

**DOSE AND DOSE-RATE EFFECTIVENESS FACTORS
FOR LOW-LET RADIATION
FOR APPLICATION TO NIOSH-IREP**

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DEDICATION

The co-authors of this report dedicate this comprehensive review of the state of knowledge of DDREFs to the memory and legacy of its principal author, Dr. John R. Trabalka, whose untimely death on February 23, 2014, occurred prior to completion of the final manuscript. Dr. Trabalka's keen intellect, broad knowledge of radiation physics and biology, and relentless pursuit of relevant information were the driving forces behind this work.

ACRONYMS AND ABBREVIATIONS

AECL	Atomic Energy of Canada Limited
ALL	Acute lymphocytic leukemia
AML	Acute myelogenous leukemia; acute myeloid leukemia
ATB	At time of bombings (Hiroshima and Nagasaki)
ATM	Ataxia Telangiectasia Mutated (protein kinase)
BEIR	Biological Effects of Ionizing Radiation (Committee of National Research Council)
bp	Base pairs
CERRIE	Committee Examining Radiation Risks of Internal Emitters (U.K.)
CI	Confidence interval
CIRRPC	Committee on Interagency Radiation Research and Policy Coordination
CLL	Chronic lymphocytic leukemia
CML	Chronic myelogenous leukemia; chronic myeloid leukemia
CT	Computed tomography
d	Day
DDREF	Dose and dose-rate effectiveness factor
DHHS	U.S. Department of Health and Human Services
DNA	<u>D</u> eoxyribo <u>n</u> ucleic <u>a</u> cid
DOE	U.S. Department of Energy
DREF	Dose-rate effectiveness factor
DS02	Dosimetry System 2002 (Japanese atomic-bomb survivors)
DS86	Dosimetry System 1986 (Japanese atomic-bomb survivors)
DSB	Double-strand break
EAR	Excess absolute rate
EEOICPA	Energy Employees Occupational Illness Compensation Program Act
EPA	U.S. Environmental Protection Agency
EPRI	Electric Power Research Institute
ERR	Excess relative risk
eV	Electron volt
FISH	Fluorescence <i>in situ</i> hybridization
G	Giemsa (G-band, G-banding)
GM	Geometric mean
GSD	Geometric standard deviation

Gy	Gray
h	Hour
HM	Harmonic mean
hgp _{rt}	<u>H</u> ypoxanthine- <u>g</u> uanine <u>p</u> hosphor <u>o</u> bosyl <u>t</u> ransferase
HPA	Health Protection Agency (U.K.)
HPRT	<u>H</u> ypoxanthine <u>p</u> hosphor <u>o</u> bosyl <u>t</u> ransferase
HR	Homologous recombination
IAEA	International Atomic Energy Agency
IARC	International Agency for Research on Cancer
ICRP	International Commission on Radiological Protection
ICRU	International Commission on Radiation Units and Measurements
INWORKS	<u>I</u> nternational <u>N</u> uclear <u>W</u> ORK <u>E</u> rs <u>S</u> tudy
IREP	<u>I</u> nteractive <u>R</u> adio <u>E</u> pidemiological <u>P</u> rogram
kerma	Kinetic energy released per unit mass
kVp	Peak kilovoltage (x-ray tubes)
LD ₅₀	Lethal dose from ingestion in 50% of test sample
LDEF	Low-dose effectiveness factor
LET	Linear energy transfer
LNT	Linear no-threshold (dose-response model)
LQ	Linear-quadratic (dose-response model)
LQE	Linear-quadratic-exponential (dose-response model)
LSS	Life Span Study (Japanese atomic-bomb survivors)
mFISH	Multifluor fluorescence <i>in situ</i> hybridization
min	Minute
MLE	Maximum likelihood estimate
nc	Non-coding
NCRP	National Council on Radiation Protection and Measurements
NHEJ	Non-homologous end-joining
NIH	National Institutes of Health
NIOSH	National Institute for Occupational Safety and Health
NRC	National Research Council
NRPB	National Radiological Protection Board (U.K.)
NRRW	National Registry for Radiation Workers (U.K.)
ORNL	Oak Ridge National Laboratory

P	P-value: probability of obtaining result equal to or more extreme than actually observed, assuming that null hypothesis is true
PC/AS	Probability of causation/assigned share
RBE	Relative biological effectiveness
RBE _M	Maximal RBE at low doses
REF	Radiation effectiveness factor
REF _L	REF at low doses or low dose rates
RERF	Radiation Effects Research Foundation (Hiroshima, Japan)
RNA	<u>R</u> ibon <u>a</u> nucleic <u>a</u> cid
RR	Risk ratio
SE	Standard error
SSA	Single-strand annealing
Sv	Sievert
TRDS	Techa River Dosimetry System
UNSCEAR	United Nations Scientific Committee on the Effects of Atomic Radiation
UV	Ultraviolet (radiation)
y	Year

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EXTENDED SUMMARY

INTRODUCTION

This report describes a study for The National Institute for Occupational Safety and Health (NIOSH) to re-evaluate dose and dose-rate effectiveness factors (DDREFs) for low-LET radiation (photons and electrons) that are incorporated in cancer risk models in the Interactive RadioEpidemiological Program (IREP). The objective of this study was to develop recommendations that provide unbiased representations of the current state of knowledge of DDREFs for low-LET radiation.

NIOSH uses IREP to estimate the probability of causation/assigned share (PC/AS)¹ of diagnosed cancers in nuclear energy workers who were exposed to ionizing radiation. IREP estimates PC/AS of a diagnosed cancer in an individual with known radiation exposures as $PC/AS = ERR/(ERR + 1)$, where ERR is the excess relative risk of incidence of the individual's cancer type associated with the known exposures. Models to estimate risks (ERRs) of cancer incidence in IREP are based primarily on studies of Japanese atomic-bomb survivors [the Life Span Study (LSS) cohort] who received an acute exposure mainly to high-energy photons, with a small contribution from neutrons, at doses to the colon up to about 4 Gy.² DDREFs are incorporated in cancer risk models in IREP to account for the possibility that the effectiveness of low-LET radiations in inducing cancer in humans at low doses or low dose rates differs from the effectiveness of those radiations at high doses and high dose rates.

As in all recent analyses of cancer risks in the LSS cohort, assumptions in IREP about DDREFs for solid cancers and the dependence of risks of solid cancers on dose differ from the assumptions for leukemias. Risks of solid cancers from exposure to low-LET radiation are estimated in IREP by assuming a linear, no-threshold (LNT) dose-response model modified by a DDREF. The risk of a solid cancer per unit dose at low doses or low dose rates of low-LET radiation, R_L , is estimated as $R_L = R_H/DDREF$, where R_H is the risk per unit dose at high doses and high dose rates, as estimated primarily on the basis of fits to dose-responses in the LSS cohort assuming an LNT model. Two DDREFs for solid cancers are used in

¹ The version of IREP used by NIOSH refers to the estimated probability that a diagnosed cancer in an individual was caused by exposure to ionizing radiation as "probability of causation," whereas the working group that developed IREP (Land et al. 2003a) preferred the term "assigned share" to indicate that the quantity calculated in IREP (1) is based on estimates of cancer risks obtained from epidemiological studies of exposed populations and (2) is a property of the population group to which an individual belongs that is assigned to that individual but may not be the true probability that an individual's cancer was caused by known radiation exposures.

² Doses to members of the LSS cohort are neutron-weighted doses, which usually are calculated as the sum of the absorbed dose from photons and 10 times the absorbed dose from neutrons to account for the greater biological effectiveness of neutrons in inducing cancer in humans at high acute doses. The highest neutron-weighted doses to some organs (e.g., bone marrow, breast, thyroid) exceeded 4 Gy.

IREP, one for breast and thyroid cancers and one for all other solid cancers. Both DDREFs are described by probability distributions to represent their uncertainty (Land et al. 2003a).

In contrast to the approach to estimating risks of solid cancers, a DDREF is not used explicitly in IREP in estimating risks of leukemias from exposure to low-LET radiation. In cases of acute exposure to low-LET radiation, risks of leukemias are estimated by assuming a linear-quadratic (LQ) dose-response model, which incorporates a DDREF >1 implicitly. In an LQ model, the risk, \mathfrak{R} , from acute exposure at dose D (Gy) is estimated as $\mathfrak{R} = \alpha D + \beta D^2$, where α (Gy⁻¹) and β (Gy⁻²) are the model coefficients. With this assumption, DDREF = R_H/R_L is a dose-dependent quantity given by $(\alpha + \beta D)/\alpha = 1 + (\beta/\alpha)D$, where the quantity β/α , referred to as the curvature parameter, represents the extent to which the dose-response departs from linearity. In estimating risks of all leukemias (excluding chronic lymphocytic leukemia, CLL) or specific types of leukemia in IREP, the coefficients α and β in the LQ dose-response models are assumed to be equal, so that, for example, DDREF is about 2 at an acute dose of 1 Gy.³

In cases of chronic exposure to low-LET radiation, a DDREF is applied in IREP in estimating risks of solid cancers at any total dose. In cases of acute exposure, a DDREF is applied in estimating risks of solid cancers only at doses below an uncertain dose, D_L , in the range of 30–200 mGy. This range was intended to represent the uncertainty in radiobiological and epidemiological data that could be used to define a “low” acute dose, i.e., an acute dose below which a DDREF should be applied. At acute doses of low-LET radiation less than 30–200 mGy, the DDREFs for solid cancers in IREP are assumed to vary smoothly with dose, starting from the value 1 with no uncertainty at dose D_L and reaching 99.9% of the DDREF for chronic exposure at a dose of about 1 mGy. In estimating risks of leukemias, the LQ model described above is assumed to apply in all cases of acute exposure (i.e., at any dose), and only the linear term in the modeled dose-response for acute exposure is assumed to apply in cases of chronic exposure.

The main purpose of this study was to evaluate the scientific basis for developing DDREFs and to provide NIOSH with a recommendation on revising the probability distributions of DDREFs for solid cancers in IREP. More generally, our intent was to develop a probability distribution of a DDREF for solid cancers that could be used in any cancer risk assessments that account for uncertainty. We also evaluated the adequacy of the LQ dose-response model for all leukemias (excluding CLL) and specific types of leukemia in IREP and application of the LQ model to chronic as well as acute exposures. This study involved a comprehensive review of microdosimetric, radiobiological, and epidemiological data on low-dose and low-dose-rate extrapolations of cancer risks associated with exposure to low-LET radiation.

³ In modeling risks of leukemias in the LSS cohort, the LQ dose-response model is of the form $\alpha(D_\gamma + 10D_n) + \beta D_\gamma^2$, where D_γ and D_n are the absorbed doses from photons and neutrons, respectively, and the dose-response from neutrons (high-LET radiation) is assumed to be linear. The weighted dose from neutrons ($10D_n$) is small compared with the dose from photons and has little effect on the dependence of the implicit DDREF on dose.

USE OF LINEAR-QUADRATIC DOSE-RESPONSE MODEL TO ESTIMATE DDREFS

Use of a DDREF in estimating cancer risks at low doses or low dose rates of low-LET radiations has been based mainly on an assumption that the dose-response from acute exposure to those radiations is inherently LQ in form, even when dose-responses for cancer in humans appear to be essentially linear. This assumption was based largely on acute dose-responses for various endpoints in cells, especially induction of dicentric chromosome aberrations, that appeared to be LQ in form. Since the response per unit dose in an LQ model decreases with decreasing dose, there was a perceived need to apply a reduction factor in estimating cancer risks in humans using a linear dose-response model at doses in the essentially linear (low-dose) region of an LQ model that are below limits of epidemiological detection (e.g., at doses to the colon less than about 100 mGy for all solid cancers the LSS cohort). As noted above, an LQ model with an implicit DDREF >1 is often used to represent an observed non-linearity in the dose-response for all leukemias in the LSS cohort. Although dose-responses for solid cancers in the LSS cohort usually can be described by a linear model, an LQ model is often used to assess possible departures from linearity for the purpose of estimating a DDREF. However, a DDREF can be estimated for any functional form of a dose-response relationship; an assumption of an LQ dose-response model is not required.

Since microdosimetric considerations imply that the initial radiation damage at very low doses should be independent of dose rate, a DDREF that is estimated by analyzing possible non-linearities in acute dose-responses using an LQ model usually is assumed to represent a reduction in risks per unit dose at low dose rates as well. However, results from various radiobiological studies have suggested that the effects of dose protraction may not be adequately represented by a DDREF that is derived by assuming an LQ dose-response model for acute exposures and, further, that an LQ dose-response may not be a universal expectation for radiation carcinogenesis in either laboratory animals or humans.

The basis for estimating a DDREF, especially the use of DDREFs that are derived from analyses of the curvature in acute dose-responses assuming an LQ model, is called into question by recent developments in radiation cytogenetics. Studies of chromosome aberrations using multifluor fluorescence *in situ* hybridization (mFISH) indicated that most of the curvature in acute dose-responses that could be represented by an LQ model when aberrations were scored using conventional Giemsa staining was due to the competing influences of multiple endpoints with different dose-response relationships, none of which is LQ in form, rather than the curvature in an LQ dose-response for a single endpoint. Studies of chromosome aberrations using mFISH also showed that the apparently linear dose-response for simple aberrations depended on dose rate; i.e., the response per unit dose from chronic exposure was substantially less than the response per unit dose from acute exposure, contrary to expectations based on an LQ model that a linear dose-response should not depend on dose rate.

A significant dependence on dose rate also was observed in some studies of cancer induction and life-span shortening in laboratory animals in which the dose-response from acute exposure appeared to be linear. Other studies of cancer induction in animals showed more complex dose-responses, such as U- or J-shaped dose-responses or a concave downward curvature at lower doses that suggested a supralinear dose-response ($DDREF < 1$). These results do not conform to expectations based on an LQ model.

We think that results from studies in cells and laboratory animals described above indicate that a $DDREF$ for cancer in humans should not be estimated based solely on an analysis of non-linearities in dose-responses from acute exposure, such as an analysis of the curvature in dose-responses in the LSS cohort assuming an LQ model. Results from studies in cells and animals indicate that comparisons of dose-responses from acute and chronic or protracted exposures also should be taken into account.

UNCERTAINTY IN LOW-DOSE RESPONSES DUE TO COMPLEXITY OF BIOLOGICAL SYSTEMS AND RESPONSE MECHANISMS

It is generally recognized that induction of cancer by ionizing radiation is initiated by damage to cellular DNA, especially DNA double-strand breaks. However, studies of various phenomena reviewed in this report indicate that radiation carcinogenesis in humans is a complex, multistage process that may not be adequately represented by an LQ dose-response model that is essentially linear at low doses.

Biophysical arguments for the LNT hypothesis at low doses are plausible only if single cells that are genetically altered by radiation act autonomously to produce a cancer. However, those arguments were developed largely without knowledge of epigenetic factors, intercellular interactions, and homeostatic mechanisms that appear to play a significant role in radiation carcinogenesis. Current information also indicates that a tumor is a heterogeneous population of cells, with differing tumorigenic and metastatic potentials, not a homogeneous clone that is derived from a mutation or chromosome aberration induced in a single cell, as implied by biophysical arguments for an LNT model.

RECENT CHALLENGES TO LNT MODEL

The importance of cellular and tissue- or organ-level responses to radiation *in vivo* and the extent to which those responses and their outcomes are different at low doses than at high doses is the subject of considerable debate and research at the present time. The assumption of an inherently LQ dose-response for low-LET radiation, with an essentially linear response at low doses or low dose rates and an implied $DDREF > 1$, has been challenged in many ways.

Some investigators (e.g., UNSCEAR 2008) cited results from a variety of studies, including modeling of data in the LSS cohort and results from epidemiological studies involving chronic exposure,

as evidence for linearity in the dose-response for cancer over a large dose range, with no reduction in risks at low doses or low dose rates (DDREF \equiv 1). Others (e.g., Little et al. 1999; UNSCEAR 2000) argued that the dose-response for some cancer types may have a threshold (DDREF = ∞). Still others (e.g., Snyder 2003; Hooker et al. 2004) believe that the LQ model underestimates risks at low doses, based on observations of bystander effects, inverse dose-rate effects, and suggestions of supralinearity in dose-responses in some epidemiological studies (DDREF $<$ 1), and that use of a DDREF $>$ 1 with an LNT model serves to exacerbate an underestimation of cancer risks. Proponents of hormesis (e.g., Calabrese and Baldwin 2001, 2003; Feinendegen 2005) cite evidence that there are beneficial effects of radiation exposure at low doses or low dose rates, including a reduction of adverse health effects. The French national academies (Aurengo et al. 2005) rejected the biophysical argument for the LNT hypothesis and argued that different biological mechanisms are active at low doses, such that the LNT model greatly overestimates risks at doses of low-LET radiation $<$ 100 mGy and even more so at doses $<$ 10 mGy.

Our re-evaluation of DDREFs currently used in IREP assumes that an LNT dose-response model for cancer will continue to be used in IREP and other cancer risk assessments. However, recent data on adaptive responses, non-targeted and delayed effects (e.g., bystander effects, genomic instability), and other phenomena raise the possibility that the form of the dose-response at low doses or low dose rates is highly uncertain, and that a simple linear extrapolation from higher doses, even including a DDREF, may not be appropriate. Although basic knowledge of these phenomena is increasing rapidly, the extent to which they affect cancer induction in humans at low doses remains largely a matter of speculation. A better understanding of the underlying mechanisms, the extent to which they are active *in vivo*, and how they are interrelated is needed before they can be incorporated quantitatively into methods of estimating cancer risks in humans at low doses or low dose rates. We think that this lack of understanding leads to a greater uncertainty in DDREFs than is represented by probability distributions derived from an analysis of dose-responses from acute exposure in the LSS cohort.

