCRP, 1993b). The NCRP then noted that while many, but not all, scientific data support this assumption (NCRP, 1995), the probability of effects at very low doses such as are received from ubiquitous low-LET background radiation (NCRP, 1987; 2015) is so small that it may never be possible to prove or disprove the validity of the LNT assumption at those dose levels.

The International Commission on Radiological Protection (ICRP) published a science evaluation report, Publication 99 (ICRP, 2005b), on low-dose extrapolation of radiation-related cancer risks and issued updated radiation protection recommendations based on the conclusion that "while existence of a low dose threshold does not seem unlikely for radiation- related cancers of certain tissues, and cannot be ruled out for all cancers as a group, the evidence as a whole does not favor the existence of a universal threshold, and there seems to be no particular reason to factor the possibility of a threshold into risk calculations for purposes of radiation protection (ICRP, 2007)." ICRP concluded that a LNT theory, combined with an uncertain DDREF for extrapolation of risk from high doses received acutely remains a prudent basis for radiation protection at low doses and low dose rates (ICRP, 2005b).

The United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) evaluates the evidence of radiation-induced health effects from studies of the health of survivors of the atomic bombings of Japan and of other exposed groups. It also reviews advances in understanding of the mechanisms by which radiation-induced health effects can occur. These assessments provide the scientific foundation used by the International Commission on Radiological Protection (ICRP) and other protection organizations in developing their recommendations on radiation protection. UNSCEAR has concluded that the simplest representation of tumorigenic response is a linear relationship, which is consistent with much of the available mechanistic and quantitative data and strongly supports the scientific rationale for the LNT model as used in radiation protection (UNSCEAR, 2000; 2006). A departure from linearity was noted for leukemia data, for which a linear-quadratic function was used. It was noted that linear or linear-quadratic functions are used for representational purposes only in evaluating possible radiation risks and that the actual response may involve multiple and competing processes that cannot be separately distinguished.

Based on the available epidemiologic data, UNSCEAR derived risk estimates and noted, as a first approximation, linear extrapolation of the estimates at 1 Sv could be used for estimating solid cancer risks at lower doses. The rationale was re-evaluated in the UNSCEAR 2006 Report, Effects of Ionizing Radiation Vol. 1 (UNSCEAR, 2008), that included several new cancer sites and used Bayesian methods for the incorporation of dose uncertainty in the atomic-bomb survivor cohort risk, and concluded that "the data reviewed for its 2006 report do not necessitate changes in its current risk estimates for cancer and the hereditary effects of radiation." However, this conclusion was based primarily on the LSS dose-response data following a high dose rate brief exposure and not on an evaluation of cancer excesses after exposure at low dose rates.

The National Academies (NA) published the Biological Effects of Ionizing Radiation (BEIR) VII report (NA/NRC, 2006) that concluded that the available biological and biophysical data support a LNT risk model, whereby the risk of cancer proceeds in a linear fashion at lower doses without a threshold. The U.S. Environmental Protection Agency (EPA) in evaluating radiogenic risk models (EPA, 2011) noted that in general, results from epidemiologic and radiobiologic research are consistent with an LNT dose-response model in which the risk of inducing a cancer in an irradiated tissue by low doses of radiation is proportional to the dose to that tissue, while acknowledging that new research might conceivably lead to revisions in the future. In contrast, a report from the French Academy of Sciences (Tubiana *et al*., 2005) that focused primarily on radiobiology raised doubts about the validity of using the LNT model for evaluating carcinogenic risks at low doses and suggested that since biological mechanisms and responses appear different at low doses and high doses, an empirical relationship of linearity validated at only doses >150 mSv may lead to an overestimation of risks at low doses.

Box (1979) concluded that "all models are wrong but some are useful". The LNT model is an assumption that has not been and likely cannot be scientifically validated in the low-dose range. Other dose-response relationships for the mutagenic and carcinogenic or detrimental effects of low-level radiation cannot be excluded, and there are notable exceptions to the LNT relationship seen in experimental and epidemiologic studies (Boice, 2015c; Dauer *et al*., 2010). Nonetheless, on the basis of the scientific knowledge to date the current judgment by national and international scientific committees is that no alternative dose-response relationship currently appears more pragmatic or prudent for radiation protection purposes than the LNT model.

2.2 LNT and the Estimation of Cancer Risk

As part of the process for developing nominal dose limits for radiation protection purposes, it is the current practice of ICRP, for example, to calculate total health detriment values for exposure to low doses and low dose rates of radiation (ICRP, 2007). Detriment values are based largely on the risk estimates for fatal cancers, nonfatal cancers and heritable effects (so-called stochastic effects) and also factors such as quality of life and adjustment for DDREF. Until recently, little consideration has been placed on noncancer effects (harmful tissue reactions, previously called deterministic effects) for the calculation of nominal risk, largely because it has been assumed that noncancer effects have quite large threshold responses and that cancer is dominant at low doses and low dose rates. This assumption is being reassessed, most specifically for cataracts and cardiovascular diseases (ICRP, 2012; NCRP, 2007). How to use this information, if indeed it is to be used, for noncancer responses in a detriment calculation remains a matter of scientific debate and clearly requires additional human data on radiation-induced adverse health outcomes.

The process of estimating risks for adverse health outcomes (cancer and noncancer) has relied almost exclusively on the available human epidemiology data from exposed populations, in particular the survivors of the atomic bombs in Japan, but with additional support from other exposed populations, including those exposed occupationally, environmentally, or from medical diagnostic and treatment procedures. Rather little use of the extensive radiobiology data has been made in the risk assessment process, with the exception of calculations of the DDREF and radiation weighting factors.

The general approach used by ICRP, EPA, NA/NRC (2006) and NCRP for cancer risk estimation used for protection purposes has been to develop a dose-response curve for all solid cancers assessed in the LSS following acute exposures that are highly influenced by the mid to high dose ranges and to extrapolate from this range to estimate cancer frequencies at low doses assuming no threshold, a LNT extrapolation. A DDREF is

applied to the slope of the linear extrapolation to estimate the cancer risk at low dose rates and often also for low doses. It is important to note that the use of an LNT extrapolation model is really a default approach because of a lack of definitive evidence to the contrary (Preston, 2003). Considerations of nonlinear extrapolations for solid cancer risk from high-to-moderate doses are continually being investigated and received some support from the recent studies on solid cancer incidence and mortality for the LSS (Grant *et al*., 2017; Ozasa *et al*., 2012).

A number of uncertainties are associated with the current approach to apply the scientific evidence for radiation protection, especially for DDREF and also with the model chosen for extrapolation (LNT) (NCRP, 2012). It is difficult to conduct epidemiology studies that will allow for direct measurement of adverse health outcomes at low doses and dose rates, although the ongoing Million Person Study (Boice, 2012a; 2017) can enhance the assessment at low doses and low dose rates. The way forward is most likely to include an integration of epidemiology and radiobiology data (NCRP, 2015).

2.3 Objective and Scope

This Commentary is to provide a review of recent data from new epidemiologic studies and data of populations exposed to radiation at low dose rates and to review the new data from the Life Span Study of atomic-bomb survivors. The purpose is to determine whether these epidemiologic studies broadly support the LNT model of carcinogenic risk as used in radiation protection or, on the contrary, whether there is sufficient evidence that the LNT model is inappropriate? The strength of support for the LNT model is evaluated for solid cancer incidence or mortality and secondarily for low dose-rate studies of leukemia. The focus is on new human studies on low doses and low dose rates. In addition, the report will briefly review current evidence regarding certain noncancer outcomes, such as cardiovascular diseases, and risk from childhood exposure and heritable radiation risk.

This Commentary was written by a committee of multi-disciplinary experts based on a comprehensive review of recent (within approximately 10 y) relevant epidemiologic studies, especially those that have been extensively studied, with attention paid to epidemiologic methodology, dosimetry and statistical approaches. The Committee performed a critical but balanced evaluation of these epidemiologic studies, including a description of their strengths and limitations, similar to the approach utilized in recent related reviews by UNSCEAR (2008; 2013). The present evaluation includes a detailed assessment of the dosimetric and statistical approaches employed for the epidemiologic study. The aim was to develop a perspective for each study and evaluate its strength with regard to radiation protection implications. Future directions and ongoing research needs were identified.

3. Important Considerations

3.1 Epidemiologic Considerations

Epidemiologic studies of humans provide evidence that is critically important in establishing disease causation. Epidemiology is by nature primarily observational rather than experimental. Consequently, in virtually all epidemiologic studies there is always the possibility that biases or confounding factors of various sorts may give rise to spurious results. A well-designed study should attempt to minimize any potential biases and avoid or control for the effects of confounding factors.

Bias in a study can produce results or conclusions that differ systematically from the truth (Sackett, 1979). Therefore, high-quality studies will recognize and address various types of bias, including: selection and participation bias, dose-estimation bias, follow-up bias, disease ascertainment bias, recall bias, and others. Because a risk factor correlates with a disease (*e.g.*, smoking and lung cancer) does not necessarily mean it confounds the radiation association with that disease. It can confound the radiation-disease association only insofar as the risk factor is also correlated with the amount of radiation exposure. A few examples of mild (Cardis *et al.*, 2007) or even serious (Akiba and Mizuno, 2012) confounding by smoking or alcohol consumption have been seen in worker cohorts, but a few worker and environmental-exposure studies have found little evidence of such confounding (*e.g.*, the LSS, INWORKS, Mayak and Techa River studies) but individual data on specific confounding factors was often missing or only partially available and indirect ways to evaluate confounding were considered.. Confounding by indication or "reverse causation" has been seen in medical exposure studies (Berrington de Gonzalez *et al.*, 2016; Boice *et al.*, 2015b; Journy *et al.*, 2015; UNSCEAR, 2013). In high-quality studies, confounding factors can usually be addressed at the analysis stage if information on the factors is available, either through regression procedures or stratification of the data according to the levels of the confounding factor (UNSCEAR, 2008), but the confounding factor data must be available for individuals. Confounding also can be indirectly assessed by examining whether target organs of the risk factors (*e.g.*, lung for smoking, liver for alcohol or hepatitis infection) show aberrantly high or low associations with radiation dose levels.

To convincingly establish causality, a number of criteria are relevant. However, it is not necessary to show that all the criteria are met to the same extent to be able to make a causal inference about disease risk. While exposure must, of course, precede outcome, another one of the most important criteria of causation is that there be a quantitative relationship between the factor of interest and the disease. The most convincing evidence is quantitative in nature, where the quantification is based on individuals' exposure levels and health outcomes. In the case of ionizing radiation, personal data on exposure level and subsequent occurrence of

disease are needed to quantify the association. This is commonly referred to as a "dose response." Almost as important as the existence of a dose gradient, it is very important that similar studies conducted by others around the world come up with similar results, *i.e.*, that there is consistency among multiple studies (UNSCEAR, 2008). That is, if one study shows a dose response but most other studies do not, then causal interpretations are tempered. In the current evaluation of the LNT model, final conclusions will be based on consistency of results in the nearly 20 epidemiologic studies evaluated and not on a single or very few investigations.

In the context of radiation protection, comparable strength of the dose-response data across the spectrum of exposure, from the highest to the lowest would be ideal. Unfortunately, the data from epidemiologic studies do not provide a clear picture of the shape or magnitude of the dose response at all levels of exposure. Of particular interest is a better characterization of the dose response at low doses (100 mGy and below) and low dose rates because it is that part of the dose response curve where most human exposures to ionizing radiation occur today and are likely to remain so in the future, barring a major accident, terrorist event, intentional nuclear weapon detonation or natural disaster. Estimating risk in this dose range has not been possible with much certainty. A brief review of the primary epidemiologic research study designs illustrates some of the important strengths and limitations of epidemiologic methods.

There are three basic study designs that have been employed in radiation epidemiology are:

- cohort studies;
- case-control studies; and
- descriptive and/or ecologic studies.

Epidemiological investigations that quantify radiation effects are usually cohort studies and, to a much lesser extent, case-control studies. In a cohort study, a defined population (preferably with a wide range of exposures) is followed forward in time to examine the occurrence of effects. Such a study may be performed either prospectively (*i.e.*, by following a current cohort into the future) or retrospectively (*i.e.*, by constructing a cohort of persons alive at some time in the past and following it forward, possibly to the current time) (UNSCEAR, 2000). Examples of informative cohort studies include the LLS study of Japanese atomic-bomb survivors (Ozasa *et al*., 2012), the INWORKS study (Richardson *et al*., 2015), and the Massachusetts tuberculosis study of patient monitored repeatedly with x-ray fluoroscopic examinations of the chest (Boice and Monson, 1977).

In case-control studies, people with and without a specified disease (the cases and controls, respectively) are compared and differences in exposures are examined (UNSCEAR, 2000). Some case-control studies are nested within a cohort study, in that the cases and controls are selected from the cohort. The nested case-control study design is used when it is difficult to obtain estimates of radiation dose or other exposures for all members of a cohort, but possible to collect them for a smaller number of individuals (*e.g.*, Cardis *et al*., 2005; Kendall *et al*., 2013; Krille *et al*., 2015; Schubauer-Berigan *et al*., 2015; Zablotska *et al*., 2013a). Of the approximately 25 studies providing some quantitative information on radiation risk and thus relevant to LNT evaluation, there were only two referring to case-control studies which suggests a rather limited influence of this design in evaluating the LNT hypothesis for use in radiation protection.

The cohort design is less susceptible to biases than the case-control study design and has a number of important advantages over other observational designs:

- exposure is characterized without knowledge of disease status;
- disease free status is firmly established in a uniform way at the beginning of follow- up for the entire cohort;
- all cases of the disease under study are identified (with complete follow-up) incident cases and/or deaths;
- incidence/death rates can be calculated directly from the study and can be compared to assess risk across dose categories; and
- multiple outcomes can be evaluated in a single study.

A third type of observational epidemiologic study is often referred to as an ecologic study. These geographical (or temporal) correlation studies are those in which disease rates based on data aggregated over geographical areas (or time periods) are compared with aggregated data on levels of exposure. In such studies, groups rather than individuals are the unit of analysis and the correlation between disease rates and the groups' average levels of exposure is studied, with an intention to infer disease risk for individuals. These studies sometimes provide a good overview of the distribution of the disease of interest according to person (*e.g.*, age, sex and race), place and time. However, since the analyses are not based on individual-level data and are generally not able to control for possible confounding factors or effect modifiers. Such studies can be useful in generating hypotheses, but not in testing hypotheses. Because the exposure is not at the individual level, ecological studies cannot provide meaningful data regarding a dose response, and cannot be used to infer disease risk, and cannot be used to evaluate the LNT model.

In short, "When analyzing aggregated [ecological] data, we not only lose all ability to extend inferences reliably to less aggregated data but we even lose the ability to estimate the direction and magnitude of bias. We cannot rely on the addition of more grouped data to eliminate the bias" (Piantadosi, 1994). In general, "The investigator is never justified in interpreting the results of ecological analyses in terms of the individuals who give rise to the data" (Piantadosi *et al*., 1988). Studies of this type therefore are not useful in determining the shape of the radiation dose response in humans (Brenner *et al*., 1992; Greenland and Robins, 1994), and cannot substantiate or challenge the LNT model.

In addition, other types of epidemiologic studies include the randomized clinical trial (RCT), cross-sectional studies, case-cohort studies and variations of the case-control study using counter matching. An RCT, if the randomization is conducted properly, should not be subject to any biases (it is essentially a human experiment), and is generally regarded as the epidemiologic "gold standard." There are few RCTs relevant to dose-response modelling, except perhaps the high-dose studies of breast cancer treatment and resulting deaths due to cardiovascular disease.

When assessing exposure-disease associations, cross-sectional studies (also called prevalence studies) are similar to ecological studies in providing limit if any evidence on the possible shapes of dose-response relationships, and are considered to be hypothesis-generating or exploratory. Cross-sectional studies measure exposure and health outcome simultaneously. They tend to assess the presence (prevalence) of the health outcome of interest at a single point of time without regard to duration. However, these should be distinguished from cross-sectional assessments of health outcomes of individuals who had previous quantified radiation exposures. Such studies can provide legitimate estimates of radiation risk (*e.g*., Imaizumi *et al*., 2006; 2015), albeit with potential qualifications regarding follow-up bias.

3.2 Dosimetry Considerations

A major objective of this Commentary was to provide detailed reviews of the dosimetry underpinning each epidemiologic study to gain a better understanding of the study's strengths and weaknesses. Analysis of the dosimetry helped evaluate the robustness of each epidemiologic study in supporting the shape of the dose response curve at low doses and low dose rates. High quality dosimetry is essential in evaluating any dose response from radiation exposure especially at low doses (<100 mGy). because small numbers of excess cancers lead to uncertainty in the estimation of risk (*e.g*., ERR Gy^{-1}). Furthermore, it is now well established that shared dose uncertainty (*e.g*., uncertainty in a source term) can result in further underestimating the uncertainty bounds in

ERR Gy^{-1}, in addition to Berkson or random uncertainties (Kwon *et al*., 2016; Land *et al*., 2015; Stram *et al*., 2015). Further, unshared classical error (*i.e*., random individual dosimetry error), if present, can bias the dose response toward the null (Stram *et al*., 2015; UNSCEAR, 2014). However, adjustment for shared, Berkson and random measurement uncertainties is unlikely to change a significant dose response to a non-significant response, *i.e*., if the confidence bound for a risk estimate does not include the null value, the uncertainty-adjusted bound usually will not include the null value either (Stram *et al*., 2015).

There does not seem to be a reasonable case that the positive dose-response associations that are consistent with a LNT model are due to dosimetry inaccuracies, especially for studies with measured doses. If one can assume that estimated individual doses in the various studies were well correlated with the true doses, and that the estimated doses were not based on individuals' disease status (which was generally true, except possibly for the CT studies), then dose errors would be unlikely to induce an apparent dose response where one does not exist. If anything, random ('classical') dose error will tend to diminish rather than heighten the slope of the dose-response model, while unbiased shared error will have little effect on the statistical significance. On the other hand, if individual doses were imputed based on a dose reconstructions from limited information, there may be unknown biases in the shared-dose estimates, but dosimetrists involved in the major studies have devoted much effort to providing reasonably accurate estimates of shared doses.

Aspects of the dosimetry review have been reported by Till *et al*. (2017). It was carried out by a team working independently of the epidemiologic team and used evaluation criteria specifically focused on dose measurements and dose reconstructions. The criteria were divided into several categories:

- general study characteristics;
- dose assignment;
- uncertainty;
- dose confounders;
- dose validation; and
- overall strengths and weaknesses of the dosimetry.

A template created for each study addressed these criteria and subcategories within them. The templates were used in the dosimetry review which became an integral part of the evaluation of the reported dose response relationships. A matrix summarizing the dosimetry characteristics of each epidemiologic study facilitated evaluations and comparisons of dosimetry quality. A summary of the dosimetry is included in the review of each

epidemiologic study in Section 4. In general, the most likely impacts of dose uncertainty are to reduce the statistical power of a study and (particularly in the case of unshared errors) to bias risk estimates toward the null. It is important, therefore, for studies to appropriately address and provide effective allowance for the effects of uncertainty in dose estimates; this may require more than a simple measure of the uncertainty of individual dose estimates themselves (Beck *et al*., 2017; Bouville *et al*., 2015; NCRP, in press; Stram *et al*., 2015; Till *et al*., 2014; 2017). Additional comments on the importance of dosimetry in epidemiologic studies as well as recommendations for future considerations in planning and implementing studies ERR Gy^{-1} are provided in the conclusions.

3.3 Statistical Considerations

Design and analysis features are relevant when assessing the evidence for and against the LNT model hypothesis from statistical details given in published studies. The type of study design (*e.g*., cohort and case control) and the statistical analysis method applied (*e.g*., Poisson regression with grouped data or Cox regression with individual data) are important features to consider. Such methods are often regarded to be the least open to bias.

The statistical precision of a study is a key determinant of the study's contribution toward evaluating the shape and slope of the dose response risk for detrimental health outcome. The precision is related to the statistical power of the study, and both depend on study features such as: the number of persons at risk and their years of observation (person-years at risk), the number of exposed and unexposed or minimally exposed cases with the health outcome of interest, the length of epidemiologic follow-up time, dose range and dose distribution within cohort members, the magnitude of the radiation effect, the availability of information on possibly explanatory covariables (that is, confounding factors). A consideration of estimated influences of any unavailable potentially explanatory covariables that might induce bias should be included. It is important to examine the choices made for the mathematical forms applied for the radiation dose effect, the modification of the radiation effect by other variables (*e.g*., sex; time), and adequacy of modeling of the baseline rates of the outcome of interest. To assess the main dose-response model, functional forms such as linear, quadratic, linear-quadratic, nonparametric , categorical (the risk in each category of a set of predefined dose categories), and dose threshold ideally should be examined. Similarly, appropriate modeling of other sources of radiation exposure should be considered. For example, in assessing radiation related cancer risk per unit occupational gamma organ dose, adjustments may be needed to account for other types of radiation exposure, such as alpha particles or neutrons, or for other sources of external exposure, such as medical x-ray organ doses. Some investigators to not adjust but include the organ dose from other known exposures, *e.g*., the LSS of atomic-bomb survivors incorporates the small neutron dose into the measure of "weighted Gy" organ dose to colon used for analyses. Interpretation, however, becomes difficult if the

organ dose from other exposures exceeds the gamma ray dose. Analyses excluding the organs with substantial dose from other occupational exposures, *e.g.*, internal intakes of alpha particle emitting radionuclides, are also conducted.

In the baseline model it is usually appropriate to adjust for sex, age at exposure, attained age and sometimes calendar period or birth cohort to avoid confounding, as well as to explore whether those variables may be effect modifiers of the radiation dose response. When information on smoking, alcohol-intake or other lifestyle or sociodemographic factors is available, it is important to examine whether it may be a confounder and/or an effect modifier; often a measure of socioeconomic status is used in the analysis as an adjustment factor to reflect lifestyle variables, especially for the lung and other smoking-related sites.. Sometimes it may be appropriate to adjust for factors such as duration of employment in worker studies, and medical risk factors (*e.g.*, obesity or diabetes) for some types of outcomes such as cardiovascular disease.

An important activity in assessing the evidence for and against the LNT model is to look for consistency of patterns in risks between a simple parametric model and a nonparametric model (*e.g.*, Pierce *et al*., 2000) or dose-category specific risk model. The degree of consistency can either be assessed qualitatively or by applying statistical methods to provide quantitative evaluations. However, the limited statistical power of a particular study may restrict the number of parameters that can provide useful estimates, with informative confidence intervals, in both parametric and nonparametric types of models. Consequently it may be important to consider nonlinear one-parameter dose-response models, such as one purely quadratic in dose, when there is not enough statistical power to support a linear parameter and a nonlinear parameter in the same model. Epidemiologic studies are prone to many potential sources of bias and the results may be influenced by one or several of the many different possible types of bias, so thorough consideration of all sources of bias is also critically important in assessing evidence for and against the LNT model hypothesis.

The studies reviewed in Section 4 have mostly used Poisson regression analyses and have adjusted for sex, age at exposure and attained ages at risk. Cox proportional hazards analyses are also used for estimating risk, *e.g.*, ERR Gy^{-1}. Different statistical methods or notable changes in adjustment variables will be mentioned in the discussion of the individual studies when relevant.

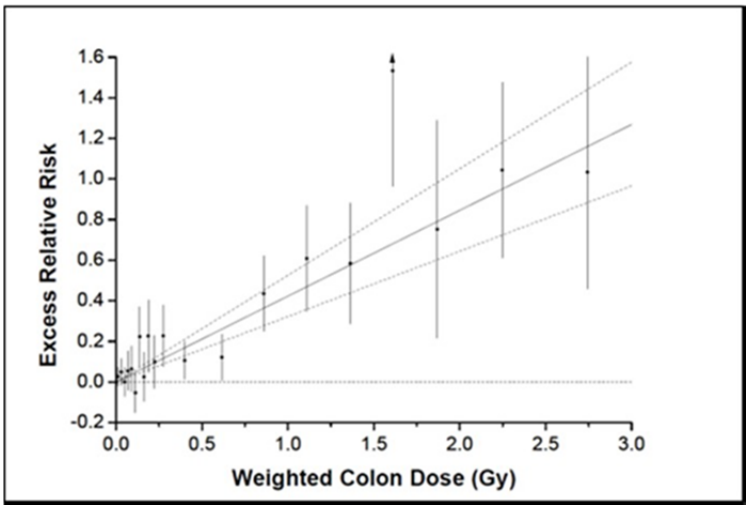
3.4 Dose-Response Considerations

3.4.1 *Dose Response and Solid Cancers: Cancer Type and Sensitivity*

As an example to demonstrate dose-response considerations, we use the dose response for all solid cancers combined as obtained from the Life Span Study (LSS) data for mortality during 1950 to 2003 among the cohort of Japanese atomic-bomb survivors is shown in Figure 3.1. The proportionality of ERR of all solid cancers to the weighted absorbed colon dose (which includes a small neutron component) received during the bombings is apparent from the figure, although this is most evident for moderate and high doses (>0.1 Gy), and the nature of the dose response for low doses (<0.1 Gy) is not clear.

However, it must be borne in mind that by considering all solid cancers combined, any individual structure that may be present in the dose responses of the component solid cancer types may have been lost. This may be appreciated from Figure 3.2 showing the dose-averaged ERR for individual sites of solid cancer. While there is clear evidence of excess risks for certain cancer types, such as bladder , breast, colon and stomach,, this is not the case for certain cancer types such as uterus, pancreas, testes, prostate, renal cell, rectum, bone and soft tissues, in part due to the relatively small numbers affected. Data on non-melanoma skin cancer incidence indicate substantial curvilinearity, consistent with a possible dose threshold of about 1 Sv to the skin (Little and Charles, 1997; UNSCEAR, 2000). Under these circumstances, whether it is valid to assume that each site of solid cancer may be adequately represented by the dose response for all solid cancers combined needs careful consideration, and at the minimum, different slopes may pertain for different sites of solid cancer, (Preston *et al.,* 2007), though there is some ambiguity in interpreting variations in slope because of statistical considerations (Pawel *et al*., 2008). Indeed, one could not safely assume, on the basis of these LSS data, that radiation can cause certain solid cancers (for example, cancer of the gallbladder in addition to those mentioned above). There is also heterogeneity in the risk estimates for different histological types of some cancers, *e.g*., the radiation risks for non-melanoma skin cancer a strong association is seen for basal cell carcinoma but there is little evidence of an association for squamous cell carcinoma (Preston *et al*., 2007). Although for the purposes of radiation protection it has been considered prudent to adopt a linear dose response without a threshold dose for all solid cancers combined, this dose response may be driven by those cancer sites having a relatively high incidence and comparatively pronounced linear dose responses (such as breast cancer and thyroid cancer).

939



940
941
942

943 **Fig. 3.1.** Dose response of all solid cancer mortality among the LSS, 1950 to 2003. The solid line is the fitted
944 linear, sex-averaged ERR dose response, and the dashed lines are its 95 % confidence range. The points are
945 categorical estimates of the ERR in dose categories and the bars are their 95 % confidence intervals. The
946 categorical estimates indicate a larger uncertainty in the risk estimate at low dose levels than that reflected in the
947 linear fit because the confidence range of the linear fit is determined mostly by the association at higher dose levels
948 (Kamiya *et al.*, 2015).

949

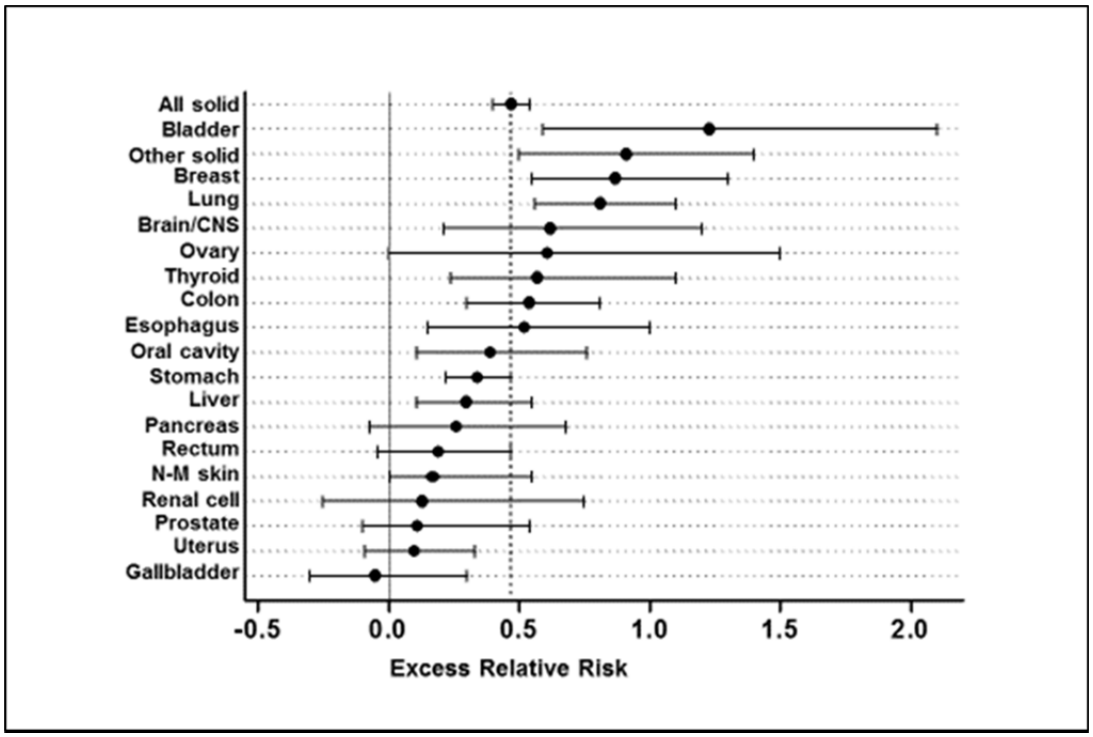


Fig. 3.2. ERR Gy^{-1} for the incidence of site-specific solid cancers in the LSS cohort. The risk is standardized as exposure at 30 y of age and estimated sex-averaged risk at age 70 y. The horizontal bars indicate 90 % confidence intervals (Kamiya *et al*., 2015; Preston *et al.*, 2007).

3.4.2 *Dose Response and Leukemia*

That the dose response may vary among different cancer types is illustrated by the difference between the dose response for all leukemias and that for all solid cancers. The dose response for leukemia is linear-quadratic in form whereas for solid cancers combined it is closer to linear, and the slope of the linear (low dose) segment of the leukemia dose response is steeper than the slope of the solid cancer dose response. Further, the dose responses for the main types of leukemia appear to differ, with acute myeloid leukemia exhibiting upward curvature while acute lymphoid leukemia and chronic myeloid leukemia show a linear dose response (Hsu *et al*., 2013),with CLL having a low sensitivity to radiation induction (and technically speaking, CLL is actually a type of low-grade non-Hodgkin lymphoma).[1] This heterogeneity seen for leukemia may well extend to the various sites of solid cancer, and this possibility must be kept under consideration when assessing the nature of the dose response for solid cancer.

3.4.3 *DDREF Considerations*

Cancer risk estimates obtained in the LSS for survivors of the atomic bombs are based on acute exposures, driven by the medium-to-high exposure levels. To predict effects at low doses and low dose rates, an extrapolation model (LNT) is used together with a DDREF that adjusts the slope of the linear curve for solid cancer. The value of this DDREF commonly used for radiation protection purposes ranges from about 1.5 (*e.g*., NA/NRC, 2006) to 2 (*e.g*., ICRP, 2007), although a value of one also has been proposed by the German Commission on Radiological Protection (SSK, 2014). The approaches for obtaining these values differ in a number of ways as do the data sets selected for use for the calculation. The data used are, broadly, cancer data from the LSS and studies with low dose rates, animal cancer data and cell and molecular radiobiology data. There is a high degree of uncertainty with the approaches used in all cases (NCRP, 2012).

[1] See https://www.lymphomas.org.uk/about-lymphoma/types/non-hodgkin-lymphoma/chronic-lymphocytic-leukaemia-cll

4. Review of Epidemiologic Studies of Cancer and Genetic Effects from Low-Dose or Low Dose-Rate Irradiation

The primary question to be addressed is whether the new epidemiologic evidence sufficiently supports a LNT model as a reasonable basis for radiation protection. This section provides brief reviews of a number of the epidemiologic studies that contribute to an evaluation of quantitative information regarding the LNT model. Because such evaluations are quantitative of necessity, most studies that rely on standardized mortality ratios (SMRs) or on other simple group comparisons were not included, as they typically do not have quantitative information regarding individual exposure levels, and SMRs of worker populations in particular have inherent biases due to "healthy worker" selection effects that can be addressed, but interpretation of results uncertain.

This review considers recent studies on occupational and environmental and a few medical radiation exposures, although most medical exposures are typically limited to select organs. Brief summaries are provided for *in utero* and childhood exposures (including pediatric CT examinations) and for heritable genetic outcomes.

As an overview of a number of the important studies described in this Commentary, four summary tables are given. The first table provides a description of the study designs, characteristics of the study populations and underlying epidemiologic databases (Table 4.1). Table 4.2 provides a summary of the types of exposures received, the dosimetry and the mean and range of doses for individual studies. Table 4.3 provides information about the statistical methods and the epidemiologic and statistical results of each study. Table 4.4 gives a summary of the strengths and weaknesses of each study as they pertain to the evaluation of the LNT model.

In Section 4 a critical review is given for each major study. The epidemiologic evaluation includes a characterization of the study design and study population, quality of the data available, data collection methodology, the degree to which potential confounding variables or biases were assessed, and the quantitative results. The critique includes an assessment of the comprehensiveness, quality and uncertainties in the dosimetry used in each study, whether the analytic methods were appropriate and whether each study considered statistical alternatives to a linear dose-response trend.. A brief statement characterizes the contribution the study makes on providing information relevant to the LNT model and to radiation protection For selected studies, a more detailed assessment of the dosimetry and the statistical and epidemiologic methodologies is hoped to be provided as subsequent publications in the literature, as was the case recently for dosimetry (Till *et al*., 2017).

The more robust studies have a number of strengths, with relatively good quality dosimetry, good cohort mortality/morbidity ascertainment, attention to potential confounding variables, and proper analysis. Nevertheless,

Table 4.1—*Study population characteristics*.

Study (Reference) [section of text]	Study Design Mortality/Incidence Country	Study population characteristics (N, PY, % female)	Mean Age at First Exposure or Study Entry (y)	Dates Follow-up (mean years of follow-up)	Information on Follow-up (F-U) and Cancer Ascertainment
1. Japanese atomic-bomb survivors (Grant *et al.*, 2017; Hsu et al., 2013; Ozasa *et al.*, 2012; Preston *et al.*, 2007) [Section 4.1]	Cohort, Mortality and cancer incidence; Japan	N = 93,741 PY = 3,079,484 F = 59 %	~29 [a]	Mort: 1950–2003 (mean = 38.0 y) Solid cancer incid: 1958–2009 (mean = 29.2 y) Hematologic cancer incid: 1950–2001	Mort: >99.5 % follow-up (F-U) and ~98 % of deceased with death certificates; Incidence: Limited to cancer registries in 2 prefectures where ~85 % live – rates adjusted for out-migration. Good ascertainment and diagnosis.
2. 15-Country nuclear workers (Cardis *et al.*, 2007) [Section 4.2.1]	Pooled cohorts, Mortality; Europe, N. America, Asia, Australia	N = 407,391 PY = 5,192,710 F = 10 %	30.7	Maximum: 1943–2000 (mean = 12.7 y)	High F-U and death certificate ascertainment
3. INWORKS nuclear workers (Leuraud *et al.*, 2015; Richardson *et al.*, 2015) [Section 4.2.2]	Pooled cohorts, Mortality; UK, US, France	N = 308,297 PY = 8,222,000 F = 13 %	30.3	Maximum: 1944–2005 Mean = 26.7 y	High F-U and death certificate ascertainment

	Study (Reference) [section of text]	Study Design Mortality/Incidence Country	Study population characteristics (N, PY, % female)	Mean Age at First Exposure or Study Entry (y)	Dates Follow-up (mean years of follow-up)	Information on Follow-up (F-U) and Cancer Ascertainment
4.	Mayak nuclear workers (Hunter *et al.*, 2013; Sokolnikov *et al.*, 2015) [Section 4.2.3]	Cohort, Incidence and Mortality; Russia	N = 25,757 PY = 950,896 F = 25 %	24.7	Employed 1948–1982, follow-up 1948–2008 (mean = 36.9 y)	23 % lost to F-U, mainly due to out-migration; Cause of death for >99 % of known deaths, but 9 % from relative reports; autopsy data for 21 % of deaths
5.	Chernobyl Russian nuclear cleanup workers (Ivanov *et al.*, 2007; Kashcheev *et al.*, 2015; Kryuchkov *et al.*, 2009) [Section 4.2.4]	Cohort, Incidence and Mortality; Russia	N = 67,568 PY = mort 993,423; incid 972,660 F = 0 %	34.8 (at exposure; study entry ~6 y later)	1992–2009 (exposures in 1986–1987); (Mean = 14.7 y)	7 % lost to F-U Causes of death confirmed by multiple documents
6.	Canadian nuclear workers (Zablotska *et al.*, 2013b)	Cohort, Mortality; Canada	N = 42,228 PY = 514,729 F = 16.8 %	30.6 y	1956–1994 (mean = 12.2)	2.4 % lost to follow-up; Cause of death for 99.9 % of deaths
7.	Japanese nuclear workers (Akiba and Misuno, 2012; Hosoda *et al.*, 1997; Iwasaki *et al.*, 2003; Murata *et al.*, 2002) [Section 4.2.5]	Cohort, mortality; Japan	N = 200,583 PY ~1,373,000 F = 0	31.7 y[c]	1991–2002 (exposure in 1957–2000) (Mean = 6.8 y)	High rate of follow-up through Japan's *koseki* system; 99.4 % cause of death ascertainment[c]

Study (Reference) [section of text]	Study Design Mortality/Incidence Country	Study population characteristics (N, PY, % female)	Mean Age at First Exposure or Study Entry (y)	Dates Follow-up (mean years of follow-up)	Information on Follow-up (F-U) and Cancer Ascertainment
8. U.S. radiologic technologists (Liu *et al*., 2014; Preston *et al*., 2016) [Section 4.2.6]	Cohort, Incidence and Mortality (but no dose response performed for solid cancer mortality data); U.S.	N = 83,538 mort, 66,915 incid PY = 1,089,502 incid F = 100 % (breast cancer)	~22 y [b]	<1940–2008 (Mean = 20.6 y)	~97 % breast cancer detection rate. Based on self-report of breast cancer; 83 % with medical record verification, only 1 % of medical records disconfirmed reported diagnoses.
9. Rocketdyne nuclear workers (Boice *et al*., 2011; 2006b) [Section 4.2.7.4]	Cohort, Mortality; U.S.	N = 5,801 radiation monitored + 41,169 non-radiation workers PY = 196,674 (+ 1,392,648 PY non-rad workers) F = 8 %	31 y	1948–2008 (33.9 y)	0.6 % lost to F-U; Death cause known, 98.1 %
10. Mound nuclear workers (Boice *et al*., 2014) [Section 4.2.7.4]	Cohort, Mortality; U.S.	N = 7,269 (4,977 monitored for radiation) PY = 293,462 F = 24.8 %	n.a.	1944–2009 (40.4 y)	1.3 % lost to F-U Cause of death known for 98 % of deceased.

Study (Reference) [section of text]	Study Design Mortality/Incidence Country	Study population characteristics (N, PY, % female)	Mean Age at First Exposure or Study Entry (y)	Dates Follow-up (mean years of follow-up)	Information on Follow-up (F-U) and Cancer Ascertainment
11. Chinese x-ray workers (Sun *et al.*, 2016) [Section 4.2.8]	Cohort, Incidence; China	N = 27,011 x-ray workers; 25,872 unexposed PY = 1,446,347 F = 20 %	25.7	1950–1995 (27.4 y)	Medical x-ray workers in 1950 at major hospitals in 24 Chinese provinces. Question of socioeconomic comparability of exposed ("medical x-ray workers") and unexposed ("physicians"). Diagnoses: 70 % histologic, remainder mainly radiologic exam.
12. Techa River, residents (Davis *et al.*, 2015; Schonfeld *et al.*, 2013) [Section 4.3.1]	Cohort, Incidence and Mortality; Russia	N = 29,730 mort; 17,435 incid PY = 927,743 mort; 472,788 incid F = 58 %	~28 (range 0 - >50)	Mort: 1950–2007 (31.2 y) Incid: (27.1 y)	16 % lost to F-U through migration, but migrants censored so not a bias. 5.7 % of non-migrants lost to F-U Cause of death for 91 % of non-migrant deaths
13. Chernobyl: Ukrainian and Belarusian childhood ^{131}I exposure (Brenner *et al.*, 2011; Tronko *et al.*, 2006; Zablotska *et al.*, 2011; [Section 4.3.2]	Cohorts, Incidence Ukraine, Belarus	Ukraine: N = 13,127 F = 51 %. Belarus: N = 11,611 F =	~10 y	Screened 1998–2000 (~13 y)	Ukraine: 67 % of subjects who could be traced were screened. Belarus: 74 % of eligible, traceable subjects were screened.

Study (Reference) [section of text]	Study Design Mortality/Incidence Country	Study population characteristics (N, PY, % female)	Mean Age at First Exposure or Study Entry (y)	Dates Follow-up (mean years of follow-up)	Information on Follow-up (F-U) and Cancer Ascertainment
14. Kerala, India, HBRA residents (Akiba, 2013; Nair *et al*., 2009) [Section 4.3.3]	Cohort, Incidence India	N = 69,958 PY = 736,586 F = 54.1	47 (exposure began in utero)	1990–2005 (10.5 y)	0.7 % lost to follow-up; 6 % out-migration. Had histopathology/cytology on 73 % of cancers
15. Yangjiang, China, HBRA residents (Sun *et al.,* 2000; Tao *et al*., 2012) [Section 4.3.4]	Cohort, Mortality China	N = 31,604 PY = 736,942 F = 49 %	31.7 (exposure began in utero)	1979–1998 (23.3 y)	Visited hospitals, reviewed medical records of deceased subjects every 3 to 4 y. When necessary, visited local village doctors, family members, or next of kin to collect further cause-of-death information. Had pathological information on 26 % of cancer deaths, and radiologic/ultrasonic on 62 %.
16. Taiwan, radiocontaminated dwellings (Hwang *et al*., 2008) [Section 4.3.5]	Cohort, Incidence Taiwan	N = 6,242 PY = 118,000 F = 34.4 %	16.9	1983–2005 (18.9 y)	Good cancer ascertainment through Taiwan National Cancer Registry
17. UK pediatric CT patients (Berrington de Gonzaléz *et al.,* 2016; Pearce *et al*., 2012) [Section 4.4.2]	Cohort, Incidence United Kingdom	N = 178,604 PY = 1,720,984 F = 45 %	~10.6	1985–2008 (9.6 y)	~97 % completeness of cancer registry.

Study (Reference) [section of text]	Study Design Mortality/Incidence Country	Study population characteristics (N, PY, % female)	Mean Age at First Exposure or Study Entry (y)	Dates Follow-up (mean years of follow-up)	Information on Follow-up (F-U) and Cancer Ascertainment
18. Australia pediatric CT patients (Mathews *et al*., 2013) [Section 4.4.2]	Cohort, Incidence Australia	N = 680,211 exposed; 10,000,000 unexposed PY = ~6,460,000 for exposed F = 47 %	(ages 0–19)	1985–2007 (9.5 y)	Cancers ascertainment nearly complete through national cancer database and death index.
19. Pooled analysis of external radiation and thyroid cancer (Lubin *et al*., 2017; Veiga *et al*., 2016) [Section 4.5.3.1]	Cohorts, Incidence Europe, Asia, U.S.	N = 61,155 exposed; 46,439 unexposed PY = 2,588,559 exp.; 1,865,957 unexp. F = 54 %	5.7 (ages 0 – 19)	1920 – 2009 (inclusive dates for various studies) (Mean n.a.)	Varies among studies, but follow-up and cancer ascertainment generally good-to-excellent.

CT = computed tomographic examinations
F = female
F-U = follow-up
HBRA = high natural background area
incid. = cancer incidence
mort. = cancer mortality
N = number of individuals studied
PY = person-years at risk

[a] Based on age distribution given in Ozasa *et al*. (2012) and assuming mean ages of age intervals and mean of 58 for those >50 y of age.
[b] Calculated from age at entry distribution for females with questionnaires as given in Mohan *et al*. (2003)
[c] Data for the subset described in Vrijheid *et al*. (2007b).

Table 4.2—Summary of dosimetry.

Study[a]	Type of Dosimetry	Types of Exposure	Mean Dose (range) - mGy	Comment on Dosimetry
1. A-bomb survivors (Cullings *et al*., 2006; 2017; Young and Kerr, 2005).	Individual dose reconstruction based on physical modeling of reported location, shielding and other factors.	Gamma and neutron dose mostly <1 % of gamma dose	~200 (0 – 4000) Uncertainties: estimated GSDs of 1.25 – 1.55.	Dosimetry validated by mock-up explosion measurements, measurements of physical samples and chromosome aberrations. Doses corrected for uncertainty by regression calibration method.
2. 15-Country (Cardis *et al*., 2005b; Thierry-Chef *et al*., 2007)	Based on film/TLD badges Developed database of correction factors for calibration practices, various dosimeters, geometries etc. to adjust and harmonize for various cohort/year combinations. Colon, RBM and lung doses estimated.	X and γ rays mainly between 100 and 3,000 Kev. Some tritium exposure. Workers with potential for substantial neutron or internal exposures excluded, as were those with high dose-rate (>250 mGy in a year) exposures.	19.4 (3.8 – 1500) Estimated uncertainty factors (K) of 1.07 – 1.99 and bias factors (B) of 1.01–2.31.	Excluding workers with neutron or internal exposures removed many of the higher-dose individuals; therefore loss of statistical power. Authors concluded that most of the uncertainty was Berkson error, which would have little effect on risk estimates.
3. INWORKS (Thierry-Chef *et al*., 2015)	Based on film/TLD badges Estimated colon, RBM and other organ doses. Evaluated dosimetry comparability across different nuclear facilities and time to identify bias and uncertainties in different dose estimates. Phantoms employed to reconstruct dose for 3 geometries (anterior-posterior, uniform rotational, and isotropic) and different energies.	X and γ rays mainly between 100 and 3,000 Kev. Small percent with tritium exposure, but not usually included in dose estimates. Those indicated as monitored for neutron (13 %) or internal exposures (17 %) were flagged, but such exposure information may have been incomplete in the early days.	Colon: 17.4 mGy among all workers; 20.9 mGy among exposed workers (90^{th} percentile 53.4, max. 1332; ~4000 PY with >500 mGy) RBM: 16 mGy, all workers (10^{th} – 90^{th} percentile, 0.0 – 40.8 mGy)	Used flags for neutron exposure in main analysis and for internal exposures in sensitivity analysis. Too little systematic information available to evaluate impact of "missed" dose in the early years or to quantify neutron doses.