GENERAL CONSIDERATIONS IN RE-EVALUATING DDREFS IN IREP

A re-evaluation of the probability distributions of DDREFs for solid cancers currently used in IREP is worthwhile when the uncertainty in a DDREF is often one of the largest contributors to uncertainty in estimates of cancer risks and PC/AS at low doses or low dose rates. If dose-responses that are modeled on the basis of data in the LSS cohort were fully representative of cancer risks at low doses (e.g., $<$ 10 mGy) and low dose rates, a DDREF might not be needed, given that most investigators concluded that there is little evidence for a departure from linearity in dose-responses for most solid cancers in the LSS cohort.

However, estimated risks of solid cancers at low doses based on analyses of data in the LSS cohort have large uncertainties, such that the slope of modeled risks at low doses is significantly greater than zero only when data in groups of survivors with doses to the colon up to 125–250 mGy are pooled. And, contrary to expectations based on an LNT model, the modeled risk based on data over this dose range may be higher than an estimated risk based on data over a wider dose range (e.g., 0–2 or 0–4 Gy), which suggests a supralinear dose-response at the lowest doses (DDREF <1). The unresolved question is whether the apparently linear dose-responses for most solid cancers in the LSS cohort over these wider dose ranges could still conceal some degree of dependence on dose or dose rate (e.g., a supralinear response) or justify the application of a DDREF >1 at low dose rates, if not at low acute doses.

To some extent, this question is related to the issue of how a low dose or low dose rate should be defined. As part of this study, microdosimetric, radiobiological, and epidemiological data that could be used to define a dose or dose rate below which a DDREF should be applied were reviewed. The available data suggest that the upper limit of the log-uniform probability distribution of the uncertain parameter D_L that is used in IREP to determine when a DDREF is applied in estimating cancer risks from acute exposure to low-LET radiation should be maintained at 200 mGy, but that the lower limit should be reduced from 30 to 10 mGy; i.e., a “low” acute dose should be defined as any dose less than an uncertain value D_L in the range of 10–200 mGy.

A parameter to represent uncertainty in defining a low dose rate from exposure to low-LET radiation, similar to the uncertain parameter D_L to represent the upper limit of a low acute dose, is not used in IREP. We think that available data do not support the development a probability distribution to represent uncertainty in the dose rate below which a DDREF should be applied. An exposure often is considered to be chronic when the dose rate averaged over a period of a few hours is less than 6 mGy h⁻¹.

The term “DDREF” embodies two distinct concepts: (1) a low-dose effectiveness factor (LDEF), which is estimated by analyzing possible non-linearities in dose-responses from acute exposure, such as a dose-response for solid cancers in the LSS cohort; and (2) a dose-rate effectiveness factor (DREF), which is estimated by comparing dose-responses from acute and chronic or protracted exposures. Most epidemiological data that have been used to estimate a DDREF, such as dose-responses in the LSS cohort, provide estimates of an LDEF. However, comparisons of dose-responses in populations that received chronic or protracted exposures (e.g., radiation workers or medical patients) with dose-responses in the LSS cohort can provide estimates of a DREF. Since microdosimetric and other theoretical considerations imply that radiation effects at doses of about 0.1–1 mGy or less should be independent of dose rate, the separate concepts of an LDEF and a DREF usually have been combined into a DDREF. Nonetheless, we have distinguished between LDEFs and DREFs in evaluating radiobiological and epidemiological data.

EVALUATIONS OF DATA TO ESTIMATE DDREFS

Evaluations of Data from Radiobiological Studies

As part of this study, data on radiation dose-responses in cells and laboratory animals that might be relevant to estimating DDREFs for cancer in humans were evaluated.

Genetic and cytogenetic data. We reviewed data on the dependence of radiation dose-responses on dose and dose rate from studies of genetic and cytogenetic endpoints, including somatic mutations, cell transformation, and a variety of chromosomal aberrations. Although these model systems often are considered to be simple, interpretation of the data can be difficult. More importantly, it is questionable whether data for various endpoints in cells can be extrapolated to cancer induction in humans.

Most LDEFs and DREFs based on dose-responses for genetic and cytogenetic endpoints are in the range of 1–10. However, some data suggest values <1 or >10 including ∞ from potentially hormetic or apparently threshold responses.⁴ A central estimate suggested by these data is in the range of about 2–6.

Use of data in cells to estimate a DDREF is based on biophysical (e.g., microdosimetric) arguments for the validity of an LNT model at doses below those at which statistically significant responses have been observed in humans. Although these arguments are considered to be plausible by many expert groups, they depend on assumptions about the ability of single cells to act autonomously in producing a cancer, assumptions which are now questionable.

Cancer induction in animals. Data on induction of several cancer types in laboratory animals exhibit varied dose-responses, most commonly linear, LQ, or threshold but also including supralinear or hormetic responses. Apparent thresholds typically occur when certain organs or tissues are targeted (e.g., bone, lung, or skin). Interpretation of dose-responses in animals (and humans as well) is often complicated by the use of different energies of low-LET radiations in different studies (e.g., ⁶⁰Co gamma rays or 180–250 kVp x rays) and an uncertain dependence of the biological effectiveness of low-LET radiations on energy. The frequent assumption that high-energy gamma rays and lower-energy x rays have the same biological effectiveness does not conform to the current state of knowledge.

The most abundant data from studies in laboratory animals are DREFs for a variety of solid tumors and hematopoietic cancers in rodents. Consideration of the effects of dose rate and dose fractionation on dose-responses expands the range of plausible values of a DDREF compared with using estimates derived from analyses of acute dose-responses only.

⁴ A DDREF for a potentially hormetic response (i.e., a response that falls below the level of controls) should have a finite, negative value. However, since risk coefficients (ERRs per unit dose) in IREP are constrained to be ≥ 0 based on the assumption of an LNT model, we assigned a DDREF of ∞ to represent hormetic or threshold dose-responses. An apparent threshold in a dose-response may not mean that there is a dose below which there is no response.

Data in laboratory animals have several disadvantages, however. For a variety of biological and methodological reasons, DDREFs derived from studies in animals vary greatly and are difficult to relate to cancer induction in humans, even when analyses are restricted to data on tumor types relevant to humans. The range of ages at exposure that have been studied is limited, and there are concerns about extrapolating responses in laboratory animals to humans (e.g., because of genetic differences and the genetic uniqueness of highly inbred animal strains). Some dose-responses are complex and difficult to interpret. In particular, effects of cell sterilization and hormonal influences appear to be important for some cancer types. Although DREFs for osteosarcomas can be estimated from studies of protracted exposures in beagle dogs, dose-responses exhibit thresholds, which limits their utility compared with most of the other data on DREFs for which central estimates and confidence intervals are finite.

As discussed previously, risks of leukemias (excluding CLL) from exposure to low-LET radiation are estimated in IREP by assuming an LQ dose-response model under conditions of acute or highly fractionated exposures or a linear model under conditions of chronic or protracted exposures. On the whole, however, data from studies of leukemias in laboratory animals do not appear to provide support for an LQ dose-response from acute exposures or a linear dose-response at low dose rates.

Life shortening in animals. Although life shortening in animals at low-to-intermediate doses (<3 Gy) and low dose rates is predominantly attributable to an accumulation of malignancies, we concluded that, with the exception of studies noted in the summary below, data on dose-responses for this endpoint should not be considered for use in estimating DDREFs for solid cancers. The range of central estimates of DREFs (about 1–13) based on dose-responses for life shortening in laboratory animals is similar to the range based on studies of cancer induction in animals. However, the spectrum of tumor types induced by protracted exposures in laboratory animals (e.g., mice) at low dose rates is different from the spectrum of tumor types induced by acute exposures. More hematopoietic cancers, which occur earlier and exhibit a higher level of lethality than solid tumors, are induced by acute exposures, whereas protracted low-dose-rate exposures of mice yield more lymphomas and ovarian tumors later in life, with much less loss of life span. In addition, not all tumors are a cause of life shortening in animals or humans. Thus, we concluded that DREFs derived from analyses of dose-responses for life shortening in laboratory animals have limited utility for the purpose of estimating a DDREF for solid cancers.

Summary of data from studies in animals. Most DDREFs based on analyses of dose-responses for solid tumors in laboratory animals are in the range of 1–15. However, some analyses indicate a DDREF <1 and others indicate a DDREF of ∞ from threshold or potentially hormetic responses. A central estimate based on those analyses appears to be in the range of about 2–4. A DDREF of 1, which is at the lower end of the range of values, was estimated in studies of life shortening in which mortality due to leukemias and thymic lymphomas was excluded. In studies of bone cancer from protracted internal

exposures of dogs and mice to beta-emitting radionuclides, estimated lower limits on a DDREF in cases of non-zero responses that exhibited a threshold are in the range of $7 \geq 18$. In a study of non-melanoma skin cancers from highly fractionated exposures in mice that also exhibited a possible threshold in the dose-response, an estimated lower limit on a DDREF is about 30.

Evaluations of Data from Epidemiological Studies

Radioepidemiological data on several types of cancers in humans can be used to estimate DDREFs. In this study, we evaluated data on dose-responses for all solid cancers as a group (incidence and mortality), female breast cancer (incidence and mortality), thyroid cancer (incidence), lung cancer (incidence and mortality), skin cancers (incidence), and leukemias (incidence and mortality). Data on bone cancer also were considered but were judged to be uninformative, due to the small number of cases in the LSS cohort (Preston et al. 2007) and lack of statistical significance of a dose-response in workers at the Mayak complex in Russia (Sokolnikov et al. 2008).

Although dose-responses for many solid cancers in the LSS cohort and in radiation workers or medical patients are approximately linear, interpretation of some dose-responses is not straightforward. Some dose-responses for solid cancers in the LSS cohort show the effects of cell sterilization in reducing risks per unit dose at the highest doses. This effect is represented by a dose-response model of the form $\mathfrak{R} = (\alpha D + \beta D^2) \exp(-\gamma D)$. Hormonal influences appear to be important in interpreting the dependence of dose-responses for female breast cancer on age. Accounting for the interaction of smoking and radiation is important in estimating risks of lung cancer. Dose-responses for incidence of non-melanoma skin cancers and basal cell carcinoma in the LSS cohort clearly are non-linear. A threshold dose-response (an LDEF of ∞) cannot be excluded on the basis of data on leukemia mortality (excluding CLL) in the LSS cohort or data on lung cancer mortality in tuberculosis fluoroscopy cohorts. UNSCEAR (2008) concluded that dose-responses for incidence of non-melanoma skin cancers and bone cancer in the LSS cohort are best represented by quadratic models, which incorporate an LDEF that approaches ∞ as the dose and dose rate approach zero. UNSCEAR (2008) also suggested that a quadratic dose-response model with an exponential cell-sterilization term may best describe leukemia mortality in the LSS cohort. Recent analyses of data in the LSS cohort (Richardson et al. 2009; Hsu et al. 2013) indicated that the apparently LQ dose-response for all leukemias (excluding CLL) is an artifact of combining an essentially quadratic dose-response for acute myeloid leukemia (AML) with approximately linear dose-responses for chronic myeloid leukemia (CML) and acute lymphocytic leukemia (ALL). Finally, uncertainties in the biological effectiveness of neutrons (high-LET radiation), for which dose-responses should be linear, can affect estimates of the curvature in dose-responses for solid cancers or leukemias in the LSS cohort, and

uncertainty in doses from neutrons and alpha particles can affect modeling of dose-responses from exposure to low-LET radiations in some radiation workers.

On the basis of an assumption that linear dose-response models for solid cancers modified by a DDREF and an LQ dose-response model for all leukemias, which incorporates a dose-dependent DDREF implicitly, would continue to be used in IREP and other cancer risk assessments, epidemiological data for solid cancers and leukemias were evaluated separately in this study.

Evaluation of data for solid cancers. We evaluated a variety of data from epidemiological studies that can be used to estimate DDREFs for solid cancers. Those studies provided data to estimate LDEFs for incidence or mortality from all solid cancers or specific solid cancers, which usually were based on analyses of the curvature in dose-responses in the LSS cohort assuming an LQ model, or data to estimate DREFs for incidence or mortality from all solid cancers or specific solid cancers, which were based on comparisons of risks to radiation workers, medical patients, or members of the public that received chronic or protracted exposures with risks from acute exposure in the LSS cohort.

DDREFs for all solid cancers or specific solid cancers that we derived from results of selected epidemiological studies are shown in Figure ES.1; central values are estimated 50th percentiles, and uncertainties are 90% subjective confidence intervals (CIs). LDEFs and DREFs for all solid cancers in the top portion of Figure ES.1 were included in our analysis to estimate a DDREF for low-LET radiation. Those LDEFs and DREFs and their bases are summarized in Table ES.1.

LDEFs and DREFs for all solid cancers shown in Figure ES.1 and given in Table ES.1 were derived from results of studies of the LSS cohort in which dose-responses were analyzed using the DS02 dosimetry system and neutron-weighted doses to the colon assuming a neutron RBE of 10; the previous DS86 dosimetry system with an assumed neutron RBE of 10 or 20 was used in several studies that were used to derive cancer-specific LDEFs or DREFs. Except for one analysis in which an LDEF for mortality from all solid cancers was based on estimates of excess absolute rates (EARs) in the LSS cohort, LDEFs or DREFs for all solid cancers were based on estimated ERRs in the study populations. LDEFs, DREFs, or DDREFs for breast and thyroid cancers were based on estimated ERRs and EARs, whereas LDEFs for lung and skin cancers were based on estimated ERRs only. Except for the LDEFs for skin cancers, LDEFs were based on estimates of the curvature in an acute dose-response assuming an LQ model.

The following points about some of the estimates in Figure ES.1 should be noted.

- The LDEFs for solid cancer incidence or mortality are based on the most recent analyses of data in the LSS cohort by various expert groups. Results from an analysis of solid cancer mortality based on DS02 dosimetry at RERF by Preston et al. (2004) are not included based on a judgment that those results are superseded by results from analyses, also at RERF, by Ozasa et al. (2012).

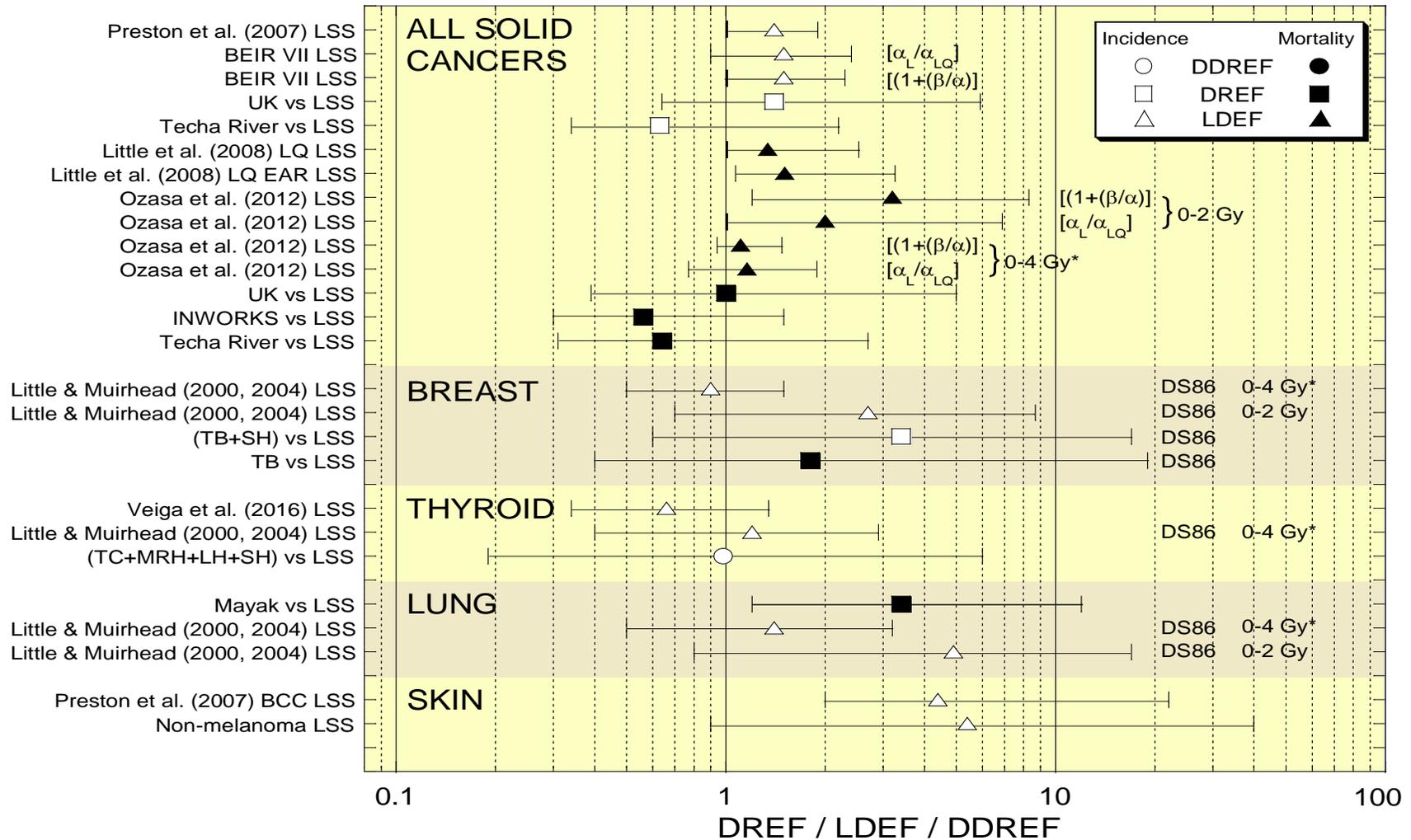


Figure ES.1. Estimates of 50th percentiles and 90% CIs of DREF, LDEF, or DDREF for all solid cancers or specific solid cancers based on selected epidemiological studies. Estimates are based on modeled ERRs and DS02 dosimetry in LSS cohort, except as noted. UK = United Kingdom workers; INWORKS = International Nuclear Workers Study; TB = tuberculosis fluoroscopy cohort; SH = skin hemangioma cohort; TC = tinea capitis cohort; MRH = Michael Reese Hospital cohort; LH = lymphoid hyperplasia cohort; BCC = basal cell carcinoma; * range of shielded kerma from photons and neutrons (neutron-weighted doses to colon for all solid cancers or identified organ otherwise).

Table ES.1. Estimates of 50th percentiles and 90% CIs of LDEFs and DREFs for all solid cancers included in analysis to develop probability distribution of DDREF

Factor	Estimate	Description
LDEF, incidence ^a	1.5 (0.9, 2.4) ^b	Calculated as α_L/α_{LQ} or $[1 + (\beta/\alpha)D]$ at 1 Gy based on analysis by BEIR VII committee (NRC 2006) of ERRs in LSS cohort at colon doses of 0–1.5 Gy
	1.5 (1.0, 2.3)	
	1.4 (1.0, 1.90)	Calculated as $[1 + (\beta/\alpha)D]$ at 1 Gy based on analysis by Preston et al. (2007) of ERRs in LSS cohort at colon doses of 0–2 Gy
LDEF, mortality ^a	1.34 (1.01, 2.53)	Calculated as $[1 + (\beta/\alpha)D]$ at 1 Gy based on analyses by Little et al. (2008) of ERRs or EARs in LSS cohort at colon doses corresponding to shielded kerma of 0–4 Gy
	1.51 (1.07, 3.26)	
	3.2 (1.2, 8.3) ^c	Calculated as $[1 + (\beta/\alpha)D]$ at 1 Gy or α_L/α_{LQ} based on analysis by Ozasa et al. (2012) of ERRs in LSS cohort at colon doses of 0–2 Gy
	2.0 (1.0, 6.8)	
	1.11 (0.94, 1.48)	
1.16 (0.77, 1.90)	Calculated as $[1 + (\beta/\alpha)D]$ at 1 Gy or α_L/α_{LQ} based on analysis by Ozasa et al. (2012) of ERRs in LSS cohort at colon doses corresponding to shielded kerma of 0–4 Gy	
DREF, incidence ^d	1.4 (0.64, 5.9)	Based on analyses of ERRs in U.K. radiation workers by Muirhead et al. (2009) and ERRs in LSS cohort by Jacob et al. (2009)
	0.63 (0.33, 2.2)	Based on analyses of ERRs in Techa River cohort by Davis et al. (2015) and ERRs in LSS cohort by BEIR VII committee (NRC 2006)
DREF, mortality ^d	1.0 (0.39, 5.0)	Based on analyses of ERRs in U.K. radiation workers by Muirhead et al. (2009) and ERRs in LSS cohort by Jacob et al. (2009)
	0.55 (0.30, 1.5)	Based on analyses of ERRs in radiation workers in France, U.K., and U.S. (INWORKS) by Richardson et al. (2015) and ERRs in LSS cohort by BEIR VII committee (NRC 2006)
	0.64 (0.31, 2.7)	Based on analyses of ERRs in Techa River cohort by Schonfeld et al. (2013) and ERRs in LSS cohort by BEIR VII committee (NRC 2006)

^a LDEFs are estimated based on analyses of the curvature in modeled linear-quadratic (LQ) dose-responses in LSS cohort. Estimates of LDEF included in analysis represent approaches to modeling by BEIR VII committee (NRC 2006), Radiation Effects Research Foundation (RERF) (Preston et al. 2007; Ozasa et al. 2012), and United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) (Little et al. 2008).

^b Estimate based on method of calculation preferred by BEIR VII committee NRC (2006).

^c Estimate based on curvature parameter (β/α) preferred by Ozasa et al. (2012).

^d DREFs are estimated as ratios of age- and sex-matched estimates of ERR/Gy from acute exposure in LSS cohort assuming linear dose-response to estimates of ERR/Gy from protracted or chronic exposures of workers or Techa River cohort. Analyses of risks in LSS cohort by Jacob et al. (2009) were independent of analyses by BEIR VII committee (NRC 2006) and approaches to modeling dose-responses by other expert groups.

- LDEFs for solid cancer incidence based on analyses by the BEIR VII committee (NRC 2006) and LDEFs for solid cancer mortality based on analyses by Ozasa et al. (2012) indicate the dependence of LDEF on the method used to derive it— α_L/α_{LQ} vs $[1 + (\beta/\alpha)D]$ at 1 Gy, where α_L is the coefficient in a linear fit to the dose-response and α_{LQ} is the coefficient of the linear term in a fit assuming an LQ model over the same range of doses.
- Four LDEFs for solid cancer mortality based on analyses by Ozasa et al. (2012) are included in our analysis to estimate a DDREF for all solid cancers even though those investigators preferred the LDEF based on an estimate of the curvature parameter (β/α) at colon doses of 0–2 Gy. The other three LDEFs were estimated from central values of risk coefficients reported by Ozasa et al. (2012) and estimates of uncertainty in those coefficients provided by D. Preston (personal communication, November 6, 2016).
- LDEFs for solid cancer incidence or mortality are based on analyses of dose-responses in the LSS cohort over various ranges of colon doses: 0–1.5 Gy (NRC 2006), 0–2 Gy (Preston et al. 2007; Ozasa et al. 2012), or a full dose range corresponding to a shielded kerma from photons and neutrons of 0–4 Gy (Little et al. 2008; Ozasa et al. 2012). The dependence of LDEF on the dose range over which a dose-response was analyzed is particularly apparent in estimates based on analyses by Ozasa et al. (2012).
- LDEFs for solid cancer mortality based on analyses by Little et al. (2008) indicate the dependence of LDEF on the measure of risk analyzed (ERR vs EAR). All other estimates of LDEF for solid cancer mortality or incidence were based on analyses of ERRs only.
- We considered that the DREF for solid cancer mortality labeled “INWORKS vs LSS,” which was derived using an estimated risk to radiation workers in France, the U.K., and the U.S. (Richardson et al. 2015), superseded all DREFs that we derived using estimated risks of solid cancer mortality from the 15-country study of radiation workers (Cardis et al. 2007). Although DREFs we derived using estimated risks from the 15-country study with all or part of the Canadian cohort included were similar to the DREF we derived using an estimated risk from the INWORKS analysis, the validity of those DREFs is questionable, due to concerns about unreliable estimates of doses to some Canadian workers (Zablotska et al. 2014) and the importance of estimated risks to those workers to results from the 15-country study with all or part of the Canadian cohort included (Cardis et al. 2007). In addition, a DREF of 0.7 (–3.1, 4.5) we derived using an estimated risk from the 15-country study with the entire Canadian cohort excluded (Cardis et al. 2007), which we considered to be the most representative estimate from that study, has a substantially larger uncertainty with a 90% CI that overlaps zero and, thus, is largely uninformative compared with the DREF we derived using an estimated risk from the INWORKS analysis.

- DREFs for solid cancer incidence and mortality we derived using estimated risks in the Techa River cohort (Schonfeld et al. 2013; Davis et al. 2015) were included in our analysis to estimate a DDREF despite concerns about the accuracy of estimated doses, which were based on modeling. We included those DREFs based in large part on the consideration that the Techa River cohort is the only cohort consisting of members of the public of all ages in which estimated risks of all solid cancers have been reported.
- In estimating the two DREFs for breast cancer incidence or mortality and the DDREF for thyroid cancer incidence labeled “(TC+MRH+LH+SH) vs LSS,” risks from exposure of medical patients to x rays were compared with risks from exposure to higher-energy photons in the LSS cohort by adjusting the former to account for an assumption of a greater biological effectiveness of medical x rays in inducing cancer in humans. Reported risks in medical patients were divided by a radiation effectiveness factor at low doses or low dose rates (REF_L) of x rays with a central value of 2 and 90% CI of (1, 3); i.e., on average, the risk per unit dose from exposure to medical x rays was assumed to be twice the risk per unit dose from exposure to higher-energy photons.
- Due to the varied conditions of exposure of medical patients in the tinea capitis (TC), Michael Reese Hospital (MRH), lymphoid hyperplasia (LH), and skin hemangioma (SH) cohorts, the entry for thyroid cancer incidence labeled “(TC+MRH+LH+SH) vs LSS” could not be identified as an LDEF or a DREF and is referred to as a DDREF.
- The DREF for lung cancer mortality labeled “Mayak vs LSS” was derived using an estimated risk in the LSS cohort that accounted for the joint effects of radiation and smoking (Furukawa et al. 2010) and data on smoking status in workers at the Mayak complex (Sokolnikov et al. 2008). We concluded that estimated risks of lung cancer in tuberculosis fluoroscopy cohorts (Davis et al. 1989; Howe 1995; UNSCEAR 2008) could not be used to estimate a DREF when CIs of those estimates overlapped zero and some CIs had unspecified lower limits.
- LDEFs for incidence of basal cell carcinoma (BCC) or all non-melanoma skin cancers were not based on analyses of possible non-linearities in an assumed linear dose-response in the LSS cohort, in contrast to the approach to estimating all other LDEFs. Rather, LDEFs for these skin cancers were estimated based on linear-spline fits to the dose-responses with a knot at 1 Gy (Preston et al. 2007). These LDEFs were calculated as the ratio of the slope of the dose-response at doses >1 Gy to the slope at doses <1 Gy. Consequently, these LDEFs would not apply if linear risk coefficients used in estimating risks of basal cell carcinoma or all non-melanoma skin cancers were based on dose-responses in the LSS cohort at doses of 0–1 Gy only.

Results of our analyses of data for all solid cancers shown in Figure ES.1 indicate the importance of taking into account DREFs that are based on comparisons of risks in populations that received chronic or protracted exposures with risks from acute exposure in the LSS cohort. Estimates of a DREF for all solid cancers expand the range of credible values of a DDREF considerably by giving substantial weight to values <1 . A DDREF <1 is not apparent in LDEFs for all solid cancers that are based on analyses of the curvature in dose-responses in the LSS cohort assuming an LQ model when all central estimates are >1 and most lower limits of 90% CIs are 1 or greater.

Evaluation of data for leukemias. The evaluation of epidemiological data on radiation-induced leukemias in this study served several purposes. The first was to investigate whether the LDEF of 2 at a dose to bone marrow of 1 Gy that is implicit in the LQ dose-response models for acute exposure in IREP is consistent with recent analyses of the curvature in dose-responses for all leukemias (excluding CLL) in the LSS cohort. We also considered whether the use in IREP of LQ dose-response models for specific types of leukemia (AML, CML, and ALL) is supported by recent data in the LSS cohort.

Second, estimated risks of all leukemias at a dose to bone marrow of 1 Gy in the LSS cohort based on an LQ dose-response model were compared with estimated risks per Gy from chronic exposure of workers or members of the public based on linear dose-response models to estimate a DREF at 1 Gy. Those DREFs were compared with LDEFs based on data in the LSS cohort.

Third, dose-responses for all leukemias from acute exposure in the LSS cohort at doses sufficiently low that the quadratic term in an LQ dose-response is unimportant were compared with dose-responses from chronic exposure of workers based on linear models to evaluate the validity of the assumption in IREP that risks of leukemias from chronic exposure can be estimated using only the linear term in an LQ dose-response model for acute exposure.

Fourth, we considered whether an LDEF for all leukemias in the LSS cohort could be used to represent an LDEF for solid cancers, given that the curvature in the acute dose-response for leukemias in the LSS cohort should be affected to a lesser extent by contributions from neutrons, which should have a linear dose-response, due to the substantially lower biological effectiveness of neutrons in inducing leukemias compared with solid cancers.

Finally, we considered whether recent data in the LSS cohort and populations that received chronic or protracted exposures indicate that CLL is radiogenic. Although CLL usually is not considered to be radiogenic, CLL is assumed to be radiogenic in the version of IREP used by NIOSH. The risk model for CLL is based on data on dose-responses for lymphoma and multiple myeloma in the LSS cohort.

Results of our evaluation of epidemiological data on radiation-induced leukemias are summarized as follows.

- Estimates of an LDEF at 1 Gy for all leukemias (excluding CLL) based on DS02 dosimetry in the LSS cohort and estimates of a DREF at 1 Gy for all leukemias based on comparisons of risks in the LSS cohort with risks in workers or risks in children exposed to gamma radiation in natural background are consistent with the LDEF of 2 at 1 Gy that is implicit in the LQ dose-response model for all leukemias in IREP. However, there is substantial uncertainty in estimates of LDEF or DREF at 1 Gy that may not be fully accounted for in the dose-response model for all leukemias in IREP, in which the coefficients of the linear and quadratic terms are assumed to be equal and no additional uncertainty is assigned to the curvature parameter (β/α).
- Recent analyses by Richardson et al. (2009) and Hsu et al. (2013) showed that the apparently LQ dose-response for all leukemias (excluding CLL) in the LSS cohort does not represent the forms of dose-responses for specific types of leukemia, including AML, which exhibits a quadratic dose-response with little evidence of linearity at the lowest doses, and CML and ALL, which exhibit approximately linear dose-responses. In contrast to the assumption in IREP of an LDEF at 1 Gy of 2 for specific types of leukemia, a quadratic dose-response implies that LDEF approaches ∞ at the lowest doses, and a linear dose-response implies an LDEF of 1.
- Given that the apparently LQ dose-response for all leukemias (excluding CLL) from acute exposure in the LSS cohort is largely an artifact of combining dose-responses for specific types of leukemia, none of which is LQ in form, estimates of an LDEF for all leukemias should not be used to represent an LDEF for solid cancers.
- Comparisons of recent estimates of risks of all leukemias (excluding CLL) in the LSS cohort at doses sufficiently low that only the linear term in an assumed LQ dose-response is important with estimated risks from chronic exposure of workers are broadly consistent with the assumption in IREP that the linear term in an LQ dose-response from acute exposure can be used to estimate risks from chronic exposure. However, uncertainties in ratios of the two risks are large, and a firm conclusion is not warranted.
- A recent analysis of data in the LSS cohort by Hsu et al. (2013) showed evidence of a statistically significant linear dose-response for CLL, which suggested that the risk of CLL might be increased at higher doses. However, the analysis was based on only 12 cases in the LSS cohort, and Hsu et al. (2013) cautioned that generalization of this finding to other populations may be unwarranted. Studies of populations that received chronic or protracted exposures are inconclusive on the question of whether CLL is radiogenic.

RECOMMENDATION ON PROBABILITY DISTRIBUTION OF DDREF FOR SOLID CANCERS

The primary focus of this study was to re-evaluate the probability distributions of DDREFs for breast and thyroid cancers or all other solid cancers that are currently used in IREP to estimate risks from exposure to low-LET radiation and to develop a recommendation for revising those distributions. Conclusions based on our evaluation of data for leukemias are summarized above.

Assumptions and Initial Conclusions

Development of a recommendation on revising the probability distributions of DDREFs for solid cancers currently used in IREP was based on an assumption that an LNT dose-response model would continue to be used in estimating risks of solid cancers. With this assumption, an uncertain DDREF is used to adjust estimated risks of solid cancers per unit dose at high doses and high dose rates of low-LET radiation to obtain estimates of risks per unit dose at low doses or low dose rates.

An important initial conclusion from this study is that a probability distribution of DDREF for solid cancers should be developed on the basis of epidemiological data only. This conclusion was based on two considerations. First, we judged that use of radiobiological data in cells and laboratory animals to estimate a DDREF for solid cancers in humans is problematic, due to (1) the large uncertainties in DDREFs that were derived on the basis of radiobiological data, (2) the limited number of cancer types that have been studied in laboratory animals and the absence of data for all solid cancers combined, (3) difficulties in interpreting some dose-responses in cells and animals, and (4) unresolved questions about the relevance of DDREFs in cells and laboratory animals to induction of cancer in humans. Second, a substantial body of epidemiological data that can be used to estimate a DDREF for solid cancers has become available since IREP was developed. Especially important, in our view, is the availability of estimates of risks of all solid cancers in radiation workers or members of the public that received chronic or protracted exposures, which can be compared with risks in the LSS cohort to estimate a DREF.

We then concluded that results of our analyses of epidemiological data for all solid cancers and specific solid cancers shown in Figure ES.1 do not support the distinction in IREP between a DDREF for breast and thyroid cancers and a DDREF for all other solid cancers. Therefore, we developed a single probability distribution of DDREF that is intended to apply to all solid cancers.

Finally, we concluded that a probability distribution of DDREF for solid cancers should be developed on the basis of estimates of LDEF or DREF for all solid cancers only. Although estimates of LDEF, DREF, or DDREF for specific solid cancers shown in Figure ES.1 are generally consistent with estimates of LDEF or DREF for all solid cancers, many of the estimates for specific solid cancers are

more uncertain or incorporate the use of DS86 dosimetry in the LSS cohort. Therefore, we judged that the data for specific solid cancers would not substantially alter the range of credible values of a DDREF based on the data for all solid cancers.

Development of Probability Distribution of DDREF for All Solid Cancers

The probability distribution of a DDREF for all solid cancers developed in this report was based on the LDEFs and DREFs for all solid cancers shown in Figure ES.1 and summarized in Table ES.1.

Estimates of LDEF or DREF were combined based on assumptions about the relative weights that should be given to those estimates to represent their relevance to estimation of a DDREF. Our assumptions in combining LDEFs and DREFs to estimate a DDREF are summarized as follows.