	Study[a]	Type of Dosimetry	Types of Exposure	Mean Dose (range) - mGy	Comment on Dosimetry
4.	Mayak (Sokolnikov *et al*., 2015; Vasilenko *et al*., 2007a; 2007b)	Film/TLD badges, urine Pu bioassays. Corrected film badge doses account for energy and angular variation for the various film badge dosimeters, and used information on the nature of the fields at various workplaces to improve dose estimates.	X and γ rays, neutrons, plutonium. Neutron dose generally not measured but inferred based on estimated neutron to gamma ratios for various workplace environments (NCRP, 2012).	354 mGy (0 - >3 Gy; 17 % >1 Gy, 35 % <0.1 Gy)	External dose estimates by unshielded dosimeters before ~1955 have large uncertainties due to range of photon energies and angular responses, and high-energy beta exposures. Prior to 1960, neutron doses substantial, particularly in the reactor complex, but would have been unrecorded. Poor agreement between plutonium dose estimates from autopsy vs. urinalysis. Tritium and polonium exposures not well characterized.
5.	Cleanup, Russia (Chumak *et al*., 2008; Kryuchkov *et al*., 2009)	Official dose records; 15 % reconstructed. Accuracy of doses differs because different methods of dose assessment were applied including use of individual dosimeters, group dosimeters, or dose-rate measurements at the work place.	γ exposures during 1986–1987	132 mGy (0.1 – 1240); 20,992 with 50–100 mGy, 572 with >300 mGy Uncertainties estimated as 0.5 to 3 times estimated doses but may be larger.	Questions regarding official film badge data, conversion of badge reading to organ dose in highly variable directional radiation fields, and uncertainty due to recall.
6.	Canadian nuclear workers (Zablotska *et al*., 2013b)	Doses from National Dose Registry of Canada, supplemented by additional review of records. Details given in Zablotska *et al*. (2004).	Gamma- and x-ray, neutron, tritium; other internal exposures rare	21.6 mSv total dose (0 – 491 mSv); 3.02 mSv tritium dose (0 – 169 mSv)	Careful review of dosimetry problems with the earlier reports on this cohort. Found that dose information from Atomic Energy Canada Limited (AECL) was incomplete before 1965.
7.	Japanese nuclear workers (Akiba and Misuno, 2012; Hosoda *et al*., 1997)	Annual dose records in "Radiation Dose Registration Center for Workers". Applied quality factors for various types of radiation.	External and internal radiation, 1957–1992 (but virtually all external); X-, gamma-, beta-rays, neutrons	12.2 mSv; (75.4 % <10 mSv, 2.6 % ≥ 100 mSv)	Harmonized dose records for technical differences/advances in dose measurements and metrics. Conducted review by facility visits and dose manuals.
8.	US radiation technologists (Simon *et al*., 2006b; 2014)	680,000 annual badge doses between 1960 and 1997, dose reconstruction based mainly on literature etc. before ~1970.	X ray	42 mGy (badge dose; 37 mGy breast dose)	Individual annual dose estimates were the arithmetic means of 1000 dose realizations to model uncertainties. ~70 % of workers had at least some annual doses estimated by dose reconstruction.

Study[a]	Type of Dosimetry	Types of Exposure	Mean Dose (range) - mGy	Comment on Dosimetry
9. Rocketdyne (Boice *et al*., 2006a; 2006b; 2011)	Film/TLD badges 38 % monitored for internal exposures: >30,000 bioassays Calculated doses to 16 organs or tissues	X or γ rays; 14 radionuclides	13.5 mSv (0 – 1 Sv)	Obtained dose information on other places worked for cohort members; Primary uncertainties: photon energy, exposure geometry, type of dosimeter
10. Mound (Boice *et al*., 2014)	Film/TLD badges. >200,000 polonium urine bioassays, also plutonium and tritium bioassays.	Gamma, alpha, beta emitters, neutrons. Polonium, plutonium, tritium exposures.	26.1 mSv (0 – 939) 4.6 % with >500 mSv	Extensive dosimetry work-up. Obtained dose information on other places worked for cohort members.
11. China x-ray (Sun *et al*., 2016)	Dose reconstruction. Simulated measurements for multiple X-ray machines, workplaces and working conditions, protective measures and work histories for 3805 (14.1 %) workers.	25–40 keV X rays	86 mGy – colon dose. 60 % had cumulative doses <50 mGy, and <1 % >500 mGy.	Used simulations to estimate average calendar year doses for x-ray workers and assigned average dose for the year to all who worked that year.
12. Techa River (Degteva *et al*., 2009)	Individual dose reconstructions based on estimated village doses (based on distance down-river and distance from shoreline) with adjustments for age, sex etc. Estimated stomach dose	γ , ^{90}Sr, ^{137}Cs and other radionuclides	35 mGy (0 – 960; <10 % of doses >100 mGy)	External dose peaked in 1951 Substantial revisions to dosimetry not yet reflected in published Epi studies.
13. Chernobyl childhood exposure (Drozdovitch *et al*., 2013; 2015; Likhtarev *et al*., 2003; 2006; 2014)	Individual measurements of thyroid activity soon after Chernobyl accident. Latest dosimetry takes into account uncertainties.	Internal ^{131}I was predominant exposure, and small external γ exposure.	Ukraine: 670 mGy (0.35 mGy to 42 Gy; 19 % with >1 Gy) 96 % had dose uncertainty GSDs <2 (geometric mean of 1.47) Belarus: 560 mGy (0 to 32.8 Gy)	Ukraine: Evaluated shared and unshared uncertainties using Monte Carlo realizations. Adjusting for dose error resulting in changes in cancer risk estimates of only –11 % to +7 %, because errors modest and partly Berkson (Little *et al*., 2014). Belarus dosimetry was similar to Ukraine dosimetry

Study[a]	Type of Dosimetry	Types of Exposure	Mean Dose (range) - mGy	Comment on Dosimetry
14. Kerala HBRA (Nair *et al*., 2009)	Took indoor and outdoor ambient spot measurements for each house in the study using NaI scintillometers. Used model incorporating estimated age/sex specific occupancy factors to calculate yearly dose and cumulative doses for each individual. Validation sample of 800 houses with quarterly TLD readings in houses for year correlated 0.97 with scintillometers.	γ and also had some radon and thoron exposures.	161 mGy, cumulative	Obtained survey of house occupancy for time spent indoors/outdoors for 2 % sample and used mean occupancies by age and sex to apply to ambient measurements to derive estimated cumulative doses. Had 160 individuals wear TLD badges for 2 months & correlated the badge readings with their modeled dose estimates. Found a correlation of 0.80, but only after discarding 15 % of the badge readings as "outliers". No dose uncertainty analysis.
15. Yangjiang HBRA (Tao *et al*., 2000)	Ambient dose rate survey: about 1/3 of houses and nearby areas in every hamlet;	γ, but also had radon and thoron exposures positively correlated with γ.	63.2 mGy – colon dose (excess above low-exposure area)	House occupancy information from 5,291 homes; developed aggregate age-sex occupancy factors.
16. Taiwan dwellings (Chen, 2002).	Exposure rates estimated from measurements of representative locations in each room; TLD measurements. Questionnaire used to reconstruct amount of time spent in each room of the contaminated apartment.	γ from ^{60}Co-contaminated rebar used in building construction	Median 6.3 mGy (<1 – 2,363 mGy)	Primary uncertainties due to recall and individual locations in room; no uncertainty analysis included. Large number of exposure rate and TLD measurements taken.

Study[a]	Type of Dosimetry	Types of Exposure	Mean Dose (range) - mGy	Comment on Dosimetry
17. UK pediatric CT (Pearce *et al*., 2012)	Doses to brain and RBM. "Obtained typical machine settings for CT in young people from UK-wide surveys undertaken in 1989 and 2003, combined those with a series of hybrid computational human phantoms and Monte Carlo radiation transport techniques to estimate absorbed doses to the RBM and brain for reference males and females for ages 0 – 22 years." (Pearce *et al*., 2012)	X-ray (CT)	2001 and after: For brain, dose 0 – 28 mGy per CT, depending on age and CT anatomical location; For RBM, dose of 0 – 9 mGy per CT depending on sex, age and CT anatomical location. Dose estimates before 2001 ~2–3 times higher because age-specific machine settings rarely used in earlier years.	No individual dosimetry. Uncertainty in reconstructed doses likely high for earlier exposure years. Recent validation work on doses vs. age, sex, size, time has been carried out (Kim *et al*., 2012).
18. Australia pediatric CT (Mathews *et al*., 2013)	Estimated "effective dose" based on literature information, and subsidiary brain and RBM doses. Effective dose modeled from anatomic scan site, year and age. Most analyses based on number of CT scans rather than dose.	X-ray (CT)	Estimated mean effective dose per CT scan: 4.5 mGy (but this would vary by year and scan site). Mean brain dose (brain CTs), 40 mGy; RBM dose, 4.6 mGy	No individual doses- estimated average doses for red bone marrow and brain and "effective dose", based on literature information—taking into account the site of CT, age, and year of scan, but no details given. Organ dose estimates used only for subsidiary analysis.
19. Thyroid cancer, pooled analysis (Lubin *et al*., 2004; 2017; Veiga *et al*., 2016)	Variety of approaches based on modeling of doses from medical radiation exposures, plus atomic-bomb dose estimation.	Mostly X ray, but γ for hemangioma radium needle study and γ + neutron for atomic-bomb study	Used only study subjects with <200 mGy to thyroid.	For x ray procedures in early days, issues of distance from primary beam, degree of beam collimation, thyroid shielding etc. are primary sources of uncertainty.

[a] Study numbers refer to studies as referenced in Table 4.1.

CT = computed tomographic examinations
RBM = red bone marrow dose
TLD = thermoluminescent dosimeters

Table 4.3—*Epidemiologic results and statistical features*.

	Study[a]	Observed Cancers (excess cancers)	Estimated ERR Gy^{-1} (95 % CI) for Solid Cancer (or all non-leukemia), and/or Leukemia	Statistical Methods	Statistical Models Evaluated	Covariate Adjustment Factors
1.	A-bomb survivors	Incid: 22,538 (992 excess)	Mort: 0.47 (0.38, 0.56); Leukemia: 3.1(1.8, 4.3) Incid: 0.64 (0.52, 0.77) –female 0.20 (0.12, 0.28) - male	Poisson regression. Sensitivity analyses for smoking, autopsy-only diagnoses, sex-related cancers	L, LQ, Q, threshold, semiparametric, nonparametric, dose categories [B]	City, sex, age at exposure, attained age, time since exposure, smoking (also, evaluated effect modification by these)
2.	15-Country	4,770	0.58 (90 % CI 0.10, 1.39) – (excluding the Canadian cohort because of it had missing dose data that created a marked bias in the results).	Poisson regression using time-dependent cumulative dose. Sensitivity analyses by sex, cohort, attained age, age at exposure, time since exposure, smoking.	L, polynomials in dose, dose categories	Sex, age, calendar period, facility, duration of employment, socioeconomic status
3.	INWORKS	19,064 non-leukemias (209 excess); 531 non-CLL leukemias	Non-leuk: 0.48 (90 % CI 0.20, 0.79) Non-CLL Leuk: 2.96 (90 % CI 1.17, 5.21)	Poisson regression using time-dependent cumulative dose. Sensitivity analyses for country, lag period, smoking (un)related cancers, neutron or internal radionuclide monitoring status, lower dose ranges; excluding lung, liver, bone	L, LQ, restricted dose ranges, nonparametric, dose categories	Country, sex, attained age, year of birth, socioeconomic status, duration of employment, neutron and internal-exposure monitoring status

	Study[a]	Observed Cancers (excess cancers)	Estimated ERR Gy^{-1} (95 % CI) for Solid Cancer (or all non-leukemia), and/or Leukemia	Statistical Methods	Statistical Models Evaluated	Covariate Adjustment Factors
4.	Mayak	1,825 – solid cancer, excluding lung, liver, bone (97 excess)	Mort: 0.12 (0.03, 0.21) adjusted, or 0.16 (0.07, 0.26) unadjusted, for plutonium exposure; Threshold: 0.2 Gy (<0, 1.3)	Poisson regression using time-dependent cumulative dose. Sensitivity analyses by Pu exposure, attained age, time since exposure	L, LQ, Q, L+cell killing, threshold, dose categories	Sex, attained age, age at exposure, time since exposure, birth cohort, smoking, Pu exposure
5.	Cleanup, Russia	Mort: 2,442 (excess 172) Incid: 4,002 Leuk: 141	Mort: 0.58 (0.002, 1.25) Incid: 0.47 (0.03, 0.96) Leuk: 0.44 (–1.68, 2.56)	Poisson regression; SMRs and SIRs; No sensitivity analyses	Linear, nonparametric, dose categories	Calendar year period, region, age at exposure, attained age
6.	Canadian nuclear workers (Zablotska *et al*., 2013b)	Mort: 324 solid cancers (excess n.a.); 12 non-CLL leukemias	–1.20 (< –1.47, 2.39), solid cancer; 9.79 (< –1.49, 107), non-CLL leukemia	Poisson regression; examined effect modification by facility, sex, attained age, time since first exposure	Linear, dose categories	Sex, attained age, calendar period, duration of monitoring, facility, monitoring status, socioeconomic status

	Study[a]	Observed Cancers (excess cancers)	Estimated ERR Gy^{-1} (95 % CI) for Solid Cancer (or all non-leukemia), and/or Leukemia	Statistical Methods	Statistical Models Evaluated	Covariate Adjustment Factors
7.	Japanese nuclear workers (Akiba and Misuno, 2012; Hosoda *et al*., 1997; Iwasaki *et al*., 2003)	Mort: 2,636 non-leukemias; (Excess n.a.). 80 leukemias	1.26 (–0.27, 3.00) – cancers except leukemia; 0.20 (–1.42, 2.09) – cancers except alcohol-related and leukemia; –1.93 (–6.12, 8.57) – all leukemia	Poisson regression; sensitivity analyses for smoking and alcohol consumption	Linear, dose categories; no LQ model	Attained age, calendar year period, geographic region. Adjusted for smoking and alcohol consumption. Had data on but did not adjust for socioeconomic level, medical radiation exposures and other hazardous occupational exposures.
8.	US rad techs	1,922 incident breast cancers (54 excess); 586 breast cancer deaths	0.7 (0.3, 3.9) – breast cancer incid. Effect confined to cohort that had worked before 1950; perhaps because low doses after 1950 limit statistical power.	Poisson regression using time-dependent cumulative dose.	L, LQ	Attained age, birth cohort, duration of employment, no. live births, menopausal status, age menarche, obesity, family breast cancer, alcohol intake, hormone replacement therapy, race, marital status, smoking
9.	Rocketdyne	Mort: 651 non-leukemias; (excess n.a.)	–0.2 (–1.8, 1.7) [c] Non-CLL leukemia: 0.6 (<0, 12.3)	Cox regression using time-dependent cumulative dose. No sensitivity analyses.	Loglinear; Used 10y lag.	Years of birth and hire, sex, hourly/salary pay, duration of employment, rocket toxicant exposure

Study[a]	Observed Cancers (excess cancers)	Estimated ERR Gy^{-1} (95 % CI) for Solid Cancer (or all non-leukemia), and/or Leukemia	Statistical Methods	Statistical Models Evaluated	Covariate Adjustment Factors
10. Mound	Mort: 26 non-CLL leukemias	Non-CLL leukemia: 0.4 (–3.7, 7.1) [d]	Cox regression using time-dependent cumulative dose. Cox analyses based on the radiation-monitored only, since the unmonitored had a different risk profile.	Loglinear 10y lag, except 2y lag for leukemia.	Year of birth, year of hire, sex, race, education level
11. China x-ray	1,643 non-leukemia (excess n.a.)	0.87 (0.48, 1.45) Male and female risk coefficients similar.	Poisson regression, but based on only 4 dose categories.	Linear, 5y lag;nonparametric, dose categories	Birth year, sex, year 1st employment, age started work, attained age, calendar period
12. Techa River	Mort: 2,303 (50 excess); Incid: 1,933 (61 excess)	Mort: 0.61 (0.04, 1.27) Incid: 0.77 (0.13, 1.5)	Poisson regression using time-dependent cumulative dose. Sensitivity analyses: examined effect modifiers of sex, age entry, attained age, time since exposure; examined risk excluding bone and colon	L, LQ, Q, spline with knot at 0.1 Gy, threshold, dose categories; LQ not significantly (p = 0.2) better than L, nor was spline better than L; Q fit as well as L (p >0.5)	Gender, ethnicity, entry period, calendar time, attained age, age at entry, time since 1st exposure, smoking. Effect modifiers: risk did not vary (incidence) or increased significantly with older age at exposure – not as expected.

Study[a]	Observed Cancers (excess cancers)	Estimated ERR Gy^{-1} (95 % CI) for Solid Cancer (or all non-leukemia), and/or Leukemia	Statistical Methods	Statistical Models Evaluated	Covariate Adjustment Factors
13. Chernobyl childhood exposure	Ukraine: 45 prevalent (excess 34); 65 incident; Belarus: 87	Ukraine: 5.25 (1.70, 27.5) for prevalence, 1.91 (0.43, 6.34) for incidence; Belarus: 2.15 (0.81, 5.47) for dose range 0–5 Gy was linear, but negative exponential at higher doses.	Logistic regression, Poisson regression; Belarus: Binomial odds model (yielded excess odds ratio estimates)	L, LQ, L-exponential, nonparametric, dose categories	Age at screening; sex; place of screening & residence; urban/ rural; marital status; personal history of cancer, thyroid diseases in self or relatives, iodine prophylaxis.
14. Kerala HBRA	1,349 (no excess)	–0.13 (–0.58, 0.46) (Dose group with >500 mGy cumulative dose "had no evident risk.")	Poisson regression; 10 y lag; Exclusion of lung cancer (because of radon/thoron exposure) did not alter risk.	Linear	Sex, attained age, education, occupation, income, bidi smoking, tobacco chewing
15. Yangjiang HBRA	941 (excess n.a.)	0.19 (–1.87, 3.04) – excluding leukemia and liver cancer (liver disease common, and diagnosis as cancer or cirrhosis varied by region)	Poisson regression	Linear (used 10 y lag)	Sex, attained age, calendar year.
16. Taiwan dwellings	106 solid cancers (excess n.a.) 10 y lag	0.4 (90 % CI –0.3, 0.8) [e]	Cox regression; No sensitivity analyses; (CI seems narrower than expected, based on number of cancers.)	Linear (loglinear)	Sex, attained age, birth cohort

Study[a]	Observed Cancers (excess cancers)	Estimated ERR Gy^{-1} (95 % CI) for Solid Cancer (or all non-leukemia), and/or Leukemia	Statistical Methods	Statistical Models Evaluated	Covariate Adjustment Factors
17. UK pediatric CT	74 leukemia; 135 brain tumors	Leukemia or myelodysplastic syndrome: 36 (5, 120) [Leukemia only: 19 (–12, 79)] Brain: 23 (10, 49)	Poisson regression with time-dependent cumulative dose. Sensitivity analyses: age at exposure, attained age, lag period, calendar year	L, LQ, L-exponential, nonparametric, dose categories (p >0.4 for LQ and L-exponential models for both leukemia and brain)	Sex, age at exposure, years since first and last CT scan
18. Australia pediatric CT	Leuk | Brain CT group: 211 | 283 Control group: numbers not reported, but ~20 times as many as in CT group.	Brain (after brain CT): 21 (14, 29) – for 5-y lag Leukemia (all CT exams): 39 (14, 70) – 1-y lag	Poisson regression with time.	L, nonparametric, time-dependent cumulative dose; main analysis used 1 y lag.	Age at exposure, sex, year of birth, year of exposure, time since exposure, socioeconomic status. No information on Down Syndrome or other markers of cancer susceptibility.
19. Thyroid cancer, pooled analysis	Exposed, 252; unexposed, 142	Thyroid: 11.1 (6.6, 19.7) – for 0–200 mGy range Dose threshold: 0 (95 % CI <0, 44 mGy)	Poisson regression. Sensitivity analyses: sex, no. of dose fractions, age at exposure, random effects model.	L, LQ, threshold, semiparametric, parametric, dose categories	Study, age at exposure, time since exposure, attained age, calendar year, number of radiation treatments, plus other variables specific to certain studies.

CT = computed tomographic examinations
Leuk = leukemia
non-CLL = leukemia excluding chronic lymphocytic leukemia
[a] Study numbers refer to studies as referenced in Table 4.1.

[b] L = linear, LQ = linear-quadratic, Q = pure quadratic, Semiparametric = empirical dose-response without assuming a shape, Nonparametri c = Risk estimates and CI for individual dose categories.

[c] Based on linear extrapolation of HR at 100 mGy of 0.98 (95 % CI 0.82, 1.17). For non-CLL leukemia, HR at 100 mGy = 1.06 (0.50, 2.23).

[d] Based on HR at 100 mGy = 1.04 (0.63, 1.71).

[e] Based on HR at 100 mGy = 1.04 (90 % CI 0.97, 1.08)

Table 4.4—Study strengths and limitations.

	Study [a]	Strengths	Limitations
1.	A-bomb survivors	Large cohort, both sexes, exposed at all ages, with long F-U and wide dose range. Representative sample of general population. Low-dose data: 30,000 survivors with colon doses between 5 and 100 mGy. Evaluated shape of the dose-response curve, jointly and singly by sex Evaluated risk modifications by sex, age at exposure, attained age, smoking history Examined risk comparability for subsets of tumor types. Found statistically significant dose response over the range 0 – 100 mGy; dose threshold analysis consistent with no threshold.	Only one acute, high dose-rate exposure, not protracted exposures. Study started in October 1950, >5 y after the bombings, so early data missing. Possible "healthy survivor effect", particularly at high doses. Low proportion of men of military age. Malnourished Japanese population at time of bombing and for several years thereafter. Retrospective dosimetry and some doses uncertain. Incidence data for solid cancer available only beginning 13 y after exposure. Out-migration: could not ascertain tumor incidence outside of Hiroshima and Nagasaki prefectures, but mortality data available for all of Japan. Curvature is attributable to male data in the range of 0.2 to 0.75 Gy, not for 0 to 0.2 Gy; reasons for that unclear.
2.	15-Country	Extensive dosimetry effort. Large cohort of workers, some with long F-U (up to 62 y).	Dosimetry data provided were incorrect for a fraction of the Canadian cohort, which biased the risk estimates. Elimination of those with internal exposures or larger neutron exposures restricted the dose range of workers and reduced the statistical power. Exclusion of some workforces could have introduced bias. Suggestions that analyses confounded by worker socioeconomic status and duration of employment. Some confounding by smoking.

Study [a]	Strengths	Limitations
3. INWORKS	Large study sample with long, high-quality mortality F-U and personal dosimetry. Dosimetry based on an extensive effort. Overall, doses well characterized and uncertainties relatively small. Analyses restricted to those with <200, <150 or <100 mGy were statistically significant. Showed good correspondence with a linear model and could reject curvilinearity. Results apparently not affected by smoking or asbestos exposure, since similar results after lung and pleural cancers removed from endpoint.	Dosimetry for the early time period includes relatively greater uncertainty, due to early technologies, and "missed" photon and neutron doses. Influence of excluded neutron and internal doses, and of "missed" doses, on reported dose response uncertain. Results regarding neutron exposure contrary to expectations; may represent confounding.
4. Mayak	Cohort with wide range of external doses from protracted exposures. Individual external dose measurements and detailed work histories. Long follow-up of high quality for Ozyorsk residents. Risk assessments adjusted for smoking; not adjusted for alcohol intake, but preliminary data show little correlation between alcohol intake and dose. Showed good correspondence with a linear model.	Autopsies more frequent among higher dose individuals, and cause of death obtained from a variety of sources, including 9 % from family members. Incidence data only available for Ozyorsk residents. Only ~38 % of workers with potential Pu exposure had Pu bioassay measurements. Issues of dose inaccuracies in early years due to dosimeter limits regarding photon energies, angular responses, high-energy betas and no/inaccurate neutron measurements. 70 % of workers had one or more years with reconstructed doses. Possibility of surveillance bias – that higher dose workers were paid greater attention than others.

	Study [a]	Strengths	Limitations
5.	Cleanup, Russia	Majority of doses measured by personal dosimeters. 80 % of workers with recorded doses. Large cohort and fairly high cumulative doses.	Accuracy of "official" recorded doses unknown, and >15 % based on dose reconstructions. Reliability sample: ~17 % of the official doses deviated 10-fold from RADRUE-estimated doses. Organ dose not used in the analyses of either solid cancers or leukemia. No information on smoking or alcohol consumption Nonlinear dose-response models not investigated. Potential difficulties of accurately following a large number of people over a wide geographical area, and of surveillance bias – greater attention paid to higher dose cleanup workers.
6.	Canadian nuclear workers	Fairly large, well-defined cohort. Good individual dosimetry and elimination of AECL subgroup with missing doses. Excellent follow-up rate and cause of death determination. Had worker socioeconomic information.	Could not find the missing dose information for the AECL subgroup. Had no data on smoking, alcohol consumption or other lifestyle variables. Nonlinear models not investigated.
7.	Japanese nuclear workers	Large cohort with good individual dosimetry. Had information on smoking and alcohol consumption for a substantial subset. High rate of follow-up and cause of death determination.	Apparent confounding by alcohol consumption and/or smoking but had analyses to consider these. Short follow-up. Study design weakness had potential survivor bias (follow-up began 30+ y after first exposure for some). Had data but did not adjust for socioeconomic level or medical radiation exposure.

Study [a]	Strengths	Limitations
8. US rad techs	Large nationwide cohort with individual dose estimates, long-term follow-up, detailed information on potential confounders, and high medical confirmation rate. Modeled both shared and unshared dose uncertainties for incorporation into analyses.	Only breast cancer and skin cancer analyzed with dose data to date (plus cataract with less accurate dosimetry). Substantial dose uncertainties for workers before ~1960 because had to rely on literature reports of doses for radiologic technologists. Potential intrinsic confounding between estimated cumulative breast dose and birth year (r = –0.58)
9. Rocketdyne	Doses well-characterized, including internal radionuclide exposures, and doses received at other places of employment. High rate of follow-up (99.4 %) and cause of death ascertainment (98 %). Lengthy follow-up.	Couldn't evaluate shape of dose response because risk estimate was negative for solid cancer. Relatively small study of radiation workers and thus relatively low statistical power. No lifestyle information.
10. Mound	Long F-U – up to 60 y Captured doses before and after Mound employment. High F-U rate and high percent with known cause of death Adjusted for education Had large amount of polonium bioassay data.	Relatively small number of workers. No lifestyle information. Uncertainties of polonium and other radionuclide measurements.
11. China x-ray	Substantial range of doses with long-term exposure and long F-U.	Dose response based on only 4 dose categories. Limited diagnostic accuracy (70 % with histology; others based on radiological exams) Assigned average estimated calendar-year doses to workers. Question about socioeconomic comparability of exposed and unexposed groups.

Study [a]	Strengths	Limitations
12. Techa River	Extensive dose reconstruction Unselected population; Large numbers with long follow-up; Many with ^{90}Sr measurements to help estimate individual exposures Could examine data for confounding by ethnicity, smoking. Evaluated L, LQ and Q models.	Intrinsic uncertainties in dosimetry; Recent revisions in dosimetry not reflected in published studies No personal gamma measurements Unusual age-at-exposure pattern of risk. Too little statistical power to discriminate between L and Q models. 16 % of cohort migrated away from the catchment area, thus reducing the effective sample size and power of the study, but there is no reason to believe that migration was a confounding factor.
13. Chernobyl childhood exposure	Fairly low thyroid dose uncertainties because of individual thyroid radioactivity measurements. Had detailed uncertainty analysis that took shared/unshared and other errors into account. Ultrasound and palpation screening with a standard protocol provided consistent, blinded assessment, and had cytologic indication for cancer before surgery. Non-participation rates of 26–33 % did not vary significantly by dose, so unlikely to bias the results.	Whereabouts, consumption details, etc. based on questionnaires with possible recall error. Direct thyroid measurements were conducted under difficult conditions within a few weeks after the accident.
14. Kerala HBRA	Had ambient measurements of external exposure for ~94 % of homes. Fairly high cumulative dose at a low dose rate. Used various resources to ascertain cancer. Have data on several potential risk factors, including smoking. Medical exposure infrequent, so little potential of dose-response bias from this source of exposure.	Dosimetric uncertainties because of having to use aggregate house-occupancy factors; had personal dosimetry on only a few individuals. No dose uncertainty analysis. Possible diagnostic bias: 72.4 % of cancers in 0–49 mGy group, and 64.8 % in >200 mGy group, had histologic diagnosis. Cancer incidence rates increased more slowly than expected with age (2.4 power), suggesting under-diagnosis in older individuals. Access to adequate medical care potentially limited and unequal. No account for migration. Potential confounding in comparing largely coastal residents with largely inland residents.

Study [a]	Strengths	Limitations
15. Yangjiang HBRA	Dose groups did not differ regarding diet, drinking water, pesticide residue, aflatoxin in food, medical usage, smoking, alcohol intake. Indoor ambient measurements for ~1/3 of dwellings in each hamlet, and outdoor measurements in hamlet. Age/sex specific occupancy factors estimated from ~5,300 interviews. Stable population.	Dose was inversely related to mortality from external causes, TB and liver cancer – suggests potential bias. May have been geographic differences in quality of cancer ascertainment. Diagnosis weak: 26 % of cancer deaths based on pathological information, 62 % on radiography/ultrasound, remainder clinical impression etc.
16. Taiwan dwellings	Extensive ambient measurements made in dwellings but no personal measurements. Good quality tumor registry to ascertain cancers.	Low dose distribution, contributes to low statistical power and precision. No information on lifestyle or socioeconomic factors. Small sample size, young ages, so relatively few cancers.
17. UK pediatric CT	Large study. Mainly well-designed. Good cancer ascertainment.	Possible missed doses from retakes due to patient movement were not considered. No individual dosimetry. Information not available as to reasons for CTs or other clinical variables – susceptible to biases due to confounding by indication and reverse causation. Likely missed CT exams performed on study subjects at health care facilities not in the study. Myelodysplastic syndromes (MDS) included with leukemias; leukemia effect not significant without the MDS cases.

Study [a]	Strengths	Limitations
18. Australia pediatric CT	Very large study. Good cancer ascertainment.	Information not available as to reasons for CTs or other clinical variables – susceptible to biases due to confounding by indication and reverse causation. Main risk estimates based on lagging only 1 y after exposure; thus risk estimates likely exaggerated by reverse causation. Found implausible results, *e.g.*, elevated risks for melanoma and Hodgkin lymphoma, but not for breast cancer; elevated risk for brain tumors after CT to sites other than the head. Possible missed doses from retakes due to patient movement not considered. Missed CT exams, including: "nearly all CT scans in state based tertiary hospitals" (where the majority of Australian CT scans are performed), and CTs before 1985 or after age 20. Estimated organ doses used only in subsidiary analyses.
19. Thyroid cancer, pooled analysis	Large number of exposed individuals, thyroid cancer cases and comparable controls. Adjusted for a variety of risk factors. Evaluated low-dose part of dose-response curve. Based on a number of high-quality studies with good follow-up and histologic verification of cancers.	Could not adjust for dose measurement error, although the 2 most influential studies had data corrected for measurement error, and measurement error uncertainty probably fairly small. Could not directly assess the possibility of differential medical surveillance by dose, but analyses suggested it was not a biasing factor.

[a] Study numbers refer to studies as referenced in Table 4.1.

CT = computed tomographic examinations
F-U = follow-up
HBRA = high natural background radiation area

it is recognized that all observational studies have limitations, mostly ranging from minor to moderate, that contribute to the evaluation of the LNT model. Except for the study of Japanese atomic-bomb survivors, the studies reviewed here have low doses, low dose rates, or both. The individual low-dose studies intrinsically have limited statistical power and precision in risk estimation. Therefore, a synthesis of study results regarding the LNT model, with consideration of study quality, will be the most informative epidemiologic evidence that can be provided for radiation protection purposes.

4.1 Japanese Atomic-Bomb Survivors

Highlights

The Life Span Study (LSS) cohort of atomic-bomb survivors has provided important data because it is a large cohort (~94,000 survivors of all ages) with relatively accurate dosimetry, a wide dose range (0 to 4 Gy, including ~68,000 with doses <100 mGy), over 60 y of high-quality follow-up for mortality and cancer incidence, and nearly 1,000 excess solid cancer cases, besides leukemias. These features provide relatively high statistical power and precision of risk estimates, including a statistically significant dose response for all incident solid cancer over the dose range 0 to 100 mGy and no evidence of a dose threshold. Data are available on sociodemographic, lifestyle and other disease risk factors to assess confounding, and limited data suggest that neither atomic-bomb fallout exposures nor medical radiation exposures confound the results. In the latest analysis, cigarette smoking did not confound the association of radiation with solid cancer incidence.

Unlike most other studies reviewed in this report, the LSS assesses the effects of a single, brief dose and the associated low dose effectiveness factor (LDEF), but not protracted doses so as to examine a dose rate effectiveness factor (DREF). Though a pure quadratic dose-response curve provided a poor fit to the data, the most recent solid cancer mortality and incidence data provide evidence of linear-quadratic upward curvature at lower doses, implying a LDEF > 1 and suggesting a shallower dose-response slope at low doses than at higher doses. However, the fact that curvature was seen only in males, and that it was mostly because of a flat response between about 200 and 750 mGy, makes the curvature difficult to interpret.

4.1.1 *Dosimetry Considerations*

The cohort of survivors received a wide range of doses essentially instantaneously. Individual doses are estimated based on reported location, shielding, and other factors at the time of the bombing using complex radiation transport codes and the estimated height and yield of the two devices (Young and Kerr, 2005). Radiation doses have been estimated for about 87,000 of the 94,000 atomic-bomb

survivors for 15 different organs or tissues. Doses could not be estimated for the remaining 7,000 because of complex shielding situations (Cullings *et al*., 2006).

The dosimetry has been refined periodically over a 50 y period with Cullings *et al*. (2017) representing the most recent update; this included a review of the original paper records to improve the accuracy of the location and shielding information that was used in the Dosimetry System 2002 (DS02) calculations (Young and Kerr, 2005). An electronic geographic information system was used to locate study subjects with greater accuracy on new orthophotographic maps which corrected for biases present in the original army maps dating from circa 1945, and a vastly improved method to estimate terrain shielding was applied (Cullings *et al*., 2006; 2017).

Extensive validation efforts of external gamma doses and neutron fluence have included thermoluminescent dosimetry (TLD) of roof tiles, sulfur activation of power line insulators, and activation of building materials and copper. Electron spin resonance of tooth enamel and fluorescence in situ hybridization (FISH) have been used to validate dose estimates for internal and external exposures (Nakamura *et al*., 2012; Young and Kerr, 2005).

Young and Kerr (2005) summarized the DS02 uncertainty range in individual doses as a coefficient of variation (CV) = 0.24 to 0.43 for Hiroshima and 0.28 to 0.47 for Nagasaki. Based on those data, 35 % was used as an uncertainty correction factor in estimating the doses for analyses. A revised method to estimate dose-response relationships that incorporates both individual ("classical") and grouped (also called "Berkson") dose measurement error has been proposed (Pierce *et al*., 2008) but not yet routinely applied in papers. In test cases, with an individual CV of ~40 % and a grouped uncertainty CV of ~20 %, this method showed results only slightly different from the previous method that corrected for only individual measurement error.

One issue with the dosimetry is the role of neutron exposures in the radiation effects observed. Neutron exposure levels were thoroughly studied as part of the DS02 (Young and Kerr, 2005) revision of the atomic-bomb dosimetry, but the relative biological effectiveness (RBE) of the neutrons is uncertain. In estimating doses, RERF applies a quality factor of 10 for the neutron component, whereas others have advocated 20 to 30 or a sliding RBE ranging up to 100 for neutron exposures at low total doses (Rühm and Walsh, 2007; Sasaki *et al*., 2016). One recent analysis suggested an important role for neutron dose (Walsh, 2013) in atomic-bomb risk estimates, though another suggested intrinsic uncertainties because neutron and gamma doses are substantially correlated and neutrons are only a small fraction of the total dose (Cullings *et al*., 2014).

Other potential sources of uncertainty in radiation doses include possible additional exposure to some individuals from "rainouts" from the radioactive plumes of the bombs, or by neutron activation of soils. Available

exposure measurements suggest that radioactive fallout was not widespread (Okajima, 1987; Okajima *et al*., 1987), except significant fallout did occur in the Nishiyama area of Nagasaki where one to two thousand resided, and those in the Koi-Takasu area of Hiroshima may have experienced a small amount of fallout. An analysis correlating reported fallout exposures with subsequent mortality and cancer incidence rates did not find significant associations (Sakata *et al*., 2014). Significant exposure to radionuclides from neutron activation of soils would have occurred primarily to any who went quite near the hypocenter within a few days after the bombings (NCRP, 2012), but individual information about "early entrance" to the proximal area is very limited.

Although the dosimetry for the atomic-bomb survivors is considered to be fairly accurate, particularly in comparison to dose estimates for most other environmental dose reconstructions, the accuracy is still limited by the uncertainty in location and structural shielding for various individuals due to recall error and inability to precisely characterize shielding configurations. Furthermore, shielding configurations have greater uncertainty for the Nagasaki factory workers who comprise a large portion of the relatively high dose survivors in that city (Cullings *et al*., 2006).

Information on diagnostic medical radiation exposures was obtained for Adult Health Study (AHS; a dose-stratified random sample of LSS subjects in the catchment areas of Hiroshima and Nagasaki cities) participants from 1964 to 1982 (Yamamoto *et al*., 1986). Those data did not show a correlation with atomic- bomb doses, so medical irradiation did not appear to be a confounding variable. There are relatively few socioeconomic or other barriers to utilization of medical care because it is free and available for essentially all atomic-bomb survivors.

More information about dosimetry uncertainties for atomic-bomb survivors is presented in NCRP Report No. 171 (NCRP, 2012).

4.1.2 *Epidemiologic Methods and Uncertainties*

The Life Span Study of ~94,000 atomic-bomb survivors includes ~54,000 who were within 2.5 km of the bomb hypocenters, a sampling of ~40,000 who were between 2.5 and 10 km away, matched on city, age and sex, as well as ~26,000 similarly matched individuals who were not in either city at the time of the bombing. The cohort was assembled based primarily on the 1950 Japanese census data which included a question about residence at the time of the bombing. The death certificate cause-of-death accuracy before and during the 1970s found some incompleteness of cancer death coding and still more inaccuracy of coding heart disease and certain other causes of death (Ron *et al*., 1994), but cause-of-death accuracy has improved in more recent decades. The Hiroshima and Nagasaki city/prefecture (regional) tumor registries provide high-quality tumor incidence data. A limitation is that

such data are available for only the two prefectures, but AHS participation data provide a way to estimate the prefecture out-migration rates by age, sex and temporal period, so the incidence denominators are adjusted for population migration. Migration rates were not differential by dose.

Information on sociodemographic, lifestyle and other disease risk factors is available for about two-thirds of the atomic-bomb survivors. Certain analyses have been conducted to account for possible biases associated with lifestyle activities such as smoking habits (Furukawa *et al*., 2010; Grant *et al*., 2017), but smoking habits did not alter the risk estimates materially (Grant *et al*., 2017). Sociodemographic variations, such as urban/rural differences, have been examined to a limited extent. Data on a number of medical and lifestyle risk factors such as smoking, alcohol consumption, and dietary effects for heart disease, cataracts, and other noncancer effects are available for AHS subjects and have been used to adjust pertinent results in that subcohort. Broadly speaking, little confounding by lifestyle variables has been seen, because their distributions tend not to vary across the dose range. A more detailed summary of epidemiologic uncertainties is available in NCRP Report No. 171 (NCRP, 2012).

Background disease rates in Japan have historically differed from those in western populations (*e.g*., higher Japanese rates of stomach cancer, liver cancer and stroke; lower rates of breast cancer, colon cancer and ischemic heart disease), which creates uncertainties about how to extrapolate atomic-bomb survivor risk estimates to western populations. This has usually been approached as an across-the-dose-range generalization issue (*e.g*., ERR vs. EAR extrapolation), and there is no information about how this might affect low-dose risk estimation.

4.1.3 *Statistical Results*

The analyses of the LSS data have generally used fine gradations of dose (about 20 categories) and have incorporated adjustments for city, sex, age at exposure and attained age, plus various other factors in sensitivity analyses. Various past analyses of the LSS cohort had indicated that the dose response for all solid cancer incidence or mortality fits a linear model across the full dose range better than a linear-quadratic (upward curvature) or pure quadratic function. In the latest LSS report of mortality through 2003, a linear-quadratic model did not improve the fit ($p = 0.36$) for all solid cancer across the full dose range, and a purely quadratic model provided a significantly poorer fit than the linear model (Ozasa *et al*., 2012). The estimated lowest dose range with a significant ERR for all solid cancer was 0 to 0.20 Gy, and a formal dose-threshold analysis indicated no threshold; *i.e*., zero dose was the best estimate of the threshold.

However, the mortality report (Ozasa *et al*., 2012) showed that when the data were analyzed over the range of 0 to 2 Gy, there was statistically significant upward curvature, with a ratio of the dose-squared to linear dose

coefficients (α/β ratio) of 0.81 (95 % CI 0.08, 8.6) (Ozasa *et al*., 2012). Nevertheless, since curvature could be a result of nonlinear deviations in various parts of the dose range, an analysis was needed to clarify the risk and degree of uncertainty specifically in the low-dose range.

An important issue regarding the LNT model is the nonparametric slope of the dose response in the low-dose range. About 68,000 LSS survivors had estimated colon doses less than 100 mGy. Evaluating the low dose uncertainties is especially problematic, because conventional parametric LNT model analyses implicitly assume the absolute width of the confidence intervals gets narrower as the dose goes lower (Figure 3.1), an assumption that is unlikely to be true. Figure 4.1 shows the confidence band at doses less than 500 mGy based on a nonparametric method that does not utilize the best-fitting LNT model for the most recent solid cancer mortality data. The 95 % confidence band is broad and compatible with no excess risk below about 150 mGy but is more compatible with the LNT model throughout the lower dose range. Another relatively nonparametric approach to fitting a model of the solid cancer incidence data for 1958 to 1998 (Preston *et al*., 2007) found the nonparametric fit over the entire dose range was virtually identical to the best-fitting linear model (Furukawa *et al*., 2015). But when doses of 200 mGy and under were examined, Furukawa *et al*. (2015) found that the confidence band in that dose range was considerably wider than the estimate from the best-fitting linear model. Their semiparametric analysis indicated clear excess risk above 100 mGy, but below 100 mGy the confidence bounds did not exclude either no risk or a linear dose response, though the slope was generally positive below 200 mGy.

As seen in Figure 4.1 for solid cancer mortality, up to about 200 mGy the risk estimates for the LNT and nonparametric models were essentially identical, but above that level the nonparametric slope was flatter than the linear model. Examination of the dose response for the full dose range or the 0 to 2 Gy range suggests that excess risk was relatively depressed compared to the linear model over the range of roughly 0.2 to 0.7 Gy for unknown reasons, and this at least partly explains the significant upward curvature over the 0 to 2 Gy range (Ozasa *et al*., 2012).

New update of cancer incidence: An 11 y update of solid cancer incidence in the LSS cohort was recently reported (Grant *et al*., 2017), representing follow-up through 2009, 64 y after the atomic bombings. After reductions due to cancer or death before the incidence study began in 1958, or inability to estimate radiation doses, 105,000 were included in the study cohort. As of 2009, 63 % of the cohort was deceased. The analysis utilized the improved individual dose estimates mentioned above and for the first time included smoking as a potential confounder or effect modifier. They estimated 992 excess solid cancers were attributable to radiation exposure.

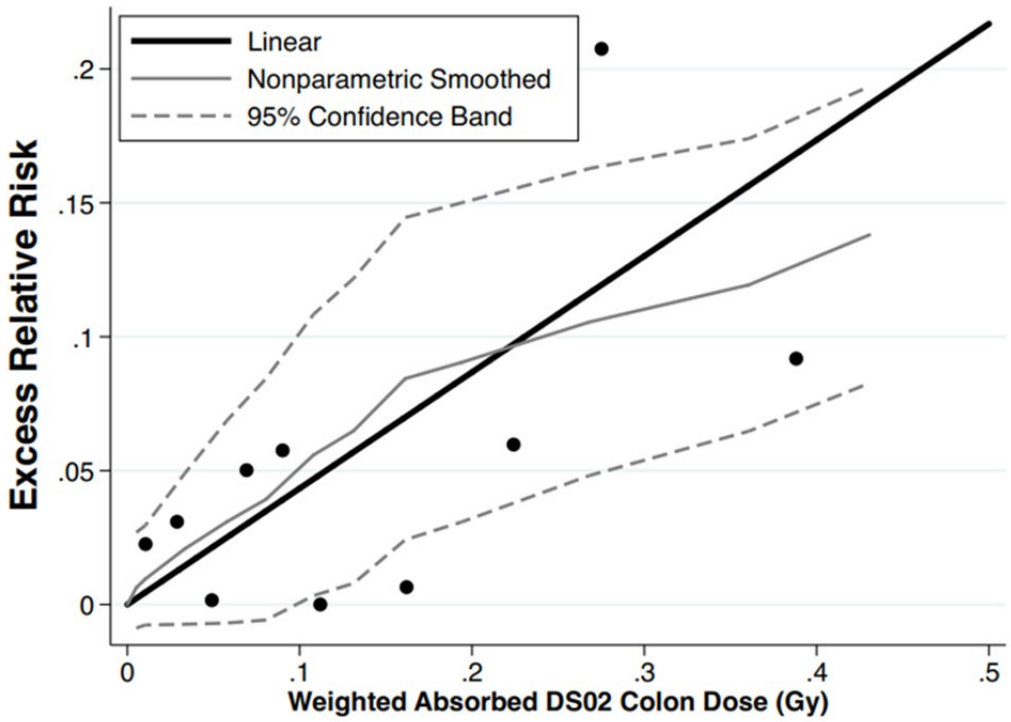


Fig. 4.1. Solid cancer mortality risk during 1950 to 2003 over the weighted absorbed colon dose range of 0 to 0.5 Gy, from the LSS cohort of atomic-bomb survivors (Ozasa *et al*., 2012). The dark solid line represents the linear fit over the full dose range. The lighter solid line is a nonparametric, lowest- smoothed fit to the 0 to 0.5 Gy data with 95 % CI shown by the dashed lines. (Based on Report 14 mortality data available online at http://www.rerf.jp)

Some important patterns of risk have continued. The ERR Gy^{-1} for total solid cancers is greater for those young at exposure, decreasing by 21 % per decade of age at exposure. The EAR estimates were likewise greater for those young at exposure. The ERR Gy^{-1} also decreased with attained age, independent of age at exposure, and the decrease was significantly steeper in males than in females; the sex-averaged decrease in the ERR with attained age was proportional to age to the power of 1.66. They reported a decreasing ERR estimate with increasing attained age which occurred because, while the excess rates increase with increasing age, their rate of increase is slightly less than the increase in baseline rates (Grant *et al*., 2017).

The modeled sex-averaged ERR of 0.50 Gy^{-1} (95 % CI 0.42, 0.59) for all solid cancer, with exposure at age 30 and follow-up at age 70, was very similar to the prior report of 0.47 Gy^{-1} (Preston *et al*., 2007). Taking account of smoking made only a small difference in the radiation risk estimate (ERR Gy^{-1} of 0.47, 95 % CI 0.39, 0.55 using a multiplicative smoking-radiation model). As in the prior report, females had a higher ERR Gy^{-1} (0.64, 95 % CI 0.52, 0.77 for females; 0.27, 95 % CI 0.19, 0.3.7 for males) based on linear models. Part, but not all, of the sex difference was attributable to the higher baseline cancer rates in males. The excess absolute risk (EAR per 10,000 person-years) was 42.9 for males and 54.7 for females at 1 Gy, but the EAR for males at 100 mGy was only about 55 % as large as for females because of the significant quadratic component of the male risk.

The lowest dose range that showed a statistically significant dose response using the sex- averaged linear ERR model was 0 to 100 mGy with an excess relative risk estimate of 0.49 Gy^{-1} (95 % CI: 0.026 to 1.01; $P = 0.049$), virtually identical with the estimate of 0.50 over the full dose range. For the sexes combined, over the full dose range the linear-quadratic model fit the data better than the pure quadratic model ($p < 0.001$), indicating there is a positive slope at low doses. Tests for a dose threshold did not indicate a statistically significant threshold.

The main difference in risk estimation from the prior cancer incidence report (Preston *et al*., 2007) was increased evidence of upward curvature in the dose-response curve ($p = 0.03$, sex- averaged). There was relatively strong evidence of curvature among males (α/β ratio of 1.3, $p = 0.002$) but no evidence of curvature among females (α/β ratio of 0.08); the male/female difference in curvature was statistically significant ($p = 0.02$). Similarly, when the excess absolute rate (EAR) model was examined, there was significant curvature in men but not in women.

Closer examination of the dose-response curve for males indicated that the upward curvature occurred mainly because of a flat dose response over the range of about 0.2 to 0.75 Gy, whereas there was an upward slope below 0.2 Gy. The dose-response slope for males over the low-dose range of 0 to 100 mGy, while quite uncertain, was 0.33 Gy^{-1} which was nominally higher than the male ERR Gy^{-1} estimate over the full dose range of 0.27.

The interpretation of the gender-related difference in curvilinearity is complex. When sex- specific cancers were removed, the curvature increased among females, though not significantly, likely due to removing breast cancer which has linear dose-response characteristics, and also suggesting that different subsets of cancer types have varying degrees of curvilinearity.