- The three LDEFs for solid cancer incidence were combined by giving 25% weight to each of the two distributions based on an analysis by the BEIR VII committee (NRC 2006) and 50% weight to the distribution based on an analysis by Preston et al. (2007). These assumptions give equal weight to LDEFs from the BEIR VII report (NRC 2006) and Preston et al. (2007).
- The six LDEFs for solid cancer mortality were combined by giving 25% weight to each of the two distributions based on an analysis by Little et al. (2008), 15% weight to each of the two distributions based on an analysis by Ozasa et al. (2012) at colon doses of 0–2 Gy, and 10% weight to each of the two distributions based on an analysis by Ozasa et al. (2012) at a shielded kerma of 0–4 Gy. These assumptions give equal weight to LDEFs from Little et al. (2008) and Ozasa et al. (2012).
- The two DREFs for solid cancer incidence were combined by giving 80% weight to the distribution based on an analysis of risks to U.K. radiation workers by Muirhead et al. (2009) and 20% weight to the distribution based on an analysis of risks in the Techa River cohort by Davis et al. (2015).
- The three DREFs for solid cancer mortality were combined by giving 40% weight to the distribution based on an analysis of risks to U.K. radiation workers by Muirhead et al. (2009), 40% weight to the distribution based on an analysis of risks to radiation workers in France, the U.K., and the U.S. (INWORKS) by Richardson et al. (2015), and 20% weight to the distribution based on an analysis of risks in the Techa River cohort by Schonfeld et al. (2013).

The result of combining the individual distributions of LDEFs or DREFs was two distributions of LDEF and two distributions of DREF.

The assumption that lower weights should be given to the LDEFs for solid cancer mortality based on an analysis by Ozasa et al. (2012) at a shielded kerma of 0–4 Gy was based on the consideration that those investigators preferred an LDEF based on an analysis at colon doses of 0–2 Gy. The assumption that low weights should be given to the DREFs for solid cancer incidence or mortality based on analyses of risks in the Techa River cohort was based mainly on concerns about uncertainties in estimated doses. Other concerns about estimated risks in that cohort are discussed in Section 5.2.2.3 of this report.

The approach we used to combine individual probability distributions of LDEFs or DREFs for solid cancer incidence or mortality was to calculate weighted averages of those distributions using the relative weights given above. Assumptions about the form of probability distributions of individual LDEFs or DREFs or probability distributions of risk coefficients that we used to derive those LDEFs or DREFs, as well as details of the approach we used to calculate weighted averages of individual LDEFs or DREFs, are described in Sections 6.3.2.1 and 6.3.2.4 of this report.

We did not combine individual probability distributions of LDEFs or DREFs by weighting each distribution by the reciprocal of its variance, as was done, for example, in an analysis by Jacob et al. (2009) to compare estimated risks of solid cancers in several cohorts of workers or members of the public with estimated risks in the LSS cohort. That approach would give greater weight to estimates with smaller uncertainties and lesser weight to estimates with larger uncertainties. For example, in combining the individual distributions of LDEF for solid cancer mortality, the greatest weight would be given to the LDEF based on an analysis by Ozasa et al. (2012) at a shielded kerma of 0–4 Gy and calculated as $[1 + (\beta/\alpha)D]$ at 1 Gy, rather than the relatively low weight of 10% we assumed. Our judgment that a reciprocal-variance approach to weighting of individual distributions of LDEF or DREF should not be used was based mainly on the consideration that this type of weighting is most appropriate when distributions are statistically independent. However, this condition is not met when all LDEFs and DREFs included in our analysis were based on much the same data in the LSS cohort (e.g., estimates of dose based on DS02 dosimetry, follow-up of rates of solid cancer incidence or mortality for similar periods).⁵

⁵ Differences in LDEFs for all solid cancers in Figure ES.1 and Table ES.1 that were estimated using DS02 dosimetry in the LSS cohort are due to differences in several factors that affected analyses of a dose-response by the various investigators. These include, for example, differences in (1) the size of the LSS cohort, (2) the approach to modeling dose-responses by different expert groups, (3) the cancer types included in “all solid cancers,” (4) the response under study (mortality vs incidence of solid cancers), (5) the measure of risk that was analyzed (ERR vs EAR), (6) assumed uncertainties in estimated doses to survivors, (7) whether survivors with an estimated shielded kerma >4 Gy were included in a dose-response analysis, (8) the period of follow-up of survivors (1958–1998 for solid cancer incidence vs 1950–2000 or 2003 for mortality), (9) the range of doses over which the non-linearity in a dose-response was analyzed using an LQ model, (10) the approach to estimating an LDEF, as in the analyses by the BEIR VII committee (NRC 2006) and Ozasa et al. (2012), and (11) the assumed dependence of risks on age at exposure and attained age or time since exposure. These differences also can affect estimates of DREF.

- The combined LDEFs and DREFs for solid cancer incidence should be given substantially greater weight than the combined LDEFs and DREFs for solid cancer mortality. Relative weights of 2:1 were assigned to incidence- and mortality-based estimates of the combined LDEFs and DREFs.

The result is a single distribution of LDEF and a single distribution of DREF that represent estimates for solid cancer incidence and mortality combined. Our judgment that substantially greater weight should be given to LDEFs and DREFs for solid cancer incidence was based on several considerations: (1) accuracy of disease ascertainment is a greater concern in estimating risks of cancer mortality; (2) cancer mortality, but not incidence, can depend on the level and intensity of medical treatment; (3) estimates of mortality generally are less reliable for cancers that usually are non-fatal (e.g., thyroid cancer); and (4) use of LDEFs and DREFs based on data on cancer incidence is compatible with modeling of risks of cancer incidence in IREP. However, we also judged that substantial weight should be given to LDEFs and DREFs for solid cancer mortality.

- Estimates of LDEF and DREF that were obtained by combining estimates for solid cancer incidence and mortality were given equal weight in estimating a probability distribution of DDREF for all solid cancers.

Although there could be unknown biases and complicating factors in estimating DREFs by comparing risks of solid cancers from chronic or protracted exposures in radiation workers or members of the public with age- and sex-matched risks from acute exposure in the LSS cohort, there also are concerns that extrapolations of observed risks at higher acute doses (e.g., >1 Gy) in the LSS cohort to lower doses where risks are not observable (e.g., using an LQ dose-response model) may not be reliable.

- The probability distribution of DDREF for all solid cancers obtained as summarized above was truncated by removing values less than 0.2 and greater than 20.

Truncation of the probability distribution of DDREF was based on our judgment that the weight of evidence from all the data in humans and the data in animals discussed in Section 4.3 of this report, assuming a linear no-threshold dose-response for cancer in humans, is that a DDREF for all solid cancers outside the range of 0.2–20 is not credible. However, truncation removed only about 1.3% of the values in the DDREF distribution without truncation and had only a small effect on estimated CIs.

Selected percentiles of the probability distribution of a DDREF for all solid cancers that was developed on the basis of the assumptions summarized above and the lognormal probability distribution

that provides the best fit to that distribution are given in Table ES.2. The best-fit lognormal distribution, which should be suitable for general use in cancer risk assessments that account for uncertainty, gives a good fit to our probability distribution. Deviations of the best-fit lognormal distribution from our distribution are most pronounced at the very lowest percentiles (below about 0.2) and at percentiles above the 95th, where the lognormal distribution underestimates our DDREF distribution; underestimation of a DDREF results in overestimation of risks and PC/AS of diagnosed cancers. Lower values in a DDREF distribution are the more important to NIOSH when upper 99th percentiles of uncertain estimates of ERR and PC/AS calculated in IREP are used in adjudicating claims for compensation for cancer (DHHS 2002).

Table ES.2 also gives the harmonic mean of the probability distribution of DDREF developed in this report and the best-fit lognormal distribution. Because DDREF is a divisor in an equation to estimate cancer risks, the arithmetic mean of an uncertain estimate of risk, which is an important and commonly used measure of central tendency, is proportional to the reciprocal of the harmonic mean of DDREF, rather than the reciprocal of the arithmetic mean. For example, using the harmonic mean of the DDREF distribution in Table ES.2, the arithmetic mean of an estimated risk of solid cancers per unit dose at low doses or low dose rates is $1/1.1 = 0.91$ times the arithmetic mean of an estimated risk per unit dose at high acute doses. This reduction in mean risks is rather modest (about 10%). Use of the reciprocal of the arithmetic mean of DDREF would underestimate the arithmetic mean of risks per unit dose at low doses or low dose rates.

Estimates of LDEFs and DREFs for all solid cancers that were used in our analysis and a comparison of the probability distribution of DDREF for all solid cancers developed in this report with probability distributions developed by Jacob et al. (2009) and the BEIR VII committee (NRC 2006) are shown in Figure ES.2. Also shown is the probability distribution for solid cancers other than breast and thyroid currently used in IREP.

Table ES.2. Summary of probability distribution of DDREF for all solid cancers developed in this report and lognormal distribution that gives best fit to DDREF distribution

Distribution	Percentile of probability distribution					Harmonic mean ^a
	2.5th	5th	50th	95th	97.5th	
DDREF distribution	0.39	0.47	1.3	3.6	5.6	1.1
Best-fit lognormal distribution (GM = 1.31, GSD = 1.80) ^b	0.41	0.50	1.3	3.4	4.2	1.1

^a When probability distribution of DDREF is used in cancer risk assessments, arithmetic mean of uncertain estimate of risk at low doses or low dose rates is proportional to reciprocal of harmonic mean of DDREF.

^b GM = geometric mean; GSD = geometric standard deviation.

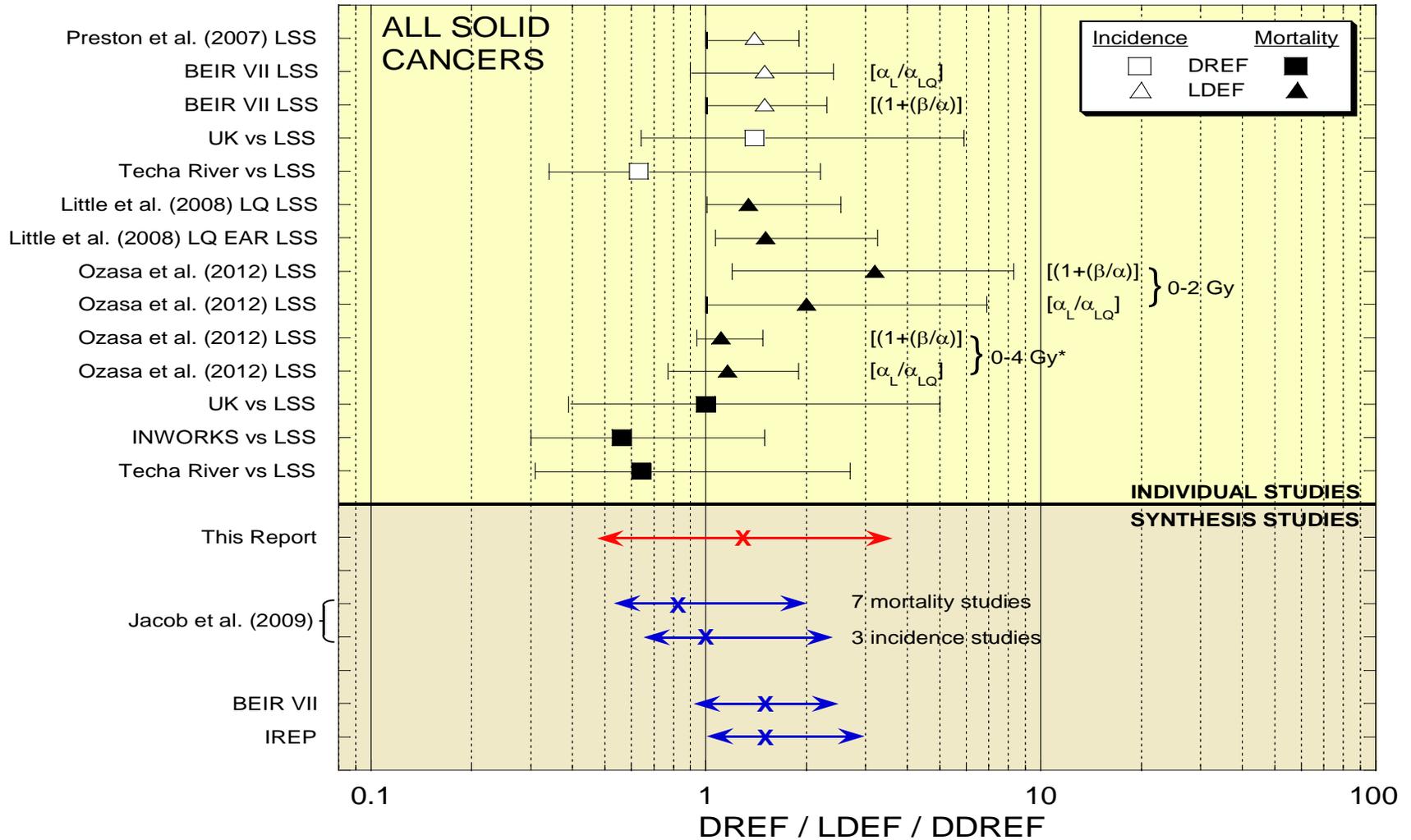


Figure ES.2. Estimates of 50th percentiles and 90% CIs of DREF or LDEF for solid cancer incidence or mortality used to develop probability distribution of DDREF for all solid cancers in this report (top) and comparison of our preferred distribution with DDREF distributions developed by Jacob et al. (2009) and BEIR VII committee (NRC 2006) and DDREF distribution for most solid cancers currently used in IREP (bottom). Distributions at top of figure are given in Figure ES.1. * Range of shielded kerma from photons and neutrons; range of neutron-weighted doses to colon in analyses by Ozasa et al. (2012) otherwise.

In analyses by Jacob et al. (2009) summarized in Figure ES.2, risks of solid cancer mortality or incidence in several cohorts of workers or members of the public that received chronic or protracted exposures at low doses were compared with risks in the LSS cohort. Because CIs of estimated risks in several worker cohorts overlapped zero, Jacob et al. (2009) calculated ratios of risks to workers or members of the public to risks in the LSS cohort, which were referred to as “risk ratios”; a risk ratio is the reciprocal of a DREF. Risk ratios based on results from individual studies were combined by weighting each risk ratio by the reciprocal of its variance. Three combinations of risk ratios were calculated: (1) one for cancer mortality that was obtained by combining results from seven studies with a larger number of cancer cases, which Jacob et al. (2009) considered to be their main result; (2) one for cancer mortality that was obtained by combining results from four studies with a smaller number of cancer cases; and (3) one for cancer incidence that was obtained by combining results from the three studies of that endpoint. The results shown in Figure ES.2 are reciprocals of the reported central values and 90% CIs of two of the combinations of risk ratios; the risk ratio based on four studies of cancer mortality is not shown.

If a risk ratio (RR), as defined by Jacob et al. (2009), were used in cancer risk assessments, risks per unit dose at low doses or low dose rates of low-LET radiation would be estimated as $R_L = R_H \times RR$. We think that use of a risk ratio in cancer risk assessments that account for uncertainty has certain advantages over use of a DDREF, including that (1) the arithmetic mean of a probability distribution of R_L is proportional to the arithmetic mean of a risk ratio, but is not proportional to the reciprocal of the arithmetic mean of DDREF, and (2) probability distributions of DREFs based on ratios of risks in the LSS cohort to risks in cohorts that received chronic or protracted exposures include a value of infinity when the CI of the risk from chronic or protracted exposure overlaps zero and, thus, are unstable. The latter concern led Jacob et al. (2009) to calculate risk ratios, rather than DDREFs, in their analyses.

The probability distribution of DDREF developed by the BEIR VII committee (NRC 2006) was based mainly on an analysis of the curvature in the acute dose-response for solid cancer incidence in the LSS cohort, which gives an LDEF. The probability distribution based on the committee’s analysis of data in the LSS cohort was modified slightly by taking into account into account data in laboratory animals.

We note the following points about the DDREFs shown at the bottom of Figure ES.2.

- Substantial weight (nearly 30%) is given to an assumption that the risk of solid cancers per unit dose at low doses or low dose rates of low-LET radiation is greater than the risk per unit dose at higher acute doses in the LSS cohort. Since LDEFs based on analyses of possible non-linearities in dose-responses in the LSS cohort generally are >1 , this property of our probability distribution is a consequence of including DREFs for solid cancer incidence or mortality that were based on comparisons of risks to workers or members of the public with risks in the LSS cohort. We think

that a credible estimate of a DDREF for solid cancers must take into account estimates of risks from chronic or protracted exposures that suggest a DDREF <1.

- The probability distribution of DDREF developed in this report includes higher values than the distributions based on analyses by Jacob et al. (2009), whereas the latter distributions give greater weight to values <1. The main reason for these differences is that the analyses by Jacob et al. were based on comparisons of risks to workers or members of the public that received chronic or protracted exposures at low doses with risks in the LSS cohort only.
- The probability distribution of DDREF developed by the BEIR VII committee (NRC 2006) did not take into account risks to workers or members of the public that received chronic or protracted exposures. Consequently, the BEIR VII distribution gives only a small weight to values <1.
- The probability distribution of DDREF developed in this report and the distribution for all solid cancers excluding breast and thyroid currently used in IREP have similar 50th percentiles (1.3 vs 1.5), but our distribution is substantially broader. The 90% CI of the DDREF for breast and thyroid cancers currently used in IREP is the same the 90% CI of the distribution for all solid cancers other than breast and thyroid shown in Figure ES.2.

We reiterate that the probability distribution of DDREF for all solid cancers developed in this report is intended to be applied in estimating risks of specific solid cancers at low doses or low dose rates of low-LET radiation only when a linear dose-response from acute exposure over a wide range of doses, e.g., at doses in the LSS cohort up to about 2 Gy or higher, is assumed. If a non-linear dose-response from acute exposure is assumed, such as the linear-spline dose-responses for non-melanoma skin cancers and basal cell carcinoma developed by Preston et al. (2007) and the quadratic dose-response for bone cancer developed by UNSCEAR (2008), our DDREF for all solid cancers would not apply.

The probability distribution of DDREF for all solid cancers developed in this report gives substantially greater weight to values <1 than the two distributions for solid cancers currently used in IREP. Consequently, 99th percentiles of uncertain estimates of ERRs and PC/AS used in adjudicating claims for compensation for cancer would increase if our distribution replaced the probability distributions of DDREF currently used in IREP. We emphasize, however, that it was not our intent to develop a probability distribution of DDREF that would be biased toward overestimation, or underestimation, of ERRs and PC/AS. Rather, our intent from the outset was to develop, on the basis of a review of available information, a probability distribution of DDREF for all solid cancers that is an unbiased representation of the current state of knowledge.

1. INTRODUCTION

1.1 BACKGROUND

The Interactive RadioEpidemiological Program (IREP) is used by the National Institute for Occupational Safety and Health (NIOSH) to estimate the probability of causation/assigned share (PC/AS) of diagnosed cancers in nuclear energy workers who were exposed to ionizing radiation (NIOSH 2002; Land et al. 2003a; SENES 2003; Kocher et al. 2008).¹ Estimates of cancer risks used in IREP were based primarily on epidemiological studies of Japanese atomic-bomb survivors [the Life Span Study (LSS) cohort] who received an acute exposure mainly to high-energy photons (low-LET² radiation), with a small contribution from neutrons. To account for the effectiveness of low-LET radiations (photons and electrons) in inducing cancer in humans at low doses or low dose rates relative to the effectiveness of those radiations at high doses and high dose rates, dose and dose-rate effectiveness factors (DDREFs) are applied to risk coefficients (risks per unit dose) for specified types of solid cancers that were derived from the epidemiological data by assuming a linear, no-threshold (LNT) dose-response model, as depicted in Figure 1.1, curve a. A DDREF is not used in estimating risks of leukemias in IREP, because those risks are estimated using a linear-quadratic (LQ) dose-response model that incorporates a DDREF implicitly.

The justification for use of a DDREF to estimate cancer risks at low doses or low dose rates is tied to an expectation that the dose-response relationship for low-LET radiation is inherently LQ, as depicted in Figure 1.1, curve b. At high doses and high dose rates, the influence of the quadratic (dose-squared) term increases the effectiveness per unit dose of low-LET radiation (the slope of the dose-response curve), as in the high-dose portion of curve b. Because estimated risks of radiation-induced cancers are based primarily on epidemiological data in the LSS cohort at organ doses up to 5 Gy or more at a high dose rate, there is a perceived need to apply a reduction factor (a DDREF) to modify risks associated with exposures at low doses (the low-dose portion of curve b), where an LNT dose-response relationship often is assumed to apply. Since microdosimetric considerations discussed in Section 2.1 imply that the initial radiation damage at very low doses should be independent of dose rate, a DDREF also is assumed to account for a reduction in risks at low dose rates. When a DDREF is applied in estimating cancer risks using an LNT

¹ NIOSH-IREP refers to the calculated probability that a diagnosed cancer in an individual was caused by exposure to ionizing radiation as “probability of causation,” whereas the working group that developed IREP (Land et al. 2003a) preferred the term “assigned share” to indicate that the quantity calculated in IREP (1) is based on estimates of cancer risks due to radiation that are obtained from epidemiological studies of exposed populations and (2) is a property of the population group to which an individual belongs that is assigned to that individual but may not be the true probability that an individual’s cancer was caused by known radiation exposures.

² LET (linear energy transfer) is the energy transferred per unit length of a radiation track.

dose-response model, the risk per unit dose at low doses or low dose rates of low-LET radiation, R_L , is estimated as $R_L = R_H/DDREF$, where R_H is the risk per unit dose at high doses and high dose rates, as estimated primarily from data in the LSS cohort.

DDREFs are expressed in IREP as probability distributions to represent their uncertainty (Land et al. 2003a). Although probability distributions of DDREFs in IREP were developed for use in estimating the PC/AS of diagnosed cancers in exposed individuals, they are intended to be suitable for use in any assessments of cancer risks that attempt to fully account for uncertainty. In contrast, a DDREF of 2 with no uncertainty was developed for use in radiation protection (ICRP 1991) and subsequently adopted by regulatory authorities. Probability distributions of a DDREF also were developed by NCRP (1997), the U.S. Environmental Protection Agency (EPA 1999), Grogan et al. (2000), and the BEIR VII committee (NRC 2006). The various probability distributions are discussed in the following sections.

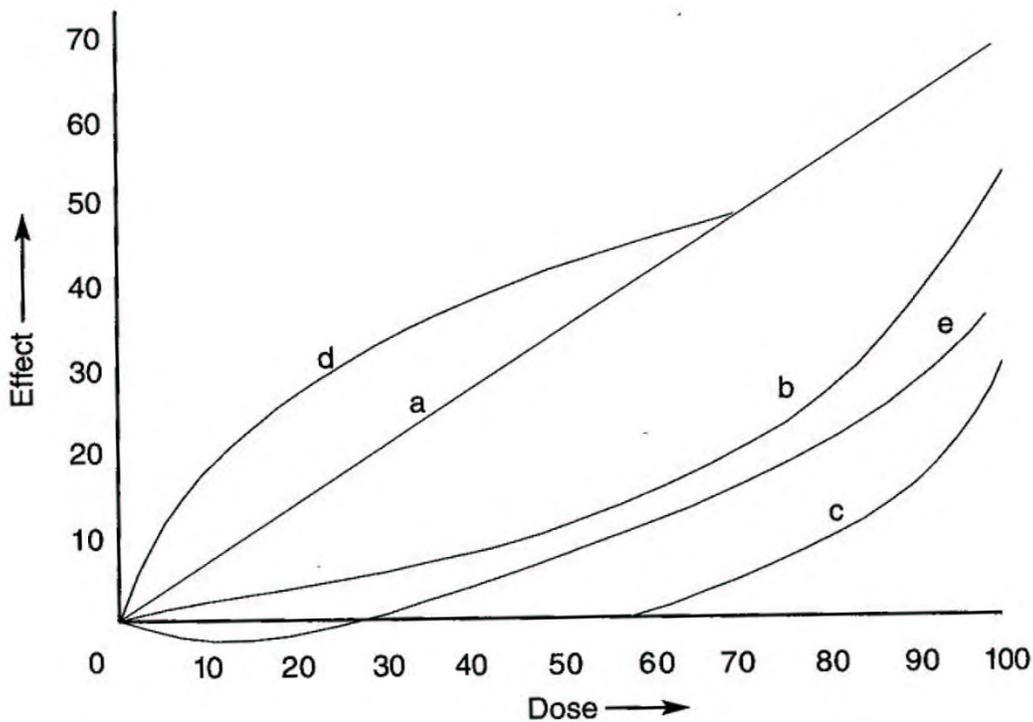


Figure 1.1. Schematic representation of different dose-response relationships: (a) linear no-threshold relationship over entire dose range; (b) linear no-threshold relationship only at low-to-intermediate doses, above which the curve bends upward, as in a linear-quadratic relationship; (c) threshold relationship, in which there is no response at doses below the threshold indicated by the intercept; (d) supralinear relationship, in which the response per unit dose at low doses exceeds the response per unit dose at higher doses; (e) hormetic relationship, in which the frequency of the response is reduced below the background (baseline) level at low doses and increases only at higher doses (NCRP 2001).

1.1.1 Probability Distributions of DDREF in IREP

In IREP, two discrete probability distributions of DDREF shown in Figure 1.2 are used to estimate risks of incidence of solid cancers at low doses or low dose rates. Those distributions were influenced by the apparent linearity in the dose-response for mortality from all cancers in the LSS cohort and by indications of a possible supralinearity in the response at doses below 0.5 Sv (Pierce et al. 1996a; Land et al. 2003a). For solid cancers other than breast and thyroid, the distribution includes non-zero probabilities at DDREFs between 0.5 and 5. In the distribution for breast and thyroid cancer, a greater probability was assigned to a DDREF of 1 and the upper limit was lowered to 4. Use of a separate DDREF distribution for breast and thyroid cancer was justified in part on the grounds that there was a greater tendency for a linear dose-response for those types of cancers in epidemiological data and in some animal data. The greatest weights were assigned to DDREFs of 1.5 and 2 in the distribution for all solid cancers except breast and thyroid and 1.0 in the distribution for breast and thyroid cancers. Mean values of the distributions are 1.6 for breast and thyroid cancer and 1.8 for all other solid cancers, and the median value and subjective 95% confidence interval (CI)³ in both distributions are 1.5 (0.7, 4.0). The distributions of DDREF in IREP were based to a significant extent on judgment.

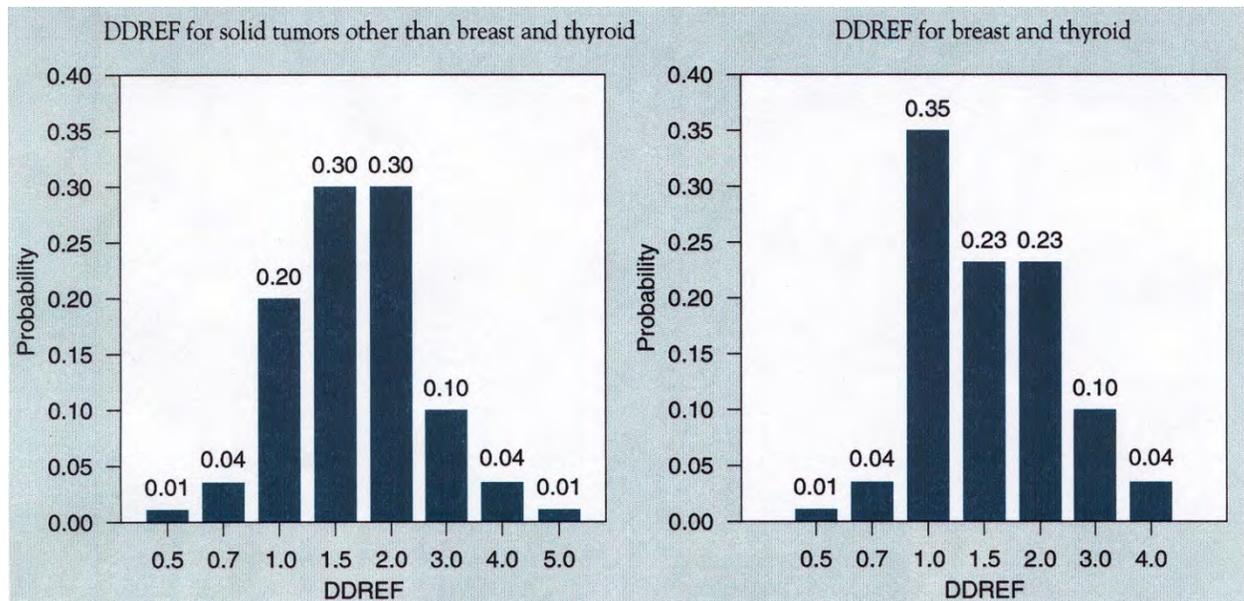


Figure 1.2. Discrete probability distributions of DDREF used in IREP (Land et al. 2003a).

³ In this report, the terms “confidence interval” and “confidence limit” describe probability distributions that are based to a significant extent on scientific judgment, as well as distributions based on statistical analyses of data sets.

The DDREFs in Figure 1.2 are applied in all cases of chronic exposure (i.e., at any total dose), but are applied in cases of acute exposure only at doses below 30–200 mGy. This dose range represents the uncertainty in radiobiological and epidemiological data that bear on the question of what constitutes a low dose, i.e., an acute dose below which a DDREF should be applied (UNSCEAR 1993, 2000). In cases of acute exposure, DDREF is assumed to vary as a logistic function of decreasing dose, starting from the value 1 with no uncertainty at an uncertain dose of 30–200 mGy, reaching 99.9% of the DDREF for chronic exposure at 1 mGy, and approaching the DDREF for chronic exposure at zero dose.

The probability distribution of DDREF for most solid cancers in IREP also is used to estimate risks of lymphomas and multiple myeloma at low doses or low dose rates. However, a DDREF is not used in estimating risks of leukemias, because those risks are estimated in IREP using an LQ dose-response model that incorporates a DDREF implicitly. The risk of leukemias at low doses based on the LQ model used in IREP (Land et al. 2003a) is consistent with the DDREF of 2 that has been recommended for use in radiation protection by ICRP (1991, 2007), NCRP (1993a), and the National Radiological Protection Board (NRPB) of the United Kingdom (U.K.) (Cox et al. 1995).

1.1.2 Probability Distributions of DDREF Developed by Other Investigators

Continuous probability distributions of DDREF developed by NCRP (1997), EPA (1999), Grogan et al. (2000), and the BEIR VII committee (NRC 2006) are shown in Figure 1.3. Distributions developed by NCRP (1997) and Grogan et al. (2000) were used in calculating lifetime risks of all cancers following whole-body irradiation, whereas the distributions developed by EPA (1999) and the BEIR VII committee (NRC 2006) were used in calculating lifetime risks of solid cancers only. The BEIR VII committee's distribution, which was based in part on data on myeloid leukemia in animals and is discussed further in Appendix B, has the narrowest range (smallest uncertainty) of any DDREF distribution developed to date.

Grogan et al. (2000) also developed separate probability distributions of DDREF for four specific cancer types: lung, liver, bone, and leukemia. However, the distributions for liver and bone cancer are identical to the distribution for all cancers. In estimating risks of leukemia at low doses or low dose rates, EPA (1999) and Grogan et al. (2000) used a linear dose-response model with a DDREF specific to leukemia, whereas the BEIR VII committee developed an LQ dose-response model for leukemia that incorporates a DDREF implicitly (NRC 2006).⁴

⁴ In EPA's current cancer risk models (EPA 2011), the probability distribution of DDREF developed by the BEIR VII committee (NRC 2006) is used to estimate risks of solid cancers, and the committee's LQ dose-response model is used to estimate risks of leukemias. Discussions of the distribution used previously by EPA (1999) are retained in this report to provide a historical perspective on the development of DDREFs that account for uncertainty.

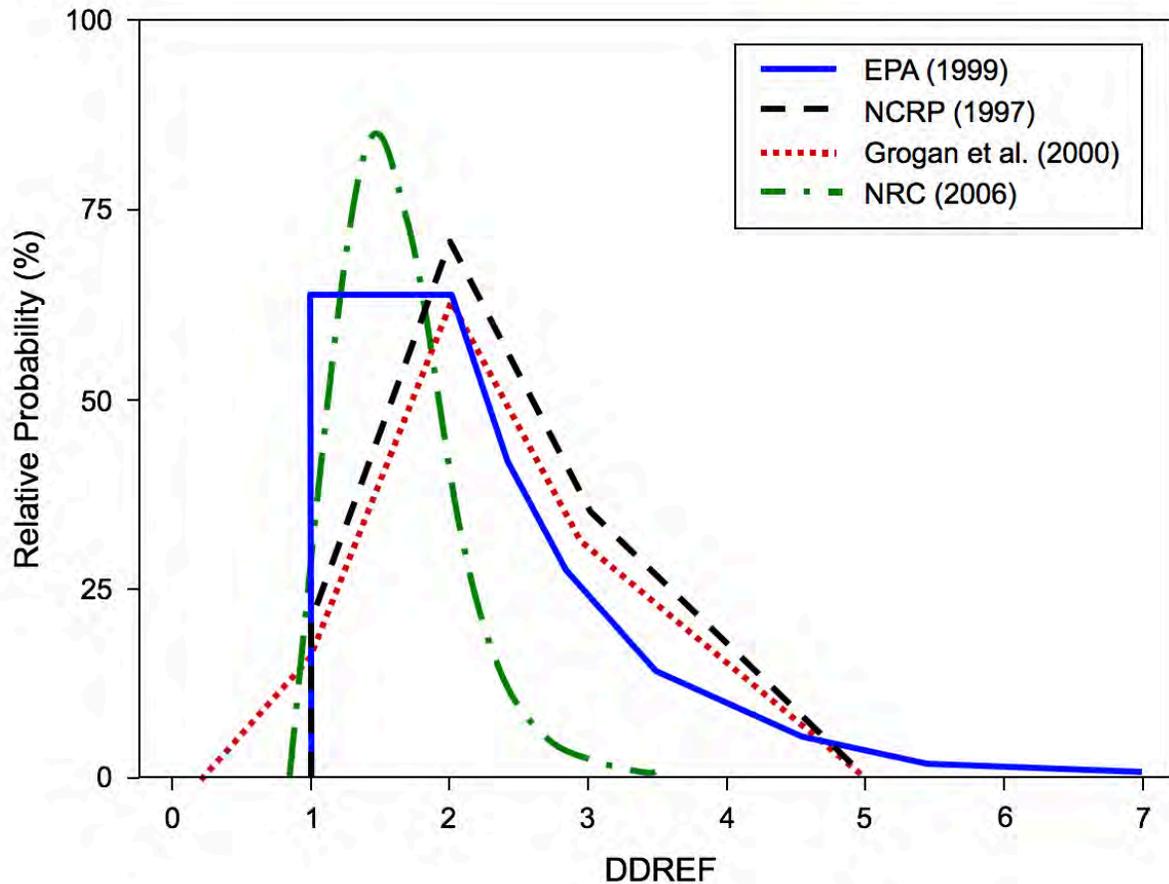


Figure 1.3. Probability distributions developed by different investigators to represent subjective uncertainty in DDREF [modified from Land et al. (2003a)].

Subjective judgment played a major role in developing all the probability distributions of DDREF shown in Figures 1.2 and 1.3. Although the various distributions differ in form, they all assign the greatest weight to DDREFs between 1 and 3. Equal weights were assigned to DDREFs between 1 and 2 by EPA (1999), the median value in the BEIR VII distribution is 1.5, and a DDREF of 2 was assigned the greatest weight by NCRP (1997) and Grogan et al. (2000).

The distributions developed by NCRP (1997) and Grogan et al. (2000) in Figure 1.3 are essentially the same at DDREFs greater than 1. However, NCRP's distribution was truncated at 1, whereas the range was extended down to 0.2 by Grogan et al. (2000) to account for a possible supralinear dose-response.