A major factor that drove the tendency for curvilinearity in these updated analyses was the newly revised dosimetry, which featured the incorporation of more extensive terrain shielding factors and improved accuracy of the dose data (Cullings *et al*., 2017). Another indication of the role of changed dosimetry in the newfound curvature was the fact that, when the new dosimetry was applied to the data of the prior tumor incidence report through 1998, curvature also was found in those data, unlike with the previous dosimetry (Preston *et al*., 2007). The upward curvature seen in males does not necessarily argue against LNT; it may rather suggest a LDEF > 1, *i.e*., a lower slope at low doses than at high doses.

It also is possible that shapes of the dose-response curves may differ for various individual cancer sites (Section 3.4.1). However, the relatively small number of cancers for individual sites means that the statistical power to detect nonlinearity is limited. In the Preston *et al*. (2007) analysis of the incidence of solid cancers, no evidence for nonlinearity was found ($p \geq 0.4$) for stomach, colon, liver, breast, bladder or brain/central nervous system cancers. There was strong evidence of radiation risk, along with weak suggestions of convex curvature for lung cancer ($p = 0.2$) and thyroid cancer ($p = 0.1$), and a clear indication of upward curvature for non-melanoma skin cancer ($p = 0.005$). However, a new LSS report of lung cancer incidence, adjusted for smoking, found an ERR Gy^{-1} for lung cancer of 0.81 (95 % CI 0.51, 1.18) but no indication of quadratic curvature ($p > 0.5$) (Cahoon *et al*., 2017a). As was noted in a previous NCRP report, "For analyses of various subtypes of cancer or other disease, the numbers are much smaller than for total solid cancer or broad categories of noncancer disease, so it is difficult to assess the specificity versus generality of particular shapes of the dose-response functions" (NCRP, 2012).

4.1.4 *Study Strengths and Weaknesses*

The LSS cohort of atomic-bomb survivors has provided important data because it is a large cohort with accurate dosimetry, a wide dose range, all ages at exposure and over 60 y of high-quality follow-up, a relatively large number of excess cancer cases (992) and cancer deaths (527), and features that enable relatively high statistical power and precision of risk estimates, including a statistically significant dose response for all incident solid cancer over the dose range 0 to 100 mGy. Regarding the LNT model, the LSS is limited to assessing the effects of a single, brief dose (a low-dose effectiveness factor, LDEF) and not protracted doses (dose-rate effectiveness factor, DREF). Analyses of earlier LSS data had suggested a single linear dose-response function

from doses of 2 to 3 Gy down to doses of 200 mGy or below. There are certain limitations to the LSS data, including that it provides data only on acute exposures; there may be some residual sample selection effects; the (especially historical) coding of cause-of-death on death certificates has uncertainties; out-migration of study subjects, which affects the denominators of the tumor incidence data, is only estimated; and the dose-response patterns may differ by tumor type. However, those methodological limitations tend to be minor, and the study represents a benchmark for other radiation epidemiology studies.

4.1.5 *Implications for the LNT Model and Radiation Protection*

A pure quadratic model provided a significantly poorer fit to the dose-response data than a linear model for both solid cancer incidence and mortality, and there was no evidence of a significant dose-response threshold for either endpoint. An analysis of the most recent mortality data indicated excess risk over the range of 0 to 200 mGy that was congruent with the LNT slope, and the new tumor incidence data showed a statistically significant dose-response slope over the range of 0 to 100 mGy. Nevertheless, the most recent solid cancer mortality and incidence data provide some evidence for upward curvature at lower doses among males but not females. This suggests a shallower dose-response slope at low doses than at higher ones and would imply a LDEF > 1. However, little or no curvature is seen in the dose response for females. In summary, the study provides strong indirect support for the use of a LNT model, with consideration of a DDREF factor, for use in radiologic protection. More direct evidence will have to come from the studies with low dose rates or many small dose fractions.

4.2 Worker Exposure Studies

Highlights

Radiation worker studies assess risks in worker groups exposed largely to many low doses received at a low dose rate, providing direct evidence of the validity of the LNT model. Further, cumulative doses, derived from dosimeter readings, can be moderate to high, especially for workers in early periods, so that studies can offer reasonable statistical power.

Large studies combining data from workers from more than one nuclear installation have now been conducted in a number of countries, and the largest study is the International Nuclear Workers Study (INWORKS), which has included workers from sites in the United States, United Kingdom, and France. INWORKS found associations between the cumulative dose from external sources of photons to the red bone marrow (RBM) and leukemia (excluding CLL) mortality, ERR Gy^{-1} = 2.96 (90 % CI: 1.17, 5.21), and the external dose to the colon and mortality from all solid cancers combined, ERR Gy^{-1} = 0.47 (90 % CI: 0.18, 0.79). For solid

cancer there was no evidence of nonlinearity ($p = 0.44$). These risk estimates are compatible with predictions based upon LSS data.

The Russian Mayak workforce also is of particular interest because of the high cumulative doses received (mainly at a low dose rate) by many workers during the early years of operations at this installation. An association has been found between the external dose to the RBM and leukemia (excluding CLL) incidence, ERR $Gy^{-1} = 3.57$ (90 % CI: 1.55, 8.22). For external dose to the colon and mortality from all solid cancers excluding lung, liver and bone (*i.e.*, excluding cancers at the major sites of plutonium deposition), ERR $Gy^{-1} = 0.12$ (95 % CI: 0.03, 0.21) with no indication of nonlinearity ($p > 0.5$)

Overall, the nuclear worker studies lend support to the inference that an excess risk of cancer exists following protracted exposure to low doses received at a low dose rate, and the excess risk is compatible with a LNT model. Though there are dosimetry uncertainties, particularly for early periods when occupational doses tended to be highest, the best worker studies provide the strongest support currently for a LNT model based on low doses and dose rates. Several worker studies are reviewed, with greater detail accorded to the more important studies. The studies include the15-Country study (Section 4.2.1), INWORKS study (Section 4.2.2), Mayak worker study (Section 4.2.3), Chernobyl cleanup worker study (Section 4.2.4), U.S. Radiologic Technologists study (Section 4.2.5), Million Worker study (Section 4.2.6), and Chinese medical x-ray worker study (Section 4.2.7). In addition to the text below, further systematic information is provided for most of these studies in Tables 4.1 to 4.4.

4.2.1 *15-Country Study*

As a context for recent radiation worker studies, the earlier Three-Country and 15-Country Worker Studies are summarized here. In 1988 the International Agency for Research on Cancer (IARC) agreed to coordinate an international collaboration aimed at increasing the statistical power of radiation workers studies (Wakeford, 2014). The first outcome of this work appeared in 1995 and involved seven cohorts of workers from three countries, three from the United States (including Hanford), three from the United Kingdom (including Sellafield) and one from Canada (the workers of Atomic Energy of Canada Limited, AECL) (Cardis *et al*., 1995). The Three- Country Study found a significantly elevated dose response for the risk of mortality from leukemia (excluding CLL) and the cumulative dose from external sources of radiation (ERR $Sv^{-1} = 2.18$, 90 % CI: 0.13, 5.7), but the equivalent estimate for all cancers except leukemia was slightly, and nonsignificantly, negative (ERR $Sv^{-1} = -0.07$, 90 % CI: –0.39, 0.30). The confidence intervals for both leukemia (except CLL) and other cancers were quite wide and compatible with a range of possibilities at low doses, including for other cancers either no risk or risks larger than the estimates from the atomic-bomb study (Cardis *et al*., 1995).

The study was later extended to 15 countries, and reported in several publications (Cardis *et al*., 2005b; 2007; Thierry-Chef *et al*., 2007; Vrijheid *et al*., 2007a; 2007b). While the number of countries that contributed data on workers was considerably expanded in the 2007 reports, updating of the cohorts that contributed to the 1995 analysis was incomplete. In particular, the U.S. cohorts contributed the same underlying data to the 15-Country Study as they had to the Three-Country Study, but a number of exclusions were made in the 15-Country Study of data that had been used in the Three-Country Study. Workers with substantial exposures to internal emitters and/or neutrons were excluded (Vrijheid *et al*., 2007b), which was important because these workers tended to have the highest external doses.

4.2.1.1 *Dosimetry*. The dosimetry for the Three-Country Study (Cardis *et al*., 1995; Fix *et al*., 1997) evolved from three separate investigations of dose response relationships for worker cohorts in the United States (Gilbert *et al*., 1993), the United Kingdom (Carpenter *et al*., 1994) and Canada (Gribbin *et al*., 1993). The dosimetry for the 15-Country Study (Cardis *et al*., 2005b) that evolved from the Three-Country Study incorporated an analysis of exposure conditions in the workplace (predominant energy and geometry of exposure), dosimetry technology, calibration practices, and administrative procedures and is described by Thierry-Chef *et al*. (2007). Accounting for these factors in the dosimetry was important because of major changes in the evolution of radiation protection methods and policies over the years 1943 through the 1980s. This work by Thierry-Chef *et al*. (2007) was a significant improvement in the overall dose estimates available for epidemiologic study.

The 15-Country investigators developed bias factors (B, systematic error) and uncertainties (K, characterizing the uncertainty/spread of the values) following principles described by the 1.05 to 1.2 (among lung, red bone marrow, and colon). Each source of uncertainty applied to the dosimetry record was considered and identified as shared or unshared, as was the uncertainty resulting from variation in the correct bias factor among workers (Thierry-Chef *et al*., 2007). Despite these improvements, there are concerns about doses recorded during early time periods of the study, especially between 1944 and 1957 when annual recorded doses tended to be higher than in later years and major changes were occurring in dosimetry measurement technology and administrative practices. Furthermore, the impact of neutron dose and internal dose on the dose response is not clear, and there is a distinct possibility that better accounting of these doses could affect the estimates of risk. The methods of accounting for doses that were below the limits of detection were another source of uncertainty. In summary, although the 15-Country Study dosimetry effected a significant improvement in the overall dose estimates, questions of underestimation of dose due to missed dose, neutron dose, and internal dose remain, as acknowledged by the dosimetry investigators (Thierry-Chef *et al*., 2015).

4.2.1.2 *Epidemiologic Methods, Findings and Issues*. The 15-Country Study included radiation workers from 154 different facilities. For inclusion, each facility cohort had to meet certain defined criteria regarding completeness of the cohort, routine external radiation monitoring, socioeconomic status (*e.g.*, blue/white collar), and adequate vital status and cause of death information (Vrijheid *et al*., 2007b). The epidemiologic analyses were adjusted to take into account the main sources of potential confounding: sex, attained age, calendar period, facility, and in some analyses, duration of employment and socioeconomic status. Although the trend of risk with cumulative external dose was positive for mortality from leukemia excluding CLL, somewhat surprisingly, given the findings of the Three-Country Study, it was not statistically significant (ERR Sv^{-1} = 1.93, 90 % CI < 0, 7.1). However, the association with external dose for all other cancers was both positive and significant (ERR Sv^{-1} = 0.97, 95 % CI: 0.14, 1.97). Tests for nonlinearity were nonsignificant. The high risk estimate for cancers other than leukemia was barely compatible with the prediction of standard risk models (*e.g.*, Preston *et al*., 2007); however, including the cohorts without socioeconomic-status data or removing the statistical adjustment for duration of employment decreased the risk estimate by 40 to 70 % (Cardis *et al*., 2007), indicating potential confounding.

The interpretation of the 15-Country Study was not straightforward for several reasons (Boice, 2010; Dauer *et al*., 2010; Shigematsu, 2005; UNSCEAR, 2008; Wakeford, 2005; 2009), especially the surprisingly large influence of the Canadian workers on the risk estimate for all cancers except leukemia. Although the Canadian workers contributed around 4 % of the deaths, the exclusion of these workers caused a ~40 % reduction in the risk estimate (Wakeford, 2005) because of their anomalously high risk coefficient (Ashmore *et al*., 2007; UNSCEAR, 2008). When cancers of the lung and pleura are removed from the 15-Country analysis of cancers other than leukemia, the statistical significance disappears (ERR Sv^{-1} = 0.59, 95 % CI: –0.29, 1.70). Among other issues, some of the concerns included bias, confounding (mixed evidence regarding smoking), the selection of workers to include (or exclude) from the study, analytical issues and low statistical power (Boice, 2010). Scrutiny of the previous findings, including the Three-Country Study (Cardis *et al*., 1995), revealed an apparent upward change in risk estimates for the group of all cancers except leukemia that coincided with the start of the use of the Canadian National Dose Registry (NDR) data for analyses (Wakeford, 2009). Ashmore *et al.* (2010) examined the NDR data for the Atomic Energy of Canada, Limited (AECL) workers and identified a number of possible deficiencies in the AECL worker data used in the 15-Country Study, particularly those relating to the data before 1971.

Zablotska *et al.* (2013b) recently reported the findings of an updated study of Canadian nuclear industry workers following a detailed check of dosimetry and employment records, which resulted in several changes in the AECL data in the NDR. It was suggested that findings of high risk for the early AECL workers was probably due to missing dose information, rather than a real effect of radiation exposure, and they believed that use of the pre-1965 AECL worker data could not be justified until further investigation is undertaken. When the early

AECL workers were excluded, there was a notable reduction in the ERR Sv^{-1} for mortality from all solid cancers in the Canadian cohort. The Zablotska *et al*. (2013b) findings confirmed that both the original Canadian and the 15-country solid cancer risk coefficients appear to be anomalously high. When the Canadian data were removed from the 15-Country analysis, the dose response for cancers other than leukemia was no longer statistically significant (ERR Sv^{-1} = 0.58, 95 % CI: –0.22, 1.55), though the risk estimate was still as high or higher than for the matched worker subset of the LSS.

4.2.1.3 *Study Strengths and Weaknesses*. The Three-Country and 15-Country Studies were the first major attempts at examining international pooled data on protracted radiation exposures and cancer risk and were successful in eliciting extensive international collaboration. The 15-Country Study investigators realized the importance of improving and harmonizing the dosimetry data and made a first attempt to do so. However, questions remain regarding underestimates of dose, due to missed dose and unincorporated neutron exposures, as acknowledged by the dosimetry investigators (Thierry-Chef *et al*., 2015). An undetected problem with the dosimetry in the Canadian cohort led to issues of bias in the derived risk estimates. There were also questions about subject selection procedures: the exclusion from the analyses of certain cohorts (because occupational status information considered inadequate) or workers who had received substantial internal or neutron exposures (which eliminated many of the higher dose workers).

4.2.1.4 *Implications for the LNT Model and Radiation Protection*. The recent re-evaluations illustrate the care that must be exercised in collating worker data and the problems that can arise, especially when using data that may have been collected for purposes other than epidemiology (Wakeford, 2014). The pooled 15-Country Study does not at this time provide sufficiently reliable information upon which to evaluate the LNT model for radiation protection purposes. However, the 15-Country Study has been superseded by the INWORKS study.

4.2.2 *INWORKS Study*

The International Nuclear Workers Study (INWORKS) is the latest international collaboration to be coordinated by the International Agency for Research on Cancer (IARC) for examining the health of workers in more than one country who were exposed occupationally to ionizing radiation (Daniels *et al*., 2017; Gillies *et al*., 2017; Hamra *et al*., 2016; Laurier *et al*., 2017; Leuraud *et al*., 2015; Richardson *et al*., 2015; Thierry-Chef *et al*., 2015). The following summary considers the study's contribution to the evaluation of the LNT model. INWORKS combines three large cohorts of radiation workers from five nuclear facilities in the United States, nuclear industry workers in France, and workers included in the U.K. National Registry for Radiation Workers (NRRW), the results

of which have already been individually reported (Metz-Flamant *et al*., 2013; Muirhead *et al*., 2009; Schubauer-Berigan *et al*., 2015). These represent updated data from those available for the 15-Country Study.

The INWORKS findings published to date address mortality from leukemia and other hematopoietic and lymphatic cancers or all cancers except leukemia (or all solid cancers in the French study) and from cardiovascular diseases in relation to doses received in the workplace from external sources of photons (mainly gamma rays). The INWORKS study includes a total of 308,297 workers monitored for exposure to external sources of ionizing radiation, with 8.2 million person-years of follow-up. Follow-up ran from 1944 (or the start-up of the facility) to 2005 in the United States, from 1955 to 2001 in the United Kingdom, and from 1968 to 2004 in France.

4.2.2.1 *Dosimetry*. The INWORKS study included dosimetry for 20 different nuclear sites/organizations in three countries (Thierry-Chef *et al*., 2015). Dosimetry was based on individual personal dosimeter readings dating from 1944 to 2005, which provided an extraordinarily large dataset. Although the availability of individual dose information is a clear strength of INWORKS, the dosimetry is complex, with mixed radiation fields including varying gamma/x-ray energies, neutron exposure and internal exposure. The long time period presents a technical challenge due to changes in dosimetry technology, and the evolution of administrative exposure policies and recording practices. Furthermore, the dosimetry is difficult to verify from the open literature because it is builds upon dosimetric work performed for a series of independent epidemiologic studies that reach back almost four decades, and the original dosimetry is mostly inaccessible.

The methods used to extract doses from the original records estimating systematic and random uncertainty and bias were described by Fix *et al*. (1997) and Cardis *et al*. (1995) for the Three-Country Study and by Thierry-Chef *et al*. (2007) and Cardis *et al*. (2005b; 2007) for the 15-Country Study. However, none of the published articles supporting INWORKS dosimetry provide sufficient details to completely understand all aspects of the methodology used, which requires a review of supporting literature back to its origins. Even this approach does not give a clear picture of the dosimetry history, but it allows us to make some observations about strengths and weaknesses of the methodology. For our review, we found it helpful to consider the individual facilities, when possible, which was critical to evaluate consistency in dosimetry among different sites and countries.

The U.S. cohort of INWORKS consisted of 101,428 workers from five sites, each site having different administrative policies and methods for recording dose and exposure conditions. The Hanford site accounted for the largest number of workers (34,278) and highest cumulative collective gamma dose (~880 person-Sv) in the combined U.S. cohort (Schubauer-Berigan *et al*., 2015). The characteristics and dosimetry of Hanford workers

were documented extensively in studies led by Gilbert (Gilbert and Marks, 1979; Gilbert, 1990, 1991; Gilbert *et al*., 1989; 1993). Later, the importance of accounting for random and systematic errors and bias in the dosimetry was recognized (NA/NRC, 1989) which resulted in revised dose estimates (Fix *et al*., 1994; 1997; Gilbert, 1998; 2009; Gilbert and Fix, 1995; Gilbert *et al*., 1996). These revisions significantly improved the quality of the dosimetry and accounted for a number of potential factors affecting individual exposures that were not specifically documented in the records. For the ORNL cohort (Frome *et al*., 1997; Schubauer-Berigan *et al*., 2015; Wing *et al*., 1991; 1993) a methodology was developed by Watkins *et al*. (1997) to adjust doses for uncertainties and bias similar to that at Hanford but applying site-specific parameters. Dosimetry for workers from Portsmouth Naval Shipyard (Daniels *et al*., 2004), Idaho National Laboratory (Schubauer-Berigan *et al*., 2005), and the Savannah River Plant (Richardson *et al*., 2007) has also been reported but not as thoroughly investigated for uncertainties and bias as Hanford and Oak Ridge. Those sites included radiation workers beginning in 1952, 1952, and 1949, respectively.

The U.K. cohort included some 175,000 workers from 11 organizations. It was based on the National Registry for Radiation Workers (NRRW) and is documented in a series of reports (Kendall *et al*., 1992; Muirhead *et al*., 1999; 2009). The largest number of workers (40,284) was employed by British Nuclear Fuels Ltd. (BNFL) and accumulated a collective dose of 2,159 person-Sv. Sellafield is the most important of the five BNFL sites, contributing approximately 1,700 person-Sv. The French study (Metz-Flamant *et al*., 2013) included 59,021 workers from four organizations with a cumulative collective dose of about 1,327 person-Sv. Among these cohort groups that form the INWORKS study, the dosimetry at Hanford and Sellafield are especially important to scrutinize because of their relative importance in contribution to cumulative dose and number of workers during early time periods compared to other facilities.

As mentioned above, considerable improvements in dosimetry were made over time in both the U.S. and U.K. cohorts in addressing uncertainty and bias in recorded doses. Another adjustment to improve dose estimates was in the U.S. Oak Ridge and the U.K. cohort to account for missed dose. Missed dose in this context refers primarily to large numbers of workers whose dose was recorded as zero because readings were less than the level of detection. For example, dosimeters were exchanged weekly (or even daily) in many facilities until the late 1950s and, as in the case of Hanford workers, as many as 75 % of the workers were noted to have been assigned zero dose (s) in one or more years (Gilbert, 1990). In the early years the level of detection for film badge dosimeters was high at most facilities, ranging between 0.3 to 0.5 mGy, which with weekly badge readings could theoretically amount to even as much as 25 mGy of missed dose in a year. Recognition of the potential importance of missed dose among early nuclear workers in epidemiologic studies and methods for estimating missed dose have been reported (Inskip *et al*., 1987; Kneale *et al*., 1991; Maienschein and Peelle, 1992; Smith and Inskip, 1985; Strom, 1986; Strom *et al*.,

1996; Tankersley *et al*., 1996). Although the amount of total dose missed for many individuals may be small, if missed dose is not addressed appropriately the cumulative missed dose in the early time period could be significant for some individuals. The extent to which missed dose was accounted for in INWORKS, if at all, is not clear. In one of the INWORKS cohorts, US Oak Ridge workers, a detailed analysis led to the conclusion that the effect of missing doses was to introduce an upward bias in the dose-response risk estimates (Frome *et al*., 1997), but comparable analyses are not available for other individual cohorts in the study.

Considerable effort has been invested in the assessment of radiation exposures in the workplace by the 15-Country and INWORKS dosimetry teams (Thierry-Chef *et al*., 2007; 2015). Various types of dosimeters were evaluated over the periods of exposure, and panels of experts were convened to characterize workplace conditions, monitoring routines, photon energies and exposure geometries over the periods of the study. A database of correction factors was developed to address geometries of exposure, energies of photons, and various other sources of bias and uncertainty (Thierry-Chef *et al*., 2007). Administrative practices such as failure to document measured doses, missing (or not worn) badges, and the treatment of doses below the limit of detection were also evaluated, but were considered to be of minor importance by the INWORKS investigators. Additionally, some workers had recorded doses from neutrons (13 % of workers) or from internally deposited radioactive materials ("internal emitters"; 17 %), but these doses were not included in the dose estimates used in INWORKS. The dose records were used to derive absorbed doses to the RBM for the analyses of hematopoietic and lymphatic malignancies, and doses to the colon for analyses of all cancer other than leukemia (Thierry-Chef *et al*., 2015). The average estimated cumulative dose to the colon among all workers was 17.4 mGy, or among the 257,166 exposed workers was 20.9 mGy (90^{th} percentile 53.4 mGy, maximum 1331.7 mGy) and the collective dose was 5,370 person-Gy. The mean RBM dose for all workers was 16 mGy (10^{th} percentile 0.0, 90^{th} percentile 40.8 mGy) (Leuraud *et al*., 2015).

The estimated uncertainties in the INWORKS dosimetry were generally quite low (K values for individual *Hp*(10) doses ranging from 1.2 to 1.7, corresponding to geometric standard deviations (GSDs) of 1.1 to 1.3 or CV from ~0.2 to ~0.3) compared to other large scale dosimetry studies, especially environmental studies. These low values are to be expected because of the widespread availability of personal dosimetry data. An analysis of the various sources of shared and unshared uncertainty (Thierry-Chef *et al*., 2007) concluded that most of the uncertainty was Berkson error and thus would probably introduce little attenuation into the risk estimates. Although no specific uncertainty was assigned to the bias factors used to correct film badge readings, the uncertainty in bias (B) is included in the estimates of uncertainty (K) for individual doses based on badge readings, as is explained by the National Research Council (NA/NRC, 1989). However, the authors' assessment of uncertainties sometimes did not take into account potential "missed doses" below the limits of detection, nor the neutron or internal doses.

514

515 Addressing neutron exposure and internal exposure is complex for any analysis of dosimetry, especially when
516 these exposures occurred during the early years when measurement technology was far less advanced than today.
517 One complication is differences in recording practices between different facilities and countries at the time. Another
518 challenge is the effectiveness of neutron dosimeters at various energies. None of the dosimeters was able to measure
519 the full energy range, and some workers with the potential for receiving doses from neutrons may not have been
520 monitored for such exposure. This deficiency is noteworthy because the highest exposures likely occurred during
521 these early years. These technical deficiencies could result in the potential for considerable underestimation of dose
522 from neutrons and internal exposure. Although this underestimation is acknowledged by Thierry-Chef *et al*. (2015)
523 and considerable effort was expended trying to resolve this question of dose from neutrons and internal dose, there
524 remains a question of the underestimation of dose from these sources during the early years of the study. If
525 excluded neutron doses and internal doses are positively correlated with included photon doses, the dose response
526 reported in INWORKS for photon dose will be an overestimate because of the excluded doses.

527

528 To summarize, while the availability of dose information on an individual basis is a clear strength of this
529 INWORKS, the dosimetry is complex and presents a technical challenge to researchers because of the long time
530 period covered, changes in dosimetry technology, evolution of administrative exposure and recording policies,
531 mixed radiation fields including varying gamma/x-ray energies, internal exposure, neutron exposure, and missed
532 dose. Some important details of the dosimetry are very difficult to verify from the open literature because they
533 involve several layers of dosimetry efforts that reach back almost four decades and because of the inaccessibility
534 of the original dosimetry. Even after our review to date, it is still not clear whether the individual dosimetry
535 records included adjustments by previous investigators and how bias and uncertainty were addressed among the
536 various cohort groups in the study. The technical challenge of the dosimetry and the positive findings of the
537 epidemiology stress the importance of making the dosimetry as state-of-the-art, complete, thorough and
538 transparent as possible, since minor variations in the cumulative dose could impact the outcome of the study.

539

540 It is extremely important to pay particular attention to the doses and their uncertainties for the early periods of
541 exposure (1940s and 1950s) when doses tended to be highest, since those with higher cumulative doses tend to
542 drive the analytic results. But this is the period when the least information from the historical records is available,
543 so uncertainties potentially would be the greatest. It is unclear how adequately the investigators surmounted this
544 challenge.

545

546 **4.2.2.2** *Epidemiologic Methods, Findings and Issues*. Characteristics of the INWORKS consortium (nuclear
547 workers in France, United Kingdom, and United States, 1944 to 2005) are given in Table 4.5, and further details are

548 Table 4.5—*Characteristics of cohorts included in the INWORKS consortium (nuclear workers in*
549 *France, United Kingdom, and United States, 1944* to *2005)*.
550

Characteristics	
Calendar years of follow-up	1944 – 2005
Workers (no.)	308,297
Exposed workers (no.) [a]	257,166
Person years (millions)	8.2
All causes of death	
Collective dose (person Gy)	5370.3
Average individual cumulative dose (mGy)[b]	20.9
No. workers with cumulative dose >100 mGy (percentage of all workers)	18,384 (6.0 %)
All causes	66,632
All cancer	19,748
All cancer other than leukemia	19,064
Solid cancer	17,957
Solid cancer other than lung cancer	12,155
Leukemia, excluding chronic lymphocytic type	531
Ischemic heart disease	17,463
Cerebrovascular disease	4,444

[a]Workers with cumulative dose greater than zero.

[b]Average estimated cumulative dose to the colon, among exposed workers

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given in the original publications (Gillies *et al*., 2017; Hamra *et al*., 2016; Leuraud *et al*., 2015; Richardson *et al*., 2015; Thierry-Chef *et al*., 2015). The table shows that 257,000 out of the 308,000 workers in the study monitored for exposure to radiation had at least one recorded dose greater than zero. The epidemiologic methods of cohort composition, occupational record compilation, follow-up and mortality documentation are described in the original cohort publications or the pooled analysis reports for the individual countries (Metz-Flamant *et al*., 2013; Muirhead *et al*., 2009; Schubauer-Berigan *et al*., 2015). The length of follow-up was up to 61 y, with a mean of about 27 y.

The analyses of the data were conducted using conventional Poisson regression methods, with adjustment for attained age, country, sex, year of birth, socioeconomic status, duration of employment or radiation work, and neutron monitoring status. Nonlinear dose-response models were compared to the linear model, and a variety of sensitivity analyses were conducted, including analyses of the low-dose part of the dose-response curve.

The principal results thus far from INWORKS are for all cancers excluding leukemia (or for French workers, only solid cancers) and for all leukemias excluding CLL, which are summarized below. Table 4.6 compares the risk estimates reported in the original studies that constitute this study with the results of the pooled INWORKS analysis.

One superficially puzzling feature of the INWORKS results shown in Table 4.6 is that the ERR Gy^{-1} estimates seem to be higher than might be predicted from the estimates reported by the separate studies of individual countries for the ERR Sv^{-1}. Though some of the differences in risk estimates may be caused by different selection factors for inclusion in the studies (INWORKS, but not the original studies, used a minimum of 1 y of work at a nuclear facility), the primary explanation for the differences in risk estimates is likely to be the difference in the doses used in INWORKS and in the original studies. The original studies used the recorded *H*p (10) doses based on personal dosimeters, with no adjustment to derive organ/tissue-specific doses. INWORKS derived absorbed doses to the colon for the analysis of all cancers other than leukemia, and absorbed doses to the red bone marrow for the analysis of leukemia (Thierry-Chef *et al*., 2015). Because the INWORKS study used estimated doses for deeper tissues (colon or RBM) instead of the *H*p (10) estimates of the original studies, the doses would be lower and consequently the risk estimates per unit dose would be higher. Thierry-Chef *et al*. (2015) have tabulated summary data for the organ/tissue-specific doses used in INWORKS; overall the mean *H*p (10) dose was 25.2 mGy while the mean estimated colon dose was 17.4 mGy and that to the RBM was 14.9 mGy. For all cancer except leukemia (or solid cancers in the French study), the ERR estimate was 0.47 (90 % CI 0.18, 0.79) using estimated colon doses and 0.33 (90 % CI 0.12, 0.56) using the *H*p (10) doses (Richardson *et al*., 2015).

Table 4.6—*ERR/Sv (ERR/Gy in INWORKS) estimates as presented in the original studies of French (Metz-Flamant et al., 2013), United Kingdom (Muirhead et al., 2009), and United States (Schubauer-Berigan et al., 2015) workers, respectively; and in INWORKS (Richardson et al., 2015).*

	France [*H*p(10) dose]	United Kingdom [*H*p(10) dose]	United States [*H*p(10) dose]	INWORKS [*H*p(10) dose]	INWORKS (colon dose)
All cancers	N/Aa	0.28	0.14	0.35	0.48
excluding leukemia		(0.02, 0.56)b	(–0.17, 0.48)	(0.14, 0.57)	(0.20, 0.79)
Solid cancers	0.34	N/A	N/A	0.33	0.47
	(–0.56, 1.38)			(0.12, 0.56)	(0.18, 0.79)
All leukemias	3.96	1.71	1.7		2.96
excluding CLL	(<0, 16.82)	(0.06, 4.29)	(–0.22, 4.7)		(1.17, 5.21)

[a] N/A not available
[b] 90 % CI, except 95 % CI for the U.S. study.

A comparison was made in INWORKS (Richardson *et al*. (2015), supplement) of risk estimates for all cancers other than leukemia (or for France, solid cancers) using colon doses with those using doses from original records. The ERR Gy^{-1} and ERR Sv^{-1} estimates are shown in Table 4.6, where the first INWORKS column uses doses from original dose records and the second INWORKS column uses colon doses.

For the U.K. and U.S. workers (the cohorts that drive the INWORKS findings) the ERR Sv^{-1} result based on *H*p (10) doses from INWORKS (ERR Gy^{-1} of 0.33) is still notably above the two ERR Sv^{-1} values from the original studies, namely, 0.275 (90 % CI 0.02, 0.56) and 0.14 (90 % CI –0.17, 0.48), respectively. The reasons for this are unclear, though the inclusion of more short- term workers and of doses from neutrons and (some) beta-particle doses in the original studies but not INWORKS may affect the ERR Sv^{-1}, depending on the distribution of such doses relative to the included photon doses.

Table 4.7 shows several reported variations in INWORKS risk estimates according to which covariables were included in the model. The alternate risk estimates are 20 % to nearly 60 % lower than the main reported ones, depending on the covariables included. Particularly notable is the inclusion/exclusion of workers flagged for recorded neutron exposure in the last row of the table. The overall INWORKS ERR Gy^{-1} estimate of 0.48 for all cancer except leukemia includes an adjustment based upon their neutron monitoring flag (neutron exposure: no indication, >0 to <10 mGy, ≥ 10 mGy), but if no such adjustment is made (*i.e*., all workers are included, but no account is taken of neutron monitoring status) then the ERR Gy^{-1} estimate reduces to 0.20 (90 % CI: –0.03, 0.45). The reasons for this large shift in ERR estimates from 0.48 to 0.20 Gy^{-1} are unclear, but may relate to some confounding, especially since one might expect missing neutron doses in the risk modeling to cause overestimation, rather than underestimation, of risk if there was a positive correlation among workers between the neutron doses and external gamma doses, as might be expected. The potential for confounding is highlighted in the updated BNFL data for Sellafield (Gillies and Haylock, 2014).

Linear and categorical risk estimates are shown for the INWORKS study in Figure 4.2. The linear ERR coefficient in the INWORKS study was 0.47 (90 % CI 0.18, 0.79) Gy^{-1} for all cancer except leukemia. An added quadratic term was not statistically significant (p = 0.44). The INWORKS analysis of solid cancers other than lung, liver and bone gave an ERR Gy^{-1} of 0.51 (90 % CI: 0.15, 0.91), very similar to the risk estimate for all solid cancers. The exclusion of cancers of the lung, liver and bone excludes those sites of cancer most affected by doses from the internal deposition of plutonium, suggesting that internal plutonium doses did not have a marked effect upon the ERR Gy^{-1} estimates. A parallel finding was that an analysis adjusted for a flag for any known internal emitter exposure also showed only negligible changes in the ERR Gy^{-1}. The authors indirectly examined the

Table 4.7—*INWORKS Study: Comparison of risk estimates showing the effects of adjusting for different choices of covariables*.

Cancer Grouping	Primary Estimate[a] ERR (90 % CI) Gy^{-1}	Partially Adjusted Estimate ERR (90 % CI) Gy^{-1}
Solid cancer	0.47 (0.18, 0.79)	0.37 (0.14, 0.62)b
Solid cancer other than lung	0.46 (0.11, 0.85)	0.35 (0.07, 0.65)[b]
Cancer except leukemia	0.48 (0.20, 0.79)	0.20 (–0.03, 0.45)[c]

a The primary estimates reported by Richardson *et al*.(2015) were adjusted for country, age, sex, birth cohort, socioeconomic status, duration employed, and neutron monitoring status.
b These estimates were adjusted for country, age, sex and birth cohort, but not for socioeconomic status, duration employed, or neutron monitoring status.
c This estimate was adjusted for all the covariables listed in footnote A except for neutron monitoring status.

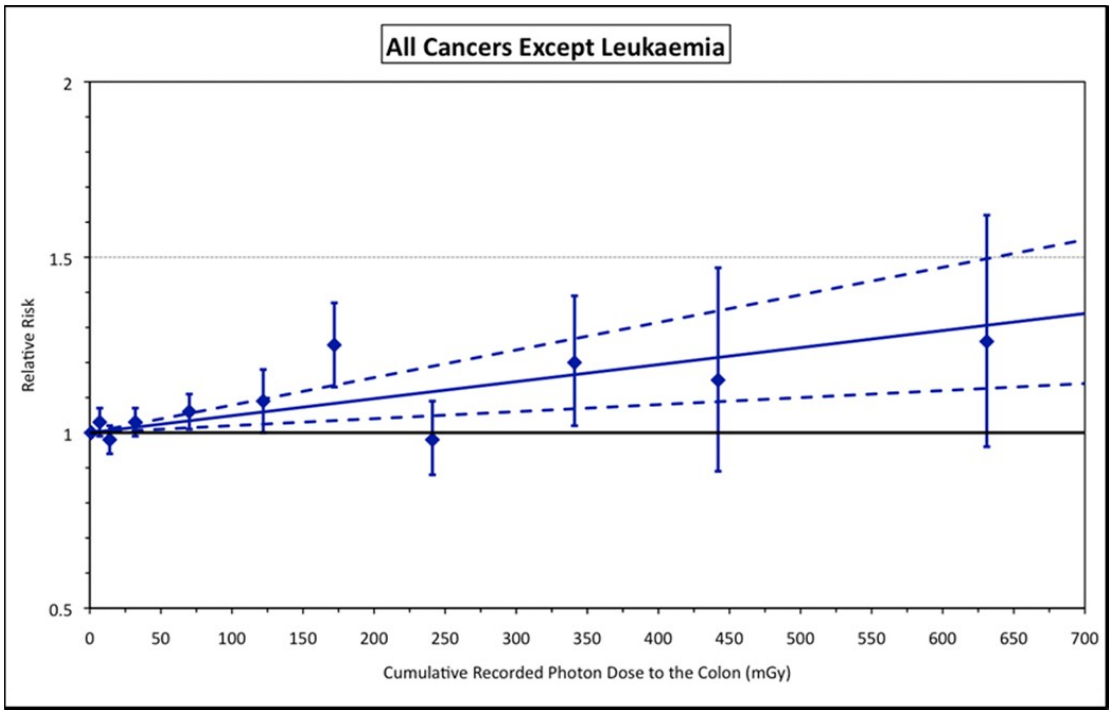


Fig 4.2. Relative risk of all cancer mortality other than leukemia by cumulative colon dose, lagged 10 y. Points and vertical lines are estimates and 90 % CI for dose categories; dashed lines are = 90 % CI for the linear model (adapted from Richardson *et al*., 2015)

possible confounding effects of smoking and asbestos exposure by examining the risk when excluding lung cancer, or both lung and pleural cancer, and found that the risk estimates did not change materially.

Richardson *et al*. (2015) examined the risk estimates for all cancers except leukemia (or all solid cancers for the French cohorts) for restricted ranges of worker dose (Table 4.8). Notably, even over the range of 0 to 100 mGy the risk was statistically significant (using their criterion of $p < 0.05$ on a one-tailed test). Thus there appears to be risk consonant with LNT in the lower dose ranges for all cancer except leukemia. However, the full picture of solid cancer risks will not be apparent until risk estimates from INWORKS for individual sites of cancer based on appropriate organ/tissue-specific doses become available.

Regarding the INWORKS leukemia findings, Leuraud *et al*. (2015) reported that for leukemia (excluding the chronic lymphocytic type; non-CLL) the linear ERR Gy^{-1} was 2.96 (90 % CI 1.17, 5.21). This compares to the atomic-bomb LSS estimated ERR Gy^{-1} of 2.60 at 60 y of age after exposure at age 30, for non-CLL leukemia incidence (Hsu *et al*., 2013). Leuraud *et al*. (2015) indicated that linear-quadratic or pure quadratic models did not substantially improve the model fit for non-CLL leukemia, although the dose response had too little precision to discriminate between the model fit of a pure linear and a pure quadratic model. They also showed that when the analyses were restricted to data for <300 mGy or <100 mGy, the risk estimates for non-CLL leukemia were essentially the same as for the entire dose range.

4.2.2.3 *Study Strengths and Weaknesses*. Owing to the size and nature of the workforces included in INWORKS, this study is the most statistically powerful of the radiation worker studies conducted to date; the major installations included in the study were largely established in the early years of the nuclear industry, when occupational doses were relatively high, and a substantial number of these workers employed in these early years, many with cumulative doses >100 mGy, have now died and thereby have contributed to the information and statistical power of the study. Attention was given to improving and harmonizing the dosimetric information. The high-quality follow-up of the worker cohorts was for up to 61 y, with good ascertainment of death due to malignancies. The statistics were strong, with examination of linear and linear-quadratic models and a number of sensitivity analyses.

A principal strength of INWORKS is that cumulative individual photon dose estimates are provided for over 300,000 workers using personal dosimeter data. This dosimetry is based on several decades of epidemiologic investigations and continued improvements in the dose assignments and associated uncertainties. The dosimetry is thorough, and technical methods applied seem to be advanced. Photon dosimetry was based on an extensive effort to harmonize a large database of dose measurements. However, the dosimetry was limited by uncertainties about

Table 4.8—*INWORKS study, excess relative risk estimates for mortality from all cancer except leukemia over restricted colon dose ranges*.

Dose Range (mGy)	ERR Gy^{-1} (90 % CI)
Full range	0.47 (0.18, 0.79)
0 – 200	1.04 (0.55, 1.56)
0 – 150	0.69 (0.10, 1.30)
0 – 100	0.81 (0.01, 1.64)

occupational doses received in the early years of the nuclear industry in general, which includes the photon doses that were the subject of the INWORKS analyses published to date.

A special concern pertains to neutron doses which were measured poorly in the early years due to technical limitations, and there will have been neutron exposures that were not recorded. The limited neutron information was used only semi-quantitatively in the analysis, and there was a puzzling result associated with the analysis of a semi-quantitative surrogate of neutron exposure. Further, in addition to neutron doses, doses from intakes of radioactive materials were also excluded from the analyses conducted in INWORKS. The impact of these dose exclusions and uncertainties upon the published findings of INWORKS will depend upon the degree of correlation between the included and excluded doses. If more actual doses were missed/underestimated in the early years, which is possible given that dose uncertainties were the greatest for the years when the photon doses also tended to be highest, this would reduce the ERR Gy^{-1} estimates that have been reported from INWORKS. The study also does not have any information on medical radiation exposures or on possible confounding lifestyle factors, but it is doubtful that these would change the radiation risk estimates much.

4.2.2.4 *Implications for the LNT Model and Radiation Protection*. Because of its size and the availability of personal dosimetry information, INWORKS (Richardson *et al*., 2015; Thierry-Chef *et al*., 2015) has the potential to contribute significantly to our understanding of radiation effects at low doses and low dose rate. There are uncertainties about the magnitude of risk in the INWORKS study associated with dose uncertainties and some variant results in the sensitivity analyses. Nevertheless, all the risk estimates are positive and commensurate with risks from the LSS cohort of atomic-bomb survivors, even for restricted low dose ranges. There is no indication of upward curvature or a dose threshold in the dose-response curve. Further, the ERR Gy^{-1} estimates from INWORKS are based on doses received at a low dose rate as many small doses over a number of years. Thus, this large study provides one of the strongest pieces of epidemiologic evidence that the LNT quantitative model is useful for radiation protection.

4.2.3 *Mayak Worker Study*

The Mayak Production Association (hereafter called "Mayak") was the first and largest weapons-grade plutonium (^{239}Pu) production plant in the U.S.S.R. It began operations in 1948 and includes radiochemical and plutonium production plants and nuclear reactor and auxiliary facilities. A large number of early workers were exposed to high levels of external gamma rays or internal alpha particles, or both. The studies have nearly 60 y of follow-up and individual dose estimates. Several recent reports have characterized radiation risks from low-LET exposures in the Mayak worker cohort, covering the incidence (Hunter *et al*., 2013) or mortality (Sokolnikov

et al., 2015; 2016) of solid cancers other than liver, lung and bone (to minimize the impact of plutonium exposure on risk estimates for external exposure), and hematopoietic cancer incidence (Kuznetsova *et al*., 2016). The full cohort consisted of about 25,000 Mayak workers (mortality study, or 22,000 in the incidence studies) who were first employed during 1948 to 1982.

4.2.3.1 *Dosimetry*. The 2008 Mayak Worker Dosimetry (MWDS-2008) provided annual external dose estimates for various organs for each cohort member. About 80 % of the external doses were based on personal dosimeter data and 20 % on reconstructed doses (Sokolnikov *et al*., 2015). Although only crude estimates of uncertainties were made, the GSD was reported as only 1.26 (Vasilenko *et al*., 2007a; 2007b). The raw film badge data were corrected for changes in badge types over time, photon energies and angular responses. For pre-1955 badges, fairly large and uncertain corrections were required to separate the high-energy beta response from the gamma response (Vasilenko *et al*., 2007b). Doses from medical fluoroscopic and x-ray examinations were also estimated but have not been used in most cohort analyses; however, they are not highly correlated with worker cumulative doses, so have little potential to confound the data.

About 15 % of the workers had indications of some exposure to neutrons. Neutron doses were very uncertain and mostly based on estimated ratios of neutron to gamma for a particular workplace (NCRP, 2012). Prior to 1960, neutron doses could have been substantial, particularly in the reactor complex, but were largely unrecorded.

Systematic urine monitoring for plutonium (^{239}Pu) was not performed until the early 1970s. Internal doses from plutonium exposures were calculated using biokinetic models and urine and autopsy analyses. As a result, plutonium dose estimates are available for only 38 % of the 16,995 workers in the radiochemical and plutonium plants, the principal facilities with plutonium exposure. On average there were 7.51 (SD = 7.47) urinalysis measurements per worker among those who were measured (Azizova *et al*., 2015). The estimation of time-dependent plutonium body-burdens and organ doses was based on elaborate models that were subject to substantial uncertainties and biases. Agreement between autopsy and urinalysis measurements of internal doses was poor, suggesting possible errors in the biokinetic models. Only a fraction of the cohort was monitored for plutonium via urinalysis, and monitoring selection may have been biased. For the 10,513 workers who were assessed as having nontrivial exposure to plutonium, but were unmonitored, six surrogate plutonium exposure categories were used, based on the worker's employment history (Shilnikova *et al*., 2003). Tritium and polonium exposures were not well characterized.

Only crude uncertainty estimates were provided for individual external exposures in the form of uncertainty bounds and no individual uncertainty estimates were made for internal exposures. Shared and unshared uncertainty

was not evaluated and dose uncertainty was not considered in any of the reported epidemiologic investigations. Considerable shared uncertainty is likely for internal doses. The overall quality of the external exposure data base is not well established because of limited access to the raw data.

The mean cumulative external gamma *Hp* (10) dose was 0.51 Gy (0.54 Gy for men and 0.44 Gy for women (Hunter *et al*., 2013). Over 3,800 workers had a cumulative dose of at least 1 Gy and 95 workers had >4 Gy).

In summary, the overall quality of the MWDS-2008 data base remains to be assessed adequately. Other sources of dose uncertainty from medical fluoroscopic and x-ray examinations and from stack releases to those dwelling in Ozyorsk were not fully addressed (Koshurnikova *et al*., 2012).

For internal doses, the MWDS is being revised and more accurate internal doses are estimated using improved biokinetic models (Vostrotin *et al*., 2016). MWDS-2013 will also account for doses from Mayak stack releases, particularly thyroid doses to residents of Ozyorsk. The MWDS-2013 dose system investigates uncertainty in great detail and uses multiple realizations to separate shared and unshared uncertainty. The new dose system appropriately models both shared and unshared errors, making it possible to explicitly account for the impact of shared uncertainties on risk estimates for external dose.

A strength of the study is that most workers likely to have been exposed externally wore personal dosimeters (film badges or later TLDs). Overall, the weaknesses in the MWDS-2008 dosimetry, and in particular, the plutonium dosimetry, may have limited the accuracy of the risk estimates in the studies published to date more than the evaluation of LNT. But the newer MWDS-2013 as well as additional improvements in a projected MWDS-2017 should allow a better evaluation of LNT.

4.2.3.2 *Epidemiologic Methods, Findings and Issues*. Follow-up was until 2004 for cancer incidence or 2008 for mortality (mean of ~37 y of follow-up). About 23 % were lost to mortality follow-up because of migration from the closed city of Ozyorsk after 2003 or other reasons. Hunter *et al*. (2013) investigated the incidence of other solid cancers (excluding lung, liver and bone because of plutonium exposure, and nonmelanoma skin cancers) for 1948 to 2004 among 22,366 Mayak workers of both sexes, first employed at the site during 1948 to 1982. They identified 1,447 other solid cancer cases among workers who lived in Ozyorsk at the time of diagnosis, so data completeness was restricted by inability to identify cancer diagnoses after workers migrated from Ozyorsk, which neighbors Mayak, so a worker's follow-up was censored at that time. About 41 % had migrated from Ozyorsk by the end of 2004. About 91 % of known cases had morphological diagnosis (91.2 %), with autopsies for about 30 % of cancer deaths. In the first decades of Mayak operation, about 60 % of cancer deaths had postmortem or medico-

legal reports, but currently about 15 % are autopsied, with autopsies more likely to be performed on workers who had higher levels of plutonium exposure (Hunter *et al*., 2013). It is unclear whether cancers discovered only at autopsy are included, and, if so, the degree to which that introduces a bias. Smoking information was available for 89 % of cohort members and alcohol consumption for 78 %. Poisson regression analyses were conducted of "other solid cancers" (excluding lung, liver, bone and nonmelanoma cancers). External doses were obtained from individual film badges and expressed as *H*p (10), while internal doses from plutonium were the estimated liver doses. A total of 1,447 incident cases of other solid cancers was registered among workers who were diagnosed during 1948 to 2004. Potential confounder covariates considered for the analyses included sex, particular Mayak plant, calendar year, attained age, age at first exposure, smoking, alcohol consumption and internal exposures. The final model for analyses of external dose needed adjustment only for attained age, sex and smoking status, and included estimated plutonium dose (measured dose or dose surrogate) as other additive sources of risk.