All distributions developed prior to the BEIR VII committee's distribution, including the distributions in IREP, include DDREFs between 1 and 4, and DDREFs up to 7 or more are included in some distributions. However, DDREFs less than 1 were assigned zero probability by NCRP (1997) and

EPA (1999) and in the distribution for leukemia developed by Grogan et al. (2000), which is not shown in Figure 1.3. Values slightly less than 1 are included in the BEIR VII committee's distribution, which has a 95% CI of (0.8, 2.7), but values greater than 3 are assigned a very low probability (NRC 2006). The upper limit is 7 in the distribution for leukemia developed by Grogan et al. (2000) (not shown) and approximately 7 in EPA's distribution for all cancers except leukemia shown in Figure 1.3 (EPA 1999). In EPA's distribution, a decreasing exponential function was assumed at values greater than 2. That distribution extends to values greater than 7, albeit with a very low probability.

Grogan et al. (2000) cited the analysis of data on cancer mortality in the LSS cohort by Pierce and Vaeth (1991) as the source of information they used to develop their DDREF distribution for leukemia. That distribution is log-triangular, with a most probable value of 2 and lower and upper limits of 1 and 7, respectively. EPA (1999) assumed a lognormal distribution of DDREF for leukemia with a geometric mean of 2.5 and geometric standard deviation of 1.5. Although EPA also cited the analysis of data on cancer mortality in the LSS cohort by Pierce and Vaeth (1991) as the primary source of information they used to develop their DDREF distribution for leukemia, an analysis of data on leukemia mortality in nuclear workers (Cardis et al. 1995) and a preliminary analysis of data on leukemia in Mayak nuclear workers and Techa River residents in Russia (UNSCEAR 1993) also were used.

In the DDREF distribution for lung cancer developed by Grogan et al. (2000), the central estimate is 4, rather than 2 as in their distribution for all cancers shown in Figure 1.3, and the upper limit was extended from 5 to 10 to be consistent with the higher central estimate. That DDREF distribution was greatly influenced by the excess relative risks (ERRs) for lung cancer reported by Howe (1995) in a study of the Canadian fluoroscopy cohort, which suggested a DDREF of 8. However, Grogan et al. (2000) modified the suggested DDREF because it conflicted with data in the LSS cohort. EPA (1999) interpreted the data from Howe (1995) somewhat differently, concluding that because the use of an excess absolute rate (EAR) model would reduce the projected risk in a North American population by about a factor of four, those data would be consistent with a DDREF of 2. In effect, EPA (1999) opted to incorporate a larger uncertainty in their risk estimates for lung cancer due to modeling of the transfer of risks between populations, in lieu of a separate and higher DDREF for lung cancer.

1.2 PURPOSE AND APPROACH

The main purpose of the study described in this report was to evaluate the scientific basis for developing DDREFs and to provide NIOSH with an alternative to the probability distributions of DDREFs for solid cancers currently used in IREP. The probability distribution of DDREF for solid cancers developed in this report is intended to provide an unbiased representation of DDREF, i.e., a

representation that would not intentionally over- or underestimate an uncertain DDREF. Such a DDREF distribution would be suitable for use in cancer risk assessments that account for uncertainty.

Our evaluation involved a comprehensive analysis of information on low-dose and low-dose-rate extrapolations of cancer risks obtained from a variety of sources. A re-evaluation of the DDREF distributions currently used in IREP is important when the uncertainty in DDREF can be a significant contributor to the uncertainty in estimates of cancer risks at low doses or low dose rates (NCRP 1997) and, therefore, to the uncertainty in estimates of PC/AS of diagnosed cancers in exposed individuals. Given that decisions about awarding compensation to nuclear energy workers in the U.S. often are based on the upper 99% confidence limit of an uncertain estimate of PC/AS of a diagnosed cancer (DHHS 2002), a proper accounting of uncertainty in DDREF clearly is important. For purposes of awarding compensation, it is especially important to account for a credible lower limit of a DDREF, because of its effect on the upper limit of an estimated risk and PC/AS. More generally, including an uncertainty in DDREF is important in any cancer risk assessment that attempts to fully account for uncertainty.

A significant amount of new information that can be used to estimate DDREFs for solid cancers has been obtained since the distributions in IREP were developed. Furthermore, the assumption that risk coefficients that are derived from epidemiological data at intermediate and high doses and dose rates and applied using an LNT relationship modified by a DDREF can adequately represent dose-responses for induction of cancer at low doses (e.g., <200 mGy) and low dose rates has been challenged in many ways. Although such challenges are not new, a substantial body of knowledge from use of new tools for elucidating the effects of ionizing radiation on biological systems (such as x-ray and ion microbeams and exquisitely sensitive markers/assays for DNA damage and mutagenesis) and from the genomics revolution has provided additional support for alternatives to the LNT model modified by a DDREF >1, including:

- A supralinear response at low doses or low dose rates, which implies that risks are underestimated by assuming a linear response in the low-dose region ($0 < \text{DDREF} < 1$; Figure 1.1, curve d);
- A strictly linear response over the entire dose range ($\text{DDREF} \equiv 1$; Figure 1.1, curve a);
- A sublinear response at low doses, which implies a reduction of risks estimated by assuming a purely quadratic dose-response (akin to an extension of the high-dose portion of curve b in Figure 1.1 to zero dose; $\text{DDREF} \rightarrow \infty$) or a threshold in the dose-response (Figure 1.1, curve c; $\text{DDREF} = \infty$);
- A hormetic response, which implies that there are beneficial effects of radiation exposure, including a reduction of risks below ambient levels, at low doses or low dose rates ($\text{DDREF} < 0$; Figure 1.1, curve e).

- Other, more complex (e.g., U- or J-shaped) dose-responses, which imply that risks at very low doses or dose rates are comparable to risks at high doses and high dose rates.

The current debate is concerned with whether sufficient information is available to reject the LNT hypothesis in favor of an alternative model (Johannson 2003; Hei 2006; Brenner et al. 2007; Tubiana et al. 2007, 2008; Feinendegen et al. 2008; Leonard 2008; Mossman 2008; Preston 2008; Averbek 2009; Brenner 2009; EPRI 2009; Dauer et al. 2010).

Based on these considerations, a re-evaluation of DDREFs used in IREP also should take into account concerns about the validity of the underlying dose-response model. Addressing those concerns required an evaluation with a much broader scope, including not only the data needed to establish DDREFs for use with the LNT model but also emerging information on a diverse array of biological and radiobiological phenomena that are thought by some to call into question the continued use of the LNT model as the standard paradigm in radiation protection and risk estimation at low doses or low dose rates.⁵ Such phenomena include adaptation (e.g., from inducible stress responses and stimulation of the immune system), low-dose hyper-radiosensitivity or induced radioresistance, and a variety of non-targeted and delayed effects (e.g., bystander effects, genomic instability). If an LNT relationship derived from an LQ model is a questionable representation of the response at low doses or low dose rates, uncertainties in DDREFs could increase substantially.

In this study, we used reviews and evaluations of radiobiological and epidemiological data by such expert groups as the Académie des Sciences – Académie Nationale de Médecine of France, the Committee to Assess Health Risks from Exposure to Low Levels of Ionizing Radiation of the National Research Council (NRC) of the National Academies (referred to as the BEIR VII committee), the International Commission on Radiological Protection (ICRP), the National Council on Radiation Protection and Measurements (NCRP), the U.K.'s National Radiological Protection Board (NRPB) and Committee Examining Radiation Risks of Internal Emitters (CERRIE), and the United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR), as well as reviews and evaluations by individuals who are recognized experts. However, because of the rapidly evolving state of knowledge in some areas, we performed an independent evaluation of some of the primary literature, with an emphasis on publications since 1999.

Methods and mathematical relationships used in deriving DDREFs, along with uncertainties introduced by questions about the nature of the dose-response and the possibility that DDREF depends on the energy of low-LET radiations, are discussed in Section 2.

⁵ Strictly speaking, the linear-quadratic (LQ) model, which becomes an LNT relationship at low doses or low dose rates, is the principal paradigm; see Section 2.1 and Goodhead (2000, 2007).

Information that might support alternatives to, or modifiers of, the LNT model is discussed in Section 3. Discussions of the LNT model are preceded by a presentation of background information on biophysical, molecular, and cellular phenomena of importance to determining the biological effects of ionizing radiation, as well as recent information on epigenetic and homeostatic mechanisms that appear to play a much larger role in radiation carcinogenesis than previously considered. Maintenance and expression of the genome and, thus, the link between initial genomic damage and the subsequent development of a cancer may be far more complex than previously thought. These issues are relevant to cancer research in general, having led the editor-in-chief of *Science* (and former president of the National Academy of Sciences) to call for a greater focus on deciphering the detailed mechanisms of apoptosis and DNA repair, in particular (Alberts 2008).

Radiobiological and epidemiological data that we considered for use in developing a probability distribution of DDREF for all solid cancers in IREP are reviewed and evaluated in Sections 4 and 5. Those sections discuss estimates of DDREF based on studies prior to the BEIR VII report (NRC 2006) and additional data that were obtained from studies of largely *in vitro* (e.g., cell culture) systems and studies of radiation carcinogenesis in laboratory animals and humans.

Section 6 describes the development of our preferred probability distribution of DDREF for all solid cancers. Our DDREF distribution is intended to represent uncertainties in potentially relevant data and uncertainties in the many judgments involved in evaluating those data. Section 6 also includes a summary of information related to defining low doses and low dose rates at which a DDREF should be applied. That information is presented in more detail in Appendix A.

Finally, Appendix B presents a review and critique of the approach used by the BEIR VII committee (NRC 2006) to develop a probability distribution of DDREF on the basis of epidemiological data and data in laboratory animals.

2. DERIVATION OF DDREF

2.1 INTRODUCTION

The justification for use of a DDREF in estimating cancer risks at low doses or low dose rates of low-LET radiation has been linked to an assumption of a linear-quadratic (LQ) dose-response model for those radiations. In an LQ model, the response (\mathcal{R}) is represented by $\mathcal{R} = \alpha D + \beta D^2$, where D is the absorbed dose (Gy) and α (Gy^{-1}) and β (Gy^{-2}) are the coefficients of the linear and quadratic terms, respectively. Data on radiation-induced chromosomal exchange aberrations, in particular, provided the basis for the standard LQ paradigm that has been used by expert committees to extrapolate observed effects in simple systems to cancer induction in humans (Goodhead 2000). The linear and quadratic terms in an LQ dose-response model for exchange aberrations have been ascribed to single-track and two-track induction of pairs of DNA double-strand breaks (DSBs), respectively, which undergo exchange as a result of misrepair (Goodhead 2000). At low doses and low dose rates of interest in radiation protection and many cancer risk assessments, a linear no-threshold (LNT) dose-response relationship ($\mathcal{R} = \alpha D$) usually is assumed, because the contribution from the quadratic term (βD^2) is expected to be negligible and arguments based largely on microdosimetric considerations discussed in Appendix A, Section A.2.2, suggest that a threshold is implausible (Sachs et al. 1997; Mossman 2001; Preston 2004). Thus, the LNT model and such concepts as DDREF (and relative biological effectiveness, RBE) represent expectations based on data and analyses of dose-responses for chromosome aberrations (Goodhead 2000; Bedford and Dewey 2002; Cox et al. 2005; ICRP 2005; NRC 2006).

Microdosimetric considerations imply that the response at very low doses (about 0.1–1 mGy or less) of low-LET radiation should be determined solely by the linear term (αD) in an LQ dose-response relationship. Because the initial damage is associated with a single track of low-LET radiation, it follows that the sum of the effects of a series of such low doses, widely spaced in time, also should be a linear function of dose. Since a chronic exposure can be thought of as a sequence of very small fractionated exposures, the dose-response also should be linear if the dose rate is sufficiently low that effects are produced by single radiation tracks only. The assumption of an LQ dose-response combined with microdosimetric theory thus provides the justification for incorporating an expected reduction in responses per unit dose at low doses or low dose rates, compared with responses per unit dose at high doses and high dose rates, into a single factor, the DDREF (EPA 2011).

2.2 METHODS USED TO DERIVE DDREF

The reduction factor embodied in the term DDREF has been called a dose-rate effectiveness factor (DREF) (NCRP 1980, 2001; Rossi 1990), a linear extrapolation overestimation factor (UNSCEAR 2000), a linear risk overestimation factor (Pierce and Preston 2000), or a low-dose extrapolation factor (Pierce and Vaeth 1991; Little and Muirhead 2000, 2004). Some estimates of DDREF have been based on analyses of possible non-linearities in dose-responses in studies in which subjects received a single acute exposure (e.g., analyses of dose-responses in the LSS cohort). In this report, the reduction factor estimated from analyses of data for single acute exposures is called a low-dose effectiveness factor (LDEF).

In other studies, the effectiveness per unit dose at high dose rates was compared with the effectiveness per unit dose at low dose rates, typically over the same range of total doses (e.g., in many studies of cancer in animals). Such comparisons yield a DREF. Many animal studies provide data on induction of cancer at dose rates similar to the dose rate below which an exposure is assumed to be chronic in IREP. Studies in which dose-responses at high dose rates are compared with dose-responses from highly fractionated acute exposures (many low-dose fractions) also should yield DREFs.

Estimates of DREF and LDEF also have been derived by analyzing dose-responses for several genetic or cytogenetic endpoints obtained mainly *in vitro*, including somatic mutations, cell transformation, and chromosomal aberrations. There are a number of drawbacks to the use of such data, including complex dose-responses that often are difficult to interpret and concerns about the relevance of observed responses in cells to induction of cancer in humans.

Strictly speaking, only DREFs derived from comparisons of dose-responses from acute exposure with dose-responses from chronic or highly fractionated exposures are suitable for use in estimating a DDREF for chronic exposure. However, given the limited data from epidemiological studies of populations that received chronic or highly fractionated exposures, LDEFs derived from analyses of possible non-linearities in acute dose-responses, especially analyses of the curvature in dose-responses assuming an LQ model, are often used as surrogates for DDREFs for chronic exposure (NRC 2006). The use of such LDEFs to estimate DREFs is usually justified on the basis of microdosimetric considerations and the assumed universal applicability of the LQ dose-response model.

If the dose-response from acute or high-dose-rate exposures is LQ in form, as shown in the example in Figure 2.1, and no information on effects at low doses from such exposures is available, an LDEF may be estimated from the mathematical relationship:

$$\text{LDEF} = (\alpha D + \beta D^2)/\alpha D = 1 + (\beta/\alpha)D . \quad (1)$$

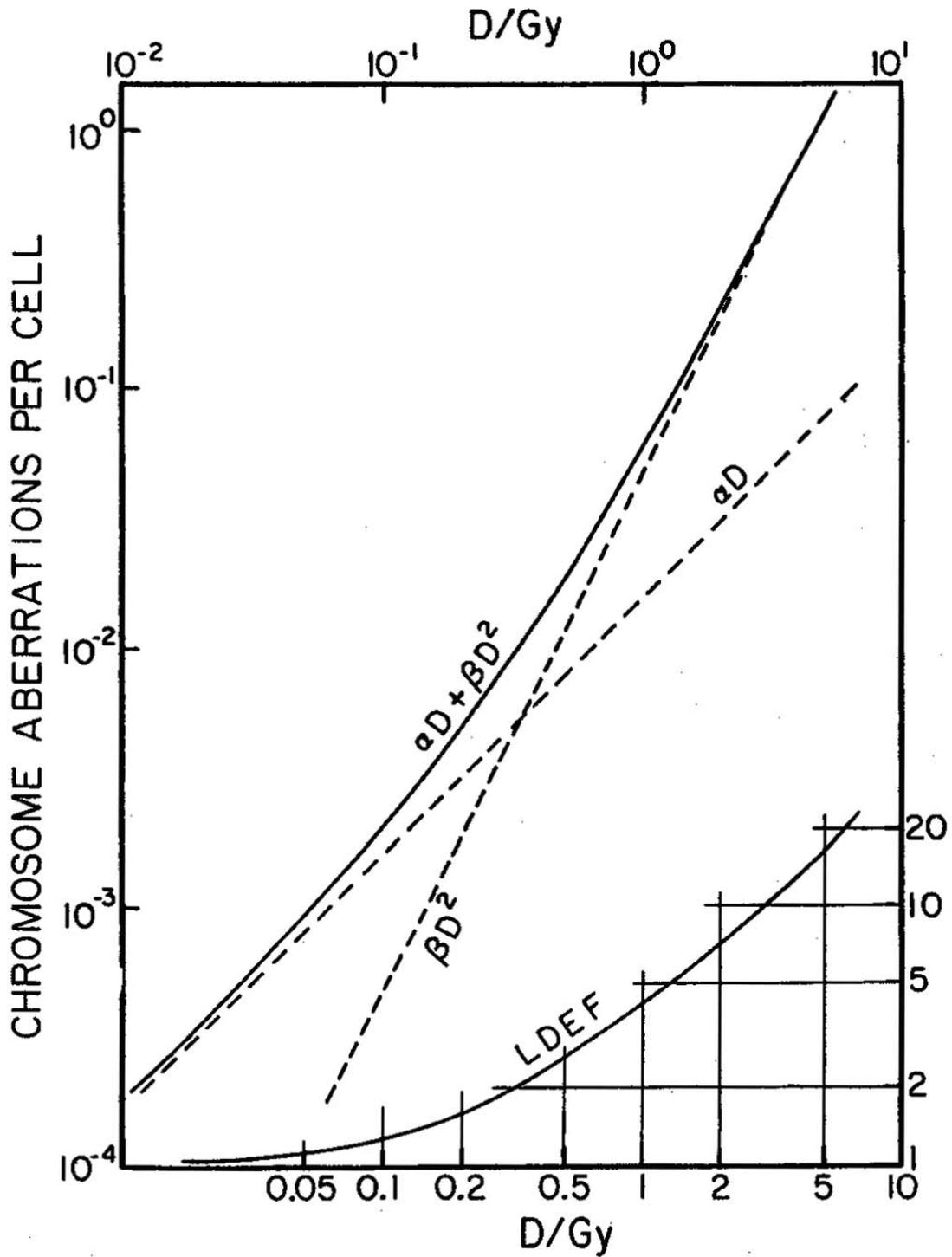


Figure 2.1. Representation of data on dicentric chromosome aberration frequency vs absorbed dose in human lymphocytes to illustrate dependence of low-dose effectiveness factor (LDEF) on dose assuming linear-quadratic (LQ) dose-response; plot also shows linear and quadratic terms in modeled dose-response [modified from Rossi (1990)].