There was no statistically significant association between the incidence of other solid cancers and internal liver dose for plutonium monitored workers (ERR Gy^{-1} = 0.10; 95 % CI: –0.02, 0.26) or using plutonium exposure surrogate categories for unmonitored plutonium workers ($p > 0.5$) (Hunter *et al*., 2013). A borderline statistically significant dose response for other solid cancers and cumulative external dose (0 y dose lag) was found (ERR Gy^{-1} = 0.07; 95 % CI: 0.01, 0.15), and no substantial change was found when 5, 10, 15, or 20 y dose lags were used (Figure 4.3). When adjusting for monitored internal dose to the liver from plutonium, the external dose ERR Gy^{-1} became 0.06 (95 % CI: –0.01, 0.14; $p = 0.12$), or 0.07 (95 % CI –0.005, 0.15) when the surrogate exposure categories for unmonitored plutonium exposure also were adjusted for. There was no evidence of nonlinearity in the dose response for external exposure. Adding a quadratic term to the model did not improve the fit ($p > 0.5$) overall or when external dose was restricted to <3 Gy ($p > 0.5$).

Sokolnikov *et al*. (2015) examined mortality from "other solid cancers", excluding cancers of the lung, liver and bone, among 25,757 Mayak workers who were first employed during 1948 to 1982. A total of 1,825 deaths from these other solid cancers was recorded during 1948 to 2008; for those workers who had emigrated from Ozyorsk to other parts of the Russian Federation, follow-up stopped at the end of 2003 because of difficulties of determining vital status in the rest of Russia from 2004 onwards. The external dose used was the estimate of the dose to the colon. The internal dose from deposited plutonium was the dose to the liver. The dosimetry was based on the MWDS-2008, but whereas Hunter *et al*. (2013) used MWDS-2008 external doses expressed as Hp (10), Solkolnikov *et al*. (2015) used colon doses, which will be less than Hp (10) doses because of tissue shielding and may thereby yield a larger risk estimate.

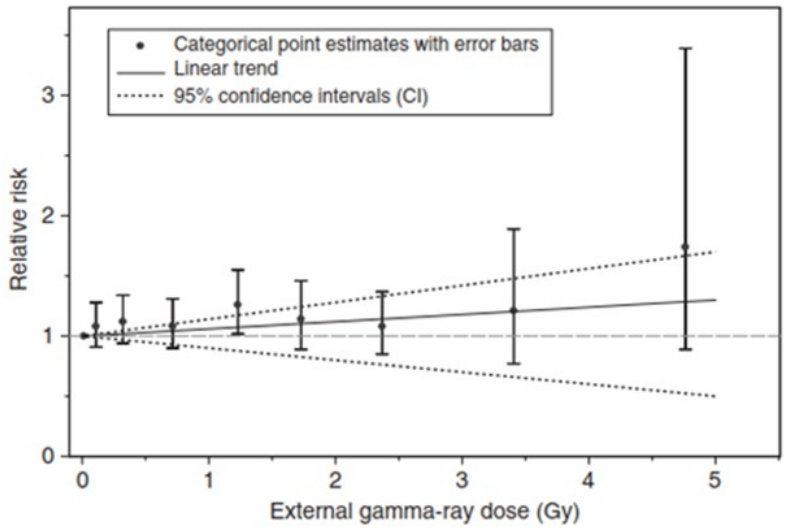


Fig. 4.3. Relative risks of the incidence of solid cancer (except lung, liver and bone) in relation to external exposure [$H_p(10)$] categories and the linear trend (and 95 % CI), having adjusted for internal exposure (based on 0 y lag) (Hunter *et al*, 2013).

The dose response for mortality from other solid cancers and cumulative external colon dose with a 5 y dose lag was statistically significant (ERR Gy^{-1} = 0.16; 95 % CI: 0.07, 0.26; $p < 0.001$) (Figure 4.4) (Sokolnikov *et al*., 2015). When the external dose response was adjusted for internal dose to the liver from plutonium and plutonium exposure surrogate categories, the ERR Gy^{-1} for external irradiation became 0.12 (95 % CI: 0.03, 0.21; $p = 0.01$). Given that the age-adjusted rates of cancer mortality were 24 % higher among plutonium-exposed workers, the investigators examined subsets of workers to evaluate the effects of external doses, absent plutonium exposure (Sokolnikov *et al*., 2016). For plutonium workers the ERR Gy^{-1} was 0.15 (95 % CI 0.06, 0.25), while for other workers it was 0.19 (95 % CI 0.02, 0.39). The risk estimates did not show statistical heterogeneity, so they concluded that concomitant plutonium exposure did not confound the external radiation estimates (although adjusting for it did reduce the risk estimate by about 25 %).

There was no statistical indication of nonlinearity for external radiation, although most of the low-dose points suggested there might be less effect per unit dose in that range. Adding a quadratic term did not improve the fit of the model ($p > 0.5$). The estimate of a dose threshold was compatible with no threshold; the maximum likelihood estimate of a threshold was 0.2 Gy (95 % < 0, 1.3).

Kuznetsova *et al*. (2016) have reported on radiation dose to the RBM and the incidence of leukemia, lymphoma and multiple myeloma during 1948 to 2004. Based on 31 cases of leukemia, excluding CLL, the linear ERR Gy^{-1} estimate was 3.57 (90 % CI 1.55, 8.22) for cumulative external radiation dose to the RBM, adjusted for the internal RBM dose from plutonium. The LQ model fit marginally better than the linear model ($p = 0.11$), and the pure linear and pure quadratic models fit about equally well. The risk estimate for internal plutonium was not significant, nor were risk estimates for external irradiation and lymphoma or multiple myeloma.

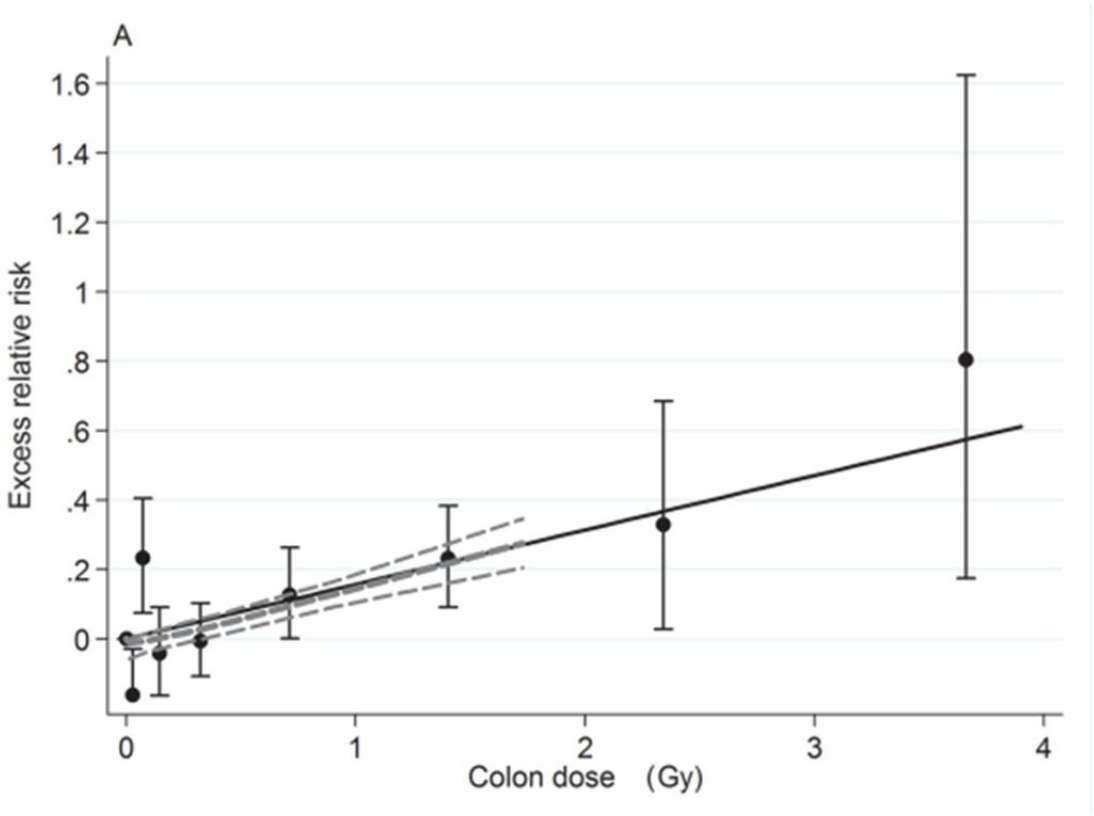


Fig. 4.4. External exposure dose response for solid cancer mortality, other than lung, liver and bone. The solid line is the fitted linear dose response, the points are ERR estimates in dose categories, with 95 % CI. The thick dashed line is a nonparametric smooth fit to the categorical estimates while the thin dashed lines indicate plus or minus one standard error from the smoothed curve. The models used in this analysis were not adjusted for plutonium exposure (Sokolnikov *et al.*, 2015).

293
294 **4.2.3.3** *Study Strengths and Weaknesses*. This fairly large cohort, with up to 60 y of follow-up, has a considerably
295 wider dose distribution than any other worker study that reported a dose-response analysis. However, the estimated
296 doses to the early workers have large uncertainties. A newly revised dosimetry, that has not yet been applied to the
297 epidemiology, may change the risk estimates by some unknown degree. For the majority of individuals, who have
298 remained in Ozyorsk, the follow-up for both cancer mortality and incidence is excellent. However, there is concern
299 over possible bias in cancer detection due to dose-dependent rates of autopsy, the high levels of concomitant
300 plutonium exposure for a subset, and the fact that about 60 % of those with potential plutonium exposure had no
301 plutonium measurements. The investigators found evidence for a linear model of solid cancer (excluding lung,
302 liver and bone), but at this time there is no obvious explanation as to why their risk estimates are lower than those
303 in most other large worker studies, although dose misclassification ('measurement error') may be one factor. The
304 discrepancy between the risk estimates of the INWORKS study and the Mayak worker study is explored further in
305 Shore *et al*. (2017).
306
307 **4.2.3.4** *Implications for the LNT Model and Radiation Protection*. The studies of solid cancer risk supported a
308 linear dose-response function with no clear evidence for a dose threshold. At face value, the solid cancer risk
309 estimate in this study, by comparison to the atomic-bomb LSS risk estimate, does suggest that a DREFDREF >1
310 would be appropriate, *i.e*., a lesser dose-response slope for protracted exposure than for the LSS acute exposure.
311 However, the uncertainties in dosimetry, concomitant plutonium exposures, and concerns about possible out-
312 migration biases suggest caution in the interpretation of the dose response.
313
314 **4.2.4** *Japanese Worker Study*
315
316 **4.2.4.1** *Dosimetry*. Dosimetry for the Japanese nuclear worker studies was based on individual doses from
317 personal dosimetry as recorded in the Radiation Dose Registration Center for Workers (RADREC) with records
318 beginning in 1957 (Akiba and Minzuno, 2012; Hosoda *et al*., 1997; Iwasaki *et al*., 2003). As with other worker
319 studies, dose measurement instrumentation, methods, units, facility types, and administrative policies changed
320 over time and these changes were accounted for in the RADREC system. A radiation dosimetry committee was
321 formed to evaluate the quality, consistency and procedures employed and concluded that the doses recorded were
322 of sufficiently high quality and documentation that they could be used to support an epidemiologic study.
323
324 Internal exposure to workers was very limited and not considered to be a confounder in the dosimetry.
325 Neutron exposure was also taken into account but the number of workers affected was very small. Although
326 doses below the limit of detection (~0.1 mSv) were assigned values of zero dose (Iwasaki *et al*., 2003), it is

unlikely this resulted in any significant bias in reported cumulative doses. For dose records that were missing, the respective facilities reconstructed the dose based on the worker's job assignment and exposures received by workers in a similar position. The mean cumulative individual dose was approximately 12 mSv. The distribution of doses was heavily skewed towards lower doses with ~ 75 % of the workers having a cumulative dose less than 10 mSv and only about 2.6 % receiving doses greater than 100 mSv or more (Akiba and Mizuno 2012). No uncertainties were estimated in the dosimetry nor was an evaluation of the importance of shared/unshared uncertainty. Investigators did a thorough job of considering inconsistencies that ordinarily increase uncertainty in other studies of workers over long time periods. In addition, the fact that exposures to the cohort began in 1957 when methods and procedures for estimating dose were greatly improved over earlier time periods suggest that uncertainties would generally be smaller by comparison. Given that the exposures were almost exclusively external gamma radiation and that doses were based almost entirely on measured personal dosimetry with good quality assurance, the dosimetry was thus of relatively high quality.

4.2.4.2 *Epidemiologic Methods, Findings and Issues*. Akiba and Mizuno (2012) have documented the mortality among 200,583 Japanese male nuclear workers from 1991 through 2002. The cohort was based on those included in a nationwide registry of nuclear workers as of 1989. Cancer mortality data for 1986 to 1990 had been obtained for an earlier publication (Iwasaki *et al*., 2003) but was not included in the Akiba and Mizuno (2012) data. Mortality follow-up was through the Japanese *koseki* system which is very complete. Follow-up duration was only 6.8 y on average and did not begin until over 30 y after first exposure for some workers. During 1997 to 1999 questionnaires were obtained from 48,000 workers pertaining to lifestyle factors, medical radiation exposures and occupational history (Murata *et al*., 2002), with a subsequent survey in 2003 and 2004 of about 45,000 workers. Murata *et al*. (2002) found that radiation dose was positively associated with both smoking and alcohol consumption, but those in higher dose groups received less medical radiation exposure than those in lower dose groups. These differences may reflect variations by socioeconomic variables (*e.g*., job status) that are correlated with dose.

The Poisson analysis of all cancer except leukemia, which stratified on attained age, calendar year period and geographic region, yielded an ERR Sv^{-1} of 1.26 (95 % CI –0.27, 3.00, n = 2636). However, when alcohol-related cancers (upper digestive tract and liver) were excluded, the ERR Sv^{-1} was 0.20 (95 % CI –1.42, 2.09, n = 1946). The difference between the risk estimates of these two analyses suggests there was confounding by levels of alcohol consumption. For all leukemia the ERR Sv^{-1} was –1.93 (95 % CI –6.12, 8.57, n = 80). No analyses were reported to examine nonlinearity, a dose threshold or risk by time since exposure.

4.2.4.3 *Study Strengths and Weaknesses*. The study consists of a large cohort of workers who have had high-quality individual exposure monitoring and high rates of follow-up and death ascertainment. For a substantial fraction of workers, information was available on lifestyle factors, other occupational hazards and medical radiation exposures. Since there was some indication of confounding by alcohol consumption, they presented a risk estimate deleting alcohol related tumor sites. However, the cohort follow-up was short and began years after the inception of radiation exposures for some workers which introduces a potential for survival bias.

4.2.4.4 *Implications for the LNT Model and Radiation Protection*. Although this is a large cohort with individual radiation exposure documentation and high-quality mortality follow-up, a short follow-up period, potential survivor bias, and apparent confounding by lifestyle variables reduce the study's informativeness regarding the LNT model and radiation protection.

4.2.5 *Chernobyl Cleanup Worker Study*

Follow-up of the Russian cohort of Chernobyl emergency cleanup workers (1986 to 1987) was most recently updated from 1992 to 2009 by Kashcheev *et al*. (2015) for both cancer incidence and mortality. The study includes ~67,000 cleanup workers. Information on health status, both cancer incidence and mortality, was available for 1992 to 2009. The mean age of the cohort was 34 y at the time of exposure.

4.2.5.1 *Dosimetry.* A variety of methods were used to estimate dosimetry for Chernobyl emergency cleanup workers, including individual dosimeters, group dosimeters, or dose-rate measurements at the work place. Individual dosimeter readings provided the most direct method and were used for 85 % of the doses. Group dosimeters and dose rate measurements in the work place were used to reconstruct doses for the remaining 15 % and were associated with more uncertainty (Pitkevitch *et al*., 1997). The mean dose of the approximately 67,000 workers was estimated as 132 mGy (median, 102 mGy), ranging up to 1240 mGy; 20,992 workers received 50 to 100 mGy; 572 had >300 mGy. Estimated uncertainties in doses ranged from factors of 0.5 to 3, depending on the dosimetric method used, the working time, and the work location (Kashcheev *et al*., 2015).

The reported doses are based on "official" film badge data. The quality of the official doses is suspect (Chumak *et al*., 2008; Kryuchkov *et al*., 2009). An attempt to validate the official doses found some large discrepancies, so there may be substantial uncertainty in the official doses that were used in the epidemiologic study. These concerns led to the development of RADRUE (Kryuchkov *et al*., 2009) which estimated doses that on average are about 40 % lower than the official doses. The RADRUE technique is a reconstruction of external dose based on calculations of the product of the exposure rate and irradiation time, with shielding taken into account.

They reported GSD estimates measurement error of 1.1 to 5.8 (mean of 1.9) for individual dose estimates. Considering questions regarding the official film badge data, the conversion of badge reading to organ dose in directional highly variable radiation fields, and uncertainty due to recall, the uncertainties in dosimetry may be underestimated.

4.2.5.2 *Epidemiologic Methods, Findings and Issues*. Follow-up was undertaken through the Russian National Medical and Dosimetric Registry (RNMDR) which was established in relation to the Chernobyl accident. The RNMDR obtained cancer mortality and incidence data from regional hospitals and clinics in Russia. About 7.2 % of the cohort was lost to follow-up. There were 2,442 solid cancer deaths and 4,002 incident solid cancers. The analyses were adjusted for calendar year, region, age at exposure and attained age. The linear dose response for solid cancer yielded ERRs of 0.58 Gy^{-1} (95 % CI 0.002, 1.25) for mortality and 0.47 Gy^{-1} (95 % CI 0.03, 0.96)f or incidence (Kashcheev *et al.,* 2015). Only a linear model was fitted, but from the data presented it appears that a linear-quadratic model also should have been considered.

Leukemia incidence also was examined in a nested case-control study within the Ukrainian cohort of 110,000 Chernobyl cleanup workers (Zablotska *et al*., 2013a). The individual cleanup worker doses were estimated using the RADRUE algorithm for cases diagnosed in 1986 to 2006 and for approximately five controls per case matched on place of residence and year of birth. The mean dose for cases was 132.3 mGy (range 0 to 3220), while that for controls was 81.8 mGy (range 0 to 2600). For 52 non-CLL leukemia cases and their controls the ERR Gy^{-1} was 2.21 (95 % CI 0.05, 7.6), while for 65 CLL cases it was 2.58 (95 % CI 0.02, 8.4). For all leukemia, tests for a quadratic, exponential or power deviation from linearity were all nonsignificant (p = 0.93, 0.92 and 0.27, respectively). In summary, within the limits of the dose uncertainties and the modest number of cases, the data tend to support the LNT model.

4.2.5.3 *Study Strengths and Weaknesses*. Study strengths included a fairly large sample size and higher dose range than most other studies with protracted exposures; multiple sources of medical information to document cancer mortality and incidence, and recorded doses. Kashcheev *et al*. (2015) investigated whether the imputed doses may have created a bias and found that incidence rates were similar for those with measured and imputed doses. Limitations of the Kascheev *et al*. (2015) study include the uncertainties in dosimetry; lack of data on smoking, alcohol use or sociodemographics; possible bias due to increased medical surveillance of the most heavily exposed; and failure to evaluate nonlinear dose-response models for solid cancer. The study of leukemia by Zablotska *et al*. (2013a), however, had data on smoking, alcohol use, sociodemographics, medical radiation exposures and evaluated several shapes for the dose-response association.

4.2.5.4 *Implications for the LNT Model and Radiation Protection*. Although the Kashcheev *et al*. results suggest that exposures at low dose rates confer radiation risk, the uncertainties regarding dosimetry and possible variations in health surveillance, plus failure to consider alternate dose-response models, lessen the contribution of the study for the LNT model and radiation protection. The Zablotska *et al*. leukemia study provides better support for the LNT model, though it is limited by having dosimetry uncertainties and only a moderate number of cases.

4.2.6 *U.S. Radiologic Technologists Study*

The x-ray technologist study was begun in 1983, with baseline questionnaires completed by ~90,000 radiologic technologists who had been registered by the American Registry of Radiologic Technologists during 1926 to 1980 (Boice *et al.*, 1992). It inquired about lifetime work history as a radiologic technologist, with details about procedures performed, practices, and protective measures plus sociodemographic and lifestyle information, and employment, reproductive and medical histories. Subsequent questionnaires updated those data and provided information on health endpoints.

4.2.6.1 *Dosimetry.* Because radiation dose measurements were unavailable for many individual technologists, especially in the earlier years when exposures were often higher, self- reported work history data were used to construct categorical proxy measures of radiation exposure. Individualized cumulative dose estimates were developed (Simon *et al*., 2006b; 2014) based on a combination of badges, when available, inference of exposure from self-reported work history and protective measures used, and literature estimates of exposures during the early years.

A dosimetry update (Simon *et al*., 2014) includes many more badge readings than the earlier 2006 analysis and calculated doses to 12 organs and tissues. The 2014 study included numerous methodological improvements that reduced the uncertainty in doses substantially. For example, the GSD for individual cumulative occupational female breast doses ranged from 1.5–3.0, depending on particular information available, whereas Simon *et al*. (2006) had estimated the uncertainty in individual "badge-equivalent" doses as GSD = 2.4 to 3.9). The 2014 analysis utilized additional information on apron shielding as well as more accurate dose conversion coefficients than the earlier dosimetry and included a more comprehensive assessment of uncertainties. As a result of the improved dosimetry, Simon *et al*. (2014) found higher badge doses than the earlier dosimetry (median cumulative badge dose 47 mGy vs. 29 mGy). A validation sub-study showed a positive correlation between imputed bone marrow doses and frequency of chromosome translocations, though the size of the correlation was not provided (Simon *et al*., 2014).

462 **4.2.6.2** *Epidemiologic Methods, Findings, and Issues.* Mortality follow-up was conducted using the technologist
463 registry information and mortality sources, including the U.S. National Death Index. Data have also been
464 published on the incidence of various types of cancer, based on self- reports with verification of a fraction of the
465 reports with medical records. The most recent mortality analysis for the U.S. technologist cohort was published by
466 Liu *et al*. (2014). There were 9,566 deaths (3,329 cancer and 3,020 circulatory). The work history from the
467 baseline questionnaire was used as a categorical proxy for radiation exposure. The conclusion was that
468 technologists working before 1950 had increased mortality from a few cancers (breast cancer, leukemia) and some
469 cardiovascular diseases, based on observing SMRs >1. Other reports have examined cancer mortality or incidence
470 in relation to work in interventional radiography (Linet *et al*., 2006; Rajaraman *et al*., 2016) or nuclear medicine
471 (Kitahara *et al*., 2015), again based on categorical proxies for dose. To date, only a few U.S. radiologic
472 technologist publications have used the individual dose estimates that were developed: for cataract (Chodick *et*
473 *al*., 2008), skin cancer (Lee *et al*., 2015), and breast cancer (Preston *et al*., 2016). The mean estimated dose to the
474 breast was 47 mGy overall, but means ranged from 6 mGy among those who began work in the 1980s to
475 1,168 mGy among those who began before 1930.
476
477 **4.2.6.3** *Study Strengths and Weaknesses*. Dosimetry weaknesses included the use of questionnaires to determine
478 work history, shielding, use of protective devices, and badging, which can result in unreliable information. The
479 high imputed doses during the early years were based mainly on early literature, so uncertainty estimates may be
480 too low for some individuals. It also is unknown how faithfully dosimetry badges were worn in some settings. The
481 most significant source of uncertainty was associated with dose estimates prior to 1977 when only a very limited
482 amount of individual monitoring data for cohort members was available. Other significant sources of uncertainty
483 involved radiological exam procedures, badge placement, spatial homogeneity of the radiation fields, the energies
484 of radiations, and use of protective devices. On the other hand, a strength of the dosimetric work is the detailed
485 investigation of uncertainty and the calculation of multiple realizations of individual doses that account for shared
486 vs. unshared uncertainty.
487
488 This large cohort has good mortality ascertainment and a wide range of doses delivered in a protracted fashion
489 the investigators have attempted to reconstruct individual doses and model dose uncertainties. Weaknesses include
490 inaccuracy of long-term recall of exposure-related information, inability to verify the dosimetry in the early period
491 when doses were higher, and reliance on self-reports for much of the cancer incidence data.. The greatest
492 limitation has been the use of self- reported work history as a surrogate for dose in nearly all publications to date.
493 Only a few papers have actually used quantitative dosimetry, and it has not yet been applied to the study of total
494 solid cancer or leukemia risks.
495

4.2.6.4 *Implications for the LNT Model and Radiation Protection*. Because nearly all the publications have relied on self-reported, categorical data from work histories rather than having individual dose estimates for quantitative dose analyses, the study currently does not address the LNT model [except for the one report on breast cancer (Preston *et al*., 2016)], nor does it contribute quantitatively to radiation protection issues.

4.2.7 *Million Worker Study*

Highlights

A critically important gap in knowledge surrounds the health consequences of exposure to radiation received gradually over time, which in the past was studied only piecemeal in the United States. The Million Worker Study (MWS) is an active study of U.S. workers and veterans to address the effects of radiation when doses are delivered gradually over years. The study is ongoing and will ultimately include historical cohorts of DOE workers, U.S. atomic veterans, nuclear power plant workers, industrial radiographers and medical radiation workers.

The relatively great statistical power and precision of the study will be related to the large numbers, a broad dose distribution, standard methods used across all exposed cohorts and comprehensive dose reconstruction. The dose distribution is broader than for most occupational studies, with more workers with cumulative doses greater than 50 mGy than reported among atomic-bomb survivors. The follow-up started as early as 1940 for Manhattan Project workers. Recent studies of leukemia among nuclear power plant workers and industrial radiographers are consistent with a linear dose-response below 100 mGy, thus providing support for use of the LNT model in radiation protection.

4.2.7.1 *Introduction*. The Study of One Million U.S. Radiation Workers and Veterans (MWS) (Boice, 2012a) was conceived over 25 y ago following an NCI request to the NRC to consider creating a radiation worker registry based on the NRC requirement that nuclear power plant licensees report radiation doses received by their employees (Boice, 2012a; Muirhead *et al*., 1996). Subsequently, the MWS was expanded to include 115,000 atomic veterans who participated in above-ground nuclear weapons testing (Boice, 2012b; 2014; Caldwell *et al*., 2016), 360,000 workers during the Manhattan Project years (Boice, 2013c; Boice *et al*., 2006b; 2014), 250,000 early radiologists and medical workers, 150,000 nuclear power plant workers (Boice, 2013a; 2016a; Boice *et al*., 2017), and 130,000 industrial radiographers. The follow-up started as early as 1940 for Manhattan Project workers. The overriding goal of the MWS is to estimate the risk of organ-specific cancers from radiation doses received at low dose rates over the course of years. These risk estimates from healthy American workers and veterans are deemed more valid for American workers than those from the atomic-bomb survivor study which involved a brief, acute exposure to a Japanese 1945 population living in a war torn country. The MWS is providing risk estimates that are more valid for American workers than is the atomic-

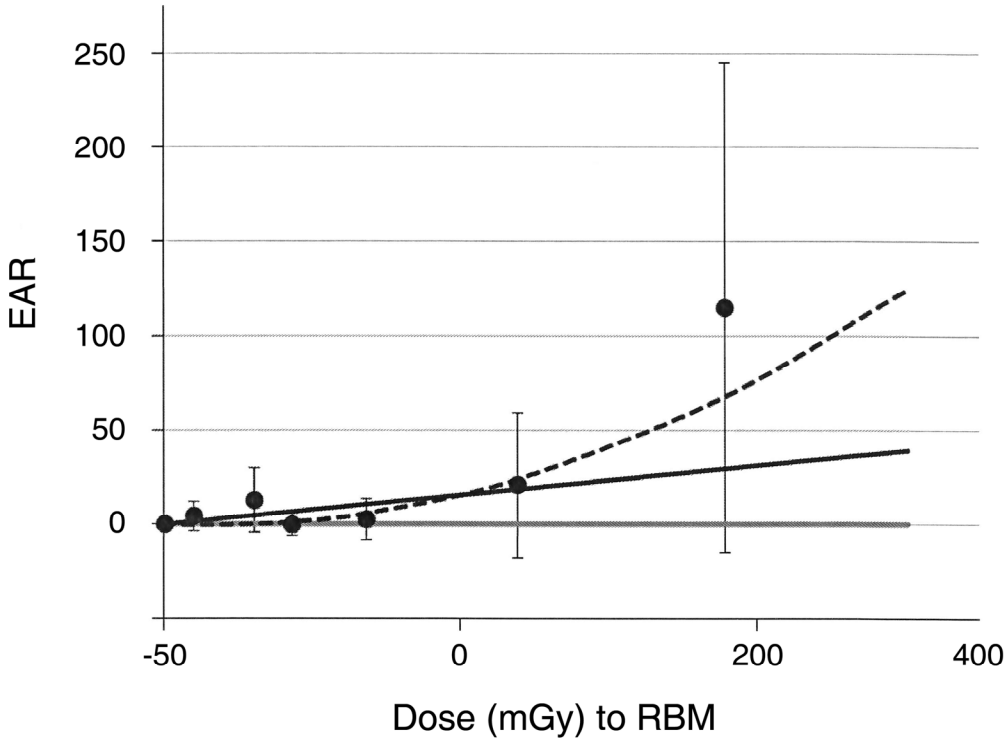
bomb survivor study which involved a brief, acute exposure to a Japanese population, who lived in a war-torn country with deprivation, malnourishment and infectious diseases, and who also have a profile of cancer types and other health conditions that differs from the U.S. population.

Initial publications stressed the importance of dosimetry for both the DOE facility workers (Boice *et al*., 2006b; Leggett *et al*., 2005), the atomic veterans (Beck *et al*., 2017; Till *et al*., 2014), and overviews of the entire dosimetry approaches for all cohorts studied (Boice, 2013b; 2014; 2016a; Bouville *et al*., 2015). Statistical issues of uncertainty are being addressed (Stram *et al*., 2015). Publications have included evaluations of the Rocketdyne (Atomics International) (Boice *et al*., 2011) and Mound workers (Boice *et al*., 2014). Papers have been submitted on the risk of male breast cancer among atomic veterans (Beck *et al*., 2017) (Boice *et al*., 2017c), and on leukemia among nuclear power plant workers (Boice *et al*., 2016b). The statistical power and precise risk estimates will come from the combination of the study cohorts. The earlier publications, while informative, are not sufficiently powerful to address radiation risks in the low-dose domain or the consistency or lack of consistency with an LNT model. However, as seen in Figures 4.5 and 4.6, more recent analyses of leukemia among the large populations of nuclear power plant workers and industrial radiographers have sufficient statistical ability to provide direct information on dose response relationships (Boice, 2017b) as the entire population epidemiology and dosimetry will eventually be combined into the large compiled effort. To date, subpopulations include: Rocketdyne Workers, Mound Workers, Mallinckrodt Workers, Atomic Veterans, Nuclear Power Plant Workers, Interventional Radiologists, and Medical Workers. Brief descriptions of the subpopulations that have been addressed to date and the results are provided below.

4.2.7.2 *Dosimetry*. The approach to estimating occupational doses received by individuals included in the MWS follow the procedures outlined by Boice and colleagues (Boice, 2001; Boice *et al*., 2006b; 2014). NCRP has undergone a review of both the dosimetry methods and the uncertainty associated with the reconstructions for the MWS and has provided an initial summary (Bouville *et al*., 2015). A full report has been reviewed by the Council and is expected to be published in 2017. Specific details on the dosimetry aspects for each subpopulation are included in that report.

4.2.7.3 *Epidemiologic Methods, Findings and Issues*. A brief summary of several of the MWS subpopulations, their exposures and results that have been or are being obtained are given below.

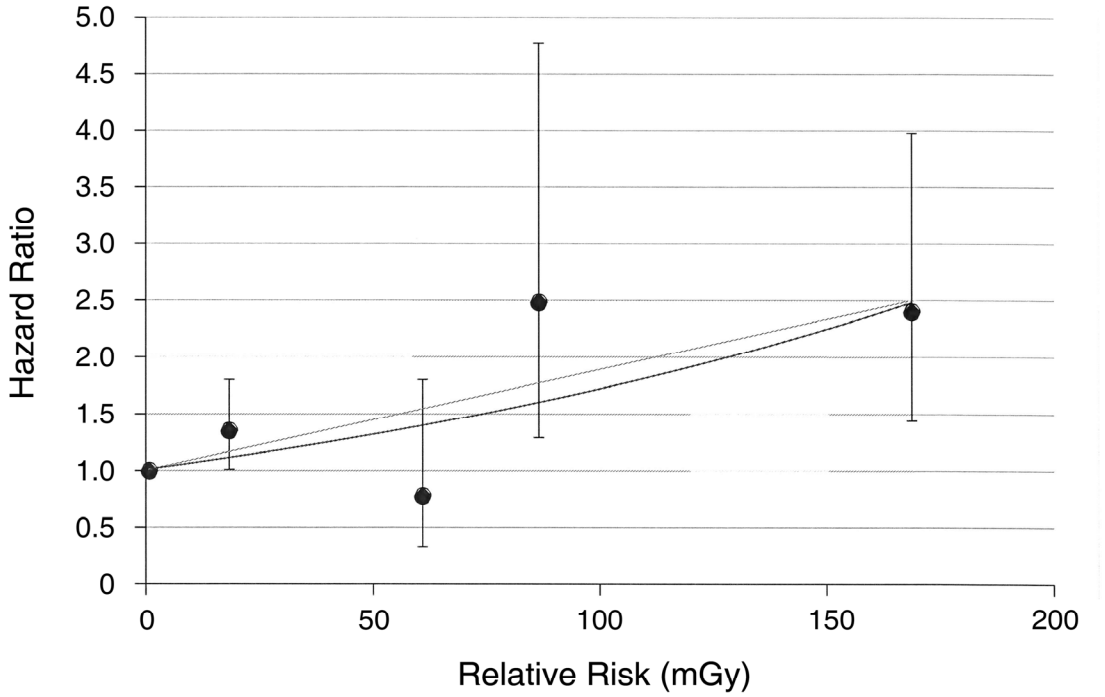
Rocketdyne Workers (Boice *et al*., 2006a; 2006b; 2011). Between 1948 and 1999, thousands of Rocketdyne/Atomics International workers were involved in a wide range of activities such as sodium-cooled



550

551 **Fig. 4.5.** Excess absolute risk (EAR) dose response among nuclear power plant workers (preliminary $n = 320$)
552 for leukemia (other than CLL). The dark solid line is the best linear slope, the dashed line is the linear-quadratic fit,
553 and estimates (dots) and 95 % CI (vertical lines) are shown for individual dose categories (Boice, 2016b).

554



555

556 **Fig. 4.6.** Hazard ratio dose response among industrial radiographers (preliminary) for leukemia (other than
557 CLL). The upper sloped line shows the best linear fit and the lower line the linear-quadratic fit. Hazard ratios for
558 individual dose categories are shown by dots, with the 95 % CI shown by vertical lines.[2]

559

[2] John Boice, unpublished, 2017

560 breeder reactor technology, uranium fuel fabrication, spent fuel evaluation, radiography, hot lab chemistry,
561 plutonium fuel fabrication and storage of nuclear material (Boice et al., 2006a; 2006b; 2011). During the 52 y
562 covered by the study, 5,801 workers were monitored for external or internal radiation at Rocketdyne and
563 1,833workers were monitored at other facilities. Results were adjusted for year of birth, year of hire, sex, pay type
564 (hourly/salary), duration of employment, and work as a test stand mechanic (which involved exposure to
565 toxicants). Only 0.6 % were lost to follow-up, and cause of death was available for 98.1 % of deaths. There were
566 651 deaths from all cancer except leukemia. The Cox regression hazard ratio (HR) at 100 mGy was 0.98 (95 % CI
567 0.82, 1.17) which extrapolates to an ERR Sv^{-1} of –0.2 (95 % CI –1.8, 1.7).[3] Given the null results, no analysis for
568 nonlinearity was conducted. Similarly, for all leukemia other than CLL the HR_{100mSv} was 1.06 (95 % CI 0.5, 2.23)
569 which was extrapolated as an ERR Sv^{-1} of 0.6 (95 % CI –5 to 12.3). Cox regression analyses revealed no
570 significant dose-response trends for any cancer. Strong conclusions could not be drawn because of small numbers
571 and relatively low career doses.
572
573 **Mound Workers** (Boice *et al*., 2014). Cancer mortality was examined among 7,270 workers at the Mound nuclear
574 facility near Dayton, OH where ^{210}Po was used (1944 to 1979) in combination with beryllium as a source of
575 neutrons for triggering nuclear weapons, including the Trinity and Nagasaki bombs (Boice *et al*., 2014). Other
576 exposures included external gamma radiation and to a lesser extent ^{238}Pu, tritium and neutrons. Radiation
577 monitoring was conducted on 4,977 workers who also were followed up over the years 1944 to 2009. Lifetime
578 occupational doses from all places of employment were sought and incorporated into the analysis. Over 200,000
579 urine samples were analyzed to estimate radiation doses to body organs from polonium and other internally
580 deposited radionuclides. The cohort was well defined from available records. Vital status of the cohort was
581 achieved for 98.7 % of the cohort. There were 968 cancer deaths, including 31 leukemia cases (26 non-CLL).
582 Analyses were adjusted for sex, educated, year of birth and year of hire, and age at risk defined the follow-up time
583 in the Cox regression analysis. External radiation dose-response analyses showed no significant association with
584 death from any a priori cause. For leukemia (excluding CLL) the ERR was approximately 0.4 Gy^{-1} (95 % CI –3.7,
585 7.1). Combined internal and external radiation was not associated with lung cancer mortality ERR = 0.0 Gy^{-1} (95 %
586 CI –0.3, 0.4). Cox regression analysis revealed a significant positive dose-response trend for esophageal cancer
587 [HR = 1.54 (95 % CI 1.15 to 2.07) at 100 mGy] and a negative dose- response trend for liver cancer HR = 0.55
588 (95 % CI 0.23 to 1.32) at 100 mGy], but these are viewed as unexpected and possibly artifacts of chance or other
589 factors.
590

[3] The ERR at 100 mSv was derived from the HR, *i.e*., $ERR_{100\ mSv} \approx (HR_{100mSv}) - 1)$. That ERR estimate was then extrapolated to an ERR Gy^{-1} by multiplying by 10. The assumption of the approximate equivalence of the ERR ≈ (HR – 1) at a low dose seems justified by the reasonably close correspondence shown in Cardis *et al*. (2007), Table 6.

Mallinckrodt Workers (Boice, 2017a; Golden *et al*., 2016). An extended follow-up with comprehensive dose reconstruction was conducted of 2,514 white males employed at the Mallinckrodt Chemical Works in St. Louis, the earliest uranium processing facility in the United States, between 1942 through 1966 (Dupree- Ellis *et al*., 2000; Golden *et al*., 2016). Workers processed pitchblende, a naturally occurring radioactive material containing uranium and silica. Over 75 % of the workers died during the up to 70 y of follow-up with cause of death known for 99 %. There was some evidence of a healthy worker effect, with the standardized mortality ratio (SMR) of 0.94 for all causes, 0.97 for all cancer and 0.89 for all heart disease.

The only significant radiation dose-response relationship was for kidney cancer [RR = 1.88 (95 % CI 1.13 to 3.11) at 100 mGy] and was suggested for nonmalignant kidney diseases [RR = 1.36 (95 % CI 0.98 to 1.89) at 100 mGy], such as nephritis. No notable observations were seen for any other cancer, leukemia or heart disease. Conceivably, dust could distort the association between kidney disease and radiation, related to nonradiogenic properties of uranium and silica (both kidney toxins), but the evidence was inconclusive.

Nuclear Power Plant Workers (Boice, 2013a; 2016a; Boice *et al*., 2017). In 1957 the United States became one of the first countries to produce electricity using nuclear power reactors. To date, 150,000 early workers in the nuclear industry, employed prior to 1985, have been selected for study from NRC files (the Radiation Exposure and Reporting System) and from dosimetry records from Landauer, Inc. Additional records, including early microfilm files, may be used to enhance the population size. Over the years, feasibility studies have been conducted utilizing NRC, Landauer, Inc., and utility records (Jablon and Boice, 1993; Muirhead *et al*., 1996). A mortality study was conducted of 146,727 workers employed at nuclear power plants in the United States between 1957 through 1984. Over 6 % of nuclear power plant workers had had cumulative exposure greater than 50 mGy. Follow-up through 2011 identified 30,993 deaths from all causes, including 68 from CLL and 320 from leukemia other than CLL. The SMR was not increased for CLL (0.90) or for non-CLL (1.02). Cox regression analyses revealed no evidence of a dose- response relationship for CLL. For non-CLL, preliminary results indicate a pattern of risk that was consistent with both a linear and linear-quadratic relationship with no elevation in the relative risk (hazards ratio) below 100 mGy and a nearly two-fold risk for exposures >250 mGy (Figure 4.6). A linear relationship between dose and leukemia could not be rejected, and the study is consistent with, though not strongly supportive of, the LNT model for radiation protection. Analyses are not yet available for solid cancers.

Industrial Radiography Workers (Boice, ?) Industrial radiographic nondestructive testing typically utilizes ^{192}Ir and ^{60}Co sources. Industrial radiographers receive external irradiation, generally in an anterior- posterior (AP) geometry. Information on annual recorded dose has been collected by the MWS for 127,910 industrial radiographers. The average cumulative recorded dose for these industrial radiographers is ~20 mGy, with 10 % of

them receiving a cumulative recorded dose >50 mGy. Over 32,000 of the industrial radiographers are also known to have worked in naval shipyards. Approaches to follow-up, dose reconstruction, mortality ascertainment and analyses were similar to the study of nuclear power plant workers. Preliminary analyses for leukemia, other than CLL, have been conducted and the dose-response model is being assessed (Figure 4.6). The industrial radiographers include nearly 300 leukemia cases, in comparison with the atomic-bomb survivor data in adult males, *i.e.*, 94 cases, and the dose response curve is consistent with both a linear and a linear-quadratic model. Currently, the preliminary leukemia analyses for nuclear power plant workers and industrial radiographers are consistent with a dose response under 100 mGy and with the LNT model as used in radiation protection. For leukemia other than CLL, the MWS is consistent with a linear relationship for both the nuclear power plant workers and the industrial radiographers. A linear relationship would be expected when radiation is received gradually over time as these workers experienced. It might be considered an evaluation of the linear component of the linear quadratic relationship seen at higher dose rates. Thus, these data are consistent with the LNT model as used in radiation protection today.

Nuclear Weapons Test Participants (Atomic Veterans) (Beck *et al*., 2017; Caldwell *et al*., 2016; Till *et al*., 2014). The United States conducted over 200 above-ground atmospheric nuclear weapons tests during the Cold War, many of which involved military maneuvers at the Nevada Test Site and the Pacific Proving Grounds (*e.g*., Bikini Islands). A recent update of the SMOKY and PLUMBBOB veteran's studies included detailed dose reconstructions (Beck *et al*., 2017; Caldwell *et al*., 2016; Till *et al*., 2014). There were 12,219 veterans at the PLUMBBOB test series, including 3,020 at the SMOKY nuclear test. Mortality follow-up was through 2010 and observed causes of death were compared with expected causes based on general population rates. Radiation dose to red bone marrow was based on individual dose reconstructions. Leukemia risk, initially reported to be significantly increased among SMOKY participants, remained elevated, but this risk diminished over time. Despite an intense dose reconstruction, the risk for leukemia was not found to increase with increasing levels of radiation dose to the red bone marrow. Based on a linear model, the estimated ERR mGy^{-1} was −0.05 (95 % CI –0.14, 0.04). The observed null result for leukemia could be related to chance due to small numbers (27 cases) and low doses, or possibly to subtle biases in the data by lifestyle variations or other factors.

For the Atomic Veterans, a full cohort study was also conducted of 114,270 military participants at over 100 atmospheric nuclear weapons tests in Nevada, New Mexico (the Trinity test) and the Pacific from 1945 through 1962 (Boice *et al*. 2017). Mortality follow-up was through 2010 and vital status for nearly 97 % of the veterans was determined. Radiation dose was based on comprehensive dose reconstructions included contributing causes of death (Beck *et al*., 2017). No significant trends with dose were found, probably because of the dose uncertainties and the mostly small doses.

659
660 **4.2.7.4** *Study Strengths and Weakness*. For the MWS subpopulation studies, follow-up is generally long, with high
661 success rates in follow-up and cause of death ascertainment. Dose reconstructions are detailed, they include
662 individual badge measurements, individual internal dose evaluations from bioassays (where appropriate), and
663 address specific uncertainties (Bouville *et al*., 2015; NCRP, 2017). Organ doses are calculated for up to 16
664 organs/tissues. Most studies can adjust for occupational status, sex, and other potential occupational radiation
665 exposures (using information from other facilities before and after employment at the facility under study). The
666 weaknesses for individual subpopulation studies are primarily the small numbers of cancers, appreciable dose
667 uncertainties for some of the studies, and relatively low career doses that preclude strong conclusions. Data are
668 often not available on smoking or other lifestyle sociodemographic factors. For the overall MWS, it is planned that
669 subpopulations will be combined with other studies to generate the statistical power envisioned for dose response
670 curves relevant to low dose risk estimation.
671
672 **4.2.7.5** *Implications for the LNT Model and Radiation Protection.* For each of the MWS subpopulation studies,
673 because of the relatively small doses and number of deaths, and consequent wide confidence bounds, the individual
674 studies make only a small contribution to the evaluation of the LNT model or radiation protection. Although
675 several of the subpopulation studies include internal alpha emitters, and external photon exposures, and some study
676 results have provided risk estimates for leukemia (with wide confidence intervals) most have not yet estimated
677 quantitative risks for all solid cancer. At this time the individual studies provide little information relevant to
678 considerations of LNT from low-LET irradiation. However, when all of the subpopulations are eventually
679 combined, the statistical power will be much greater and it is expected that important information will likely be
680 obtained along with a rigorous evaluation of associated uncertainties.
681
682 **4.2.8** *Chinese Medical X-Ray Worker Study*
683
684 A total of 27,011 medical x-ray workers and 25,872 non-radiologist physicians in China between 1950
685 and 1980 were followed up through 1995 for the incidence of all cancers excluding leukemia (Sun *et al*.,
686 2016).
687
688 **4.2.8.1** *Dosimetry*. Personal dose monitoring did not begin until 1985. Therefore, earlier worker doses were
689 estimated for 3,805 workers based on a simulation of multiple x-ray machines, workplaces, working conditions
690 and protective measures used. Smoothed yearly averages, across all those conditions, without any individual
691 information, were then applied to all active workers for each year of 1950 through 1995. For each work-year
692 before 1949, the estimated 1949 average dose was applied. The mean cumulative *H*p(10) dose was 0.25 Gy

(median, 0.12 Gy; ~60 % with cumulative dose <0.05 Gy, <1 % with >0.5 Gy); the corresponding mean colon dose was 0.086 Gy. However, for those who began work before 1950, the mean estimated cumulative colon dose was 0.583 Gy.

Since average yearly doses were applied to all workers, estimates of individual doses have substantial uncertainties, though they would be largely Berkson dose errors that would not be expected to bias the associations with risk. The use of colon dose for estimating risk to some organs may not be valid for low energy x rays, since the colon is one of the deepest organs.

4.2.8.2 *Epidemiologic Methods, Findings and Issues*. Investigators found 795 cancer cases in the exposed cohort and 848 in the unexposed cohort. Histologic information was available for about 70 % of cancers; the remaining were diagnosed mainly from radiographic evidence. Investigators calculated an ERR of 0.87 Gy^{-1} (95 % CI 0.48, 1.45) based on estimated colon dose. They also showed risks by dose category but provided only linear ERR and EAR risk estimates.

4.2.8.3 *Study Strengths and Weaknesses*. Strengths include the fact that the exposed and unexposed groups came from the same hospitals, thereby controlling for regional differences. They observed differences between the exposed and unexposed in rates of lung, esophageal and liver cancers, which they surmised might be due to differences in smoking and hepatitis infection. However, an analysis with lung and liver cancer deleted gave a risk estimate very similar to the all solid cancer estimate.