The LDEF in equation (1) is the response per unit dose at a high dose, $(\alpha D + \beta D^2)/D$, relative to the response per unit dose at a low dose, $\alpha D/D$, assuming an LQ dose-response. The ratio β/α is referred to as the curvature parameter. The lower the value of the curvature parameter, the lower the degree of curvature in the dose-response at high doses (or high dose rates). A purely linear response is approached as $\beta/\alpha \rightarrow 0$.

Figure 2.1 and equation (1) indicate that an LDEF derived by assuming an LQ dose-response relationship is not a constant but, rather, depends on the dose (or dose range) from which the response is linearly extrapolated to the origin ($D = 0$). In theory, LDEF is nearly unity at low doses, where the influence of the quadratic term in the assumed dose-response is negligible ($\beta/\alpha \approx 0$), and LDEF increases to a value of two at the dose where the contributions from the linear and quadratic terms are equal.⁶

For the data shown in Figure 2.1, there are no large doses at which LDEF reaches a constant value. In principle, an LDEF estimated from an LQ fit to an acute dose-response that is intended for use in IREP should be obtained from data over a dose range compatible with risk coefficients in IREP, which were derived using fits to data in the LSS cohort at organ doses up to about 4 Gy or more, depending on the cancer type. The approach defined by equation (1) would still produce a dose-dependent LDEF within this dose range.

An LDEF can be estimated for any form of the dose-response from acute exposure. In general, LDEF can be estimated as the ratio of the slope of a linear extrapolation to zero dose of responses to high doses to the slope of an assumed dose-response at low doses.

Since microdosimetric considerations imply that the initial radiation damage at very low doses (about 0.1–1 mGy or less) should be independent of dose rate and, thus, that LDEF and DREF should be the same, the two concepts usually are combined into a DDREF. However, research employing new tools for elucidating the effects of ionizing radiation at the level of chromosomes has raised questions about whether (1) the dose-response relationship is inherently linear-quadratic, even at the level of early DNA damage and repair, and (2) an LDEF derived by assuming such a response should always be the same as a DREF, especially at low dose rates (Trabalka and Kocher 2007).

2.3 APPLICABILITY OF LINEAR-QUADRATIC DOSE-RESPONSE MODEL FOR CANCER

The dose-response for dicentric chromosome aberrations shown in Figure 2.1 has been considered the most reliable and reproducible method of comparing biological responses over a wide range of doses and qualities of ionizing radiation, particularly when blood from the same donor is used (Loucas and Cornforth 2001; Guerrero-Carbajal et al. 2003; Hill 2004). However, the dose-response for dicentrics has

⁶ This equality occurs at a dose of 1 Gy in the LQ dose-response model for leukemias in IREP (Land et al. 2003a); hence, that dose-response incorporates a DDREF of 2 at 1 Gy implicitly.

several limitations that raise questions about its usefulness as a predictive tool for cancer induction in humans. First, cells that carry unbalanced chromosomal exchanges, such as dicentrics, complex aberrations, or substantial chromosomal losses, are not expected to contribute to the viable post-irradiation cell population,⁷ while cells that carry small deletions or balanced exchanges, such as reciprocal translocations, are likely to remain viable, with some such cells potentially contributing to the development of a cancer (NRC 2006). The essential correctness of this point of view has been confirmed by long-term cell-culture after irradiation (Duran et al. 2009). Second, research described below that employed new tools, such as mFISH,⁸ has shown that most of the curvature in acute dose-responses for exchange aberrations that are assayed using conventional techniques is associated with complex, potentially non-transmissible forms,⁹ which can obscure the true dose-response.

Assays of chromosomal aberrations induced by acute exposure using mFISH showed that the apparently LQ dose-response for total exchange aberrations is a composite of several dose-response relationships, each of which is subject to modification by competition for reactive chromosome breaks and none of which is LQ in form (Loucas and Cornforth 2001; Loucas et al 2004; Cornforth 2006). The acute dose-response for simple (transmissible) exchanges (e.g., translocations) lacked significant upward curvature, which is consistent with a one-lesion mechanism for producing these aberrations. However, this conclusion was at odds with the observation of a large decrease in the induction of aberrations when exposures were protracted. Dose-responses for simple aberrations in human lymphocytes and fibroblasts

⁷ Dicentric aberrations are eliminated with each cell division, when they have an equal chance of falling free or producing a lethal anaphase bridge (NRC 2006). Although dicentrics are not considered transmissible, dicentrics and symmetrical translocations, which are considered transmissible, are thought to be produced by the same mechanisms, with the outcome determined by chance on average, and, thus, are expected to occur with equal frequency. Some studies have indicated that the ratio of simple (e.g., viable) symmetrical translocations to dicentrics is about one, consistent with these expectations, which suggests that data on induction of dicentrics might have predictive value for induction of transmissible aberrations. However, other investigators concluded that the ratio of translocations to dicentrics is substantially greater than one and could be at least two (Griffin et al. 1995; Loucas and Cornforth 2001; Loucas et al. 2004). Mestres et al. (2008) reported that β/α in the dose-response for dicentrics in human lymphocytes exposed at acute doses of 0.05–3 Gy was about four times greater than β/α for apparently simple translocations, which suggests that a DDREF based on data for dicentrics might be poorly constrained.

⁸ Multifluor fluorescence in situ hybridization (FISH)-painted chromosome analysis.

⁹ For many years, it was assumed that virtually all radiation-induced exchanges are simple, in that they involve just two exchange breakpoints. Until recently, the degree of complexity of radiation damage to chromosomes could be defined cytogenetically only by simple Giemsa staining and G-band analysis, which indicated that complex aberrations, defined as aberrations that involve a minimum of three breaks in two or more chromosomes, were relatively rare events. Such events were rarely identified using conventional Giemsa staining, and only a few were detectable using G-banding techniques. However, certain rearrangements previously classified as simple translocations or dicentric types (maximum of two breaks in two chromosomes) have since been shown to be “hidden” complex aberrations, which indicates that complex exchanges are much more common than previously thought. The introduction of FISH techniques indicated that many apparently “simple” exchanges, such as dicentrics and reciprocal translocations, resulted from multiple events that produced complex aberrations (Griffin et al. 1995; Anderson et al. 2000; Tawn et al. 2007). Complex dicentric aberrations would not have been distinguished in studies using conventional scoring techniques, which generated the dose-response in Figure 2.1.

were linear, or nearly so.¹⁰ The upward curvature in the dose-responses for total exchange aberrations was primarily associated with complex aberrations that were produced only at higher doses and required as many as 11 chromosome breaks, depending on the dose.

Loucas et al. (2004) concluded that even the acute dose-response for simple aberrations could not be described adequately by a simple polynomial (LQ) function. That is, the limited curvature they observed was due to the competing influences of multiple endpoints (simple plus complex exchanges) with different dose-response relationships, none of which was LQ in form, rather than a curvature in the dose-response relationship for a single endpoint (simple exchanges). Thus, “the acute dose response for the production of simple exchanges does not owe its apparently linear shape to a one-track/one-lesion mechanism,” as would be expected if a simple LQ dose-response relationship applied.

Although an LQ model might describe the acute dose-response for simple exchanges, the presence of complex exchanges distorts the dose-response for simple exchange aberrations. Loucas et al. (2004) further concluded that it would be “naïve to expect that any upward curvature in its shape would obey kinetics described by a second order polynomial, even though, statistically, it may provide an adequate fit to the data” and “fitting the high dose rate data ... to the relationship $\alpha D + \beta D^2$ to extract from it the initial slope may well produce misleading results.”¹¹ Those investigators argued that the coefficient α could be estimated only in studies in which doses were delivered at low dose rates.

The results described above clearly are inconsistent with expectations from a simple LQ model. They call into question whether such a model is a valid paradigm for estimating dose-responses for viable chromosomal aberrations that are thought to be predictive of cancer induction (Goodhead 2000, 2009b). At a minimum, those results cast doubt on the validity of the current calculational basis for a DDREF (as well as estimates of RBE based on those dose-responses) and, in particular, the use of any DDREF derived solely from analyses of curvature in acute dose-responses assuming an LQ model. If that model does not represent the acute dose-response for a relatively simple endpoint, such as the formation of

¹⁰ Simpson and Savage (1995) were the first to use FISH to estimate the frequency of “simple” exchanges induced in human lymphocytes by x rays and predicted that the dose-response for simple dicentric and translocations was essentially linear with dose, contrary to the common belief at that time. In other words, almost all of the curvature in the dose-responses, including dose-responses for dicentric that were scored by conventional Giemsa staining, was due to complex exchanges (Loucas et al. 2004). This prediction was later verified by Loucas and Cornforth (2001) using mFISH, which allows each of the 24 types of chromosomes in the human genome to be uniquely identified and permits ambiguities about the nature of some “simple” exchanges to be resolved.

¹¹ Kellerer and Rossi (1971) and Kellerer and Brenot (1974) also cautioned against over-interpretation of the primary damage model that led to the LQ relationship. Kellerer and Brenot (1974) noted that “these relations are only approximations even if one disregards saturation effects [e.g., due to cell sterilization] at higher doses,” while Kellerer and Rossi (1971) noted that “the various factors which influence the relation between primary damage and the overall cellular effect vary from system to system and may also depend on environmental conditions. It is, therefore, in general not possible to derive explicit dose-effect relations from the kinetics of the primary lesions.”

chromosome exchange aberrations, it is questionable whether it can be considered relevant to an interpretation of data on radiation carcinogenesis, which is a much more complex endpoint.

The near-linearity of the acute dose-response for simple aberrations observed by Loucas et al. (2004) might have called into question whether DDREF is significantly greater than one, were it not for the significant effect of dose rate in their study. As shown in Figure 2.2, a DREF of about 6 was obtained by comparing responses at dose rates of 0.8 mGy and 1.1 Gy min⁻¹. In another study in cells, Tanaka et al. (2009) reported that the linear coefficient in the dose-response for dicentrics plus centric rings induced in mouse splenocytes at doses of 0.1–1 Gy of ¹³⁷Cs gamma radiation decreased when the dose rate was reduced from 0.28 to 0.014 mGy min⁻¹. This result also did not conform to expectations based on an LQ dose-response model.

A significant effect of dose rate also was seen in acute dose-responses for induction of cancers and life-span shortening in laboratory animals, which, as in the mFISH data in cells, apparently were linear (Upton et al. 1970; Ullrich and Storer 1979a, 1979b, 1979c; Gragtmans et al. 1984; Ullrich and Preston 1987; Carnes et al. 1989; Edwards 1992; CIRRPC 1995; NCRP 1993a, 2001; UNSCEAR 1993). If the mFISH data for chromosome exchange aberrations are predictive of cancer induction, those data may help to explain why such dose-responses are often observed in animal data. With regard to the observation of nearly linear dose-responses for most solid cancers in the LSS cohort, NCRP (1993a) cautioned that “[t]he fact that the linear fit appears appropriate for the data over a broad range of doses does not preclude a dose-rate effect. In animal experiments, significant dose-rate effects have been noted for the response of certain tissues in which a linear fit to the data obtained at a high dose rate was considered the best fit.” Thus, in estimating risks from chronic exposure, a DREF would still need to be applied to risk coefficients derived from the nearly linear dose-responses for acute exposure in humans and animals.

We concluded that it is not possible to obtain credible estimates of DDREF based only on an analysis of dose-responses from acute exposure in humans and animals, without also considering data on responses at low dose rates or from highly fractionated acute exposures. We think that a distinction should be made between LDEFs derived from an analysis of the curvature in dose-responses from acute exposure and DREFs derived from comparisons of dose-responses from acute and chronic or highly fractionated acute exposures. Because of concerns raised by mFISH studies and a variety of other data which indicate that induction of cancer by ionizing radiation is too complex a process to be modeled reliably by simple extrapolations from acute dose-responses in individual cells, we think that DREFs derived from data in humans or animals should be given the greatest weight in defining probability distributions of a DDREF.

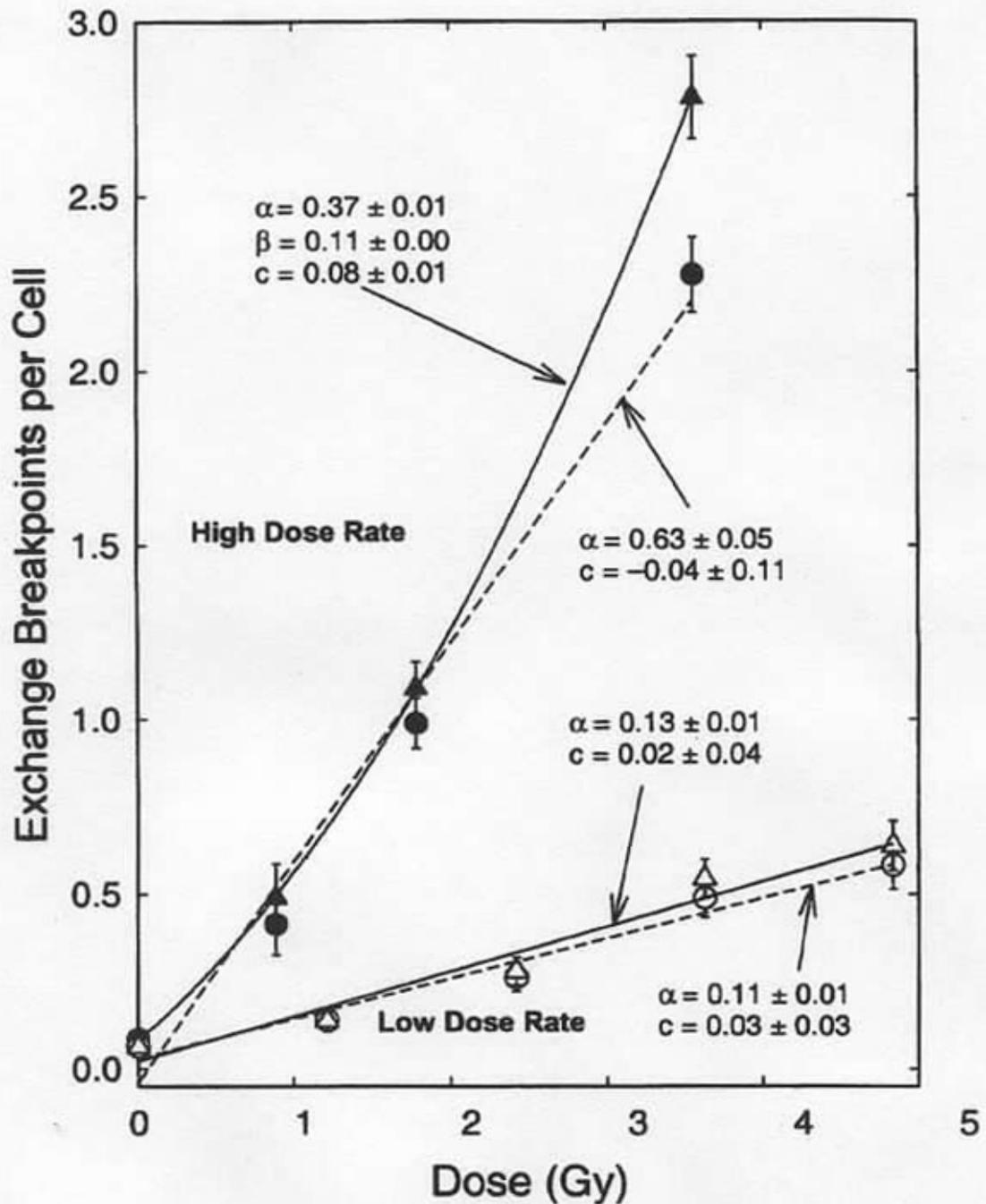


Figure 2.2. Exchange breakpoints per cell vs dose from acute or chronic exposure measured using mFISH (Loucas et al. 2004); data were considered to best represent effects of complex aberrations on the dose-response. Triangles are data for total chromosomal exchanges (simple plus complex), and circles are data for simple exchange aberrations only. At high dose rates, nearly all the curvature in the dose-response is due to breakpoints from complex exchanges produced by three or more breakpoints, whose contribution to total chromosomal damage becomes significant only at doses above 2 Gy. At limiting low dose rates, there is no evidence of upward curvature in the dose-response.

2.4 COMPLICATIONS IN ESTIMATING DDREF

Several factors discussed below and in Section 4 can complicate estimation of a DDREF from data on dose-responses. Acute dose-responses for cancer in laboratory animals are more complex than suggested by simple models, due to cell sterilization¹² and other phenomena that can suppress cancer induction at high doses or mediate apparent threshold responses. The LQ dose-response for acute exposure shown in Figure 2.1 represents data based on a cytogenetic assay in which chromosome aberrations were scored before cells undergo multiple divisions after irradiation (Lloyd et al. 1992). Thus, there is little opportunity for cells with non-transmissible aberrations to be lost, as they would be in irradiated whole animals over time.¹³ A substantial body of other information indicates that induction of cancer in humans and animals is a complex process that cannot be described comprehensively using simple models. Responses at low dose fractions (about 10 mGy per fraction) and low dose rates (e.g., $<0.1 \text{ mGy min}^{-1}$) do not always fit patterns suggested by simple models of acute dose-responses. To complicate matters further, there is some evidence that DDREF and RBE for low-LET radiations depend on energy (Trabalka and Kocher 2007), and estimates of risk and a DDREF for low-LET radiations could be influenced by uncertainty in the RBE for neutrons in exposures of the LSS cohort.