Weaknesses of the study include the fact that the occupational radiation dose assigned to individual workers was the estimated average annual dose for all workers and that the medical diagnostic information was limited. They noted that the completeness of follow-up for cancer was uncertain. There is also concern that the exposed group of mixed radiologists and radiation technologists may have differed in socioeconomic status from the unexposed group consisting only of physicians, which might affect the risk estimate.

4.2.8.4 *Implications for the LNT Model and Radiation Protection*. Though the study shows an essentially linear dose-response association, the uncertainties in both dosimetry and cancer documentation mean it provides relatively weak information regarding the LNT model and radiation protection.

724 **4.3 Environmental Exposure Studies**
725

Highlights

Several epidemiologic studies described below have been conducted to investigate whether exposure to ionizing radiation from a variety of environmental sources increases the risk of developing or dying from cancer. Between 1949 and 1956 the Russian Mayak nuclear weapons facility released radioactive waste into the Techa River and exposed approximately 30,000 residents to relatively low doses at low dose rates from gamma rays (external) and ^{137}Cs and ^{90}Sr (internal). A recent paper on cancer incidence among residents near Techa River reported an ERR Gy^{-1} estimate for all solid cancer of 0.77 (95 % CI 0.13, 1.5). Although the shape of the dose response was uncertain, especially at doses below about 100 mGy, the study provides fairly strong evidence that exposures at low dose rates confer risk for solid cancers.

New studies of cohorts of children in Ukraine and Belarus who had thyroid measurements of ^{131}I activity shortly after the Chernobyl accident and systematic thyroid screening have added appreciably to our knowledge about thyroid cancer risk after protracted internal exposure. Both studies showed strong linear dose-response functions with no evidence of nonlinearity. The risks per unit dose were somewhat lower than, but statistically compatible with, those found for acute external radiation exposures.

Studies of residents of high natural background radiation have been conducted in Kerala, India and Yangjiang, China. However, it is difficult to conduct a study of background radiation, *e.g.*, to find a suitable low exposure control group with highly similar lifestyles and natural disease rates to whom the highly exposed group may be compared. The better and larger of the two studies, the Kerala study of cancer incidence, included 70,000 individuals and over 1,300 cancers from high-background or low-background radiation areas. The dosimetry was based on measurements of ambient levels within and near homes, coupled with aggregate house-occupancy factors by age and sex. They reported an ERR Gy^{-1} of –0.13 (95 % CI –0.58, 0.46) for all cancer except leukemia. The leukemia cases were too few to be informative. The Yangjiang study reported a positive, but nonsignificant, risk coefficient for cancer, excluding leukemia and liver cancer (ERR Gy^{-1} of 0.19, 95 % CI –1.87, 3.04) . These studies are nominally more supportive of little or no effect after low dose-rate exposures rather than the LNT model. However, the uncertainties in dosimetry, the weaknesses in cancer ascertainment, the low rates of histological verification of cancer cases, questions about the comparability of the low- and high-dose populations, and the wide confidence intervals on the risk estimates mean they need to be interpreted with caution.

A number of environmental studies are reviewed, with greater detail accorded to the more important or informative studies. The studies include Techa River residents (Section 4.3.1), Chernobyl residents (4.3.2), Kerala, India High Background Radiation Area (HBRA) residents (4.3.3), Yangjiang, China HBRA residents (4.3.4), Taiwan residents of radiocontaminated buildings (4.3.5), and radiation fallout studies (brief reviews)

(4.3.6) of Japan atomic-bomb fallout, Marshall Islands atomic testing fallout, Nevada Test Site (NTS) atomic fallout in Utah, Atomic testing fallout across the United States, Semipalatinsk fallout, Hanford ^{131}I fallout, Mayak fallout, Three Mile Island fallout and Fukushima Dai-Ichi fallout.

In addition to the text below, further systematic information is provided for the Techa, Chernobyl, Kerala, Yangjiang and Taiwan studies in Tables 4.1 to 4.4.

4.3.1 *Techa River Resident Cohort*

Between 1949 and 1956 the Mayak Production Association, which is located in the southern Ural Mountains, released radioactive waste into the Techa River as part of the process of producing plutonium for the Soviet nuclear weapons program. Approximately 30,000 residents of 41 villages along the river were potentially exposed to radiation from these releases. External exposures were due to gamma rays from contaminated shorelines and flood plain soil. Internal exposures were from the consumption of water, milk and food contaminated with ^{137}Cs, ^{90}Sr, ^{89}Sr and other uranium fission products (Davis *et al*., 2015; Degteva *et al*., 2012; Kossenko *et al*., 2005; Napier, 2014; Tolstykh *et al*., 2011). This review updates the reviews by UNSCEAR (2008) and the BEIR VII committee (NA/NRC, 2006) of Techa River studies.

4.3.1.1 *Dosimetry*. Analyses utilized dose estimates computed using the Techa River Dosimetry System 2009 (TRDS-2009) (Degteva *et al*., 2009), which is an improved version of TRDS-2000 (Degteva *et al*., 2000). External exposure was estimated using exposure rate measurements available at various locations along the river bank, and a model of the river and flood plain contamination based on source term estimates (releases) derived from historical records of the facility. Doses from external exposure decreased with the distance along the Techa River and distance from the shoreline. Additional factors were characteristics of the riverbank, residence history, average gender- and age-dependent behavioral factors, and age-related coefficients to convert air to organ doses. (Degteva *et al*., 2000; Schonfeld *et al*., 2013). Exposure levels peaked in 1951 and since then have declined over time. The mean estimated cumulative stomach dose was 0.035 Gy (range 0 to 0.96 Gy).

Exposures to internal radionuclides (primarily ^{90}Sr and ^{137}Cs) also were estimated taking into account factors such as residence history and drinking water sources. Whole-body measurements of ^{90}Sr were available for some residents and were used to calibrate the model calculations.

While no formal uncertainty analysis was conducted and more precise individual doses and associated uncertainty are clearly preferred, using such individual dose estimates probably results in mostly Berkson

(grouped) errors, which introduces increased variance and reduced statistical power, but little bias provided the grouped estimates are unbiased. Less than 10 % of the person-years were at cumulative doses over 100 mGy, which indicates it is primarily a low-dose study.

TRDS-2009 suffers from certain limitations. The ^{90}Sr whole-body measurements, of necessity, were made decades after intake. Individual bone reabsorption rates vary by time, sex and other factors, and doses from the short-lived fission products had to be inferred with limited data. The source term for the activity in the river was not well established, and the river model itself has subsequently been revised substantially. Although diagnostic examinations were not accounted for in the dosimetry, evidence indicates they were not highly correlated with Techa River doses, so would not introduce substantial bias.

External dose estimates were crudely validated on the village level using physical measurements of thermoluminesence in bricks. Tooth enamel electron spin resonance (ESR) was also used to validate the cumulative external exposure. Comparison with available but limited measurements was used to validate the river model. The consistency between the model calculations and the results of actual whole body counter measurements in humans was used to assess the reliability of the model used in TRDS-2009D for the calculation of internal doses due to strontium. FISH data in 2009 were considered preliminary but were roughly consistent with estimated doses.

TRDS-2009 is being replaced by a more accurate and precise dose system (TRDS-2017) that among other improvements incorporates a more accurate river model and a more accurate source term. TRDS-2017 also includes estimates of confounding exposures from medical irradiations, exposure to the Kyshtym accident and Mayak stack releases, an improved internal dosimetry model for ^{90}Sr bone dose, as well as other improvements. TRDS-2017 will provide more accurate individual doses along with shared and unshared uncertainty estimates based on multiple realizations of doses using a two-dimensional Monte-Carlo simulation.

4.3.1.2 *Epidemiologic Methods, Findings and Issues*. The study cohort consisted of approximately 28,000 individuals of either sex, 80 % of whom lived in villages along the Techa River between 1950 and 1953, the time of the greatest exposures, and met other eligibility requirements (Schonfeld *et al*., 2013). About 40 % were under age 20 at the time. Vital status was determined from oblast (region) address bureaus, periodic contact letters to individuals, tax and passport records and personal interviews. About 22 % were lost to follow-up, mainly due to out-migration, but this was accounted for by censoring of the follow-up time. Cause of death information was obtained from oblast Civil Registrars Offices and was known for 91 % of deaths. Cancer incidence data were obtained from regional oncology dispensaries and a central cancer hospital and were thought to have nearly 100 % ascertainment, except for out-migrants from the region. Distant out-migrants tended to have higher doses, and

death and cancer incidence data were less known for them (Kossenko *et al*., 2005), but the follow-up censoring in effect removed this as a biasing factor.

The study of solid cancer mortality in the Techa River cohort during 1950 to 2007 included 2,303 deaths. Analyses adjusted for sex, ethnicity, attained age, birth cohort, and oblast (region). The linear ERR Gy^{-1} was 0.61 (95 % CI 0.04, 1.27) (Schonfeld *et al*., 2013). Adding a quadratic term to the linear one did not improve the fit of the model ($p > 0.5$). Nevertheless, a pure quadratic model fit the data as well as the linear model. To further focus on nonlinearity, the authors fit a spline model with a knot at 100 mGy; it suggested curvature but did not fit the data better than a pure linear model. The best estimate of a dose threshold was at 0.05 Gy, which had a lower confidence bound of <0 and was therefore compatible with a nonthreshold model. It was reported that the highest risks were seen for the esophagus and uterus, findings at variance with other studies; however, given that there was a total of only 50 radiation-associated excess solid cancer deaths, variations by individual cancer type may not be meaningful. The investigators reported that those exposed at older ages had borderline larger risks (ERR) than those exposed or observed when young, which runs counter to other studies; it may simply represent small sample variation. In fact, the age effects were unstable, depending on how the background rates were modeled, but the age and tumor type findings temper the conclusions that can be drawn.

The other major Techa River cohort report is of cancer incidence, 1956 to 2007 (Figure 4.7) (Davis *et al*., 2015). The cohort consisted of about 17,000 rather than 28,000 because cancer incidence could be determined in only one oblast; in addition, 21 % had out-migrated while another 6 % was lost to follow- up. With adjustment for smoking, the linear ERR y^{-1} for all solid cancer was 0.77 (95 % CI 0.13, 1.5). It was estimated that about 3 % (or 61) of the 1,933 incident solid cancers were statistically associated with the radiation exposure. There was considerable uncertainty about the shape of the dose response, though at low doses there was no indication that a linear-quadratic model fit any better than a simple linear model ($p = 0.2$). On the other hand, the pure quadratic model fit as well as the linear dose-response model ($p > 0.5$), with an estimated ERR of 0.022 (95 % CI 0.005, 0.04) at 100 mGy, which was less than half as large as the linear model estimate (0.077) at that dose level. Using a two-stage clonal expansion (TSCE) biological model with follow-up data through 2003, Eidemüller *et al*. (2010) reported ERRs of 0.85 (95 % CI 0.36, 1.38) Gy^{-1} for all cancer mortality and 0.91 (95 % CI 0.35, 1.52) Gy^{-1} for cancer incidence. These values are somewhat higher than, but statistically compatible with, the empirical-model estimates by Schonfeld *et al*. (2013)and Davis *et al*. (2015).

Krestinina *et al*. (2013) analyzed leukemia incidence in the Techa River cohort. The RBM doses ranged up to 2 Gy (0.3 Gy mean). The mean RBM dose rate decreased from 40 mGy y^{-1} in 1950 to 1951 to 8 mGy y^{-1} in 1960, and about 92 % of the total RBM dose was from internal exposure, primarily ^{90}Sr. There were 70 cases of

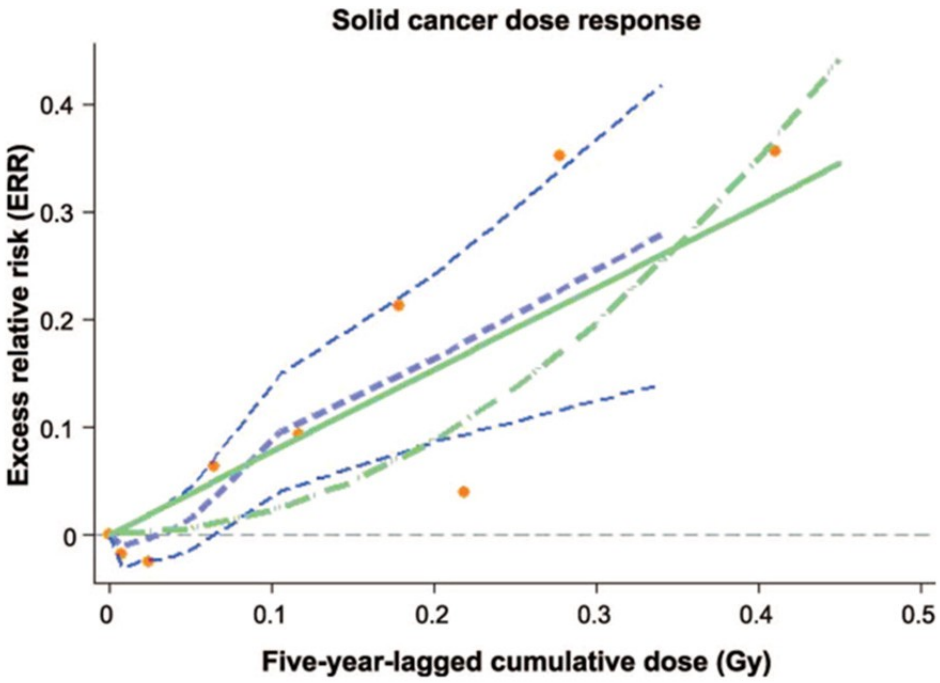


Fig. 4.7. Techa River dose response for solid cancer incidence. All results shown are based on models with adjustment for smoking in the baseline rates. The green solid lines are the fitted linear (solid) and quadratic (dash-dot-dot) dose-response curves. The orange points are ERR estimates in dose categories while the thick-blue-dashed curve is a nonparametric smooth fit to these points. The outer blue-dashed curves represent approximate (pointwise) +/– standard error limits on the nonparametric smooth (Davis *et al.*, 2015).

non-CLL leukemia. Most leukemias (81 %) were diagnosed by qualified hematologists. The linear estimate of ERR Gy^{-1} was 4.9 (95 % CI 1.6, 14). There was no indication of non-linearity ($p > 0.5$); the estimated curvature was close to 0. About 59 % of the non-CLL cases were estimated to be associated with radiation exposure.

4.3.1.3 *Study Strengths and Weaknesses*. The Techa River studies consist of a relatively large, unselected population of men, women and children with a long follow-up such that approximately 75 % have died. The range of estimated cumulative doses was fairly broad. It was possible to adjust for several covariables in the analysis, including smoking and ethnic differences. Though the mortality study had limitations in histopathologic verification of cancer deaths, it is notable that the risk estimates for solid cancer mortality and incidence, where the latter had better histopathologic verification, were similar. The study suffers from uncertainties in dose reconstruction, potential medical screening bias, concomitant radiation exposure from medical screening, losses to follow-up, and uncertain quality and completeness of outcome ascertainment (NCRP, 2012). While the dose reconstruction methodology is commendable, it has considered uncertainties because of the wide range of assumptions required. The measurements, of necessity, were made decades after intake. Another problem is that radiation exposures from medical fluoroscopic examinations were not accounted for, and those were sometimes very substantial and were correlated with Techa River exposure levels (Degteva *et al*., 2007).

The epidemiologic methods also had limitations: >20 % of the Techa River population was lost to follow-up, mainly due to out-migration, cause of death was missing for 9 % of deaths, and in the earlier years ~35 % of the solid cancer cases were morphologically or radiologically confirmed though since 1990 over 80 % have such confirmation (Davis *et al*., 2015; Krestinina *et al*., 2007). The small number of excess cancers limits the statistical precision and thus tempers interpretations when comparing results with larger studies. The dosimetric and epidemiologic limitations constrain the weight attached to this study in informing LNT and radiation protection (UNSCEAR, 2000; 2008).

4.3.1.4 *Implications for the LNT Model and Radiation Protection*. Studies based on the TRDS-2009 dosimetry provide only modest support for the LNT model, particularly for leukemia where internal dose from ^{90}Sr is important. It is expected that new studies based on the upcoming TRDS-2017 will allow a better evaluation of the LNT model. The Techa River studies are quite important in showing that low dose-rate exposures over time may increase the risk of cancer in human populations. The recent studies of the Techa River Cohort have reported associations between radiation dose and incidence and mortality rates for solid cancers and non- CLL leukemia that appear to be linear in dose response (Davis *et al*., 2015; Krestinina *et al*., 2013a; Schonfeld *et al*., 2013).

However, the small number of cancer cases, the challenging dosimetric issues, the possible confounding influence of medical irradiation, the peculiar inconsistency with other studies in age patterns and types of excess cancers, and other methodological limitations of follow-up and case ascertainment prevent strong inferences about the shape of the dose-response curves and DDREF. Thus the Techa River studies provide general support for the LNT model, but the results at doses under 100 mGy are uncertain, so implications for radiation protection are limited.

4.3.2 *Chernobyl Resident Cohorts*

The Chernobyl accident in northern Ukraine introduced a new era of concern about the effects on humans of radiation at low doses and low dose rates. There was a clear and large excess of thyroid cancer cases among those heavily exposed to radioiodine at a young age in Ukraine, Belarus and parts of Russia following the Chernobyl accident (Brenner *et al*., 2011; Jacob *et al*., 2006; Tronko *et al*., 2006; Zablotska *et al*., 2011). The data on exposure to radioactive iodines have added considerable information relative to the dose-response relationship. In 2006, the BEIR VII committee published a report of Chernobyl research activities (NA/NRC, 2006) and concluded with regard to thyroid cancer that "the linear-no-threshold model (LNT) provided the most reasonable description of the relation between low-dose exposure to ionizing radiation." UNSCEAR followed with its own comprehensive report (UNSCEAR, 2011) on Chernobyl that was consistent with that conclusion as well. An update of the key studies of defined cohorts is summarized below.

4.3.2.1 *Dosimetry*. The thyroid dosimetry for both the Ukrainian and Belarusian cohorts was based on direct measurements of thyroid activity for all study subjects supplemented by estimates from a pathway model using ground deposition data [methods described in Likhtarev *et al*. (2003; 2006; 2014)] and reports obtained by personal interviews of behavioral factors *e.g*., amount of local milk drunk at the time of the Chernobyl accident. The direct thyroid measurements were conducted under difficult conditions within a few weeks of the accident. The estimated uncertainties in thyroid doses are lower than most previous studies, mainly because of the availability of direct measurements of thyroid activity for all study subjects.

For the pathway model estimates, whereabouts of individuals, consumption details, and other variables were based on questionnaires with associated possible recall error. Although some inconsistencies have been observed, comparisons between the direct measurement-based doses and the pathway-based doses suggested that overall agreement was quite good. However, the earlier epidemiologic evaluations of the Ukrainian cohort used versions of the dosimetry that had some issues regarding thyroid mass, and the analysis did not take shared uncertainty into account. The most recent dosimetry analysis of the Ukrainian data (Likhtarov *et al*., 2014) is considered more accurate, and among other things, reflects an increased understanding of how to account for thyroid mass.

Parameters of the model used in the previous dosimetry were also substantially improved. The GSDs obtained for the 13,204 cohort members in the newer dosimetry varied from 1.26 to 10.6, with a geometric mean of 1.47 and <4 % with GSDs greater than two.

For the Belarusian studies, thyroid doses were based on methods identical to those used in Ukraine. Doses based on pathway modeling were used for validation and uncertainty estimation. Zablotska *et al*. (2011) used the deterministic doses reported by Drozdovitch *et al*. (2013). Their mean estimated dose was 0.56 Gy (range up to 32.8 Gy), based on personal thyroid exposure measured shortly after the accident. The estimated individual dose uncertainties ranged from a GSD of 1.3 to 5.1 with an average GSD of about 1.7. A more recent dosimetry study investigated uncertainties in detail and estimated the shared vs, unshared components using two-dimensional Monte Carlo with multiple realizations (Drozdovitch *et al*., 2015). They found that the GSD in individual thyroid doses varied among cohort members from 1.33 to 5.12, with a geometric mean of 1.73. The mean dose estimated by Drozdovitch *et al*. (2015), 0.68 Gy, was slightly higher than the earlier deterministic estimate of 0.56 Gy. For both the Ukraine and Belarus studies, the major sources of uncertainties were errors in the ^{131}I activities in the thyroids derived from the direct thyroid measurements and errors in assigning individual thyroid-mass values (Drozdovitch *et al*., 2015). Little *et al.* (2014) concluded that dose-error adjustment has comparatively modest effects on regression parameters in both studies.

4.3.2.2 *Epidemiologic Methods, Findings and Issues*. Among the earliest reports were ecological analyses of thyroid cancer risks. For example, a report by Jacob *et al*. (1998) showed a reasonably linear dose response relationship but at a slope lower than that for external radiation, whereas a later paper found a high linear slope with a significant negative quadratic term (Jacob *et al*., 2006). However, these studies were based on ecologic, and not individual data, that were complicated by potential goitrogenic and screening effects, and limited ^{131}I thyroid measurements. A population-based case-control study by Cardis *et al.* (2005a) found that having low levels of dietary stable iodine did augment thyroid cancer risk, but reported a radiation effect independent of stable iodine intake levels.

In the first decade or so after the Chernobyl accident, some thought that the sudden and sharp increase in thyroid cancer was mostly, if not entirely, due to aggressive screening programs instituted in the most contaminated areas, but an early case-control study showed that the increase was not merely a screening artifact (Astakhova *et al*., 1998). Since then reports of cohorts of exposed children in Ukraine or Belarus with thyroid dosimetry based on thyroid ^{131}I measurements at the time of the Chernobyl accident and systematic thyroid screening have provided decisive information that the excess of thyroid cancer and thyroid nodules is radiation related. A systematic thyroid screening study of a cohort of children exposed to ^{131}I was initiated in Ukraine (Tronko *et al*., 2006).

Approximately 13,000 individuals were exposed before age 18 and had thyroid measurements taken within two months after the accident (Likhtarev *et al*., 2003; 2006). The principal radiation exposure to the thyroid was from ^{131}I (beta) and, to a much smaller extent, external gamma. The estimated mean thyroid dose in the screenees was 0.79 Gy (median 0.26 Gy, maximum 47.6 Gy). About 53 % had estimated thyroid doses <0.3 Gy, 27 % 0.3 to <1 Gy, and 19 % ≥ 1 Gy. The GSDs of 96 % of the dose estimates were less than 2.0.

The participants were given thyroid screening by ultrasound and palpation to detect thyroid nodules and cancer between 1998 and 2000 (12 to 14 y after the accident). Forty-five pathologically confirmed cases of thyroid cancer were identified. Analyses were adjusted for sex and age at screening (or age at exposure). The dose response for thyroid cancer prevalence was essentially linear; an added quadratic term was nonsignificant ($p > 0.99$). The linear ERR dose response was 5.3 Gy^{-1} (95 % CI 1.7, 28) overall and 6.2 Gy^{-1} over the dose range of 0 to 10 Gy, risk estimates similar to those for external radiation (Veiga *et al*., 2016). The ERR estimates were nonsignificantly higher for females and for those youngest at exposure.

The Ukrainian cohort was given three more thyroid screenings at approximately 2 to 3 y intervals to evaluate the incidence of thyroid tumors (Brenner *et al*., 2011). An additional 65 thyroid cancers were diagnosed. Adjustment factors included sex, age at exposure, age at screening and calendar time, and sensitivity analyses examined oblast, urban/rural, smoking status, goiter, history of iodine prophylaxis and family history of thyroid disease. The dose response was approximately linear with no evident quadratic curvature ($p = 0.31$). They found a somewhat lower, but still compatible ERR estimate of 1.9 Gy^{-1} (95 % CI 0.4, 6.3). There were no significant interactions of radiation risk with sex, age at exposure, screening age, urinary iodine status or history of iodine prophylaxis.

A parallel thyroid cancer prevalence study was conducted in Belarus (Zablotska *et al*., 2011). Mainly between 1996 and 2001, approximately 12,000 young people who were ≤ 18 y old at the time of the Chernobyl accident were examined. The study participants were screened for thyroid cancer with ultrasound and palpation, and 85 cases were identified (excluding 53 additional cases diagnosed with thyroid cancer more than 3 y prior to the examination). The ERR was 2.2 Gy^{-1} (95 % CI 0.8, 5.5) among those with estimated doses up to 5 Gy, with a downturn in the dose response above 5 Gy. A number of covariables were examined as possible confounders and adjusted for as needed, including sex, age at screening, age at exposure, oblast of residence, urban/rural status, history of nodular goiter, past iodine deficiency and current urine iodine level.

In summary, there was a small suggestion that risk may be lower with protracted irradiation from ^{131}I than from acute external irradiation, but the risk estimates were statistically compatible. Evidence of an excess risk of thyroid

cancer in areas less affected by Chernobyl contamination was much less clear. In Finland, which was one of the countries most affected by Chernobyl contamination outside the former USSR, no increased risk of thyroid cancer after juvenile exposure was detected (But *et al*., 2006), largely because the thyroid doses of a few milligray were far lower than those received around Chernobyl.

Doses to other organs were much smaller than to the thyroid for residents downwind from Chernobyl. Because of the low and very uncertain whole-body exposure levels for individuals, mainly from ^{137}Cs, the radiation results for other organs have been null or inconsistent [for instance, see a review of leukemia findings by Howe (2007) and the Ukraine-Belarus-Russia study by an international consortium (Davis *et al*., 2006)].

4.3.2.3 *Study Strengths and Weaknesses*. The principal Ukrainian and Belarusian cohort studies of thyroid cancer prevalence and incidence in young people after exposure to ^{131}I from the Chernobyl accident included only children who had received radiation measurements of the thyroid gland shortly after the accident as the basis for individual dose reconstructions. They received several follow-up clinical and ultrasound examinations, performed blindly with respect to thyroid dose, and further fine needle aspiration cytology and surgery when indicated according to standard protocols. The cancers were verified by international pathology reviews. Limitations include some potential sample selection bias due to prior thyroid cancers, voluntary participation and losses to follow-up. In spite of the thyroid activity measurements, there were uncertainties in estimating doses due to variations in thyroid mass, uptake and retention, timing of exposure, and unreliability of behavioral and milk-intake reports.

4.3.2.4 *Implications for the LNT Model and Radiation Protection*. The thyroid cancer experienced by children in exposed areas of the Ukraine, Belarus and Russia conforms to the LNT model, though perhaps with a somewhat lower risk per unit dose than seen in studies of children exposed to external gamma radiation (Little *et al*., 2014). The UNSCEAR (2011) report on Chernobyl concluded that the thyroid risk findings were consistent with the LNT model. The dosimetry, although uncertain as described above, is believed sufficiently accurate to support that conclusion.

4.3.3 *High Natural Background Radiation Area (HBRA) Studies: Kerala Study*

Since exposure to ionizing radiation is ubiquitous, for epidemiologic studies to detect any effect of natural background radiation upon health, it is necessary for different groups of people to receive materially different doses from naturally occurring radiation sources. Differences in the doses received from naturally occurring low-LET radiation do exist, although not to the extent of the variation of lung doses from radon and its progeny. There

are areas of the world with high levels of natural background gamma radiation because of local geology, such as thorium-bearing monazite sands. Such areas occur in Iran, Brazil, India and China (Hendry *et al*., 2009). Studies of high natural background gamma radiation areas are difficult to conduct because large numbers of exposed people are required to achieve adequate statistical power to detect the predicted effects. Further, it may often be difficult, especially with studies in developing countries, to find a suitable low exposure control group with which the highly exposed group may be compared in terms of detailed lifestyles, completeness of disease ascertainment, and baseline disease rates. However, there have been updates of the two major studies of high natural background gamma radiation areas since the BEIR VII and UNSCEAR reports, described below, which might be of some use in assessing the LNT model.

For the Kerala epidemiologic study a cancer incidence registry was developed in Karunagappally, Kerala, India that compiled data between 1990 and 2005 for about 70,000 persons of ages 30 to 84 y to compare low and high background radiation areas (HBRA) (Akiba, 2013; Nair *et al*., 2009).

4.3.3.1 *Dosimetry*. The primary exposure was from external gamma radiation from thorium in the monazite sands. Doses for the Kerala region were based on measured ambient exposure rates, factoring in estimates of average house occupancy by age and sex determined for about 11 % of the cohort from interviews. Sodium iodide (NaI) detectors were used to measure indoor and outdoor dose rates for 71,674 houses (~94 % of study residences) using the mean of three dose measurements. The estimated dose rates were validated by TLDs and spot scintillometer measurements made quarterly for 1 y in 800 homes selected at random. The annual dose, estimated from TLDs worn for two months, and the personal doses, calculated by their algorithm for all subjects, showed a correlation of 0.80, but only after 15 % of dosimeter measurements were discarded as "outliers" (Nair *et al*., 2009). No uncertainties were provided for the dose estimates.

4.3.3.2 *Epidemiologic Methods, Findings and Issues*. The cancer incidence registry was based on records from a cancer hospital, other hospitals and clinics, death certificates and visits to relatives to determine missing cause-of-death information. Histopathology or cytology was available for 73 % of cases. There were 1,349 cancers other than leukemia. The dose response analysis of all cancer except leukemia yielded an ERR estimate of –0.13 (95 % CI –0.58, 0.46, $p > 0.5$) (Figure 4.8). The analysis was based on five dose categories and adjusted for sex, attained age, follow-up interval, education, occupation and bidi (home-made cigarette) smoking, as needed. There was no significant modification of the ERR by sex or age. When cancer cases were limited to those with pathological verification, the estimated ERR Gy^{-1} became larger with wider 95 % CI (but data not shown). There was no significant evidence of risk among those with 500 mGy or more. The risk estimate for leukemia was noninformative, with large uncertainties.

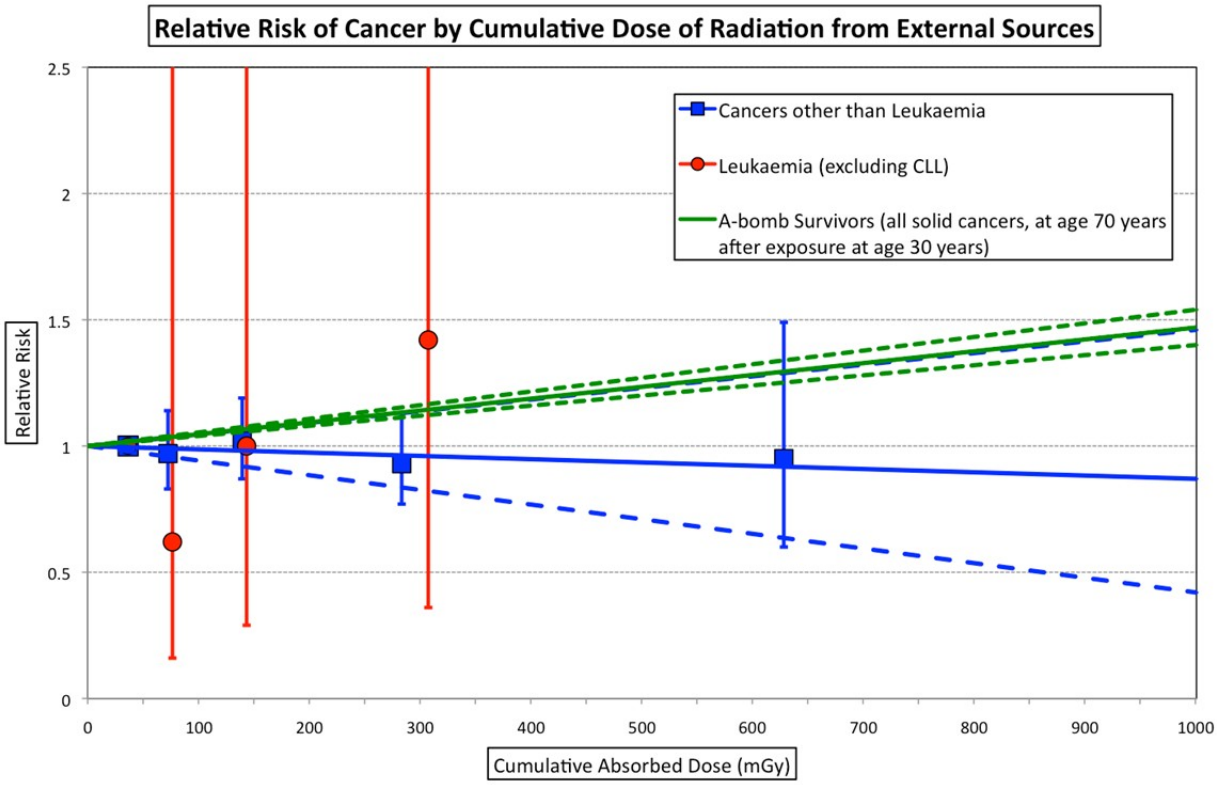


Fig. 4.8. Cancer risk by estimated cumulative external exposures in Kerala (adapted from Nair *et al*., 2009), but not shown there as a graph).

4.3.3.3 *Study Strengths and Weaknesses*. The HBRA study members had a fairly high cumulative dose (mean = 161 mGy), ranging to over 500 mGy. The investigators used various sources to try to ascertain cancers. The population was more stable than in many regions of the world, so migration did not greatly alter the estimated doses or disease ascertainment. Information was available on bidi smoking and other lifestyle and sociodemographic factors.

Over the course of the study, investigators made a considerable effort to characterize exposure levels. Nevertheless, they had to rely primarily on ambient air sampling and aggregated reports on age- and sex-specific house occupancy factors. They obtained personal dosimeters worn by 160 individuals for two months to compare with estimated doses calculated by their usual methods, but the results are difficult to interpret.

The study period was only 15 y and the number of cancers therefore was fairly small. A possible problem is that high cumulative doses occur in coastal areas where monazite sands are found, which raises the question of whether background cancer rates in coastal (fishing) communities are the same as in inland (farming) communities. Cancer incidence rates increased as the 2.4 power of attained age; this is somewhat lower than for most studies, suggesting the possibility that there may have been cancer under-ascertainment among older people, when many cancers occur. The investigators commented, "…the accuracy of information on cause of death is questionable, particularly among poor people…. One may also suspect that the social structure and medical care system in India might have made it difficult to obtain accurate information on cancer diagnosis" (Nair *et al*., 2009). International Agency for Research on Cancer (Nair *et al*., 2002) reported that the high percentages of cancer cases indicated as an unspecified or ill-defined site, or detected through the death certificate only, suggested the likelihood of cancer under-ascertainment. This raises the question of whether a non-negligible fraction of the poor people may have received little or no medical attention for their cancers, so that cancer was under-diagnosed in this study, and whether factors like individuals' distance from the sole cancer hospital might affect the degree of cancer under-diagnosis, and might even bias the results if dose levels are correlated with distance.

4.3.3.4 *Implications for the LNT Model and Radiological Protection.* This study is nominally more supportive of a dose-effect threshold than of the LNT model. However, the uncertainties in dosimetry, the weaknesses in cancer ascertainment and the wide confidence interval on the risk estimate mean it is inconclusive and needs to be interpreted with caution.

4.3.4 *Yangjiang, China HBRA Study*

Tao *et al*.(2012) reported an update on residents of a HBRA in the Yangjiang region of China for the period of 1979 to 1998. Most study families had resided there for six or more generations.

4.3.4.1 *Dosimetry*. Tao *et al*. (2000) divided the region into three dose groups (high, medium, low) on the basis of environmental dose rates per year. Sun *et al*. (2000) estimated individual annual doses and cumulative doses based on location-specific exposure data for each hamlet and distinguished between outdoor environment in the hamlet or on farmland. Arithmetic mean doses were calculated for public places and for farmland in each hamlet. Indoor doses were based on sampling one-third of houses in each hamlet. Indoor doses differed somewhat from house to house, being highly dependent on building materials and room size. A distinction was made between bedroom dose and dose in other indoor places. Sex- and age-specific occupancy factors were used to represent the time spent in bed, at other indoor places, and outside in public places or farmland. The occupancy factors were obtained from a survey of 5,291 persons. Individual dose estimates calculated using the indirect method were compared to direct measurements for 5,204 individuals that were obtained using electronic pocket dosimeters or TLDs and a good correlation was reported (Morishima *et al*., 2000). No uncertainties were calculated in the dosimetry. For the HBRA areas and the control areas the estimated mean cumulative colon doses, lagged 10 y for solid cancer, were 84.8 mGy and 21.6 mGy, respectively, a difference of about 63 mGy.

4.3.4.2 *Epidemiologic Methods, Findings and Issues*. The mortality experience of the approximately 31,000 cohort members in the Yangjiang area of China was determined for ages 30 to 74 y based on periodic staff visits to area hospitals, local village doctors, and family members (Tao *et al*., 2012). Investigators ascertained 941 deaths due to cancer excluding leukemia. Diagnoses were based on pathological determination for only 26 % of cancer deaths and radiographic or ultrasound information for 62 %. Analyses used six dose categories and adjusted for sex, attained age and follow-up interval. The estimated ERR Gy^{-1} was –1.01 (95 % CI –2.53, 0.95). However, 29 % of those deaths were coded as due to liver cancer, for which a strong negative risk estimate (ERR = –3.38 Gy^{-1}) was seen. Since that might be associated with area differences in other risk factors, *e.g*., different prevalence of hepatitis B infections, calculations were performed excluding both liver cancer and leukemia, which yielded an ERR of 0.19 Gy^{-1} (95 % CI –1.87, 3.04). Prior reports had compared socioeconomic and lifestyle factors between the high- and low-background areas and found little difference. However, a survey of the frequency of having received an x-ray examination showed about 30 % more in the low background area than in the HBRA (Tao *et al*., 2000), suggesting a differential in medical care as a possible source of bias. Furthermore, the rates of infectious disease, particularly tuberculosis, and external causes of death differed between the low- and high-background areas, again raising a question of the comparability of the low- and high-background areas.

4.3.4.3 *Limitations of the Kerala and Yangjiang HBRA Studies*. Dosimetry for the high natural background study areas is limited by the lack of personal dose information among the study populations. Although doses were based on measurement data within the regions, large uncertainties were likely within the study cohorts and little attempt was made to determine these uncertainties. Based on the dosimetry, the use of these studies is limited in furthering our understanding of LNT.

Since these studies compared persons residing in different geographical areas with relatively little migration, the area basically defines the dose. This leads to questions about the comparability of the residents in different areas regarding occupations, lifestyle and dietary habits, access to medical care, disease experience, and other factors that might confound or otherwise modify cancer risk. These uncertainties may impact the risk estimates and require caution in their interpretation.

4.3.4.4 *Implications of the HBRA Studies for the LNT Model and Radiation Protection*. The failure of the HBRA studies to find a risk for all cancer except leukemia is not supportive of the LNT model. However, the risk estimates are largely statistically consistent with the LSS risk estimate owing to their broad confidence bounds. As described above, the studies have large dose uncertainties and weaknesses in cancer ascertainment which may have attenuated the risk estimates. Furthermore, the fact that much of the dose variation is attributable to geographic locations, which may be associated with risk factors other than radiation level, introduces ambiguity into the inference regarding radiation effects. Therefore, the studies are inconclusive regarding the LNT model, but at least would tend to favor the use of a DREF greater than one in formulating radiologic protection guidelines.

4.3.5 *Taiwan Residents of Radiation-Contaminated Buildings*

Between 1982 and 1984 Taiwanese manufacturers of building construction materials incorporated radioactive 60Co into rebar reinforcing rods. The contaminated rods were used in over 180 buildings in Taiwan, which included more than 1670 apartments/houses and certain schools and industrial facilities and exposed about 10,000 individuals. The national government sponsored a program to conduct a detailed dosimetric survey of interior exposure levels in those facilities (Chen, 2002).

4.3.5.1 *Dosimetry*. A dosimetry survey was conducted from 1992 to about 2001 to estimate doses to residents of the contaminated units (Chen, 2002). They surveyed 1,607 units in 181 contaminated buildings. They measured the interior and exterior dose equivalent rate of each building. Based on the physical arrangement of contaminated reinforcement bars they measured the dose equivalent rates at the surface of the contaminated locations and at

likely person locations within the units. They measured the living room, bedroom, study room, dining room, bath and kitchen. Interviews were conducted and records of the daily living activities of the residents were collected to reconstruct the individual dose equivalent for each resident. Total cumulative doses were estimated for individuals based on the ambient exposure measurements, the time and duration of residence in the contaminated apartments and estimated occupancy-rate information. It was difficult for residents to provide explicit information on their daily activities 10 to 20 y in the past. Survey information and the use of assumed room occupancy factors (50 % living room; 33 % bedroom; 17 % others) contributed significantly to uncertainties in the individual dose reconstructions.

The estimated dose distribution was low. The mean cumulative dose was estimated to be 47.8 mGy (median 6.3 mGy, range <1 to 2,363 mGy), and the dose distribution was highly skewed, with only 15 % of the study subjects exposed to more than 50 mGy (Hwang *et al*., 2006). In general, the dosimetry effort was thorough and well conducted, and the study authors appear to have done a rigorous job in reconstructing exposures. Nevertheless, the individual estimates have considerable uncertainties due to faulty or nonspecific recall of daily activities 10 to 20 y previously, and rough extrapolations of doses at various locations within their home. Based on those dosimetry weaknesses, the study is limited in its use to evaluate dose response.

4.3.5.2 *Epidemiologic Methods, Findings and Issues*. Interviews with study subjects also obtained information on medical history, occupation, education, and detailed exposure history including dates moved in and out and lifestyles in these buildings, and exposures to occupational and medical irradiation. The cumulative dose estimates have been used to perform dose-response analyses of various health endpoints. Cancer incidence has been ascertained from the national cancer registry (Hwang *et al*., 2008), and various sub-studies of smaller groups have evaluated lens opacities, chromosome abnormalities, hematological and immunological parameters, and reproductive effects (Chang *et al*., 1999a; 1999b; Hsieh *et al*., 2002; 2010; Lin *et al*., 2010). Various papers presented categorical comparisons (*e.g*., <50 mGy vs. ≥50 mGy) and most presented dose-response analyses using Cox regression, or other statistics for continuous outcomes.

In the latest report on cancer incidence the mean length of follow-up was 19 y (Hwang *et al*., 2008). The Cox regression analyses adjusted for sex, birth cohort and years since first exposure, using dose as a continuous variable. Doses were not lagged other than allowing a minimum latency period after first exposure. The mean age was 17 y (range was from intrauterine to 87 y) at first exposure and 36 y at follow-up. There was no indication of a significant increase in risk for all solid cancers (p = 0.5; hazard ratio (HR) at 100 mGy = 1.03 (90 % CI 0.96, 1.09, n = 106; ERR $Gy^{-1} \approx 0.3$, 90 % CI –0.4, 0.9). They reported a significant dose response for non-CLL leukemia, (ERR $Gy^{-1} \approx$

1207 1.9, 90 % CI 1, 3.1, $P = 0.08$, $n = 6$) and a marginally significant dose response for breast cancer (ERR $Gy^{-1} \approx 1.2$,
1208 90 % CI –0.1, 2.1), 1.21, $P = 0.13$, $n = 17$). There was no indication of risk for thyroid, lung or stomach cancers.
1209
1210 **4.3.5.3** *Study Strengths and Weaknesses*. The dosimetry effort to reconstruct exposures was thorough, albeit the
1211 estimated doses were based on ambient exposure measurements and imputed occupancy factors. The ascertainment
1212 of cancer incidence was of reasonably good quality. The investigators determined basic phenotypic data
1213 (chromosome aberrations, blood cell counts) as well as overt health outcomes. However, the individual exposure
1214 estimates have considerable uncertainties due to faulty or nonspecific recall of daily activities 10 to 20 y
1215 previously, and necessary extrapolations of exposures at various locations within the home. The sample size was
1216 small and the dose distribution was low, so one would not expect much statistical power, yet the authors have
1217 reported a number of "positive" effects, some of them questionable. For example: they reported a narrow
1218 confidence interval for leukemia (ERR $Gy^{-1} \approx 1.9$, 90 % CI 0.1, 3.1) based on only six cases (Hwang *et al*., 2008).
1219 Also, for eosinophils, they reported $p = 0.03$ based on a mean (± SD) of 0.22 (0.17) in the exposed group and 0.21
1220 (0.19) in the unexposed group.
1221
1222 **4.3.5.4** *Implications for the LNT Model and Radiation Protection*. The investigators did not compare a linear model
1223 with quadratic or threshold models. The uncertainties associated with the dose reconstruction, small sample size
1224 and other features mean the implications regarding dose response for radiation protection purposes cannot be
1225 determined reliably .
1226
1227 **4.3.6** *Radiation Fallout Studies*
1228

Highlights

Fallout studies have been conducted in conjunction with the Japanese atomic-bomb survivors, nuclear bomb testing, nuclear production facilities and nuclear power plants (NPPs). Kim *et al.* (2016) reviewed, and conducted a meta-analysis of studies of thyroid cancer risk and residence near NPPs. Overall, they concluded that the evidence does not support an association, but noted some interpretive uncertainties. A weakness of most fallout studies has been the large uncertainties regarding fallout exposures: no individual dose information, or dose reconstructions with limited availability of individual measurements to validate the estimates, and small numbers of observed leukemias or thyroid cancers. Other issues with some radiation fallout studies have been the use of only geographic comparisons of populations (who may differ in other disease risk factors), exposure-related variations in intensity of disease surveillance, possible biases associated with self-reports of exposure-related behaviors (*e.g.*, fallout-contaminated milk consumption), and lack of information on lifestyle or other potential confounding variables. We conclude that, though a variety of fallout studies may have been needed to address public health concerns, the

studies have contributed little to our scientific understanding of the LNT model.

Epidemiologic studies of possible health effects from fallout episodes have included a brief summary of studies of health effects associated with several of the major fallout incidents follows.

4.3.6.1 *Japanese Atomic-Bomb Fallout*. The Atomic Bomb Casualty Commission (ABCC) conducted interviews of LSS members between 1951 and 1961 which included several questions about bomb fallout exposures from rain. The results were published because of recent public concerns about "black rain" exposure (Sakata *et al*., 2014). To avoid outcome-dependent biases (*i.e*., recall of exposure after a health outcome has already occurred), the primary data analyses excluded health events prior to 1962. For 1962 to 2005 there was no significant association of reported "black rain" exposure with deaths due to leukemia, all solid cancer or all causes for either Hiroshima or Nagasaki. Similarly, there were no associations for the incidence of solid cancer or leukemia. On the other hand, thyroid examinations by Nagataki *et al*. (1989) suggested an excess prevalence of thyroid nodules in the Nishiyama district of Nagasaki, where there was a known radioactive rainout event, though the excess was based on small numbers (9/184 exposed and 3/368 unexposed).

Another group of investigators from Hiroshima universities analyzed data based on a cohort of atomic-bomb survivors loosely defined in 1970, and reported positive associations of fallout with mortality through ad hoc statistical modeling techniques (Tonda *et al*., 2012) or use of reported fallout exposure information that was obtained in 2008 (and therefore subject to outcome-dependent biases) (Otani *et al*., 2012).

Limitations of the atomic-bomb fallout data include: large uncertainties regarding fallout exposures and considerable missing individual data; no indication of whether study members were protected from the rainout; no data on where individual "black rain" exposures occurred (as much of the black rain, from carbonaceous fires, contained little radioactivity); 6 to 16 y recall of a possible event that occurred when they were under heavy stress. There were further limitations of the studies by the Hiroshima universities group because of the long lapse of time before the cohort was formed (survival and migration bias) and the potential for outcome-dependent bias. Since information on individual fallout exposures was very limited, the studies are not useful for evaluating the LNT model.

4.3.6.2 *Marshall Islands Atomic Testing Fallout*. Residents of the Marshall Islands were exposed to radioiodine as a result of testing of nuclear weapons by the United States during 1946 to 1958, and particularly so by inadvertent exposure from the Castle Bravo thermonuclear test explosion in 1954 that led to assessed thyroid doses of around 20 Gy for young children living on Rongelap Island (Simon *et al*., 2010). Studies of small groups of highly

exposed residents have been conducted over the years (Howard *et al*., 1997; Robbins and Adams, 1989) but provide little information on low-dose effects. As to lower dose studies, Hamilton *et al.* (1987) screened approximately 7200 Marshall Islanders, including about 2300 who were residents of the northern Islands in 1954. They found excess thyroid nodules among the residents of the northern islands and reported a linear distance-response association based on distance from the BRAVO test. Takahashi *et al.* (1997) also found an excess of thyroid nodules among residents of the northern islands in 1954. Limitations of both studies included no individual doses and possible subject selection biases, so they provide little useful information for evaluating the LNT model.

4.3.6.3 *Nevada Test Site (NTS) Atomic Fallout in Utah*. The principal studies of potential effects of fallout from the NTS in Nevada have centered on leukemia and thyroid cancer outcomes. A large case-control study (1,177 cases and 5,330 controls) of leukemia mortality in Utah did not find a statistically significant overall association with estimated bone marrow dose categories, though a significant excess was reported among children/adolescents during 1952 to 1957 ($p = 0.02$), especially for acute lymphocytic leukemia ($p = 0.009$) (Stevens *et al*., 1990). No association was seen for those who were *in utero* during the fallout period, perhaps because of limited statistical power. The median RBM dose was estimated as 3.2 mGy among all study subjects, and 19 mGy among residents of the most highly exposed county.

Two thyroid examinations in 1965 to 1966 and 1985 to 1986 were conducted of a cohort of school children in parts of Utah, Nevada and Arizona (Rallison *et al*., 1990). Some 2500 children received both examinations. The maximum assessed individual thyroid dose was 1.4 Gy and the mean 0.12 Gy (Simon *et al*., 2006a) in Utah based on measurements of ^{131}I deposition and interview recall of amount of milk and green vegetables consumed. A detailed review of the study which revised the dosimetry and thyroid diagnoses (Lyon *et al*., 2006) and the application of a more sophisticated model for dose uncertainties found a high relative risk for total thyroid neoplasms but the risk estimate was extremely wide (ERR = 24.3 Gy^{-1}, 95 % CI 3.9, 79; $n = 20$) (Li *et al*., 2007). However, there was no clear indication of risk of thyroid cancer (ERR = 0.8 Gy^{-1}, CI < 0, 15; $n = 8$) (Lyon *et al*., 2006). Concerns about the study include possible outcome-dependent bias and having different examiners in the various geographic areas that varied by dose which might affect the consistency of diagnostic sensitivity.

The leukemia data were limited by reconstructed estimates of RBM doses and the small doses entailed. The thyroid studies were limited by the potential for subject selection factors with a considerable loss to follow-up, large thyroid dose uncertainties, limited blinding of screeners as to exposure, and the potential for outcome dependent biases because some of the interviews that defined exposure were conducted after subjects' thyroid examination

results were known. Because of wide uncertainties in individual doses and the potential for biases, the studies provide little useful information for evaluating the LNT model.

4.3.6.4 *Atomic Testing Fallout Across the United States*. Estimates of whole-body doses from external irradiation by atomic fallout for the population of the United States have been reported as ~1.2 mGy. For U.S. children born in 1951 average thyroid fallout doses from ^{131}I were estimated to be~32 mGy (Bouville *et al*., 2002). Gilbert *et al.* (2010) examined thyroid cancer rates in counties within the SEER cancer registries (SEER, 2001) in relation to estimated ^{131}I exposure levels in those counties from NTS fallout. They found a suggestive but nonsignificant exposure-thyroid cancer relationship for exposures before 1 y of age, but no indication of an association for exposures at ages 1 to 15 y. Since this is an ecological study, the potential for ecologic biases means it should not be used for evaluating the LNT model.

4.3.6.5 *Semipalatinsk Fallout*. The more than 100 above-ground nuclear tests conducted by the Soviet Union in 1949 to 1962 at the Semipalatinsk nuclear test site (SNTS) in Kazakhstan delivered fallout to residents of downwind villages. A nested case-control study of leukemia mortality (n = 22 cases) and individual estimated doses reported a significant relative risk of 1.9 for those with doses >2 Gy (Abylkassimova *et al*., 2000). A study of solid cancers among ~19,000 residents around SNTS reported a high risk for all solid cancer (ERR Gy^{-1} of 0.81) and for selected single cancer sites (Bauer *et al*., 2005). However, the dose estimates used in the study are now believed to be incorrect, so the dosimetry is being redone,[4] and the authors expressed concerns about selection biases in the unexposed group. A recent report on radiation dose and cardiovascular diseases found that all the differences observed were attributable to variation between the exposed and unexposed group and not to a dose response within the exposed group, again suggesting selection biases (Grosche *et al*., 2011).

Land *et al.* (2015) investigated thyroid disease among almost 2400 people less than 21 y of age who were resident downwind of the SNTS during 1949 to 1962. The prevalence of thyroid nodules was assessed by ultrasound screening in 1998, and 35 cases of thyroid cancer were detected. Estimated thyroid doses ranged up to several gray, with a mean of 100 to 200 mGy. Their methods for thyroid dose assessment were commendable (Land *et al*., 2015), but uncertainties were still substantial because of the limited data available. The dose responses for thyroid nodules were difficult to interpret, with small numbers and estimated risks six times as great for males as for females. The thyroid cancer results were positive, but not significantly so, for either males or females.

[4] B Grosche, personal communication, 2015

The incorrect dosimetry annuls the value of risk estimates of the cancer mortality studies regarding LNT, while the sex disparity regarding thyroid nodularity and nonsignificant risks for thyroid cancer suggest caution in the interpretation of thyroid results.

4.3.6.6 *Hanford ^{131}I Fallout*. From 1944 to 1957, the Hanford Nuclear Site in Washington State reprocessed nuclear fuel that had been stored for a comparatively short time, so that substantial quantities of ^{131}I (27 PBq) were released to the atmosphere during this period; extensive efforts were made to reconstruct the magnitude and geographic distribution of those releases (Napier, 2002). Concerns were raised about cancer risk in downwind populations. A long-term ecological study gave no indication of excess risk of mortality from all cancer, thyroid cancer, breast cancer, non-CLL leukemia or childhood leukemia during the years 1950 to 2000 (Boice *et al*., 2006c).

An extensive ^{131}I exposure reconstruction was conducted (Napier, 2002). During 1992 to 1997 Davis *et al.* (2004) conducted a historical cohort study of thyroid disease among almost 3500 people who had potentially been born during 1940 to 1946 in seven counties near the site and provided sufficient interview information on locations and habitual behaviors to estimate individual doses (mean dose of 174 mGy; median 97 mGy, maximum 2823 mGy). The doses were around an order of magnitude greater than those received locally from the Windscale Fire, but much less than the doses received after Chernobyl in heavily contaminated areas of the former USSR. The study participants were examined for thyroid abnormalities by ultrasonography and palpation by two separate thyroid specialists, blinded as to dose, plus laboratory functional thyroid tests. Based on 19 diagnosed thyroid cancer cases, the ERR Gy^{-1} was not statistically significant ($p = 0.25$), nor was it significant for all detected thyroid nodules ($p = 0.65$) or any other thyroid disease.

The authors noted that the study had sufficient statistical power to detect the magnitude of effects that had been reported elsewhere following exposure to ^{131}I. However, another group re-examined the dose assessment and other study aspects and concluded that the study results should be interpreted as inconclusive, rather than as evidence for little or no disease risk, because the uncertainties were considerable (Hoffman *et al*., 2007).

The Hanford thyroid cancer screening study is methodologically one of the best in the literature, although the ultrasound equipment was not as sensitive as that available today. The substantial uncertainties in reconstructing individual thyroid doses plus the inability to examine a third of the potential study subjects make the null findings less certain, so the study can make only a limited contribution to the question of LNT.

4.3.6.7 *Mayak Fallout*. The Mayak nuclear complex in the Southern Urals of the Russian Federation commenced reactor operations in 1948 and started reprocessing irradiated nuclear fuel in 1949. During 1948 to 1972 about 38 PBq of ^{131}I was discharged to the atmosphere from Mayak (Eslinger *et al*., 2014). A child born in 1947 in the nearby closed city of Ozyorsk and living there until 1972 is estimated to have received a cumulative thyroid dose during this period of 2.28 Gy. For young children 5 y of age living in Ozyorsk, the maximum annual thyroid dose was approaching 1.0 Gy in 1949, with annual doses decreasing to around 10 mGy by the late-1950s. Koshurnikova *et al*. (2012) studied thyroid cancer incidence during 1948 to 2009 in Ozyorsk and the neighboring city of Kyshtym and compared rates based on registries in these cities with those derived from incidence data for the regional center of Chelyabinsk during 1993 to 2006. They reported that thyroid cancer incidence rates in Ozyorsk and Kyshtym were 50 % higher than the rate in Chelyabinsk, although details of the Chelyabinsk data were not given. A thyroid screening study of 581 Ozyorsk residents born in 1952 to 1953 compared to 313 who moved to Ozyorsk after 1967 showed a RR for thyroid nodularity of 1.4 (95 % CI 1.0, 1.9), but doses were not estimated (Mushkacheva *et al*., 2006).

4.3.6.8 *Three Mile Island (TMI) Fallout*. About 550 GBq of ^{131}I were released to the atmosphere during the TMI reactor accident, leading to an estimated maximum individual thyroid dose of <0.2 mGy (Clarke, 1989). The mean dose to the TMI population living within 5 miles of TMI was estimated to be ~0.1 mGy, with ~13 % exposed to >0.2 mGy (Gur *et al*., 1983). Levin *et al*. (2013) reported an elevated incidence of thyroid cancer in the vicinity of the TMI nuclear plant (Levin *et al*., 2013), but the ecological study is difficult to interpret, particularly given that the natural incidence of thyroid cancer appears to be high in Pennsylvania (Bann *et al*., 2014).

Hatch and Susser (1990) examined rates of childhood leukemia and all childhood cancers near the TMI nuclear plant for 6 y after the accident in 1979. Based on gamma radiation levels of areas within 10 miles of the plant, they reported post-accident associations for both endpoints, but further analysis suggested that psychological stresses or selection biases due to out-migration may have been alternate explanations (Hatch *et al*., 1991). This was later debated by Wing *et al.* (1997) and Hatch *et al.* (1997). After a 17 y follow-up of a defined cohort of 32,000, no clear association with estimated radiation doses was seen, though there was a nonsignificant suggestion of associations with breast and hematopoietic cancers (Talbott *et al*., 2003). Because of small numbers, the ecological nature of the earlier analysis, and large uncertainties, the TMI studies clearly do not contribute to understanding the LNT model.

4.3.6.9 *Fukushima Dai-ichi Fallout*. Substantial quantities of ^{131}I and other radionuclides were released during the Fukushima Daiichi nuclear power plant accident in Japan in 2011, although the largest consequent thyroid doses were considerably lower than those received locally after the Chernobyl accident (UNSCEAR, 2014). To date, no

studies of health outcomes in relation to individual exposure levels from the Fukushima nuclear accident have been published. However, about 100 histologically-diagnosed thyroid cancers were identified by the Fukushima Health Management Survey (FHMS) in the first 3 y after the accident. Tsuda *et al.* (2015) advanced the hypothesis that this represents a significant 30- to 50-fold excess of thyroid cancer among those exposed before age 18 in Fukushima. This interpretation is based on their ecological study in which the primary comparison is between the FHMS cohort with ultrasensitive ultrasound thyroid screening and corresponding all-Japan rates in which few children have had thyroid screening. This represents a patent bias. However, they found no differences in thyroid screening results between children in districts of Fukushima who had the highest ^{131}I exposures vs. little exposure (odds ratio = 1.08, 95 % CI 0.60, 1.96). A recent report of the complete results of the first FHMS screening showed suspected/confirmed (from fine needle aspiration cytology) thyroid cancer rates of 33 and 35 per 100,000 in the areas with the highest and lowest levels of exposure, respectively (Suzuki, 2016). Suzuki *et al*. (2016) also noted there is a striking dissimilarity between the thyroid cancer cases around Chernobyl and in Fukushima Prefecture, in that the youngest case in Fukushima was aged 6 y at the time of the accident whereas around Chernobyl the excess cases occurred markedly among exposed infants and young children. Wakeford *et al*. (2016)have summarized a variety of other reasons why the Tsuda *et al.* (2015) interpretation does not fit the biology and epidemiology of radiogenic thyroid cancer. Hence, the Fukushima Dai-ichi studies to date do not contain information relevant to the LNT model.

4.4 Medical Exposure Studies

Highlights

Studies of patients treated with lung collapse for tuberculosis (TB) in the 1930s to 1960s are one of the few medically-exposed populations that provide consistent evidence for dose response relationships relevant to the LNT model used in radiation protection. Patients on average would receive on the order of 100 chest fluoroscopies over several years. When the studies were published in the 1970s and 1980s the data from both Massachusetts and Canada were consistent with a straight line relationship between breast tissue dose and breast cancer, adding substantial weight to the judgment on the use of the LNT model for radiation protection. Findings for lung cancer were negative and suggested that different tissues in the body respond differently to highly fractionated exposures received over a period of years. New studies have now been published from the Massachusetts and Canadian TB-Fluoroscopy cohort on cardiovascular disease. Though the dosimetry for breast was of good quality, to date that for heart and the circulatory system has been weaker. Overall, there is no convincing evidence for an association between fractionated doses to the heart and heart disease, which argues against including heart as a detriment for radiation protection.

Evaluation of epidemiologic studies of diagnostic medical exposures relative to assessment of the LNT model is particularly challenging. Medical exposures are typically limited to a relatively small portion of the body and the results of the studies are subject to significant uncertainties including, but not limited to, historical exposure data, uncertain organ dosimetry, uncertainty relative to the effectiveness of low energy photons compared to higher energy radiations, confounding by predisposing conditions, presence of disease and potential effects of associated therapy. The most recent epidemiologic studies have involved populations who had CT scanning during childhood when risk might be higher because CT doses are relatively high and children may be more radiosensitive than adults. Leukemia development has been of particular interest since there is a short latent period and non-CLL leukemia is quite radiosensitive. However, the CT studies from the U.K. and Australia, as well as other reviewed medical exposure studies, do not have the consistency, design, dosimetry, coherence or strength to provide strong evidence regarding the validity of the LNT model in the 10 to 100 mGy dose range. Hopefully, other studies currently in progress may add information over the next decade. Studies of multiple fluoroscopic examinations for tuberculosis (TB) and pediatric computed tomographic (CT) examinations are considered here.

4.4.1 *TB Fluoroscopy Studies*

In the TB fluoroscopy cohorts, patients on average would receive on the order of 100 chest fluoroscopies to monitor lung collapse (pneumothorax) and the treatment would last for several years with a fluoroscopic examination every two to three weeks. When the studies were published in the 1970s and 1980s the data from both Massachusetts and Canada were consistent with a straight line relationship between breast tissue dose and breast cancer, adding substantial weight to the judgment on the use of the LNT model for radiation protection. Findings for lung cancer were negative and suggested that different tissues in the body respond differently to highly fractionated exposures received over a period of years.

4.4.1.1 *Dosimetry*. Several investigators have estimated the cumulative radiation dose absorbed by breast, lung, RBM, and several other organs for the Massachusetts TB Fluoroscopy Study (Boice and Hoover, 1981; Boice *et al*., 1978). Based upon interviews with both the physicians who conducted the examinations and the patients themselves, probabilistic assumptions were made about duration of a fluoroscopic examination and patient orientation, and cumulative dose was based on the number of fluoroscopies, calendar year of exposure (for machine filtration), sex, age at treatment (for estimation of breast size and tissue), and phantom studies of organ-specific doses using era-specific machine exposure settings to the extent possible (Boice *et al*., 1978; Davis *et al*., 1989). Uncertainty in organ dose/R (air) was estimated by Sherman *et al*. (1978) for the Canadian TB Fluoroscopy Study and varied widely. Phantom doses were validated by Monte-Carlo simulations (Sherman *et al*., 1978).

4.4.1.2 *Epidemiologic Methods, Findings and Issues*. Since the 1970s studies of tuberculosis patients who received repeated chest x-ray fluoroscopies to monitor lung collapse (pneumothorax) have provided important information relevant to the LNT hypothesis for both breast cancer and lung cancer (Boice, 1978; Boice and Monson, 1977; Boice *et al*., 1979; Howe, 1995; Howe and McLaughlin, 1996; Miller *et al*., 1989). Linear dose-response relationships for the incidence of breast cancer were observed in both the Massachusetts and Canadian studies with dosimetry that was state-of-the-art at that time (Boice *et al*., 1978; 1981; Miller *et al*., 1989; Sherman *et al*., 1978), and the risk coefficients were similar to those for the atomic-bomb survivors study and the acute postpartum mastitis study (Boice *et al*., 1979; Preston *et al*., 2002). The Massachusetts study adjusted for age at exposure, attained age or time since exposure, calendar time and TB subcohort (Boice *et al*., 1981). The Canadian study adjusted for age at first exposure, time since exposure and province (Nova Scotia versus other provinces) (Miller *et al*., 1989).

The picture for lung cancer was different in that there was no evidence for an association between radiation dose and lung cancer mortality in either the Massachusetts or Canadian studies, despite cumulative organ doses larger than received by the atomic-bomb survivors and numbers of patients larger than the number of bomb survivors (Davis *et al*., 1989; Howe, 1995). Interpretation of the absence of a lung cancer effect is uncertain; one possibility is that tissues differ in their response to radiation when the dose is delivered in fractions over time. The studies took into account smoking histories, lungs at risk and other potentially confounding factors.

4.4.1.3 *Summary Studies of TB Patients Receiving Repeated Chest Fluoroscopies for Lung Collapse*. A strength of the TB fluoroscopy studies is that multiple realizations of dose were used to account for uncertainty, and the doses spanned a large range, for instance, in the Massachusetts study 0 to 11.6 Gy. The studies took into account smoking histories and other potentially confounding factors. However, no adjustment was made to increase the dose for patients who had special procedures that entailed lengthy fluoroscopic examinations.

4.4.1.4 *Implications for the LNT Model and Radiation Protection*. The TB fluoroscopy studies provide strong support for the LNT model for breast cancer, but the lack of a radiation association for lung cancer indicates that risk after multiple small doses may differ by cancer site.

4.4.2 *Computed Tomography Scanning Studies*

Several recent publications have reported increased risk of leukemia and cancer following exposure of children to CT scans (Huang *et al*., 2014; Krille *et al*., 2015; Journy *et al*., 2014; Pearce *et al*., 2012; Mathews *et al*., 2013). The concept is that children may be more sensitive than adults to radiogenic tumor induction, so risks might be seen

at low dose levels. A typical CT scan delivers a tissue absorbed dose to a "slice" of the patient's body in the range of about 10 to 30 mGy. There is very little scattered radiation to body parts that are not in the field of interest. Any potential cancer risk is concentrated in the directly irradiated tissues. For multiple CT scans the tissue doses can be just below the range where studies of atomic-bomb survivors have shown a statistically significantly increased risk.

Thus, large and well-designed studies are needed to discern whether there is any radiation- related effect. Information on organ doses from CT examinations in the 1980s and 1990s is sparse and may have been skewed toward "best practices". In addition to the text below, further systematic information is provided for the two major studies in tables 4.1 to 4.4.

4.4.2.1 *Dosimetry*. No individual dosimetry was collected and used in any of the cohorts. In the Pearce *et al*. (2012) study in the U.K., brain and RBM doses were estimated by reviewing typical CT settings for young people based on U.K.-wide surveys and then combining the information with hybrid computational human phantoms and Monte-Carlo techniques. Similarly, Journy *et al*. (2015) based the dose estimates on CT protocols from 916 different hospitals which they combined with computational human phantoms and Monte-Carlo methodology. Cumulative x-ray dose was estimated as effective dose, red marrow and brain dose. The uncertainties in doses were probably large, but no formal dose uncertainty analyses were conducted.

The Mathews *et al*. (2013) study in Australia used primarily estimated effective doses rather than organ doses, and then based it on the literature according to age, calendar period of CT exposure and site of irradiation. There was no correction for gender and size, but a different mean dose was assumed for exposures before 2001 as compared to those after 2001. For the time period before 2001 effective doses were estimated from the adult CT literature and a scaling factor (information not provided) applied to derive pediatric effective doses. The database they used to identify CT exposures did not include CT scans received after age 19 and was based on fewer than half the Australian hospitals, so individuals may have had additional CT scans that were not in the database. For these and other reasons Mathews *et al*. (2013) does not provide reliable evidence regarding LNT in low-dose radiation protection.

4.4.2.2 *Epidemiologic Methods, Findings and Issues*

U.K. Pediatric CT Study. Pearce *et al*. (2012) reported a retrospective cohort study of 180,000 patients in Great Britain who had CT scans while 21 y old or less. Cases of leukemia and brain tumors were identified through linkage to a national cancer registry. These two cancers were of particular interest because of the known radiation sensitivity of bone marrow to leukemia induction and because about two-thirds of the scans were head scans. They

evaluated sex, age at exposure, number of CT scans, and lagged exposures as covariables. They analyzed leukemia incidence commencing 2 y after the first CT scan and brain tumors after 5 y. Results showed an ERR of 36 Gy^{-1} (95 % CI 5, 120, n = 74) for combined leukemia and myelodysplastic syndrome (MDS), which they reported was compatible with estimates from the atomic-bomb LSS. For leukemia without MDS, the ERR Gy^{-1} was 19 (95 % CI –12, 79, n = 65). The ERR for leukemias without MDS was positive but not significant. The ERR for brain tumors was 23 Gy^{-1} (95 % CI 10, 46, n = 135), appreciably higher than that reported for the LSS. From their results, the authors calculated that children with doses of 50 to 60 mGy could triple their risk of leukemia and brain tumors.

Australian Pediatric CT study. Mathews *et al*. (2013) reported results of a cohort study from Australia. From a cohort of about 11 million people who were <20 y old at the start of 1985 or born during 1985 to 2005, about 60,500 cases of cancer were identified. Using a Medicare (Public Hospital) database it was determined that about 680,000 persons had a CT scan while less than 20 y of age. Cancer incidence in the cohort with CT scans was compared to the cohort who did not have CT scans with adjustment for sex, attained age and year of birth. Risk of all types of cancer was examined based on effective dose and beginning only 1 y after the CT scan. The calculated risks were much higher than in the LSS. For example, with their preferred 1 y lag period, after a brain scan they reported an ERR Gy^{-1} of 35 (95 % CI 26, 42) for all cancers except brain, which is highly implausible, and 29 (95 % CI 23, 37) for brain, compared to an ERR G^{-1} of about 1.7 for brain tumors after exposure at ages 0 to 5 y in the LSS (Preston *et al*., 2008). Information was not available on alcohol consumption, smoking, sun exposure or markers of cancer susceptibility.

4.4.2.3 *Strengths and Limitations*. The above CT studies (Mathews *et al*., 2013; Pearce *et al*., 2012) included a very large number of individuals and were designed to provide a direct epidemiologic assessment of low-dose radiation-associated excess cancer risk. However, the studies were subject to major biases which lead to doubt concerning the causal nature, or at least the magnitude, of the reported associations. Walsh *et al*. (2013) and Boice (2015b) have critiqued these studies and raised serious concerns about whether the relationship is causal. Among other concerns, Mathews *et al.* (2013) reported a significant increase in brain cancer risk after abdominal/pelvic and extremity CT scans, for which the brain dose was certainly negligible. They reported no increase in breast cancer, a highly radiogenic organ, but increases in Hodgkin lymphoma and malignant melanoma, sites that have not been associated with radiation exposure in other studies. In addition, they reported an increased risk for brain tumors and all other cancers in years one to four after exposure which was somewhat larger than that in later years. This implied that there was no latent period and increased the suspicion of confounding by indication (CT examination because of having a predisposing factor for cancer) and reverse causation (pre-existing but undetected malignancy). There were also major unanswered questions about missed doses.

In summary, the CT studies do not provide individual doses, and collection of the scan data and associated exposure information for individual patients was not carried out. Information on organ doses from CT examinations in the 1980s and 1990s is sparse; the estimates available may have largely reflected "best practices" rather than typical practices at the time. Thus, assigned organ doses are of questionable validity. The uncertainties in the CT doses are assumed to be large but no formal uncertainty analysis has been reported. Based on the dosimetry review, these studies are of limited use in the evaluation of LNT.

4.4.2.4 *Analyses to Evaluate Biases in CT Studies*. Krille *et al*. (2011; 2015) found that there may be reverse causation bias (pre-existing but undetected malignancy) and Journy *et al*. (2015) found evidence of confounding by indication (CT examination because of having a predisposing factor for cancer), although these confounding factors accounted only partially for the effects observed.

Berrington de Gonzaléz *et al.* (2016) analyzed predisposing factors or probable prior malignancy as biasing factors in the previously published U.K. study (Pearce *et al*., 2012) of leukemia and brain tumors after pediatric CT examinations. The study included 74 leukemia cases and 135 brain tumor cases. For leukemia, deletion of study subjects with predisposing conditions or suspicion of prior cancer derived from comparable medical sources (radiology databases and death certificates) for the CT scan and control subcohorts revealed only a small decline in the ERR Gy^{-1}, from 36 to 33 (95 % CI 4, 114). However, when the full radiologist and pathology reports were included for the leukemia cases, additional pre-existing cancers were identified and the association was no longer statistically significant (ERR Gy^{-1} was 20, 95 % CI –11, 86). A parallel pattern was seen for brain tumors: data from comparable sources reduced the ERR Gy^{-1} from 23 to 16 (95 % CI 6, 37), but additional exclusions based on the full radiologist and pathology reports for the brain tumor cases reduced the ERR further to 10 (95 % CI 2, 26). It should be noted that radiologist reports were available for only 40 % of patients and pathology reports for ~65 % of cases. Furthermore, the reporting of pre-existing conditions and diagnoses in physician records was anecdotal rather than systematic, so it is likely that some fraction of relevant information was missing. The reported reductions of risk estimates in the study due to predisposing conditions or pre-existing malignancy were about 45 % for leukemia and 55 % for brain tumors, but had the medical reports all been available and with systematic information, the reductions would likely have been larger.

4.4.2.5 *Implications for the LNT Model and Radiation Protection*. The large British and Australian CT studies and risk of cancer in children have a number of caveats. The major methodological reason to doubt the causal nature of the associations, or at least their magnitude, is bias from the absence of information on why CT scans were performed, incompleteness of dosimetry and lack of individual dosimetry and unknown number of repeat examinations or examinations performed at institutions not in the database. The published studies do not provide

strong evidence that can be used to assess the validity of LNT at doses in the 10 to 50 mGy range, although the most recent studies are beginning to address these issues (Berrington de Gonzaléz *et al*., 2016; Journy *et al*., 2015; Krille *et al*., 2015). New studies currently underway such as the EPI-CT study in Europe (Bosch de Basea *et al*., 2015; Thierry-Chef *et al*., 2013) will provide additional data and statistical power but may still have limited information on predisposing conditions, pre-existing cancer and individual doses. The new studies will permit credible insights into LNT only if the dosimetry is improved and all the potential sources of bias and missing data are carefully assessed (Walsh and Nekolla, 2015).

4.5 Childhood Exposure Studies

Highlights

An analysis of solid cancer incidence among the Japanese atomic-bomb survivors exposed prenatally or during childhood showed a clear dose response, but upward curvature ($p = 0.09$) suggested that the dose-response slope may be shallower in the low-dose range. The LSS of atomic-bomb survivors indicated a large leukemia response after childhood exposure, but the overall model showed clear upward curvature such that risk per unit dose at low doses was less than at high doses (Hsu *et al*., 2013). The data on postnatal diagnostic medical exposures and childhood leukemia risk are inconclusive (Wakeford, 2008). Studies of juvenile irradiation and breast cancer generally support a linear dose response (UNSCEAR, 2013). A recent pooled analysis of nine studies of childhood external irradiation and thyroid cancer showed a significant dose response at 0 to 100 mGy and no evidence of nonlinearity (Lubin *et al*., 2017).

For the most part, the low dose data on children are sparse, the number of specific types of cancer is small and uncertainties are large enough that such studies do not provide strong information regarding the LNT model. In the case of thyroid cancer and breast cancer, the data provide substantial support for a linear dose-response model.

In general, persons exposed at younger ages are at greater risk than those exposed as adults. One obvious reason for this is that those exposed at young ages are likely to live longer and have more time to express risk and detriment. In addition, tissue sensitivity for a given absorbed dose may vary with age. If children are indeed more radiosensitive, then review of the relevant epidemiology may shed some light on whether LNT or other dose response relationships are appropriate.

This is a complex issue and has been reviewed extensively in NCRP Report No. 136 (NCRP, 2001) and an UNSCEAR (2013) report. Studies of radiation effects on children come from a number of sources including atomic-bomb survivors, accidental exposures and post radiation therapy. Several of the key studies that report

dose-response data or risks at low-doses or low dose rates for childhood exposure will be mentioned briefly here. Studies considered include childhood atomic-bomb survivors (Section 4.5.1), childhood leukemia studies (Section 4.5.2), thyroid cancer studies (Section 4.5.3), and breast cancer studies (Section 4.5.4).

4.5.1 *Childhood Atomic-Bomb Survivors*

Preston *et al.* (2008) reported that among the ~15,000 members of the LSS cohort who were ages 0 to 5 y at exposure there were about ~650 incident cancers by age 55 y, of which 87 were estimated to be attributable to radiation. They estimated an ERR Gy^{-1} at age 50 y of 1.7 (95 % CI 1.1, 2.5), which is higher than the estimated ERR of ~0.5 at all exposure ages, but may partly reflect the fact that the denominator baseline risks are lower at younger ages. The EAR per 10,000 person-years per gray for the childhood exposure group was 56 (95 % CI 36, 79), with an estimated 87 radiation-associated excess cancers. However, there was no evidence of excess risk among those exposed to <0.2 Gy. The combined *in utero* and childhood exposure groups yielded some evidence of a linear-quadratic model [$p = 0.09$ for curvature, with an α/ß ratio = 1.0 (95 % CI –0.1, 212)].

The atomic-bomb survivor data indicate that for some tumor types (leukemia, thyroid, breast, brain), but not for all (bladder, lung), the risk is higher for those exposed in childhood than in adulthood, while for others there is too little data to draw conclusions or little radiation effect. An additional complication is that depending upon the model used (*e.g.*, time since exposure vs. attained age) differing conclusions are sometimes reached regarding the effect of age at exposure. A recent UNSCEAR (2013) report considers age effects in more detail.

4.5.2 *Childhood Leukemia Studies*

Lundell and Holm (1996) studied over 14,000 children treated with radiation therapy for skin hemangiomas using ^{226}Ra applicators or x rays. For those with a marrow dose < 10 to 100 mGy the relative risk (RR) was not elevated (0.9). For those with marrow dose >100 mGy there was a nonsignificant RR of 1.7 (95 % CI 0.7 to 3.4). Another study (Lindberg *et al*., 1995) showed a nonsignificant excess with a likely marrow dose of about 100 mGy. One recent study of childhood cancer risk after conventional radiographic examinations found no evidence of risk for leukemia and lymphoma (standardized incidence ratio = 1.05, 95 % CI 0.74, 1.45) (Hammer *et al*., 2011), while another of diagnostic radiography in early infancy reported a suggestive, but nonsignificant, increase in leukemia (odds ratio = 1.39, 95 % CI 0.87, 2.23) (Rajaraman *et al*., 2011). Neither study had estimates of RBM doses. Wakeford (2008) characterized the literature on childhood leukemia after postnatal diagnostic medical radiation exposure as equivocal and conflicting.

Studies also have been undertaken to determine if variation within the typical range of background external gamma radiation affects childhood leukemia risk, which would indicate a risk at very low doses for a sensitive cancer endpoint compatible with a nonthreshold dose response. However, since childhood cancer is rare and the exposure levels are low, the numbers of children observed would need to be very large to achieve reasonable statistical power (Little *et al*., 2010b) and other leukemia risk factors could subtly bias the results. To avoid participation bias and the impracticability of contacting many families, several recent studies have relied on using existing databases of measured areal gamma radiation levels to estimate doses at the geographic locations of childhood leukemia cases and controls (or cases and matched cohorts).

A British study (Kendall *et al*., 2013) of ~9,000 childhood leukemia cases and ~12,000 matched controls found an association with assessed gamma radiation doses, with an ERR Gy^{-1} of 120 (95 % CI 30, 220), which is compatible with the atomic-bomb LSS risk estimate of about 50 for early childhood leukemia (Hsu *et al*., 2013). On the other hand, no association of ambient gamma radiation levels and childhood leukemia was found in a French study of ~9,000 cases (Demoury *et al*., 2016), although in smaller studies of ~1,800 cases in Switzerland (Spycher *et al*., 2015) and 1,000 cases in Finland (Nikkilä *et al*., 2016) positive associations were reported. There is broad compatibility of studies of the risk of childhood leukemia and natural background gamma irradiation with a LNT model, although there are inconsistencies, owing in large part to the limited applicability of the areal radiation measurements, potential for uncontrolled confounding and limited statistical power of such studies due to dose uncertainties and low doses.

4.5.3 *Thyroid Cancer Studies*

Ron *et al*. (1989) studied over 10,800 Israeli children treated with radiation therapy for ringworm of the scalp. The average thyroid dose was about 90 mGy. In the most recent follow-up of this cohort, for up to 54 y, Sadetzki *et al.* (2006) found 103 thyroid cancers in the irradiated group and reported an ERR Gy^{-1} of 20 (95 % CI 12, 32). However, the high risk estimate in the Israeli scalp ringworm study may have been confounded by surveillance or other differences between the exposed and unexposed groups; when (Ron *et al*., 1995) fitted the dose response, accounting for the exposed-unexposed difference, the ERR Gy^{-1} was 6.6 (95 % CI < 0, 347). A linear dose response was reported for thyroid cancer ($p = 0.75$ for curvature) (Sadetzki *et al*., 2006).

4.5.3.1 *Pooled Studies of Thyroid Cancer after X- or Gamma-Irradiation.* Veiga *et al*. (2016) conducted a pooled analysis of 12 studies with primarily child/adolescent external irradiation of the thyroid gland and with a wide range of doses which represented essentially all available studies of external irradiation and thyroid cancer risk that had dose-response risk information. A subsequent analysis of radiation risk in the ranges of 0 to 200 mGy and 0 to

100 mGy was conducted to further examine thyroid cancer risk from low-dose radiation exposures (Lubin *et al*., 2017). In addition to the text below, further systematic information is provided for the Lubin *et al.* study in Tables 4.1 to 4.4.

***Dosimetry*.** One criterion for acceptance in the pooled studies of Lubin *et al.* (2017) and Viega *et al*. (2016) was that quantitative estimates of dose were required. Individual doses for the medical study cohort (treatment of childhood cancer and treatment of various benign diseases such as tinea capitis and enlarged thymus) were estimated based on the number of irradiations, irradiation equipment, and analyses of phantom exposures. For the Life Span Study (LSS) dose estimation was discussed earlier (Section 4.1.1). The doses were due primarily to X ray exposure, but γ for the hemangioma radium needle study and γ + neutron for the atomic-bomb study cohort. For x-ray procedures in early days, issues of distance from primary beam, degree of beam collimation, thyroid shielding, etc. are principal sources of uncertainty. Other dosimetric uncertainties are due to a variety of factors, including dose uncertainty in the phantom studies, random differences in sizes of children of a given age, random movements by children during treatment and missing data for ages at subsequent exposure for those with multiple treatments.

The two most influential studies in the analysis, the LSS atomic-bomb survivors (Furukawa *et al*., 2013) and children irradiated for scalp ringworm (Sadetzki *et al*., 2006), accounted for 80 % of the exposed thyroid cancer cases. The LSS results were adjusted for dose measurement uncertainty, while the evaluations of the scalp ringworm study indicated that the effect on dose response due to measurement uncertainty was fairly small (Lubin *et al*., 2004; Schaefer *et al*., 2001). Therefore, the effect of dose uncertainty on the meta-analysis dose response was probably minor for the low-dose part of the study, though there were additional uncertainties for the high-dose childhood cancer survivor participants.

***Epidemiologic Methods, Findings and Issues*.** The original pooled study (Veiga *et al*., 2016) included 9 cohort studies of children who received radiation treatments for various benign disorders, the LSS atomic-bomb survivors, and two case-control studies of patients who received radiotherapy for childhood cancer. However, only 9 studies were contributive to the analysis of individuals with a <200 mGy thyroid dose (Lubin *et al*., 2017). The nine studies relied on tumor registries and/or individual reports with medical verification to identify thyroid cancer cases, and the rates of follow-up were good to excellent. The analyses by Poisson regression adjusted for sex, age at exposure, attained age, calendar year period, plus sensitivity analyses of other variables, such as number of treatments, indicator for exposed/unexposed group, Jewish ethnicity, LSS participation in the clinical examination program etc. Although the study as a whole did not have analyses corrected for dose uncertainties, uncertainties had been evaluated in the two studies with the highest weights in the analysis, the LSS (Section 4.1.1) and the

Israel tinea capitis study (Lubin *et al*., 2004) both had assessments of dose uncertainties. After accounting for downward curvature at doses > 10 Gy, Veiga *et al*. (2016) reported an ERR Gy^{-1} of 5.5 (95 % CI 3.9, 7.5) based on 1,070 thyroid cancer cases in 5.3 million person-years of observation. When the data were limited to the subjects with ≤100 mGy, including 184 thyroid cancers, there was a statistically significant linear trend ($p < 0.01$) with no evidence of a departure from linearity ($p = 0.36$) and an ERR Gy^{-1} of 11.2 (95 % CI 4.8, 20).

The analysis of only the pooled data in the range of 0 to 200 mGy (Lubin *et al*., 2017) included data from nine studies. This analysis included 394 thyroid cancer cases among 107,594 individuals, with 252 cases among 61,155 individuals who received 1 to 200 mGy and 142 cases among 46,439 unirradiated individuals. For the range <200 mGy, RRs increased significantly with radiation dose ($P < 0.01$), with an ERR Gy^{-1} of 11.1 (95 % CI 6.6, 19.7). No departure from linearity was evident ($P = 0.77$) (Figure 4.9). A moving-average smoothing of the RRs (thick grey line) showed consistency in the linear increase. A linear- quadratic model over the dose range 0 to 200 mGy (dashed line) also showed near linearity. The results were similar for <100 mGy (inset panel), with no significant departure from linearity ($P = 0.66$) and a risk coefficient, ERR Gy^{-1} of 9.6 (CI 3.7, 17.0). The best fitting model was linear, compared to the quadratic or spline models. A dose-threshold analysis showed a maximum likelihood at 0 mGy and had a threshold upper bound of 40 mGy.

Study strengths and weaknesses. The full dose-range (Veiga *et al*., 2016) and low-dose (Lubin *et al*., 2017) meta-analyses included essentially all eligible dose-response studies of external irradiation and thyroid cancer. At least for the two most statistically influential studies the impact of the dose measurement uncertainties was small and the results were quite precise because of the large number of thyroid cancers. There might be some possibility of cancer surveillance bias since head-and-neck irradiated populations tend to be screened more often for thyroid cancer; however, sensitivity analyses reported in Lubin *et al*. (2017) suggested that there was little or no surveillance bias in the data.

Implications for the LNT Model and Radiation Protection. The analyses reported in the Lubin *et al*. (2017) paper provide strong support for use of the LNT model. They indicate that, at least for the association of radiation with thyroid cancer, there is a statistically significant dose-response over the restricted range of 0–100 mGy that is compatible with linearity. This is strongly supportive of the use of the LNT model as prudent for radiation protection.

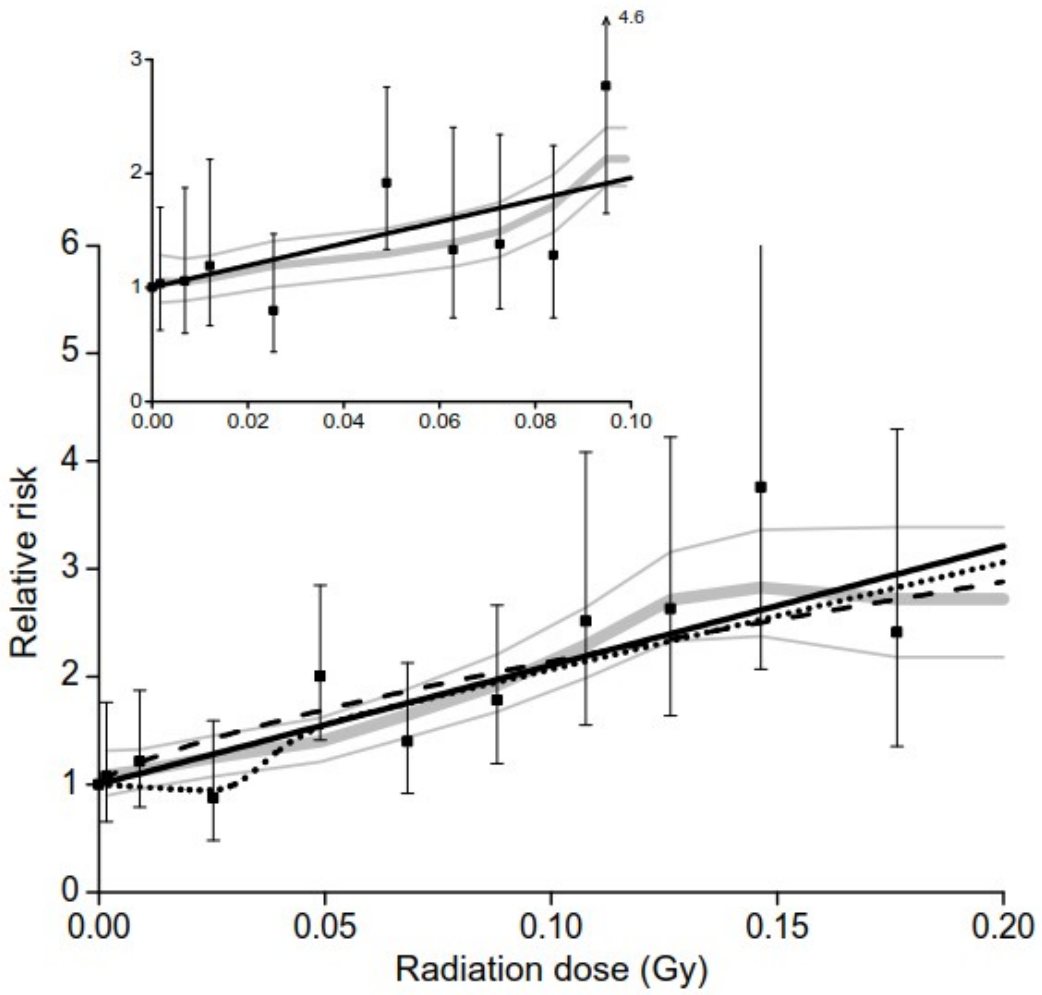


Fig. 4.9. Based on a pooled analysis of nine studies of external irradiation and thyroid cancer [Lubin *et al.*, 2017 (Fig 1)]. Shown are the models: dark solid line, linear; dashed line, linear-quadratic; thick gray solid line (with thin gray lines ± 1 standard deviation), smoothed nonparametric fit; dotted line, cubic spline.

4.5.3.2 *Other Studies of Thyroid Cancer after Childhood Exposure*. Imaizumi *et al*. (2006; 2015) reported that a long term study of the atomic-bomb survivors showed there was a significant linear dose-response relationship in the prevalence of malignant thyroid tumors, benign thyroid nodules and cysts based on a clinical and ultrasound examination. In addition there was significantly higher risk in those exposed at young ages. Three studies included a total of more than 6,000 children who were administered known amounts of ^{131}I for diagnostic purposes (giving a mean thyroid dose of 1 Gy) but did not find any excess of thyroid cancer (Boice, 2005; Dickman *et al*., 2003; Hahn *et al*., 2001; Hamilton *et al*., 1989). However, the numbers of children exposed while less than 10 y of age, who would be at most risk, were small.

In summary, children are more sensitive than adults to induction of thyroid cancer and nodules and most studies show an approximately linear dose-response relationship.

4.5.4 *Breast Cancer Studies*

The UNSCEAR 2013 report on risk from childhood radiation exposure presents a recent review of risk for breast cancer according to age at exposure (UNSCEAR, 2013).

New dosimetric estimates for the breast have been calculated for the combined Swedish cohorts of young children treated for hemangiomas and updated follow-up has been reported (Eidemüller *et al*., 2015). An analysis showed a linear dose response ($p > 0.5$ for nonlinearity) below 5 Gy and an ERR risk estimate of 0.5 Gy^{-1} (95 % CI 0.3, 0.7). A smaller French child hemangioma study (Haddy *et al*., 2010) reported a nominal increase in breast cancer risk with dose but it was not statistically significant.

An update of breast cancer risk over 57 y has been reported for 1,120 female infants irradiated for a presumed enlarged thymus gland (Adams *et al*., 2010). The median breast dose was 0.16 Gy (mean 0.72 Gy, range 0.02 to 6.2 Gy) and 96 incident breast cancers were found in the irradiated group. They found a better fit for a linear than nonlinear dose-response function, with an ERR Gy^{-1} of 1.1 (95 % CI 0.6, 1.9).

A study of 3,010 females who received multiple fluoroscopic examinations for scoliosis (estimated mean cumulative breast dose, 121 mGy) detected 78 breast cancers and reported an ERR Gy^{-1} of 2.9 (95 % CI –0.07, 8.6) (Ronckers *et al*., 2008). No significant improvement in fit was seen for linear-quadratic, pure quadratic or linear-exponential models. In the Taiwan study of individuals exposed in radiocontaminated dwellings at an average age of 17 y, a marginal breast cancer risk was reported, ERR Gy^{-1} of 1.2 (90 % CI –0.1, 2.1, $n = 17$)

(Hwang *et al*., 2008). In summary, the studies of breast cancer after (primarily) juvenile irradiation broadly support a linear model, although the small sample sizes of some studies limit their statistical power.

4.6 *In Utero* Exposure Studies

Highlights

In the atomic-bomb survivor studies, there were statistically significant dose-related increases in incidence rates of adult solid cancers among atomic-bomb survivors exposed to radiation *in utero*. Dose responses were estimated with a linear model; the data were too sparse to evaluate nonlinearity meaningfully. It appears that adult cancer risk from *in utero* exposure exists, but is not greater than that from early childhood exposure. There have been too few leukemia deaths (and data lacking on leukemia incidence during the first 4 y after the atomic bombing) to estimate the LSS radiation-related dose response for leukemia.

Although speculative, the absence of a radiation effect among the children of Mayak female workers exposed during pregnancy is also consistent with the possibility that chronic *in utero* exposures are less effective in causing solid cancers later in life than if the exposure had been received acutely, as was the case for the children of atomic-bomb survivors exposed *in utero*. However, there may be some indication of increased risks for leukemia by prenatal dose in the Mayak and Techa River cohorts.

In medicine, high doses to the embryo or fetus (*e.g*., >0.5 Gy) increase the risk of cancer in offspring exposed *in utero*. However, there is disagreement over whether the reported risk of cancer after *in utero* exposure at a low dose such as <0.1 Gy is causal, and the available data have not provided definitive information with regard to LNT. Increased risks to the human embryo or fetus have not been observed at low doses for birth defects, growth retardation, or mental and neurobehavioral effects. NCRP Report No. 174 (NCRP, 2013), includes an in-depth review of radiation risks and potential outcomes. This section briefly reviews pregnancy risks from ionizing radiation, and effects from *in utero* exposures to occupational, environmental and medical sources.

The potential effects of ionizing radiation exposure *in utero* from medical procedures or other sources of radiation are of considerable importance and concern with regard to radiation protection. The NCRP previously evaluated prenatal effects in NCRP Report No. 54, Medical Radiation Exposure of Pregnant and Potentially Pregnant Women (NCRP, 1977). NCRP also published Commentary No. 9, Considerations Regarding the Unintended Radiation Exposure of the Embryo, Fetus or Nursing Child (NCRP, 1994), in which problems were discussed that could result from the medical administration of radioactive material to pregnant or nursing women. In 1997, NCRP held its Annual Meeting on The Effects of Pre- and Postconception Exposure to Radiation, and the proceedings were published in Teratology (Boice and Miller, 1999). These reports, commentaries, and previous

guidance documents were updated and expanded more recently in the comprehensive evaluation, NCRP Report No. 174, *Preconception and Prenatal Radiation Exposure: Health Effects and Protective Guidance* (NCRP, 2013) that included an in- depth review of radiation risks for potential outcomes.

4.6.1 *Pregnancy Risks from Ionizing Radiation*

Any evaluations of prenatal radiation effects recognize the fact that pregnant women are faced with a baseline risk to the embryo and fetus for reproductive and developmental problems. The normal background rate of adverse pregnancy outcomes is considerable (NCRP, 2013). The background rate, absent radiation, for major congenital malformations is ~3 %, with another 4 % of minor malformations. Pregnancy loss (spontaneous abortion, miscarriage) in women who know they are pregnant occurs in 15 % of pregnancies with a wide standard deviation.

Increased human risks to the embryo or fetus have not been observed for birth defects, growth retardation, neurobehavioral effects, mental retardation, decreased intelligence quotient (IQ), impaired school performance, convulsive disorders, or embryonic or fetal death below a dose of 0.1 Gy (weighted uterine dose). Such effects are generally attributed to the killing or functional disruption of critical cells during important stages of embryonic or fetal development. All these effects are consistent with having a threshold dose below which there is no increased risk. The data on IQ loss are somewhat difficult to interpret but even assuming that there might not be a true dose threshold, any IQ effects at low doses would be so small as to be undetectable and therefore not of practical or clinical significance.

NCRP Report No. 174 (NCRP, 2013) summarizes the health effects from ionizing radiation exposure of the embryo or fetus during various gestational stages of pregnancy. That report also reviews cancer risk arising from fetal exposure.

4.6.2 *In Utero Exposures to Occupational or Environmental Sources*

The Japanese atomic-bomb study evaluated adult leukemia and cancer risks after *in utero* and early childhood exposure (Preston *et al*., 2008). They reported statistically significant dose- related increases in incidence rates of solid cancers through 50 y of age after both *in utero* and childhood irradiation. Following *in utero* exposure the ERR Gy^{-1} was 1.0 (95 % CI 0.2 to 2.3) (weighted uterine dose), a risk not significantly less than that for survivors exposed during the first 5 y of life, ERR Gy^{-1} = 1.7 (95 % CI 1.1 to 2.5) (Preston *et al*., 2008). The dose response was estimated with a linear model; the data were too sparse to evaluate nonlinearity meaningfully. The temporal patterns of the excess absolute rates which increased rapidly with age for early-childhood exposures did not appear

to increase following *in utero* exposure, but the difference between the two was not statistically significant ($p = 0.14$). It can be concluded that adult cancer risk from *in utero* exposure exists but probably is not greater than that from early childhood exposure. There have been too few leukemia deaths (and data lacking on leukemia incidence during the first 4 y after the bombing) to estimate radiation-related dose response (Yoshimoto *et al*., 1988).

Because there are few prospective studies of sufficient numbers of children exposed *in utero* and followed into adulthood, a recent cohort study of over 8,000 children of female workers at the Mayak Nuclear Facility is noteworthy (Schonfeld *et al*., 2012). The *in utero* gamma-ray doses were fairly small (mean 54.5 mGy; max ~800 mGy) and accumulated throughout the pregnancy, and thus not received briefly at one point in time. The exposures were measured by film badges and not estimated by dose reconstruction; a notable strength and uniqueness of the study. There was no evidence that prenatal gamma radiation received during pregnancy increased the risk of solid cancer or leukemia mortality for up to 60 y of follow-up. The small number of cancers, however, limited the precision of the study, and thus the negative findings were consistent in a statistical sense with the positive observations of 2,452 children born to Japanese atomic-bomb survivors who received comparable doses *in utero* (Preston *et al*., 2008). Although speculative, the absence of a radiation effect among the offspring of Mayak female workers is also consistent with the possibility that chronic exposures during pregnancy are less effective in causing cancer later in life than if the exposure had been received acutely, as was the case for the children of atomic-bomb survivors exposed *in utero*.

Akleyev *et al.* (2016) conducted a follow-up through 2009 of the 5,331 offspring of female Mayak PA workers and 16,821 offspring of women in the Techa River cohort who were born in 1950 to 1961. Mortality follow-up was for 1950 to 2009 and cancer incidence for 1956 to 2009. Both prenatal and postnatal individual doses were estimated for the combined cohort. The estimated mean *in utero* dose was 14.1 mGy (range 0 to 945 mGy) and the mean postnatal dose, based on living near the Techa River or working at the Mayak facility, was 11.2 mGy (range 0 to 552 mGy). Based on 369 incident solid cancers, the linear prenatal dose response was null [RR per 10 mGy of 0.98 (95 % CI 0.96, 1.01); ERR $Gy^{-1} \approx -2$ (–4, 1)], while that for postnatal dose was statistically significant [RR per 10 mGy of 1.02 (95 % CI 1.00, 1.04) ; ERR $Gy^{-1} \approx 2$ (0, 4)], with mutual adjustment for the other exposure. For solid cancer mortality, the risks were similar but not statistically significant, probably because of fewer cases. When the authors further examined digestive, respiratory and breast cancer incidence, they found a suggestion of a linear dose response for digestive cancer incidence [RR per 10 mGy of 1.04 (95 % CI 1.00, 1.07; ERR $Gy^{-1} \approx 4$ (0, 7)], but not for respiratory or breast cancers. Analyses of all-solid, digestive or breast cancers restricted to those with ≤10 mGy of postnatal exposure found only null effects, but had very low statistical power.

Schüz *et al.* (2016), in a parallel study, examined hematologic malignancies by prenatal and postnatal exposure in the Mayak and Techa sets of offspring. The ERR Gy^{-1} for leukemia by prenatal dose was approximately 4 (95 % CI 0.7, 24), based on 28 leukemias, but no risk was apparent for lymphoma. There were no significant effects for postnatal exposure or for hematologic mortality endpoints

4.6.3 *In Utero Diagnostic Radiology*

The risk of cancer in offspring that have been exposed to diagnostic x-ray procedures while *in utero* has been debated for more than 50 y. While high doses to the embryo or fetus (*e.g.*, 0.5 Gy) increase the risk of cancer, the risk of cancer in offspring exposed *in utero* at a low dose such as <0.1 Gy still has uncertainties , and the available data have not provided definitive information with regard to LNT. NCRP Report No. 174 (NCRP, 2013) extensively reviewed the risk of specific and total childhood cancers and cancer mortality in offspring of women who underwent diagnostic x-ray procedures during pregnancy. Tables 5.14 and 5.15 of NCRP Report No. 174 summarize the relative risks reported in the epidemiologic literature (NCRP, 2013).

Data from case-control studies (including two large studies that relied on medical records for exposure determination) support a statistical association between childhood leukemia in offspring and the mother's exposure to diagnostic x rays during pregnancy. The relative risk of childhood leukemia based on a meta-analysis of 32 case-control studies is estimated as 1.3 (95 % CI = 1.2 to 1.5) (Wakeford, 2008). Based on a review of the available data through 2009, IARC recently noted a causal association between fetal exposure to diagnostic x rays and the risk of childhood cancer (Ghissassi *et al*., 2009; IARC, 2012; Wakeford, 2015), however, this interpretation is not universally accepted (Brent, 2014). Although the statistical association from case-control epidemiologic studies is not generally debated, investigators have disagreed about both the etiologic significance (causality), and if the association is causal, the likely magnitude of the leukemogenic risk (ICRP, 2003; NCRP, 2013).

Meta-analyses of cohort studies (concerning exposure of mothers to diagnostic x rays during pregnancy) have found small, not statistically-significant increases of total cancer, but confidence intervals (CI) were compatible with a composite increase similar to that of the case- control studies of 30 % or a composite estimate compatible with no increase in risk. Overall, the cohort studies are characterized by limited numbers of total childhood cancer cases and the subset of childhood leukemia cases, and with insufficient statistical power, and potential uncertainties and data unreliability (Doll *et al*., 1994). These limit the ability to draw firm conclusions regarding a causal LNT association.

4.7 Genetic Studies (Heritable Effects in Human Populations)

Highlights

Heritable genetic effects have not been demonstrated for either cancer or noncancer endpoints in human studies; most notably, no effects have been found in the F1 offspring of atomic-bomb survivors. Studies of children from parents exposed to radiation (atomic bombs, accidental, environmental or medical) have been conducted over many decades using a wide range of endpoints including recently developed molecular endpoints. There is no definitive evidence for an increase in mutation frequency in the first or subsequent generations of exposed parents. The reports of increases in repetitive DNA sequences that have been proposed as evidence for transgenerational effects have been broadly discussed, resulting in the general opinion that there is insufficient evidence to conclude that these constitute an increased risk to the F1 and subsequent generations (Bouffler *et al*., 2006; Little *et al*., 2013). For these reasons, the estimates of heritable risk are based on radiation-induced mutations from mouse studies where transgenerational effects are clearly observable.

For the purposes of incorporating heritable risk into the overall risk from ionizing radiation, heritable risk is calculated for continuous low dose-rate exposures over two generations. The present heritable risk estimate, developed by UNSCEAR (2001) and ICRP (2007) essentially using the same methods, is about 0.2 % per gray. This value is more than 20-fold less than that for cancer. For radiation protection purposes heritable risk is included with cancer in the overall risk for gonads (ICRP, 2007). In essence, the estimate of genetic risk is not based on a LNT model from epidemiologic data because there is no reliable evidence of radiation-induced heritable mutations in humans.

Measures of genetic disease in the children of exposed parents include cytogenetic syndromes, single gene disorders, malformations, stillbirths, neonatal deaths, cancer, common polygenic diseases, and cytogenetic and genetic markers (Grant *et al*., 2015; ICRP, 2007; Nakamura, 2006; NA/NRC, 2006; NCRP, 2015; Tatsukawa *et al*., 2013; Winther and Olsen, 2012; UNSCEAR, 2001).

This section briefly reviews studies of cancer in the offspring of Japanese atomic-bomb survivors (Section 4.7.1), offspring after parental preconception radiotherapy (Section 4.7.2) and after environmental preconception radiation (Section 4.7.3).

4.7.1 *Studies of Atomic-Bomb Survivor Offspring*

The atomic-bomb studies have not shown any indication of heritable genetic risks from radiation exposure to either parent. No excess of birth defects was seen among about 77,000 F1 children conceived after the bombing

(Neel and Schull, 1956; Otake *et al*., 1990). Nor were dose-related excesses seen for either cancer or noncancer mortality among 75,000 F1 offspring observed for up to 62 y in relation to maternal, paternal or combined maternal + paternal doses (Grant *et al*., 2015). In the clinical study of the prevalence of noncancer diseases or conditions in the F1 offspring of atomic-bomb survivors, no associations were seen for any of the conditions—stroke, myocardial infarction, angina pectoris, hypertension, hypercholesterolemia or diabetes— in relation to either maternal or paternal radiation dose (Tatsukawa *et al*., 2013).

A number of other indicators of transgenerational effects have been evaluated over the years in the atomic-bomb survivor studies but have not shown associations with parental radiation dose, including untoward pregnancy outcomes (congenital malformations, stillbirths, neonatal deaths), cytogenetic abnormalities [chromosome number (sex-aneuploidy or Down syndrome), chromosome structure (translocations)], sex of child, growth and development, biochemical studies (electrophoretic variants and erythrocyte enzyme activity), microarray-based comparative genomic hybridization, and mutations in minisatellite or microsatellite genetic loci (Kodaira *et al*., 1995; 2004; Neel, 1998; Neel and Schull, 1956; Satoh *et al*., 1996).

4.7.2 *Studies of Offspring after Parental Preconception Radiotherapy*

A variety of human studies in Japan, Denmark, Finland and the United States of birth defects occurring in offspring of women with gonadal irradiation from radiotherapy treatment have produced null results and thus provide no information on which to judge the use of the LNT model for radiation protection. There were no excess heritable genetic changes in cytogenetic abnormalities, single gene disorders, birth defects, stillbirths, neonatal deaths, and cancer in the children of men exposed to testicular irradiation or women exposed to ovarian irradiation (Green *et al*., 2009; NCRP, 2013; Signorello *et al*., 2012; Winther and Olsen, 2012). The sex ratio among the live-born children of cancer survivors treated with radiation therapy provided no indication of a possible transgenerational or germline effect (Winther *et al*., 2003). No radiation- related excess of infant mortality was found in relation to preconception radiation exposure in Techa River residents (Ostroumova *et al*., 2005).

The molecular analyses provided no evidence of radiation-related excesses in offspring of genomic instability, inherited mutations in minisatellite DNA or mitochondrial DNA, chromosome radiosensitivity and DNA polymorphic variation, and the occurrence of cytogenetic abnormalities (Guo *et al*., 2012; Kodaira *et al*., 2004; Tawn *et al*., 2005; 2011; Wilding *et al*., 2007).

4.7.3 *Cancer in Offspring after Environmental Preconception Radiation Exposure*

Subsequent to the report by Gardner (1984) of excess childhood leukemia and non-Hodgkin lymphoma in Seascale, near the Windscale/Sellafield nuclear plant in Great Britain, a large number of studies have been performed of children around various nuclear plants throughout Europe and the United States. Gardner (1984) reported that their analyses tended to attribute the excess hematopoietic malignancies to preconception irradiation of the father, though the potential for protracted exposures means that any association might be due to preconception, *in utero*, or childhood exposure. Among alternate explanations for the initial Seascale findings was a model, with some substantiation, of an infective etiology through new-population mixing (Kinlen *et al*., 1991). Overall, there have been a few studies imputing an association of projected radiation exposures around nuclear plants (some mix of preconception, prenatal and postnatal exposure) and childhood hematopoietic malignancies (*e.g*., Kaatsch *et al*., 2008). However, a large number of null studies (Laurier *et al*., 2014) have been reported also, as ably reviewed in various reports by the British Committee on Medical Aspects of Radiation in the Environment (COMARE, 1986; 2005; 2011; 2016).

4.7.4 *Implications for Radiation Protection*

Past and recent studies of heritable effects among the children of human populations exposed to ionizing radiation have been mostly negative, with only weak positive evidence (NCRP, 2013). Extensive dosimetry for atomic-bomb survivors and for the survivors of cancer has been conducted. There is no conclusive evidence for either a radiation association or a dose response for any of the numerous measures evaluated. Thus there is little to no evidence for heritable effects among the children of atomic-bomb survivors; children of cancer survivors; children of residentially-exposed populations or children of radiation-exposed workers (NCRP, 2013).

Mouse studies continue to be used to estimate genetic risks because of the lack of clear evidence in humans that germline mutations caused by radiation result in demonstrable genetic effects in children (ICRP, 2007). For radiation protection, it is assumed to be unlikely that the human is immune to heritable effects of radiation, although the effect must be small since not detectable even at high doses. Gonadal exposure is included in the "detriment" equation but the risk of heritable effects in the whole population associated with gonadal dose is now estimated to be a factor of 5 lower than in the past, *i.e*., about 20 cases per 10,000 people per Sv rather than about 100 cases per 10,000 per sievert (ICRP, 2007).

1946 **5. Review of Epidemiologic Studies for Tissue Reactions**

1947

Highlights

Since radiation protection is designed to prevent adverse tissue reactions (deterministic effects), assessment of the LNT model for use in radiation protection is predominantly directed toward cancer induction and, to a lesser extent, hereditary effects. In the last decade, however, for a number of effects which were previously thought to have clear thresholds, newer studies suggest that they may occur at low doses and may possibly be stochastic in nature. Therefore, the dose response, particularly in the low dose range, is briefly examined.

A number of studies with data on radiation and circulatory (cardiovascular) disease at doses under 1 Gy have been published in the last 10 to 15 y. Essentially all of these studies are complicated by potential confounding factors (especially tobacco), combining diverse types of cardiovascular diseases (likely of various etiologies), uncertain diagnostic criteria and poor pathological confirmation. There also is no clear understanding of the target cells or tissues and the underlying biological processes. The reported increase in cardiovascular diseases in atomic-bomb survivors is unclear statistically below 0.5 Gy and comes from a number of diagnoses which vary substantially over time and that may have explanations other than radiation exposure. Radiation therapy studies do not show a significant increase of cardiovascular disease below 1 Gy. Studies of radiologic technologists and radiologists usually are done by questionnaire, often lack individual dosimetry, are prone to recall bias and have not demonstrated a dose response. Studies of nuclear workers are often insignificantly positive and most lack information on important confounding factors.

Study of cataracts in the atomic-bomb survivors and particularly following Chernobyl exposures have revealed development of minor lenticular opacities at doses lower than previously considered to be cataractogenic. Ophthalmologically detectable opacities are reported at doses of about 0.5 to 2 Gy or more. Review of the mechanistic studies suggests a possible stochastic phenomenon while the epidemiologic studies suggest that a threshold model may be more appropriate. Presently, the link between the mechanistic and epidemiologic evidence is not clear. At this time, the NCRP recommends use of the threshold model. While this does not apply to the use of the LNT model for exposure of tissues other than the lens of the eye, it does require that the lower apparent threshold be taken into consideration for occupational eye exposures.

The studies of noncancer thyroid effects includes radiation therapy patients, atomic-bomb survivors, exposure from weapons fallout, Chernobyl populations, and Hanford public exposure. Essentially none of the most recent and well-designed studies show any increase in thyroiditis or hypothyroidism at doses of less than 1 Gy. Occasionally, the matter is complicated by authors inappropriately applying a LNT model to data that are clearly nonlinear. Overall, studies of adverse tissue reactions or of effects that may or may not be stochastic, do not clearly

show an effect below doses of 0.5 to 1.0 Gy and thus are not the limiting factor or helpful in establishing annual effective dose limits for workers or the public. The one exception is the equivalent dose to the lens of the eye during occupational exposure.

The appropriateness of a LNT model is briefly examined for cardiovascular diseases and cataract. The cardiovascular disease studies include studies of higher doses (Section 5.1.1), TB fluoroscopy studies (Section 5.1.2), nuclear worker studies (Section 5.1.3), and studies of environmental radiation exposures (Section 5.1.4). Recent cataract studies are reviewed in Section 5.2 and thyroid noncancer effects in Section 5.3.

5.1 Cardiovascular Effects Studies

It is well established that high acute doses of ionizing radiation increase the risk of circulatory system (cardiovascular) diseases, such as heart attack and stroke (Darby *et al*., 2013; HPA, 2010; ICRP, 2012; NCRP, 2011; Shimizu *et al*., 2010; Stewart, 2012; Takahashi *et al*., 2013; 2017; Travis *et al*., 2014). The evidence for this comes from the experience of the Japanese atomic-bomb survivors and of radiotherapy patients. The underlying radiobiological mechanism is believed to be primarily cell killing by high absorbed doses (typically, the doses received by tissues from whole-body doses >1 Gy) leading to tissue damage and a consequent raised risk of cardiovascular disease that is clinically manifest some years later. However, there is growing evidence to suggest a raised risk of cardiovascular disease at lower levels of exposure to radiation, although the mechanisms for possible risk at those doses are poorly understood. Currently, the framework of radiation protection set out by the ICRP (2007) does not include an increased risk of cardiovascular disease in the exposed individual from low-level exposures. Hence, it is of some importance to understand and correctly interpret the evidence for cardiovascular disease risk associated with low or moderate dose/dose-rate exposures to radiation to ensure that the risks arising from these lower level exposures are appropriately assessed and (if necessary) incorporated into the scheme of radiation protection. Given the high background rate of cardiovascular disease in economically developed countries, a relatively small proportional increase in risk produced by low-level exposure to radiation will imply a comparatively large number of excess cases. This matter is of direct relevance to occupational exposure to radiation, for which there exists mixed evidence of increased cardiovascular disease risk. The evidence for a risk of radiation-induced cardiovascular disease will be briefly summarized below.

The literature regarding cardiovascular disease (CVD) after radiation exposure is complicated by a number of important factors. First, CVD is not a single entity and is a term used to describe a myriad of disparate conditions with different causes. As an example, heart disease includes valvular abnormalities, capillary and blood vessel lesions, aneurysms, effusions, muscle abnormalities, arrhythmia, endocarditis, malformations etc. A derivative

issue is that of disease diagnosis and classification, *e.g.*, a diagnosis of hypertension varies widely by medical practice, country, and over time, so that results of published studies about low dose radiation and CVD can be misleading. There are many potential confounding causes of CVD, such as smoking, hereditary factors, diet-related factors and concurrent conditions (*e.g.*, diabetes, obesity). Importantly, at present there is no clear understanding of the biological mechanisms for cardiovascular diseases at low doses and there is little understanding of the target cells or tissue. Without these, application of a linear dose response model at low doses and assumption that this is a stochastic process remains debatable.

5.1.1 *Higher Doses and Cardiovascular Disease*

Increased risks of cardiovascular disease (including myocardial infarction, coronary artery disease and stroke) are well documented effects after high radiation doses (>30 Gy) to the heart or neck that may occur with radiation therapy [*e.g.*, for Hodgkin lymphoma and breast cancer (Darby *et al.*, 2013; Travis *et al.*, 2014)]. Overall, however, the radiation therapy literature is of less interest for radiation protection standards than epidemiologic studies of persons exposed to lower doses.

There are several reports of increased risk of cardiovascular disease in atomic-bomb survivors. In the LSS cohort study of 8,400 heart disease deaths, researchers found an approximately linear dose response over the dose range 0 to about 3 Gy (Shimizu *et al.*, 2010). The estimated linear dose response risk estimate was an ERR Gy^{-1} of 0.14 (95 % CI 0.06, 0.23). The dose response over the range 0 to 1 Gy was statistically significant but over the range 0 to 0.5 Gy it was not. Excess risk was clear only above about 0.5 Gy. The increased risk of 14 % per gray seen in the LSS was driven primarily by the unexpected categories of heart failure, rheumatic heart disease (after heart infections), hypertension and hemorrhagic stroke, and about 30 % of the nominal risk was found to be potentially attributable to prior/concurrent diagnoses of cancer (Shimizu *et al.*, 2010). Further detailed aspects of the atomic-bomb survivor data on cardiovascular diseases are given in (Ozasa *et al.*, 2017; Takahashi *et al.*, 2017).

In the smaller atomic-bomb clinical morbidity study (Yamada *et al.*, 2004) the ERRs for hypertension, hypertensive heart disease, ischemic heart disease, aortic aneurysm and stroke all were nonsignificant. There was a linear quadratic dose response for hypertension and myocardial infarction but not a linear response.

There also are a number of issues regarding studies of atomic-bomb survivors that potentially limit the application of findings to the United States population. These include the relatively high incidence of stroke to heart disease in Japan (which is reversed in the United States), the high proportion of hemorrhagic stroke in Japan (which

is much less common in the United States and may reflect major differences in diet and hereditary background). The nature and magnitude of the risk (if any) at acute doses less than 0.5 Gy area unresolved (Takahashi *et al*., 2013).

5.1.2 *TB Fluoroscopy Studies*

A description of the Massachusetts (Boice and Monson, 1977; Boice *et al*., 1978) and Canadian (Miller *et al*., 1989; Sherman *et al*., 1978) TB fluoroscopy studies and their dosimetry is given in Section 4.4.1. The patients on average received roughly 100 chest fluoroscopies to monitor lung collapse (pneumothorax), with a fluoroscopic examination every two to three weeks, spread out over several years. The studies initially concentrated on breast and other cancers, but recent publications have examined cardiovascular disease (Davis *et al*., 1989; Little *et al*., 2016; Zablotska *et al*., 2014).

5.1.2.1 *Dosimetry*. The authors concluded that estimates of both the heart and carotid dose in the Massachusetts study may be too low or high by a factor of two (Little *et al*., 2016), but the factor could be much higher. Shared uncertainty was not investigated but could be significant in that the same dose per treatment was used for many individuals with the same characteristics: age, body size, calendar year, and beam orientation. These uncertainties apply to both the Massachusetts and Canadian studies on cardiovascular disease, though the Canadian study estimated lung doses using Monte-Carlo simulation techniques that should provide a reasonable estimate of individual radiation doses to the lung and heart (Zablotska *et al*., 2014).

A strength of the Massachusetts TB fluoroscopy study was that multiple realizations of dose were used to account for uncertainty, and the doses spanned a large range, from 0 Gy to a maximum of 11.6 Gy. Dosimetry weaknesses were that lung dose was used as a surrogate for cardiovascular diseases, actual estimates of uncertainty in individual doses were not provided, and shared uncertainty was not considered. Thus, the risk estimates could be biased by dose uncertainty. Further the inconsistencies in the Massachusetts and Canadian studies, *e.g*., a reported enhancement of risk for fewer fluoroscopies in the Canadian (Zablotska *et al*., 2014) but not the Massachusetts (Little *et al*., 2016) studies point to potential biases or uncertainties in the assumptions for derivative measures.

5.1.2.2 *Study Strengths and Weaknesses*. The epidemiologic methods are described in Section 4.4.1.2. The studies took into account smoking histories and other potentially confounding factors. These studies, overall, provide no evidence that low-dose fractionated exposures accumulating to a moderate to high dose are associated with heart or cardiovascular diseases in either the Canadian (Zablotska *et al*., 2014) or Massachusetts (Davis

et al., 1989; Little *et al*., 2016) cohorts. There are dosimetry issues that hinder interpretation of the shape of any dose-response relationship: average lung dose was used as a surrogate for heart dose and thyroid dose as a surrogate for carotid artery dose. Further, no adjustment was made to increase the dose for patients who had special procedures that entailed lengthy fluoroscopic examinations. Finally, there is no mention of how corpulmonale (enlargement of the right side of the heart due to pulmonary hypertension caused by tuberculosis), a potential confounder, was addressed.

5.1.2.3 *Implications for the LNT Model and Radiation Protection*. The studies of heart and cardiovascular disease at this time provide little evidence for an association between radiation and heart disease and much less evidence for a dose response that might be relevant in the low-dose domain.

5.1.3 *Nuclear Worker Radiation Exposure and Cardiovascular Diseases*

A number of epidemiologic studies of the risk of cardiovascular diseases (CVDs) among groups of workers exposed protractedly to radiation have been conducted and reported. These studies have been reviewed in the literature, by Little and colleagues (Little, 2016; Little *et al*., 2010a; 2012) and Kreuzer *et al*. (2015). Workforces that have been studied include nuclear industry workers, Chernobyl emergency and recovery workers, and uranium miners. The evidence from these occupationally exposed groups is summarised in Table I, which updates the studies considered in the aforementioned reviews. Table 5.1 also includes selected medical and environmental studies of relevance to low-dose and low-dose rate circulatory disease.

The studies considered are those with estimates of the slope of the CVD dose-response based on (primarily) external photon exposure. It does not include other occupational studies that have reported only Standardized Mortality Ratios (SMRs), because of the potential biases in SMRs and the fact that such studies are not based on individual doses.

ERR/Gy estimates are shown for all CVD and for major groupings of these diseases: ischemic heart disease (IHD) and cerebrovascular disease (CeVD). Other CVD groupings may be provided in some studies, but their presentation is not consistent and so these results are not given in Table 5.1. Not all CVDs are related to radiation at either high or lower doses, *e.g*., rheumatic heart disease, so future studies should focus on clinically relevant outcomes and not broad categories (Einstein *et al*., 2017).

Table 5.1—*Summary of estimates of ERR of various cardiovascular diseases per gray of cumulative whole-body external gamma-ray dose, and associated 95 % confidence intervals, obtained from studies of radiation workers and selected environmental and medical exposures. Results given for all cardiovascular diseases combined (CVD), IHD and CeVD separately, where available. Doses are lagged by 10 y, except where stated otherwise. Adaptation and update of tables presented by Little et al. (2010a; 2012)and Kreuzer et al.(2015).*

Study	Cohort Size	Mean Cumulative External Dose (Gy)	Cardiovascular Disease[a]	ERR Gy^{-1} (95 % CI)
Nuclear Workers				
INWORKS (Gillies *et al.*, 2017)	308, 297	0.025	CVD mortality IHD mortality CeVD mortality	0.22 (0.08, 0.37) [f] 0.18 (0.004, 0.36) 0.50 (0.12, 0.94)
Mayak, Russia (Azizova *et al.*, 2014; 2015a)	18 856	0.593	CVD mortality IHD incidence IHD mortality CeVD incidence CeVD mortality	0.06 (0.01, 0.12) 0.14 (0.08, 0.21) 0.05 (–0.01, 0.13) 0.49 (0.39, 0.60) 0.05 (–0.03, 0.16)
15 countries (Vrijheid *et al.*, 2007a)	275 312	0.021	CVD mortality IHD mortality CeVD mortality	0.09 (–0.43, 0.70) –0.01 (–0.59, 0.69) 0.88 (–0.67, 3.16)
NRRW-3, UK[b] (Muirhead *et al.*, 2009)	174 541	0.025	CVD mortality IHD mortality CeVD mortality	0.25 (–0.01, 0.54) 0.26 (–0.05, 0.61) 0.16 (–0.42, 0.91)
BNFL, UK[b,c] (McGeoghegan *et al.*, 2008)	38 779[d]	0.057	CVD mortality[e] IHD mortality[e] CeVD mortality[e]	0.65 (0.36, 0.98)[f] 0.70 (0.33, 1.11)[f] 0.43 (–0.10, 1.12)[f]
Idaho National Engineering and Environmental Laboratory, USA[j] (Schubauer-Berigan *et al.*, 2005)	35,833 59 021	0.131 0.023	IHD mortalityk CVD mortality IHD mortality CeVD mortality	–0.30 (–1.24,0.90) 0.31 (–0.90, 1.74)[f] 0.71 (–1.20, 3.18)[f] 0.99 (<0, 5.05)[f]
France[b] (Metz-Flamant *et al.*, 2013)				
ORNL, USA[b,g] (Richardson and Wing, 1999)	14 095	NA	IHD mortality	–2.86 (–6.90, 1.18)

Russian Chernobyl liquidators (Ivanov, 2007; Ivanov *et al.*, 2006)	61 017	0.109	CVD incidence IHD incidence CeVD incidence	0.18 (–0.03, 0.39) 0.41 (0.05, 0.78) 0.45 (0.11, 0.80)
Eldorado uranium miners, Canada (Lane *et al.*, 2010)	16 236[d]	0.052	IHD mortality[h] CeVD mortality[h]	0.15 (–0.14, 0.58) –0.29 (<–0.29, 0.27)
German uranium miners (Kreuzer *et al.*, 2013)	58 982	0.041	CVD mortality IHD mortality CeVD mortality	–0.13 (–0.38, 0.12) –0.03 (–0.38, 0.32) 0.44 (–0.16, 1.04)
French uranium miners (Drubay *et al.*, 2015)	1690[i]	0.066	CVD mortality IHD mortality CeVD mortality	0.40 (–1.8, 3.0)[j] –1.1 (–4.0, 3.2)[j] 3.7 (–0.9, 10.6)[j]
Environmental and Medical Exposures				
Dwellers near Techa River (Krestinina *et al.*, 2013b)	29,735	0.035	CVD mortality IHD mortality CeVD mortality	0.24 (–0.08,0.59) 0.40 (–0.11, 0.99) –0.14 (–0.64, 0.46)
Yangjiang, China high background radiation area (Tao *et al.*, 2012)	31,604	0.063	CVD mortality IHD mortality CeVD mortality	0.14 (–0.84, 1.29) 0.54 (–2.65, 6.13) 0.44 (–0.88, 2.08)
Canadian and Massachusetts patients with TB fluoroscopies (Tran *et al*., 2017)	77,275	~0.20	CVD mortality IHD mortality CeVD mortality	0.27 (–0.02, 0.58) 0.22 (–0.11, 0.66) 0.54 (–0.20, 1.34)

CVD = cardiovascular disease
IHD = ischemic heart disease
CeVD = cerebrovascular disease
NA = not available
CI = confidence interval

[a] Mortality data are based on underlying cause of death
[b] Substantial overlap with INWORKS and 15-country studies
[c] some overlap with NRRW-3 study
[d] men only included in analysis
[e] 15 y dose lag
[f] 90 % CI
[g] analysis conducted in terms of the cumulative dose received after the age of 45 y
[h] 2 y dose lag
[i] restricted cohort from which cases and controls drawn
[j] derived from hazard ratio obtained from nested case-control study. [j]Monitored study cohort (INEEL) adjusting for age, sex, calendar time, duration of employment, SES, migrant status, interaction between SES and migrant status, and internal dose (see Table 6-14).
[j]Overlap with INWORKS and the 15-country study. The extent of overlap is uncertain because of exclusion criteria used in the studies [*e.g.*, described in Vrijheid *et al*. (2007b) specifically for what is labelled as US-INL] and follow-up apparently started in 1960 and not 1942 when work at INEEL began or 1951 for the INEEL monitored workers.

Table 5.1 and several reviews show elevated ERR Gy^{-1} estimates for cardiovascular disease, ischaemic heart disease and cerebrovascular disease associated with exposure to external sources of gamma radiation in the workplace, and from environmental and low-dose rate medical exposures. However, a cautious interpretation is required, as discussed below, that temper conclusions.

Particular groups of workers are influential in generating the impression of a pattern of elevated ERR Gy^{-1} estimates For example two of the estimates (Muirhead *et al*., 2009; Vrijheid *et al*., 2007a) are dependent upon the significantly increased risk seen in the BNFL cohort, ERR = 0.65 Gy^{-1} (90 % CI: 0.36, 0.98) (McGeoghegan *et al*., 2008). McGeoghegan *et al.* showed that the BNFL results have heterogeneity in risk related to confounding by socioeconomic and lifestyle factors. The new report of cardiovascular disease risk in the INWORKS study (Gillies *et al*., 2017) also showed risk heterogeneity: significantly higher risk of IHDonly among white collar (ERR Gy^{-1} = 0.58, 90 % CI 0.22, 0.98) and a much lower risk among blue collar workers (ERR Gy^{-1} = 0.07, 90 % CI –0.11, 0.27), while there was a suggestion of an opposite difference for cerebrovascular disease (ERR Gy^{-1} values of 0.59 (90 % CI 0.18, 1.07) among white collar workers and a significantly low risk of –0.08 (90 % CI <0, 0.77) among blue collar workers.

Similar to BNFL, the Idaho National Engineering and Environmental Laboratory (INEEL) study (Schubauer-Berigan *et al*., 2005) is another example of overlap and heterogeneity. INEEL is included in both the 15-country study (Vrijheid *et al*., 2007b) and in INWORKS (Gillies *et al*., 2017; Hamra *et al*., 2016). The INEEL study cohort of monitored workers, followed from 1951 to 1998, showed a negative dose response for IHD (ERR Gy^{-1} = –0.30, 95 % –1.24, 0.902), and in contrast to INWORKS the blue collar workers (low SES) had higher risks than the white collar workers (high SES), *i.e*., just the reverse of INWORKS. Specifically in INEEL, "Unskilled workers, skilled manual workers, and partially skilled workers showed greater risks (*for IHD*) than the baseline risk of professional and skilled non-manual workers." Other uncertainties included different starts of follow-up (1951 for the INEEL defined study cohort and 1960 for the 15-country study), different cohort numbers, *e.g*., 64,000 for the 15-country study (Vrijheid *et al*., 2007b). Comparisons with INWORKS are problematic since few details are provided on the INEEL cohort, and a reference to the study is not provided in any INWORKS publication. In supplementary tables, however, the INEEL ERR Gy^{-1} estimates for CVD, IHD and CeVD were negative (Gillies *et al*., 2017, supplementary tables). Overlap between INEEL and the ORNL and Hanford cohorts apparently was not removed (Vrijheid *et al*., 2007b), suggesting that some workers might be counted as many as three times in the analyses.

In the case of the Mayak workers, information was available on smoking, alcohol consumption and obesity (Moseeva *et al*., 2014), but the results are difficult to interpret because of substantial differences between the

ERR Gy^{-1} values for incidence and mortality from IHDand cerebrovascular disease; the risk estimates for incidence are notably higher than for mortality, especially for cerebrovascular disease (Azizova *et al*., 2014). The Chernobyl liquidator data from Russia (Ivanov, 2007; Ivanov *et al*., 2006) are also puzzling: the number of incident cases of CeVD is surprisingly high, and the risk coefficient for incident CeVD is very high while that for CeVD mortality is low.

While cancer mortality was higher in U.K. radiologists who worked from 1897 to 1920, the mortality from cardiovascular disease was lower compared to other medical practitioners (Berrington *et al*., 2001), but there are uncertainties in the dosimetry and statistics (Smith and Doll, 1981). The studies of about 90,000 U.S. radiologic technologists have found increased risk of cardiovascular disease, particularly CeVD, in those starting work prior to 1940 compared to those starting after 1960 (Hauptmann *et al*., 2003), and other reports found weak evidence of increased CVD risk related to work in interventional radiology (Linet *et al*., 2006; Rajaraman *et al*., 2016) or nuclear medicine (Kitahara *et al*., 2015).. The most recent report on cardiovascular mortality in the entire cohort found that technologists working before 1950 had nonsignificantly increased mortality from some cardiovascular diseases (IHDand stroke) (Liu *et al*., 2014). However, none of these studies had individual dose estimates, so their relevance to the LNT model is negligible.

Table 5.2 presents estimates of ERR for all circulatory disease (CVD) and IHD per gray of cumulative whole-body external gamma-ray dose and associated 95 % confidence intervals within the currently available Million Worker Study cohorts (Boice 2017; Boice *et al.,* 2017; Bouville *et al.*, 2015).

The four cohorts presented are nuclear power plant workers, industrial workers, aboveground nuclear weapons test participants and workers at the Mound facility. They represent 387,532 or approximately 39 % of the MWS population. The overall mean dose was 20 mGy. The dosimetry was conducted following the advice from NCRP Scientific Committee (SC 6-9) as summarized in Bouville *et al.* (2015) and Boice *et al.* (2006b). The follow-up for vital status and the determination of cause of death was also the same for all cohorts within the MWS. Combining the cohorts within the MWS has begun for two cohort, Mound (Boice *et al.,* 2014) and Rocketdyne (Atomics International) (Boice *et al.,* 2006a; 2011) for cardiovascular disease (Zhang *et al.,* 2014).

Table 5.2—*Summary of estimates of ERR (and 95 % confidence intervals) of total heart disease and IHD per gray of cumulative whole-body external gamma-ray dose for cohorts within the Million Worker Study (Boice 2017; Boice et al. 2017; Bouville et al. 2015). Results given for all heart diseases combined (CVD) and ischaemic heart disease separately, where available. Doses are lagged by 10 y.*

Workforce	Cohort Size	Mean Cumulative Heart Dose (Gy)	Heart Disease [a]	ERR Gy^{-1} (95 % CI)
Occupational Exposures				
Mound (Boice *et al*., 2014; Golden *et al.,* 2017)	4,954	0.024	CVD mortality IHD mortality	–0.4 (–3.9, 3.2) –1.4 (–4.3, 1.4)
Nuclear Power Plant Workers (Boice and Bellamy, 2017; Golden *et al.,* 2017)	145,209	0.038	CVD mortality IHD mortality	0.06 (–0.5, 0.4) 0.1 (–0.5, 0.5)
Atomic Veterans (Boice 2017; Golden *et al.,* 2017)	113,813	0.006	CVD mortality IHD mortality	NA 0.06 (–0.05, 0.18)
Industrial Radiographers (Boice and Bellamy, 2017; Golden *et al.,* 2017)	123,556	0.011	CVD mortality IHD mortality	0.02 (–0.03, 0.08) 0.006 (–0.06, .05)

CVD = cardiovascular disease
IHD = ischemic heart disease
NA = not available
CI = confidence interval
[a] Mortality data are based on underlying cause of death

The ERR Gy^{-1} estimates of risk for both CVD and IHD within the four MWS cohorts were all very low and none were statistically significant, providing no evidence for an association between low dose and low-dose rate exposures. The dose-response evaluation for the industrial radiographers provides no evidence for a dose response relationship for IHD (Figure 5.1). Similar patterns are seen in the other three cohorts. The MWS studies of medical workers and additional DOE workers are ongoing and will provide substantial statistical power when combined.

5.1.4 Environmental Radiation Exposure

Few studies of environmental radiation exposure and cardiovascular diseases have individual dose information that permits them to estimate the ERR Gy^{-1}. Because of a recent indication of erroneous dosimetry,[5] the previous report of residents downwind of the Russian Semipalatinsk nuclear test site in Kazakhstan (Grosche *et al*., 2011) is not included. In the Techa River study, positive but nonsignificant ERRs were reported for ischemic heart disease mortality and all cardiovascular disease deaths (Krestinina *et al*., 2013b). There were also positive but nonsignificant risk coefficients for ischemic heart disease, cerebrovascular disease and all cardiovascular disease in the Yangjiang, China study of high natural background irradiation (Tao *et al*., 2012).

5.1.5 *Implications of Cardiovascular Disease for the LNT Model and Radiation Protection*

The study of atomic-bomb survivors had a complex pattern of types of cardiovascular disease associated with radiation exposure and did not have clear evidence of excess risk below about half a gray. The occupational data represent assessments at low doses and low dose rates. The majority of those studies were positive, but several had inconsistencies or particular problems in interpretation. In addition, most of them did not have information on smoking or other cardiovascular disease risk factors, so possible confounding could not be ruled out. The two studies with environmental exposures had low statistical power to detect a radiation effect. So at this time, the data on cardiovascular diseases at lower doses and dose rates do not present clear evidence regarding the LNT model or applicability to radiation protection.

[5] B Grosche, personal communication, 2015

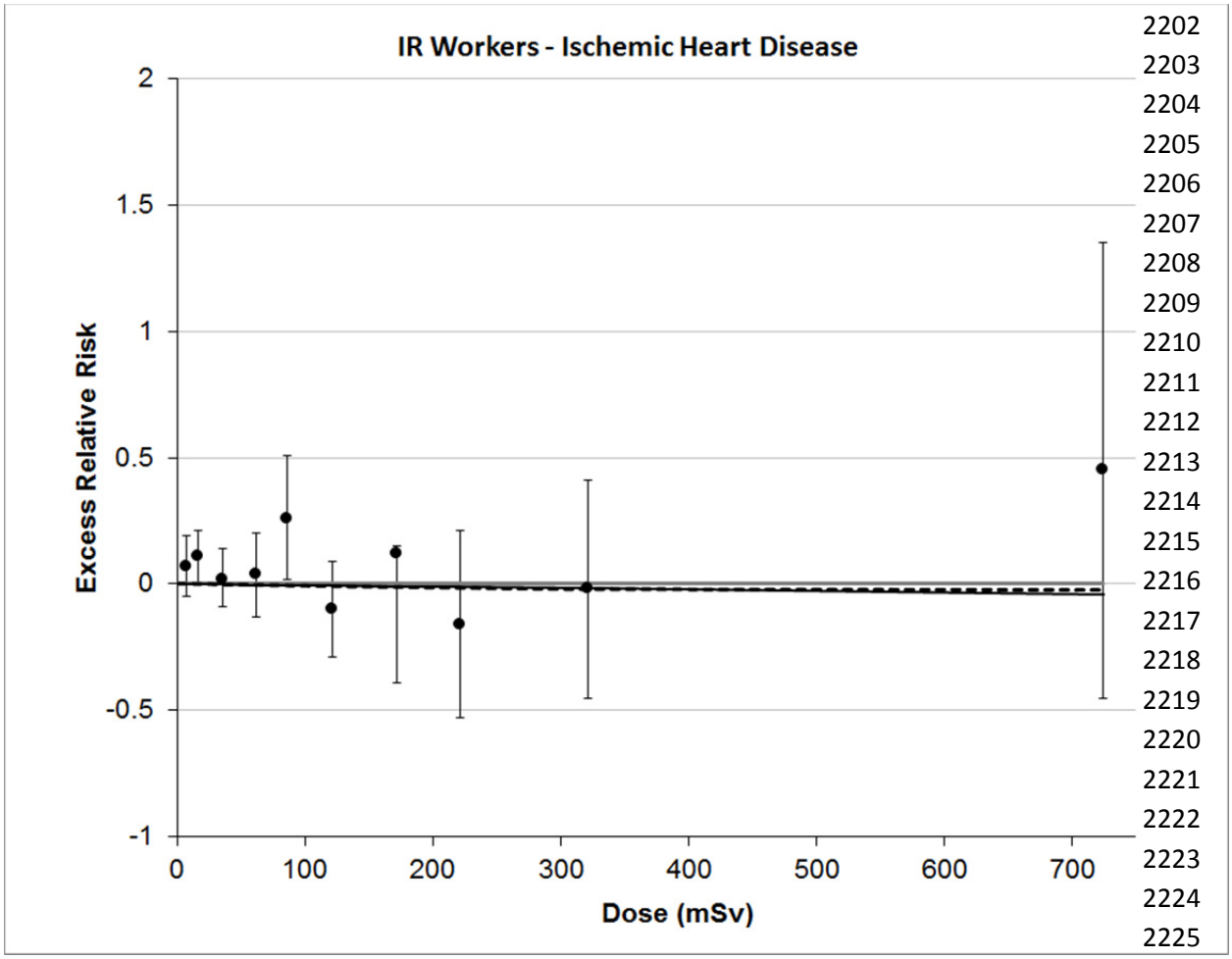


Fig. 5.1. Dose response relationship between IHD and cumulative dose to heart, industrial radiography workers. The data are fit with a linear ERR model.

5.2 Cataract Studies

Studies of lens opacities and cataracts following radiation exposure have been reviewed extensively in NCRP Commentary No. 26 (NCRP, 2016). The commentary addressed radiation protection principles with respect to the lens of the eye, summarized the current understanding of eye biology and lens effects (including ionizing radiation effects), reviewed and evaluated the current epidemiology related to ionizing radiation and cataracts, and assessed exposed populations with the potential for significant radiation exposures to the lens. It pointed to a variety of strengths and limitations in the quality of the available epidemiologic evidence. NCRP determined that a threshold model should continue to be used for radiation protection purposes for lens of eye at this time. The value of the threshold for detectable opacities or vision-impairing cataracts (VICs) is less clear, with the epidemiologic evidence currently pointing to a threshold for VICs for doses in the region of 1 to 2 Gy. However, the NCRP concluded that it is not possible to make a specific quantitative estimate of lens effect thresholds.

NCRP also concluded that while the mechanisms underlying the transition of minor lens opacifications to clinically significant VICs are still not well understood, it is prudent to regard eye exposures and the potential for lens tissue effects in much the same way as whole-body exposures, using the ALARA principle, as was previously recommended by NCRP Report No.168 (NCRP, 2010). NCRP has determined that it is prudent to reduce the current recommended annual lens of the eye occupational dose limit from an equivalent dose of 150 mGy (NCRP, 1993a) to an absorbed dose of 50 mGy (NCRP, 2016). At this time the use of the LNT model for cataracts is not justified.

5.3 Thyroid Noncancer Effects Studies

This section reviews radiation effects on thyroid function and possible thyroiditis in an effort to evaluate use of LNT versus other potential dose-response models for radiation protection purposes. There are many large sources of human data on thyroid function and autoimmune issues including atomic-bomb survivors, fallout exposures, external radiation therapy, and radionuclide treatment for thyroid conditions. At high absorbed doses the main concern is reduced production of thyroid hormone (hypothyroidism) and at lower doses thyroiditis is more of a concern. The issue of thyroiditis is usually complicated by a number of issues including increase in thyroid antibodies with age, genetic predisposition, dietary factors, concurrent diseases and the criteria used to make the diagnosis. Several studies have reported statistically significant and relatively linear dose-related increases in the prevalence of thyroid nodules and cysts (Cahoon *et al.*, 2017b; Imaizumi *et al.*, 2006; 2015; Zablotska *et al.*, 2007; 2015).

5.3.1 *Atomic-Bomb Studies*

An earlier study of atomic-bomb survivors showed a questionable increase in hypothyroidism in the 0.01 to 0.49 Gy group but not in the 0.50 to 0.99 Gy group (Nagataki *et al*., 1994). However, a subsequent, larger study among the survivors, which also included most of the individuals in the previous study, did not find any evidence of dose-related hypothyroidism (Imaizumi *et al*., 2006; 2017). Because the Nagataki *et al.* (1994) study had applied a linear-quadratic model to their hypothyroid data, that model was also examined by Imaizumi *et al.* (2006) but no quadratic curvature was found ($p = 0.86$). Since testing positive for antithyroid antibodies is strongly affected by increasing age, the subgroup of ages 0 to 9 y at the time of the bombing also was analyzed separately. Antithyroid antibody-positive hypothyroidism among the younger cohort members was not associated with radiation dose (excess odds ratio $Gy^{-1} = -0.09$, $p = 0.72$). Morimoto *et al*. (1987) also reported that in survivors under the age of 20 y at exposure and with doses 1 Gy or more there was no increase in either hypothyroidism or autoimmune thyroiditis.

5.3.2 *Chernobyl ^{131}I Fallout and Noncancer Thyroid Effects*

There are quite a number of studies regarding Chernobyl with various methodologies, different dose sources and often with conflicting results. The studies of thyroiditis are also complicated by the dietary deficiency of nonradioactive iodine. Ostroumova *et al*. (2013) reported an increase in hypothyroidism [based on thyroid-stimulating hormone (TSH), not thyroxine levels] but observed no evidence of autoimmune thyroiditis. They estimated a risk of hypothyroidism at 1 Gy based on a linear model even though the best fit to the data was not linear and there was no evidence of increased risk at doses <4 Gy. In addition, use of the linear model by the authors implies a stochastic process even though it is well known that the relationship of thyroid tissue volume to thyroid hormone or TSH is not linear.

The largest study of the Chernobyl population was performed by the Sasakawa Foundation and reported by Ito *et al*. (1995; Shibata *et al*., 2002; Shigematsu, 2002). The study included 160,000 children and did not find any increase in thyroid antibodies, hypothyroidism or hyperthyroidism that could be related to ionizing radiation.

5.3.3 *Other Studies of Radioactive Iodine Fallout and Thyroid Effects*

Fallout from nuclear testing resulted in significant deposition of radioiodine in the Marshall Islands and caused subclinical hypothyroidism in about 30 % of children who received thyroid doses of >2 Gy (Lessard *et al*., 1985). Long-term follow-up of those with thyroid doses up to 4 Gy did not show an increase in autoimmune

thyroiditis. A report on fallout of atomic tests in Nevada (Rallison *et al*., 1990) indicated an increased risk of autoimmune thyroiditis, which was supported by later analyses using corrected dosimetry (mean of 120 mGy, with a standard deviation 167 mGy) and accounting for dose uncertainties (Li *et al*., 2007), though this is in contrast to negative findings at similar dose levels in most other studies.

Davis *et al.* (2004) evaluated thyroid effects associated with low dose ^{131}I exposure from fallout from Hanford, with individual estimates of absorbed dose the thyroid gland (median of 97 mGy, mean of 174 mGy, standard deviation of 224 mGy, range of 0 to 2823 mGy) They found no evidence of dose response for either hypothyroidism (ERR Gy^{-1} of –0.006 (95 % CI –0.016, 0.047) or autoimmune thyroiditis (ERR Gy^{-1} = –0.026, 95 % CI< –0.057, 0.044).

5.3.4 *Implications of Noncancer Thyroid Effects for Radiation Protection*

The available literature on hypothyroidism has negative results at low doses, which sometimes are accompanied by upward curvature such that there is an indication of risk at doses well above 1 Gy. The data on thyroiditis from the larger, well-conducted studies is also generally negative at low doses although there are occasional scattered and conflicting small study reports. Given that hypothyroidism and immune thyroiditis are considered tissue reactions, and not stochastic effects, findings of no effects at low doses are expected.

6. Study Quality

The review of the current epidemiologic studies has identified various strengths and opportunities for improvement, as briefly outlined below.

6.1 Strengths

Quantitative risk estimates, based on estimated individual doses, of cancer mortality or incidence have been reported for nearly one million individuals with low dose rates and mostly low doses from studies of radiation workers or those exposed to elevated environmental radiation levels (Shore *et al*., 2017). The completion of the million person study will considerably augment the available information (Boice, 2012a). The strongest studies have high-quality follow-up, with a nearly complete ascertainment of cancer deaths or incidence. These studies complement the LSS of atomic-bomb survivors with its high dose rate and high dose range. Although an historic weakness of many worker and environmental radiation studies was inadequate dosimetry, in recent years investigators have been focusing more on improving the quality and accuracy of the dosimetry. For example, the million person study components (*e.g*., atomic veterans, Rocketdyne, Mound), the INWORKS, Mayak, Techa River and atomic-bomb studies have benefitted from devoting considerable resources to developing improved dosimetry, and further improvements are underway. Several studies also have examined biodosimetry data (mainly chromosome aberrations) for subsamples of the study subjects, and have broadly found validation of their dosimetry. The dosimetry improvements are essential for accurate characterization of risks and assessment of the LNT model at low doses and low dose rates.

Strengths of some of the large epidemiologic studies such as INWORKS and the LSS lie in the long follow-up and large numbers of cancers and person-years at risk. The length of follow- up of epidemiologic studies is particularly relevant since a large fraction of both spontaneous and radiation-related cancers occur after 60 y of age. Nearly all studies have adjusted for potential confounding by gender, attained age and sometimes age at exposure. There are also ongoing efforts to include other potentially explanatory variables such as life-style factors, cancer predisposing factors and other sources of radiation exposure. Most of the studies reviewed here have attempted to investigate potential sources of bias insofar as relevant data are available A few studies examined risks at restricted, lower-dose ranges to provide additional evidence regarding the applicability of a LNT model in the dose range of greatest interest. Most notably, the LSS atomic-bomb survivors study of solid cancer (Grant *et al*., 2017) and the INWORKS study of all cancer except leukemia (Richardson *et al*., 2015) found statistical evidence for risk over the dose range of 0 to 100 mGy. A pooled analysis of studies of childhood external

irradiation and thyroid cancer also showed a significant dose-response association over the dose range of 0 to 100 mGy (Lubin *et al*., 2017).

6.2 Opportunities for Improvement

Although the worker studies and key environmental studies had individual dosimetry, a number of the other studies briefly reviewed here did not (*e.g*., most fallout studies), so they provided little or no information relevant to the LNT model of risk. Most studies did not evaluate the effects of dose uncertainties on the risk estimates and their confidence bounds. Several studies did not include concomitant exposures to neutrons or internal radionuclides in their risk assessments.

For a few of the studies, a substantial fraction of the designated cancer cases were without histopathological verification, and the completeness of enumeration of cancer or other diseases also was uncertain. Issues of possible confounding effects of dose-dependent variations in health surveillance and access to medical care are also considerations in several studies. Few studies have analyzed radiation risks with control for confounding by lifestyle (*e.g*., smoking) or other disease risk factors, and few studies currently have biological samples to evaluate genetic or phenotypic biological factors in radiation risks. The studies of pediatric CT examinations are prone to confounding in that the examination may have been performed because of a suspicion of cancer or a cancer-predisposing condition; they also lacked dose estimates for individuals.

Important information for assessing the evidence for and against LNT is not currently available in some of the studies reviewed here. This is partly because some study authors tend to ignore nonlinear models when there is not enough statistical power to support both a linear parameter (which is usually applied first) and a second nonlinear parameter in the same dose- response model. Consequently it is important to consider nonlinear one-parameter dose-response models, such as pure quadratic in dose. Sometimes Excess Absolute Risk (EAR) models could provide additional information relevant to assessing LNT, but not all studies have reported results with EAR models. Attention should also be paid to temporal/age effects on the risk estimates, as the dose-response curve may vary by age, time since exposure and birth cohort (Walsh and Schneider, 2016).

7. Strength of Support for LNT in Recent Epidemiologic Studies

Support by studies for any model requires adequacy of the study components, which for epidemiologic studies could be broadly characterized as adequacy of dosimetry, epidemiology and statistics. Dosimetric criteria include, *e.g.*, personal vs. reconstructed dosimetric measurements; cumulative-dose range; accounting for neutron, internal and medical exposures; validation of dosimetry; potential for bias in dosimetry; characterization and magnitude of dose uncertainties; adequacy of dosimetry technology, calibration and administrative practices; and uncertainty in dose reconstructions for individuals. Epidemiologic and statistical criteria include, *e.g.*, appropriateness of study design and cohort definition; length of follow-up; completeness of follow-up and health outcome ascertainment, equivalent across the dose range; sources and likelihood of bias; statistical power and precision; appropriate statistical analysis method; sensitivity analyses; choices of mathematical models; types of adjustments for explanatory covariables; and consideration of risk-effect modification. However, the listed criteria are not exhaustive, as studies sometimes have unique characteristics that impinge on their ability to contribute information regarding the LNT model.

For each component of the major studies, this report has critiqued both the methods used and the adequacy of the results of those methods. To evaluate this, members of the committee made qualitative ratings of weak, medium or strong for the adequacy of the dosimetry, epidemiology and statistics components of each of the major studies or groups of studies of cancer risk after radiation exposure. Weak, medium and strong were scored as 1, 2, and 3, with intermediate ratings (1.5 and 2.5) permitted; the scores were averaged across raters. The one exception to this was that, for the dosimetry component only the ratings by the dosimetry team within the committee were considered since they were more familiar with the details of the dosimetry than most of the remainder of the Committee. Many of the implicit criteria that entered into the component ratings are given synoptically as study strengths or weaknesses in Sections 6.1 and 6.2, although the items mentioned there are not exhaustive, as some unique features may be important for a given study.

Table 7.1 summarizes the Committee's evaluation of the aforementioned components for 28 principal studies or groups of studies of cancer risk. As a minimal criterion of study adequacy, 71 % of the studies had no component on which they were scored as weak (score of 1). Fifty percent of the studies were scored moderate to strong on all three components of evaluation.

The Committee further rated each study or group of studies on their strength of support for the LNT model (Table 7.1). Eighty-two percent of the studies provided some support for the LNT model, including 18 % providing

2414 Table 7.1—*Ratings of the quality of cancer studies reviewed and their degree of support for the LNT model.*

Study (or groups of studies) [a]	Dosimetry [b]	Epidemiology [b]	Statistics [b]	Support for LNT Model [c]
Life Span Study (LSS), Japan atomic bomb (Grant *et al.*, 2017) [d]	3	3	3	4
INWORKS (UK, US, French combined cohorts) (Richardson *et al.*, 2015)	3	3	3	4
TB fluoroscopic examinations (Little and Boice, 2003)	2	3	2	4
Childhood A-bomb exposure (Preston *et al.*, 2008)	3	3	3	4
Childhood thyroid cancer studies (Lubin *et al.*, 2017)	3	3	3	4
Mayak nuclear facility (Sokolnikov *et al.*, 2015)	2	2	3	3
Techa River, nearby residents (Schonfeld *et al.*, 2013)	2	2	2.5	3
Chernobyl fallout, Ukraine and Belarus thyroid cancer (Brenner *et al.*, 2011; Zablotska *et al.*, 2011)	3	2	2	3
Childhood breast cancer studies (Eidemüller *et al.*, 2015)	2	3	3	3
In utero A-bomb exposure (Preston *et al.*, 2008)	2	3	3	3
In utero exposures, medical (Wakeford, 2008)	1	2	2	3
Canadian nuclear workers (Zablotska *et al.*, 2013b)	2.5	3	3	3
Japanese nuclear workers (Akiba and Misuno, 2012)	2.5	2	3	2
Chernobyl cleanup workers, Russia (Kashcheev *et al.*, 2015)	1	1.5	2	2
US radiologic technologists (Liu *et al.*, 2014; Preston *et al.*, 2016) [e]	1	2	2	2
Mound facility (Boice *et al.*, 2014)	2	1.5	1.5	2
Rocketdyne facility (Boice *et al.*, 2011)	2	2	2	2
Medical x-ray workers, China (Sun *et al.*, 2016)	1.5	1.5	2	2

Background radiation levels and childhood leukemia (Kendall *et al.*, 2013)	1.5	2	2	2
Taiwan radiocontaminated buildings, residents (Hwang *et al.*, 2008)	2	1.5	1.5	2
Pediatric CT examinations (Pearce *et al.*, 2012)	1	1.5	1.5	2
Childhood leukemia studies (Wakeford and Little, 2003)	1	2	1.5	2
In utero exposures, Mayak and Techa (Akleyev *et al.*, 2016)	1	1.5	2	2
US atomic veterans (Beck *et al.*, 2017)	3	3	3	1
Kerala, India, high natural background radiation area (Nair *et al.*, 2009)	2	2	1.5	1
Yangjiang, China, high natural background radiation area (Tao *et al.*, 2012)	1.5	1	1	1
Fallout studies (aggregate of 8 studies) (Lyon *et al.*, 2006)[f]	1.5	1	1.5	1
Hanford ^{131}I fallout study (Davis *et al.*, 2004)	2	3	1.5	1

[a] Studies excluded: studies of risks around nuclear sites (no dosimetry and extremely low exposures); the 15-country worker study (superseded by the INWORKS study); the Million Worker Study is not yet completed, but published components of it were evaluated separately; studies of genetic effects (since no human heritable risks have been shown); studies of tissue reactions ("deterministic effects", because these are generally not believed to be LNT).

[b] Judged quality of the Dosimetry, Epidemiology and Statistics scores: 1 = weak, 1.5 = weak-moderate, 2 = moderate, 2.5 = moderate-strong, 3 = strong.

[c] Ratings of the Support for LNT: 1 = essentially no support (null, unreliable or inconclusive), 2 = weakly moderate support, 3 = moderate support, 4 = strong support.

[d] A representative recent publication is listed for each study.

[e] The dosimetry used in the Preston *et al.* (2016) study of breast cancer, based on the Simon *et al.* (2014) dosimetry, is significantly improved and would be rated "3" compared to the dosimetry that was used in other published epidemiologic analyses of this cohort. However, since little other epidemiology has been published using the new dosimetry, for the purposes of this report these studies are limited in their support for LNT.

[f] Fallout studies were included as a group (they mostly had little or poor dosimetry and many were studies of aggregates rather than individuals; however, the Hanford ^{131}I fallout study was of better quality, so was identified separately).

strong support and 25 % rated as providing moderate support. A rating of moderate versus strong support for LNT sometimes hinged upon the size of the study or some other limitation, and not on indications of nonlinearity. The studies that provided no support for the LNT model were either totally null studies, or ones with no dose-response analysis or excessively unreliable data ("Inconclusive"). It should be noted that all the studies being considered, except for the Life Span Study of atomic-bomb survivors, had either exposures at low dose rates or multiple small exposures. Furthermore, the preponderance of study subjects had cumulative doses under 100 mGy. Thus these studies are very relevant for contemporary radiation protection concerns.

One question that could be raised is whether LNT underestimates the radiation risk of cancer. If the LNT model had grossly underestimated cancer risk there would not have been a reasonably consistent picture of dose-response slopes that were compatible with the LNT model, as was seen. Nonetheless, given the wide confidence intervals in many studies, it is possible that LNT might underestimate risk, but not to any great extent. In fact, on balance a number of the studies presented here suggest that a DREF >1 (*i.e.*, somewhat less risk at low dose rates) may be appropriate. Similarly, for a linear-quadratic response, the curve at low doses will still be a linear nonthreshold one but with a shallower slope than the overall curve at higher doses.

8. Future Directions

This section discusses several areas with regard to knowledge needs and opportunities for future research.

8.1 Epidemiology

8.1.1 *Atomic-Bomb Studies*

A number of advances in the Japanese atomic-bomb studies potentially can enhance our understanding of the magnitude of risk associated with acute radiation exposures and the shapes of dose-response curves. Some that are briefly outlined below represent a continuation of present directions and others are suggestions for new advances.

Improved organ doses. Organ doses in the atomic-bomb studies have been calculated using mathematical phantoms developed in the early 1980s and using only three prototypic ages (infant, child, adult) and a limited set of organs (*e.g.*, not including lens of the eye, heart, oral cavity, esophagus, kidney, rectum, prostate). The technology for organ dose estimation has improved significantly since then, and a more detailed set of ages, organs and other features is needed (Cullings, 2012). Until now, there has not been adequate dosimetry for the fetus, where the size and organ placement varies substantially by fetal age. This should be addressed as part of a new organ dosimetry project. Adequate dosimetry for the heart and the lens of the eye (for neutron and gamma, by posture and orientation vis a vis the bomb) is needed to improve the individual dose estimates.

Clarification of the dose-response shape and low-dose effects. Recent publications (Grant *et al*., 2017; Ozasa *et al*., 2012) have indicated more curvature in the dose response for all solid cancer and differences between males and females in the dose-response shape. Further evaluations may help clarify current discrepant views of the magnitude of the neutron RBE (Cullings *et al*., 2014; Sasaki *et al*., 2016; Walsh, 2013). A detailed analysis of possible factors involved in the curvature needs to be undertaken, *e.g*., urban/rural differences, socioeconomic factors, close examination of possible selection factors for males (*e.g*., health related selection because of the wartime male military draft), or quality of dosimetry for subsets of males in different shielding situations. Males could have different background risks from females for the influential cancers, and the interaction (or lack of it) between these background risk factors and radiation could influence the dose responses in different ways (as could confounding). The low-dose data need to be examined in more detail, using existing and new statistical methods and analytic strategies. This applies not only to all solid cancer or to leukemia, but to specific cancers or cancer groups, cardiovascular diseases, and various clinical health endpoints.

Evaluation of LNT for various organs or organ systems. Evaluate whether dose-response LNT is similar for tumors of various organs or organ systems, insofar as statistical limitations permit. This will provide evidence regarding the generality of the LNT model and the need for a low-dose effectiveness factor (LDEF) across tumor sites. Similarly, the new ophthalmological examination data currently being obtained need a careful evaluation of dose-response shape, as well as analysis by age, opacity grade, etc.

Risk at young ages (or fetal) at exposure. The mortality data and cancer incidence data for those exposed in childhood and adolescence are accruing extensively as they reach older ages, so there is increasing potential to learn more about risks following early-life exposure to radiation. Also, the most recent publication of solid cancer risk following *in utero* and early-childhood exposure yielded an intriguing result that risk following childhood exposure continues to increase over time, while it does not after *in utero* exposure (Preston *et al*., 2008). However, the difference between the two did not attain statistical significance. An update of those results is needed to clarify whether or not the difference in temporal trends continues and whether the LNT model applies to *in utero* exposure.

F1 generation risk. The risk in the F1 cohort with respect to parental irradiation has been purely null to date for cancer and noncancer mortality, for cancer incidence, and for clinical indications of cardiovascular diseases and diabetes. However, the cohort was not yet 60 y old on average, so 30 more years of observation are needed to see the full expression of disease and determine if any risk is present. Even though the numbers would likely be small, it also would be valuable to publish information on the occurrence of diseases with a strong genetic component (*e.g*., rheumatoid arthritis) in F1 clinical study subjects in relation to radiation exposure.

Bioindicators for cancer and CVD outcomes. The large bank of blood and tissue samples needs to be exploited more robustly by the biomedical community to evaluate genotypic and phenotypic alterations associated with both radiation exposure and disease risk, to thereby discover key events related to adverse outcome pathways that mediate between radiation and disease development. It is also recommended that the studies of chromosome translocations among those exposed *in utero* or at a young age be continued. If the existing *in utero* translocation findings are an indication of a drop-off of risk at moderate (rather than high) doses (Ohtaki *et al*., 2004), and if this extends after birth, then the usual extrapolation of risk from moderate-to-high doses to low doses might be modified for risk of leukemia, and possibly other cancers, after low-dose exposures at prenatal/early-childhood ages.

8.1.2 *Radiation Worker Studies*

Recent large-scale studies of radiation workers have started to make meaningful estimates of risks arising from protracted exposures to many low doses. It is important to continue to have accurate linkage to high quality cancer and mortality registries. Much of the statistical power of these studies emanates from those workers who have accumulated moderate-to-high doses over many years, and most of these workers will have started work in the early years of the nuclear industry. Therefore, the continuing follow-up of worker cohorts to obtain as much information as possible from high cumulative-dose workers is desirable, and should be pursued. International collaboration permitting the combining of worker cohorts, particularly those with reasonable numbers of high cumulative dose workers, is another valuable way of increasing the power of worker studies. Unfortunately, the earlier workers who will tend to have received the highest doses also are likely to have the greatest uncertainty attached to their doses because dose recording technologies, possibly combined with dose record keeping practices, were less advanced in the earlier years when doses tended to be highest. Therefore, careful scrutiny of dose records is necessary to identify any deficiencies in recorded doses. For example, during the 1950s the design of shielding of early reactors may have permitted neutron streaming into workspaces, but the inadequacy of personal neutron dosimeters to accurately measure intermediate and fast neutrons during this period may have led to underestimated neutron doses, or even the absence of recorded neutron exposures when neutron doses had been received. It is desirable to make use of all available dose information in the worker studies so as to identify inadequacies in dose records and to compensate for these wherever possible through, for example, dose reconstruction methods (see further discussion in Section 7.2). Reliable risk estimates depend, inter alia, upon reliable dose estimates, and this is an area that should be pursued. In addition, a further desirable refinement is the calculation of organ/tissue-specific doses for workers. Epidemiologic studies of medical workers pose problems in estimating doses because of factors such as partial-body irradiation, low photon energies, location of the dosimeter, use or non-use of the apron or other protective devices, missed dose etc.

8.1.3 *Environmental Radiation Studies*

Several improvements in the Techa River study are suggested: the new forthcoming dosimetry (TRDS-2017) will improve several aspects of the dose estimation; the shape of the dose response for solid cancer can be evaluated more fully in the low dose range; the potential for dose-related screening bias should be evaluated and, if possible, adjusted for; efforts should be made to improve the completeness of follow-up and the rate of histological verification of cancers. The Chernobyl ^{131}I studies of thyroid cancer should focus more fully on the lower dose part of their dose-response curves. The Kerala and Yangjiang studies need to increase efforts to improve their cancer ascertainment and diagnosis, and to closely examine the impact that low income/education

and distance from the principal cancer facilities may have on cancer ascertainment rates. Further carefully designed validation studies of reconstructed doses by personal dosimetry measurements would also be valuable for these studies. All of the environmental study groups should seek to implement measures to reduce individual dose uncertainties. (See further discussion in Section 6.2). Collection and storage of biospecimens from strategically defined subgroups may also be useful for future biodosimetry, molecular epidemiology and bioindicator studies.

8.1.4 *Computed Tomography Studies*

Within the next few years several major reports of the associations between pediatric CT examinations and subsequent cancer outcomes are expected to be published, including reports on cohorts in Canada, Australia and the EPI-CT study in Europe. Among other things, these studies will need improvements in the dosimetry compared to existing reports, including use of individual organ/tissue doses, more accurate characterization of historical CT doses, and accounting for all past CT examination doses. Appropriate incorporation of minimum latency periods for cancer induction is also needed. Avoiding bias: there is a fundamental need to fully disentangle radiation effects from the reasons why the CT examination was given, *i.e.*, confounding by indication (triggered by conditions that predispose to cancer) and reverse causation (pre-existing, but as yet undetectable, malignancy as the reason for the CT scan). However, owing to limitations in existing individual medical records, that may not be possible unless the impact of all of the potential sources of biases and missing sources of data are carefully assessed (Bosch de Basea *et al*., 2015). The identification of children who were not scanned for some pre-existing medical reason, such as children who are passengers in vehicles involved in collisions, is desirable to overcome confounding by indication and reverse causation, but this may be difficult with available records, especially for historically early exposures when the doses received from a scan tended to be highest.

8.1.5 *Childhood and In Utero Exposures*

The latest report on the cancer incidence of Japanese atomic-bomb survivors who were exposed prenatally or during childhood (Preston *et al*., 2008) considered cancer only through 1999 and needs an analysis of updated data. They found some indication ($p = 0.09$) of upward curvature in the dose response for all solid cancer and marginally greater risk among those exposed during childhood than prenatally, which further data may clarify. Further follow-up in the Techa River and Chernobyl studies also can yield greater statistical power to evaluate dose- response associations for cancer endpoints.

It is possible that future studies could also evaluate available data from radiation therapy patients such as those involved in the childhood cancer survivor studies (https://www.cancer.gov/types/childhood-cancers/ccss) if more accurate doses outside of the treatment fields can be ascertained (AAPM, 2017; Xu *et al*., 2008) and information on secondary malignancies can be assessed, along with the obvious confounding factors. NCRP has previously evaluated second primary cancers and cardiovascular disease after radiation therapy in NCRP Report No. 170 (NCRP, 2011) with such recommendations.

8.1.6 *Studies of Tissue Reactions*

In general, a greater understanding of the mechanisms for specific tissue reactions is needed, along with additional, quality epidemiologic data. With regard to the effects of ionizing radiation on the lens, while the currently available information has provided input on appropriate guidance with regard to radiation protection, much more work is needed to develop a complete understanding of such detriments. For the lens of the eye, NCRP (2016) recommends ongoing evaluation and additional research in the following areas: comprehensive evaluation of the overall effects of ionizing radiation on the eye; dosimetry methodology and dose-sparing optimization techniques; additional high-quality epidemiology studies; medical countermeasures; and a basic understanding of the mechanisms of cataract development. Similarly, for circulatory effects, it will be important to develop an understanding of the mechanisms for the plethora of associated diseases and to carefully address confounding factors in epidemiologic studies (especially with regard to lifestyle factors).

8.2 Dosimetry: Future Directions

The dosimetry review highlighted several recommendations about future directions of studies focusing on dose response. Clearly, individual doses based on personal monitoring technology, bioassay data, and measurements characterizing exposure scenarios provide the highest quality dose estimates. Dosimetrists must use the information available and address missing information through dose reconstruction and by taking into account uncertainties. When opportunities exist to plan dosimetry for new epidemiologic studies, the use of measurement data should be the first recourse, if available.

Ideally, uncertainties should be provided along with estimates of dose, and the dose uncertainties should be used to adjust risk coefficients and confidence intervals (Kwon *et al*., 2016; Stram *et al*., 2015; UNSCEAR, 2015; Zhang *et al*., 2017). Both individual and shared uncertainty can result in the width of uncertainty bounds of the risk estimates being significantly underestimated. Dosimetry upgrades to the Techa River and Mayak dosimetry are expected to provide better estimates of doses and multiple realizations of the doses that can be used to estimate

shared uncertainty and correct the error bounds of the estimated dose response. Future dose response analyses should include dose uncertainties in the analysis of ERR Gy^{-1}.

Most studies reviewed focused on external exposures from gamma radiation. Some of these studies also had components of external dose from neutrons and from internal exposures. The general practice followed in many studies has been to dismiss the dose from neutrons and internal dose because of the complexity and difficulty of estimating their contribution to dose. More effort should be given to exploring the impact of doses from neutrons and internal exposure.

In the future, better integration of the dosimetry and epidemiology both in the study design and implementation of the study should be achieved. When dosimetrists work closely with the epidemiologists, as in the case of the Atomic Veteran Study (Beck *et al*., 2017; Till *et al*., 2014) or the Techa River and Mayak studies (Fountos, 2016; Napier, 2014), doses and related uncertainty provided will more likely be in a form that is most useful for the dose analysis, and both groups will have a better understanding of the strengths and weaknesses of the dosimetry with respect to estimating a dose response. Integration of the dosimetry team with the epidemiologic team from the conceptual design through the implementation and documentation of any analysis of dose response is critical to the success of the effort.

8.3 DDREF: Future Directions

As noted above (Section 8.1.1), cancer risk estimates obtained in the LSS for survivors of the Japan atomic bombs are driven by medium-to-high, acute exposures. To predict effects at low doses and low dose rates, an extrapolation model (LNT) has been used together with a DDREF that adjusts the slope of the linear curve. The value of this DDREF used for radiation protection purposes ranges from about 1.5 (*e.g*., NA/NRC, 2006) to 2 (*e.g*., ICRP, 2007). The use of a DDREF has been debated extensively and the issue remains to be resolved. Further, it has been proposed that a separation of DDREF into a LDEF and a DREF more accurately reflects the extrapolation approach used (Rühm *et al*., 2015).

Without a LDEF the LNT model would be a simple linear extrapolation from medium-to-high dose to low dose. If a linear-quadratic curve is deemed to better fit the LSS cancer data (as has been proposed), then a shallower linear coefficient based on the low-dose cancer frequencies would be appropriate, which implies the incorporation of an LDEF. A recent paper by Haley *et al*. (2015) described a comprehensive analysis of 15 animal life span studies for acute and protracted exposures. The conclusions were that a linear-quadratic curve did not provide the best fit to the data sets (though there were few low-dose data) and that a direct comparison of data from

acute and protracted exposures was the preferred approach. It is considered that the question of applying an LDEF remains an open one because of a lack of pertinent data from human studies or animal and cellular studies.

Nevertheless, a DREF may be needed in the current risk estimation process, although the effect of dose rate on cancer risk has not been firmly established. However, a recently propounded view is that there is no dose rate effect per se for total cancers (*e.g.*, SSK, 2014). UNSCEAR handled this dilemma by proposing that the dose-response curve for cancers followed a linear-quadratic (LDEF; or a linear-quadratic-exponential) model, such that at low doses, where the linear component prevailed, there would be a DREF of 1 corresponding to the low-dose slope (UNSCEAR, 2008). A recent meta-analysis of solid cancers in worker and environmental studies with low dose rates found suggestive discrepancies in DREF estimates, depending on the inclusion/exclusion of two large studies (Shore *et al.*, 2017); future improvements in dosimetry and longer follow-up may reduce uncertainty in the value of DREF from epidemiologic studies.

It appears to be appropriate to separate the DDREF into its component parts, LDEF and DREF, for subsequent deliberations. It is recommended that a combined approach using low dose and low dose-rate epidemiology data together with information from animal experiments and informative bioindicators collected with human and animal models be employed to evaluate such factors (NCRP, 2015).

8.4 Key Events, Bioindicators and Risk Assessment: Future Directions

For estimating the cancer risks from exposure to environmental chemicals, the U.S. Environmental Protection Agency (EPA) has developed a mechanistic approach, in particular because human data are largely unavailable (EPA, 2005). More recently, this process has been enhanced through the inclusion of a so-called Adverse Outcome Pathway (AOP)/Key Event approach that incorporates data on key events as parameters in a Biologically-Based Dose- Response (BBDR) Model (Edwards *et al.*, 2016). An AOP "is a conceptual construct that portrays existing knowledge concerning the linkage between a direct molecular initiating event (*e.g.*, a molecular interaction between a xenobiotic and a specific biomolecule) and an adverse outcome at a biological level of organization relevant to risk assessment" (Ankley *et al.*, 2010). In this context, a Key Event is an empirically observable step, which is a necessary element of the mode of action critical to the outcome (*i.e.*, necessary, but not necessarily sufficient in its own right); key events are measurable and reproducible (Meek *et al.*, 2014). The characterization of AOPs and their associated key events is likely to require a concerted effort. However, it is a feasible task as demonstrated by the ongoing effort of the Organisation for Economic and Co-operation and Development (OECD, 2015). For radiation-induced adverse health outcomes, a clear need is to design research programs that are targeted towards a risk assessment framework that includes the identification of key events along the pathway to disease. Such key events

have been described as specific bioindicators of effect, in contrast to biomarkers that are surrogates for exposure (*e.g.*, chromosome alterations in peripheral blood) or that suggest an enhanced likelihood of disease outcome in a qualitative sense (*e.g.*, molecular alterations in nontarget tissues). Ultimately, the set of bioindicators that define the pathway from normal to malignant can be used for developing a specific BBDR model.

Recommendation: It is recommended, that in planning for new radiation biomarker studies, further consideration be given to using an adverse outcome pathway/key events approach to aid in the integration of epidemiology and radiation biology (NCRP, 2015). The aim will be to reduce uncertainty in risk assessments for low doses and low dose rates.

8.5 Other Future Direction Recommendations

Better characterization of doses to organs/tissues remote from sites of localized radiotherapy might permit a variety of new studies of radiation effects in the low-to-moderate dose range (Mazonakis *et al*., 2016; Xu *et al*., 2008), though characterizing the doses may be difficult.

Another area is background radiation. Continuing with the Kerala, India and Yangjiang, China HBRA studies is useful, but accurate dosimetry, complete and accurate diagnosis and cancer registration, and the elimination of confounding require more attention. Large numbers of cases are required (hundreds to thousands) to obtain reasonable power. Opportunities could be sought to link large historical registries of childhood cancer with dosimetric databases in regions where there is substantial variation in the ambient radiation exposure levels. Because the Kerala and Yangjiang studies are relatively recent and limited in numbers, large numbers of cancers are unlikely (*e.g.*, only ~30 cases of leukemia in the Kerala study and 15 in the Yangjiang study), so these studies would have to be conducted in other areas with well-established registries and sufficiently high doses. Such areas have not been identified at this time.

Long term opportunities for improvement include encouraging more widespread bio-banking in connection with epidemiologic studies. Information on new and as yet undiscovered biomarkers of radiation risk (rather than of exposure) of cancer or cardiovascular endpoints need to be explored as potential mediators or modifiers of radiation effects. Such studies could increase our understanding of the biology of radiation risk and have potential implications for personalized medicine. These could eventually be built into the statistical analysis of cancer risk at low doses. Analyzing epidemiologic data in conjunction with relevant radiobiological concepts and data also has the potential to provide insights into LNT that go beyond those gained from merely analyzing the empirical epidemiologic data in isolation (Eidemüller *et al*., 2015; Kaiser *et al*., 2016).

9. Conclusions

9.1 Overall Conclusion on Use of the LNT Model

While the ongoing development of science requires a constant reassessment of prior and emerging evidence to assure that the approach to radiation protection is optimal, though not necessarily perfect, NCRP concludes that, based on current epidemiologic data, the LNT model (perhaps modified by a DDREF) should continue to be utilized for radiation protection purposes. This is in accord with judgment by other national and international scientific committees, based on somewhat older data than in the present report (ICRP, 2007; NA/NRC, 2006; UNSCEAR, 2008), that no alternative dose-response relationship appears more pragmatic or prudent for radiation protection purposes than the LNT model.

9.2 Supporting Conclusions

This report has examined the evidence for or against the appropriateness of using LNT as a practical approach for managing radiation exposures to individuals. It is important to point out that there may be a DDREF involved that is greater than one, so that the LNT does not imply a single straight-line proportionality of effects from high, acute doses to low doses and/or low dose rates. Rather, low-dose or low dose-rate cumulative exposures may have a shallower linear slope than seen for high, acute doses.

Because individual studies with low doses (less than 100 mGy) almost inevitably have relatively low statistical power, the findings for radiation and solid cancer are often not statistically significant. Furthermore, studies may have sampling variation or confounding by other exposures (*e.g.*, smoking or other lifestyle factors) which can diminish the consistency or validity of findings. Nevertheless, most large and high quality low- dose studies show positive risk coefficients (Shore *et al*., 2017), suggesting there may be cancer effects at low doses, which is consistent with, though not necessarily proving, the applicability of the LNT model for radiation protection. However, it should be recognized that, the risk of cancer at low doses is small.

The most recent epidemiologic studies show that the assumption of a dose-threshold model is not a prudent pragmatic choice for radiation protection purposes. The consistency of the better-designed and larger studies with dose-response functions that are essentially linear or linear-quadratic, argues for some risk at low doses. Some studies explicitly found risk in the dose range of 100 mGy or less, *e.g.*, the atomic-bomb survivor studies, the INWORKS worker study, and the pooled radiation and thyroid cancer analysis. Several studies also performed

explicit dose-threshold analyses and found the estimates of dose thresholds to be compatible with zero dose (*i.e.*, no threshold).

The data regarding noncancer effects at low doses—cardiovascular diseases, cataracts, thyroid dysfunction, central nervous system effects—are mixed or null, suggesting at this time that an LNT assumption for radiation protection purposes for noncancer effects is not appropriate.

9.3 Radiation Protection Implications

While the LNT model is an assumption that likely cannot be scientifically validated by radiobiologic or epidemiologic evidence in the low-dose range, the preponderance of epidemiologic data is consistent with the LNT assumption, although there are a few notable exceptions. The current data are not precise enough to exclude other models, and there appears to be curvature in some datasets. The current judgment by national and international scientific committees is that no alternative dose-response relationship appears more pragmatic or prudent for radiation protection purposes than the LNT model on the basis of available data, recognizing that the risk below 100 mGy is uncertain but small (ICRP, 2007; NA/NRC, 2006; UNSCEAR, 2008).

When discussing the LNT model for radiation protection purposes UNSCEAR (2015) notes that "[t]his and the other dose-response relationships are plausible but currently none of them are definitively verifiable and therefore cannot be deemed proven or disproven." They further point out that while some have argued in support of a practical threshold for management of the risk of radiation-induced cancer, epidemiology alone will not be able to resolve the issue of whether there are dose thresholds for radiation risks, thus also supporting the need for further integrated radiobiology and epidemiology research (NCRP, 2015). Indeed, the LNT model, "…has practical advantages for radiation protection purposes in order to derive nominal radiation risk coefficients for a 'representative population'…[and are] coherent with radiobiological knowledge, epidemiologic information, and incorporate ethical judgments on the relative harm of different health effects" (UNSCEAR, 2015).

NCRP has carefully assessed the most currently available epidemiologic evidence and concludes that the LNT model (perhaps modified by a DDREF) should continue to be used for radiation protection purposes.

Glossary

acute radiation exposure: Radiation exposure received during a short time period (*e.g.*, hours).

angiography: The radiographic visualization of blood vessels following introduction of contrast material.

as low as reasonably achievable (ALARA**):** A principle of radiation protection philosophy that requires that exposures to ionizing radiation be kept as low as reasonably achievable, economic and societal factors being taken into account. The ALARA principle is satisfied when the expenditure of further resources would be unwarranted by the reduction in exposure that would be achieved.

cataract: A cataract is a clouding or opacification that occurs in the normally clear lens of the eye. Some cataracts are clinically unimportant and do not impair vision in any way. But, without intervention, cataracts remain the most common cause of blindness.

confidence interval (CI**):** A measure of the extent to which an estimate of risk, dose or other parameter is expected to lie within a specified interval (*e.g.*, a 95 % confidence interval of a risk estimate means that, based on available information, the probability is 0.95 that the true but unknown risk lies within the specified interval).

cornea: The transparent epithelial structure forming the anterior part of the external covering of the eye.

cortical cataract: Opacification that appears in the lens cortex. Associated with induction by both solar and ionizing radiation.

deoxyribonucleic acid (DNA**):** Genetic material of cells; a complex molecule of high molecular weight consisting of deoxyribose, phosphoric acid, and four bases which are arranged as two long chains that twist around each other to form a double helix joined by hydrogen bonds between the complementary components.

deterministic effects: Detrimental health effects for which the severity varies with the dose of radiation (or other toxic substance), and for which a threshold usually exists (*i.e.*, causally determined by preceding events). ICRP Publication 103 has restated this as: “Injury in a population of cells, characterized by a threshold dose and an increase in the severity of the reaction as the dose is increased further. In some cases, deterministic effects are modifiable by post-irradiation procedures including biological response modifiers.” It is common for deterministic effects to be termed tissue reactions.

detriment: Measure of stochastic effects from exposure to ionizing radiation that takes into account the probability of fatal cancers, probability of severe hereditary effects in future generations, probability of nonfatal cancers weighted by the lethality fraction, and relative years of life lost per fatal health effect.

dose: General term denoting the mean energy imparted from ionizing radiation to a tissue or organ from either an external source or from radionuclides in the body. When unspecified, dose refers to the quantity of absorbed dose, measured in gray (1 Gy = 1 J. kg–1) or rad (1 rad = 100 ergs g–1). Depending upon the context in which it is used, the generic term dose may also refer to equivalent dose, effective dose or other dose-related quantities.

dose limit: A limit on radiation dose that is applied for exposure to individuals in order to prevent the occurrence of radiation-induced deterministic effects or to limit the probability of radiation-induced stochastic effects to an acceptable level.

dose rate: Dose per unit time; often expressed as an average over some time period (*e.g.*, a year).

dosimetry: The science or technique of determining radiation dose.

effective dose: The sum of the weighted equivalent doses for the radiosensitive tissues and organs of the body. Each equivalent dose is modified by a tissue weighting factor that takes into account the relative radiation detriment for the tissue or organ. The tissue weighting factor for a particular tissue or organ represents the fraction of the total radiation detriment to the whole body attributed to that tissue when the whole body is irradiated uniformly. The tissue weighting factors have been developed from a reference population of equal numbers of both sexes and a wide range of ages. A similar quantity is effective dose equivalent (an earlier formulation of effective dose) that is also the sum of weighted doses for the radiosensitive tissues and organs of the body. These weighted doses (called dose equivalents) were also modified by tissue weighting factors (but an earlier set of factors different than used for effective dose). The SI unit of effective dose (and effective dose equivalent) is J. $kg^{-1}$with the special name sievert (Sv); 1 Sv = 1 J. kg^{-1} (see equivalent dose).

electrons: Subatomic charged particle. Negatively charged particles are parts of atoms. Both negatively and positively charged electrons may be expelled from a radioactive atom when it disintegrates.

equivalent dose: A quantity used for radiation protection purposes that takes into account the different probabilities of stochastic effects that occur with the same absorbed dose delivered by radiations with different radiation weighting factors (the factor by which the mean absorbed dose in a tissue or organ is modified to account for the type and energy of radiation in determining the probability of stochastic effects). The SI unit of equivalent dose is joule per kilogram (J. kg^{-1}), with the special name sievert (Sv) (see effective dose).

excess absolute risk: The excess risk attributed to exposure and usually expressed as the arithmetic difference between the incidence or mortality rate of disease among those exposed and that obtained in the absence of exposure. The resultant risk coefficient is usually normalized to a population base of 10,000 people and is expressed as the number of excess cases per 10,000 persons per gray (organ dose) per year at risk [*i.e.*, $(10^4 \text{ PY Gy})^{-1}$]. Absolute risk also may be presented on a lifetime (70 y) basis.

excess relative risk (ERR**):** Proportional excess risk above and beyond the baseline risk, defined as the relative risk (RR) minus one (ERR = RR – 1). It is usually stated as ERR per unit dose, *e.g.*, ERR Gy^{-1}, and is derived using a dose-response regression analysis.

exposure: Most often used in a general sense meaning to be irradiated. When used as the specifically defined radiation quantity, exposure is a measure of the ionization produced in air by x or gamma radiation. The unit of exposure is coulomb per kilogram (C kg^{-1}). The special unit for exposure is roentgen (R), where 1 R = 2.58×10^{-4} C kg^{-1}.

fluoroscopy (fluoro): The process of producing a real-time image using x rays. The machine used for visualization, in which the dynamic image appears in real time on a display screen is a fluoroscope.

fractionation: The delivery of a given total dose of radiation as several smaller doses, separated by intervals of time.

gamma radiation: Electromagnetic radiation emitted in de-excitation of atomic nuclei, and frequently occurring in decay of radionuclides. Also called gamma ray and sometimes shortened to gamma (*e.g.*, gamma-emitting radionuclides) (see photon and x ray).

genetic effects: Changes in reproductive cells that may result in detriment to offspring.

gray (Gy**):** The SI special name for the unit of the quantities absorbed dose and air kerma. 1 Gy= 1 J. kg^{-1}.

heritable effects: Changes in reproductive cells that may be passed on to offspring of persons or animals. Often called genetic effects (see genetic effects).

incidence: The rate of occurrence of a disease, usually expressed as number of cases per hundred-thousand individuals per year [or per 100,000 person-years (PY)].

ionization: The process by which a neutral atom or molecule acquires a positive or negative charge through the loss or gain of an orbital electron.

ionizing radiation: Any radiation capable of displacing electrons from atoms or molecules, thereby producing ions. Examples include alpha radiation, beta radiation, gamma or x rays, and cosmic rays. Minimum energy of ionizing radiation is a few electron volts (eV); 1 eV = 1.6×10^{-19} J.

irradiation: Exposure to ionizing or nonionizing radiation (see also exposure).

lifetime risk: The probability during one's lifetime of expressing a given health outcome.

LET: Linear-energy transfer, the average amount of energy lost per unit of particle track length and expressed in keV μm–1.

high-LET: Radiation having a high linear-energy transfer (*e.g.*, protons, alpha particles, heavy ions, and the interaction products of fast neutrons).

low-LET: Radiation having a low linear-energy transfer (*e.g.*, electrons, x rays, and gamma rays).

meta-analysis: In statistics evaluating epidemiologic studies, this comprises the use of statistical methods for contrasting and combining results from different studies reported in the literature in the hope of identifying patterns among study results, sources of disagreement among those results, or other interesting relationships that may come to light in the context of multiple studies.

neutrons: Particles with a mass similar to that of a proton, but with no electrical charge. Because they are electrically neutral, they cannot be accelerated in an electrical field.

noncancer: Health effects other than cancer (*e.g.*, cataracts, cardiovascular disease) that occur in the exposed individual.

occupational dose: The dose received by an individual in a restricted area, or in the course of employment in which the individual's duties necessarily involve exposure to radiation (medical doses involving diagnosis or treatment of the exposed individual that are not required as a condition of employment are excluded).

odds ratio (OR**):** The odds of a disease for a group is the number of people with the disease divided by the number in that group without the disease (call it pi/qi for group i). Then for two groups, i and j, the OR is (pi/qi)/(pj/qj), the ratio of the two sets of odds. The OR can be used in a case-control study where the relative risk (RR) method normally cannot be applied. With an assumption that the disease is fairly rare (in, say, a y's time), the odds ratio is a good estimate of the RR. With a continuous dose variable, rather than just two groups, the OR is usually modeled per unit dose using the logistic regression method.

photon: Quantum of electromagnetic radiation, having no charge or mass, that exhibits both particle and wave behavior, such as a gamma or x ray.

protons: The nucleus of the hydrogen atom. Protons are positively charged.

radionuclide: An unstable (*i.e.*, radioactive) nuclide. A species of atom characterized by the constitution of its nucleus (*i.e.*, the number of protons and neutrons) and the excess energy available in the unstable nucleus.

relative biological effectiveness (RBE**):** For a specific radiation (A), the ratio of absorbed dose of a reference radiation required to produce a specific level of response in a biological system to absorbed dose of radiation (A) required to produce an equal response. The reference radiation normally is x or gamma rays with an average linear energy transfer of 3.5 keV μm^{-1} or less. Relative biological effectiveness generally depends on dose, dose per fraction if the dose is fractionated, dose rate, and biological endpoint.

relative risk (RR**):** The ratio of the risk of a given disease in those exposed to the risk of that disease in those not exposed, usually expressed as a RR adjusted for ages and perhaps other factors.

risk: probability of harm, sometimes combined with potential severity of that harm.

risk coefficient: The increase in the annual incidence or mortality rate per unit dose: (1) absolute risk coefficient is the observed minus the expected number of cases per person y at risk for a unit dose, and (2) the relative risk coefficient is the fractional increase in the baseline incidence or mortality rate for a unit dose.

severe hazard: A hazard that has the potential to cause death, severe injury, or occupational illness, significant risk to the public, extensive environmental harm, or significant property damage.

severity: In the context of this Report, the quality or power of afflicting, distressing, or paining an individual or organ system from exposure to an environmental insult, such as ionizing radiation, that in the extreme would cause pain or anguish and possible clinical sequelae in the individual.

sievert (Sv**):** Special name for the SI unit of dose equivalent, equivalent dose, and effective dose. 1 Sv = 1 J. kg–1.

somatic effect: Biological effects (of radiation or otherwise) that occur in the exposed individual, as opposed to genetic (or heritable) effects which occur in the descendants of exposed individuals due to genetic mutations in the germline.

stochastic: Describes random events leading to effects whose probability of occurrence in an exposed population (rather than severity in an affected individual) is a direct function of dose; these effects are commonly regarded as having no threshold; cancer and hereditary effects are regarded as being stochastic.

tissue reaction (deterministic effect): Injury in populations of cells, characterized by a threshold dose and an increase in the severity of the reaction as the dose is increased further. In some cases, tissue reactions are modifiable by post-irradiation procedures including biological response modifiers (ICRP 2012).

Abbreviations, Acronyms and Symbols

ALARA	as low as reasonably achievable
AECL	Atomic Energy of Canada Limited
AHS	Adult Health Study (Radiation Effects Research Foundation)
ANSI	American National Standards Institute
AOP	adverse outcome pathway
ARS	acute radiation syndrome
BBDR	biologically-based dose response
BNFL	British Nuclear Fuels Limited
CVD	cardiovascular disease
CED	committed effective dose
CeVD	cerebrovascular disease
CI	confidence interval
CLL	chronic lymphocytic leukemia
CNS	central nervous system
CT	computed tomography
CV	coefficient of variation
CVD	cardiovascular disease
DDREF	dose and dose-rate effectiveness factor
DREF	dose rate effectiveness factor
DSB	double-strand break
EAR	excess absolute risk
ERR	excess relative risk
ESR	electron spin resonance
FISH	fluorescence *in situ* hybridization
HBRA	high background radiation area
INWORKS	International Nuclear Workers Study
LDEF	low dose effectiveness factor
LET	linear energy transfer
LNT	linear nonthreshold assumption or hypothesized model
LSS	Life Span Study of atomic-bomb survivors (Radiation Effects Research Foundation)
MWS	Million Workers Study
NDR	National Dose Registry (Canada)

NRRW	National Registry for Radiation Workers (United Kingdom) NTS Nevada Test Site
OR	odds ratio
RBE	relative biological effectiveness
RBM	red bone marrow
REL	recommended exposure limit
RR	relative risk
SIR	standardized incidence ratio
SMR	standardized mortality ratio
SNTS	Semipalatinsk Nuclear Test Site (Kazakhstan)
TBI	total body irradiation
TLD	thermoluminescence dosimeter/dosimetry
TMI	Three Mile Island

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