2.4.1 Joint Effects of Cell Sterilization, Dose, and Dose Rate on Dose-Responses

2.4.1.1 Representation of effects of cell sterilization

Unlike the example shown in Figure 2.1, dose-response relationships for induction of cancer in some animal and epidemiological studies exhibit a flattening and downward curvature at higher doses (typically above 2–3 Gy), due presumably to cell sterilization that reduces the pool of cells in which cancer might be initiated. The effect of cell sterilization is thought to be a stochastic phenomenon, which could be related to induction of complex (lethal) mutations or chromosomal aberrations or, in some cases, a response to hyper-radiosensitivity.

The effect of cell sterilization often is represented by an exponential modifier of the dose-response. An assumed LQ dose-response with such a modifier takes the form:

¹² Cell sterilization is defined as a loss of cellular reproductive capability (Ronckers et al. 2006). Cells need not be killed to produce the effect because they cannot become cancerous clones as long as they are unable to divide. For this reason, we prefer the term “cell sterilization” to the more common “cell killing.”

¹³ However, cells that carry some unstable or complex aberrations could be lost during chronic irradiations that last several days to several weeks, depending on the dose and dose rate.

$$\mathfrak{R} = (\alpha D + \beta D^2) \exp(-\gamma D - \delta D^2), \quad (2)$$

where γ and δ are the coefficients in the linear and quadratic terms in the exponential modifier, respectively (UNSCEAR 1993). The quadratic term in the exponential modifier usually is omitted on the grounds that dose-responses from animal and epidemiological data are too imprecise to justify such a complex function (Mole et al. 1983; ICRP 2005; Little et al. 2008).

A representation of cancer incidence from acute exposure assuming a linear-quadratic-exponential (LQE) dose-response in equation (2) is shown in Figure 2.3, curve A. However, no data on carcinogenesis in animals exhibit such a dose-response. The most comprehensive data that exhibit effects of cell sterilization in animals were best represented by quadratic-exponential dose-responses without a linear term (Mole et al. 1983; Coggle 1988; UNSCEAR 2000). Dose-responses in studies of carcinogenesis in animals suggest that doses at the four data points associated with curve A in Figure 2.3 should be in the range of about 1–3 Gy.

The dose-response for all solid cancers combined in the LSS cohort exhibits an apparent effect of cell sterilization (ICRP 2005; Little et al. 2008; Pierce et al. 2008). This effect appears as a flattening or downturn in the dose-response at doses to the colon >1.5 Gy (Pierce et al. 1996a; Preston et al. 2007; Pierce et al. 2008). However, the effect of cell sterilization on the curvature in the dose-response for solid cancers in the LSS cohort was not considered in deriving LDEFs or risk coefficients used in IREP.

An LDEF may be estimated based on the LQE dose-response model described above using a modified version of equation (1):

$$\text{LDEF} = (\alpha D + \beta D^2) \exp(-\gamma D) / \alpha D = [1 + (\beta/\alpha)D] \exp(-\gamma D), \quad (3)$$

where the quadratic term in the exponential modifier in equation (2) to account for cell sterilization is omitted.

2.4.1.2 Impact of cell sterilization on estimation of LDEF

Neglect of cell sterilization in evaluating an acute dose-response, e.g., by excluding the data points at the two highest doses in Figure 2.3, curve A, can result in an overestimation of risk and, hence, an overestimation of DDREF (UNSCEAR 1993). However, this result will be obtained only if estimation of the β coefficient in an LQ dose-response is not influenced by a downward curvature due to cell sterilization. In many cases, the analysis may be compromised by the influence of cell sterilization at doses well below the inflection point marked by the arrow on curve A, where that curve begins to bend.

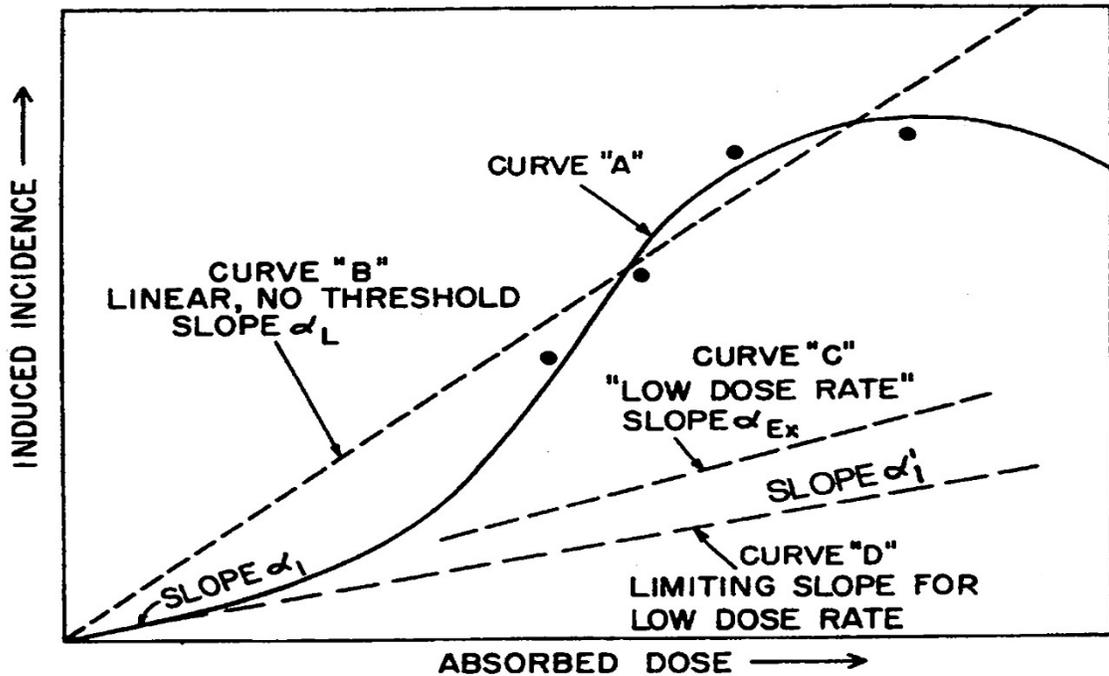


Figure 2.3. Representations of radiation dose-responses for cancer incidence (NCRP 1980). Curve A is “true” dose-response from acute exposure, which is often described by a linear-quadratic dose-response model at doses up to 2–3 Gy, above which cell sterilization and other saturation effects limit the response. Linear, no-threshold curve B with slope α_L was fitted to the four indicated data points and the origin. Slope α_1 indicates slope of dose-response in essentially linear portion of curve A at low doses, which, when extended to higher doses, is curve D. Curve C with slope α_{Ex} represents data at moderate-to-high doses but low dose rates. At very low dose rates, curve C may, in principle, approach or become indistinguishable from curve D with slope α_1' , which is the extension of low-dose portion of curve A with slope α_1 (i.e., slope $\alpha_1' = \text{slope } \alpha_1$).

An upward curvature in the assumed LQ region of the dose-response below the inflection point in curve A may be affected significantly by cell sterilization such that the quadratic term (β coefficient) is underestimated (Hoel 2015), but the effect may be obscured by uncertainties in the data. For example, as discussed in Section 5.2, the value of β in the less-complex LQ model fit to data on cancer incidence in the LSS cohort is poorly constrained unless the model is restricted to data at doses <2 Gy.

Estimates of DDREF (an LDEF) using equation (3) typically have large uncertainties, particularly when an LQE dose-response is applied to epidemiological data, due to the wide range of combinations of values of the parameters α , β , and γ that are consistent with the data (ICRP 2005). Thus, even though neglect of cell sterilization could result in an overestimation of risk, it is difficult to justify use of the more complex model on statistical grounds. This situation presents a dilemma, because statistical considerations

should not be used to justify ignoring biological reality. Thus, an effective approach to dealing with this problem needs to be developed if credible estimates of DDREF are to be obtained when dose-responses are fitted with an LQE model. [We note that a quadratic-exponential model without a linear term describes some dose-responses for leukemia and solid tumors in animals (Mole et al. 1983; Di Majo et al. 1986; Coggle 1988) and the dose-response for leukemia mortality in the LSS cohort (Little et al. 2008; UNSCEAR 2008). Such a dose-response implies that DDREF approaches ∞ as the dose approaches zero.]

There are several other problems associated with an analysis of data on acute dose-responses using an LQE model, such as that depicted as Figure 2.3, curve A, including that data in the low-dose region (e.g., <200 mGy) usually are unavailable. Even when such data are available, they generally have large uncertainties. If sufficient data were available over the entire dose range, a DDREF could be estimated by analyzing the curvature by assuming a purely LQ model and restricting the analysis to the portion of the curve below the inflection point at which the influence of cell sterilization appears to become important. This approach yields an LDEF that depends on dose.

The larger concern is that analyses described above appear to be compromised since it is now questionable that the assumption of an inherently LQ or LQE dose-response from acute exposure can predict the slope of the dose-response from chronic exposure at low doses. The same concern applies when LDEFs are estimated as the ratio of the slope of a linear extrapolation to zero dose of responses at high doses to the slope of an assumed linear dose-response at low doses.

Superposition of a curvilinear response to represent the effect of cell sterilization on a dose-response for cancer induction that could be linear, linear-quadratic, or even quadratic (Mole et al. 1983; Di Majo et al. 1986; Coggle 1988) further complicates the interpretation of the “true” dose-response and estimation of an LDEF or a DREF. Even more complex dose-responses (U- or J-shaped, or with downward curvature at lower doses suggestive of supralinearity, rather than cell sterilization) have been reported in some studies of animal carcinogenesis.

2.4.1.3 Impact of cell sterilization on estimation of DREF

Because dose-responses from acute exposure are so variable and difficult to interpret in terms of a single, universally applicable model, ratios of the slopes of dose-response curves obtained from animal data that correspond to curves B (slope α_L in a dose-response from acute exposure) and C (slope α_{EX} in a dose-response at low dose rates) in Figure 2.3 often have been used to estimate a DDREF (i.e., a DREF based on the method of derivation). This approach was used by NCRP (1980) to estimate a DREF, which was referenced by ICRP (1991), and by Edwards (1992) and UNSCEAR (1993). This approach is advantageous in that it is based on fits to dose-responses at high dose rates that often were linear or nearly

so and dose-responses at low dose rates that often were linear. Thus, it was not necessary to invoke an LQ model for the dose-response at high dose rates to estimate a DREF from such data. ICRP (1991), Edwards (1992), and UNSCEAR (1993) all characterized these estimates as DDREFs even though, strictly speaking, they are DREFs. Statistical techniques for dealing with uncertainty in such curve fits are discussed by Edwards (1992).

We emphasize that it often has been assumed that dose-responses from acute or high-dose-rate exposures are LQE and, thus, that curve B in Figure 2.3 is only pseudolinear. That is, the expectation was that curve B was derived from a linear fit to data that are not truly part of a linear dose-response. As a result, the slope of curve B (α_L) could be greatly influenced by the method of data selection. If the data used to define the linear extrapolation in curve B were obtained at doses higher than the dose range over which risk coefficients in IREP were derived (e.g., doses to animals above about 4 Gy, assuming that the radiosensitivities of laboratory mammals and humans for cancer induction are comparable), the resulting DREF could represent an overestimate or, more likely, an underestimate in humans, depending on the lowest doses at which cell sterilization becomes important.

For purposes of a comparison with a dose-response in the LSS cohort, we assume that the inflection point on curve A in Figure 2.3 occurs at a dose of about 1.5–2 Gy and that the highest dose is about 5 Gy. At the maximum in a dose-response at high dose rates of the type shown in Figure 2.3 (the data points used to generate curve B by linear extrapolation, which bracket the inflection point at which the effects of cell sterilization appear to become important), DREF will also be a maximum because the slope of curve B (α_L), which is the numerator in the calculation of DREF, is essentially at its maximum. The resulting estimate of DREF would appear to be valid for use in estimating a DDREF for chronic exposure in humans. However, if the data were obtained at doses well below or well above the inflection point in such a dose-response (i.e., outside the range of the four data points associated with curve A), linear slopes of the data at high dose rates, akin to the slope α_L shown as curve B, would be lower, and estimated DREFs could underestimate a DDREF for chronic exposure in humans.

2.4.1.4 Influence of dose rate on estimation of slope of dose-response at low doses

The selection of dose-responses at high and low dose rates can affect estimates of DREF significantly. The limiting slope of the acute dose-response at low doses shown in Figure 2.3 as curve D with slope $\alpha_1' = \alpha_1$ may differ from the slope of the dose-response at low dose rates shown as curve C. Thus, the “true” DREF may differ from a DREF estimated using ratios of the slopes of curves B (α_L) and C (α_{Ex}); i.e., a DREF estimated as α_L/α_{Ex} may not be the same as an LDEF estimated as α_L/α_1 . Due to practical limitations, the slope of curve D cannot be estimated from animal data at very low dose rates; it

can only be estimated from an analysis of the curvature in the response at high dose rates (curve A) assuming an LQ or LQE fit to the data, with all the potential problems associated with such an analysis.

To minimize the effects of age dependencies and the latency period on analyses of cancer incidence in animals, the duration of chronic exposures had to be shorter than an animal's lifetime (e.g., about one month in mice). Doses of several Gy were required to observe excess cancers at low dose rates, and the lowest practicable dose rate was about $0.03 \text{ mGy min}^{-1}$ (Edwards 1992). Because the dose rate of about $0.06 \text{ mGy min}^{-1}$ that was used in nearly all animal studies to estimate a DREF is more than two orders of magnitude higher than the dose rate from continuous exposure of a radiation worker at the current annual dose limit and about four orders of magnitude higher than an average dose rate to workers based on reported annual collective doses (Vrijheid et al. 2007), higher DREFs could apply to humans under conditions more typical of occupational exposures. Thus, we should be concerned about whether the slopes of dose-responses obtained from animal data at the higher dose rates (akin to curve C in Figure 2.3) could result in underestimates of DREF.

2.4.1.5 Summary and conclusions

The relevance of dose-responses from acute exposure and at low dose rates in animals to estimating a DREF in humans depends on the dose range over which the data were obtained, the potential influence of cell sterilization on the responses, and the dose rates used to estimate the slope of the response at low doses (Figure 2.3, curve C). There also are biological and methodological reasons why DDREFs derived from animal studies not only are quite variable but also are difficult to relate to a DDREF in humans, even when an analysis is restricted to data on tumor types relevant to humans.

Most estimates of a DREF based on data in laboratory animals were obtained from studies in which maximum doses were about 2 Gy and in no case more than 3.3 Gy. Thus, dose ranges over which DREFs were derived in animal studies appear to be compatible with the range of organ doses of about 0–4 Gy or higher, depending on the cancer type, in analyses to derive risk coefficients in IREP on the basis of modeled dose-responses in the LSS cohort (Land et al. 2003a). This conclusion probably is valid even when an analysis of dose-responses in the LSS cohort is restricted to doses of 0–2 Gy, as in some recent studies (Preston et al. 2004, 2007). Few data sets in animals show a significant effect of cell sterilization at doses up to the maximum, even though some investigators (e.g., the BEIR VII committee) assumed that the animal data at high doses are so affected. Some dose-responses from acute exposure or from chronic exposure at high dose rates were essentially linear, in contrast to the example in Figure 2.3, and estimates of DREF in those cases are essentially independent of dose.

2.4.2 Potential Energy Dependence of RBE and DDREF for Low-LET Radiations

2.4.2.1 Background

Increases in biological effectiveness with decreasing energy of photons have long been observed in radiobiological studies, especially studies of dicentric chromosome aberrations in human lymphocytes (ICRU 1986; NCRP 1990; Schmid et al. 2002; ICRP 2003; Hill 2004). Those observations appear to reinforce an expectation that variations in LET (or lineal energy)¹⁴ of photons with energy are reflected in variations in biological effectiveness, with low-energy x rays being more biologically effective, per unit absorbed dose, than high-energy x- or gamma rays. This phenomenon is thought to be a consequence of a significant shift in energy deposition patterns towards higher lineal energy with decreasing photon energy, as shown in Figure 2.4, due to the decreasing energy of secondary electrons produced (Hill 2004).

As in estimating a DDREF, RBEs for different low-LET radiations at low doses or low dose rates (RBE_M) usually are estimated by assuming an LQ dose-response model. An RBE_M is estimated as the ratio of the initial slopes (linear coefficients, α) of the dose-response curves for the radiation under study and a reference radiation. Because a DDREF and an RBE_M for low-LET radiations are derived from an acute dose-response in radiobiological or epidemiological data by assuming an LQ relationship, they are interrelated through their joint dependence on α coefficients in the dose-response model. As the α coefficient for a reference radiation decreases, RBE_M for a radiation type of concern and DDREF for the reference radiation both increase (CIRRPC 1995).

In radiation protection and in estimating cancer risks to exposed individuals, a DDREF for low-LET radiations generally is assumed to be independent of energy. However, a variety of radiobiological data suggest that DDREF may decrease with decreasing energy in a manner that parallels observed increases in biological effectiveness with decreasing energy of photons and electrons in many radiobiological studies. The importance of a possible overestimation of DDREF at low energies of photons (and electrons) is that cancer risks at low doses or low dose rates could be underestimated. The extent of underestimation could be as much as an order of magnitude depending on assumptions about biological effectiveness and DDREF (Trabalka and Kocher 2007).

¹⁴ LET is a concept of limited usefulness because it is not simply related to energy deposition in a given volume of irradiated material. Lineal energy, which is related to LET but does not suffer from most of its deficiencies, is more closely related to biological effectiveness (ICRU 1986), and lineal energy distributions for different radiation types, such as those shown in Figure 2.4, are considered to be more informative. For example, the mean lineal energies of 250 kVp x rays and ⁶⁰Co gamma rays are 3.5 keV μm^{-1} and 1.6 keV μm^{-1} , respectively, and their ratio (2.2) could approximate their relative biological effectiveness. When compared in the same way, 250 kVp x rays should be about twice as effective as the electrons and photons from decay of ¹³¹I (Brenner 1999a).

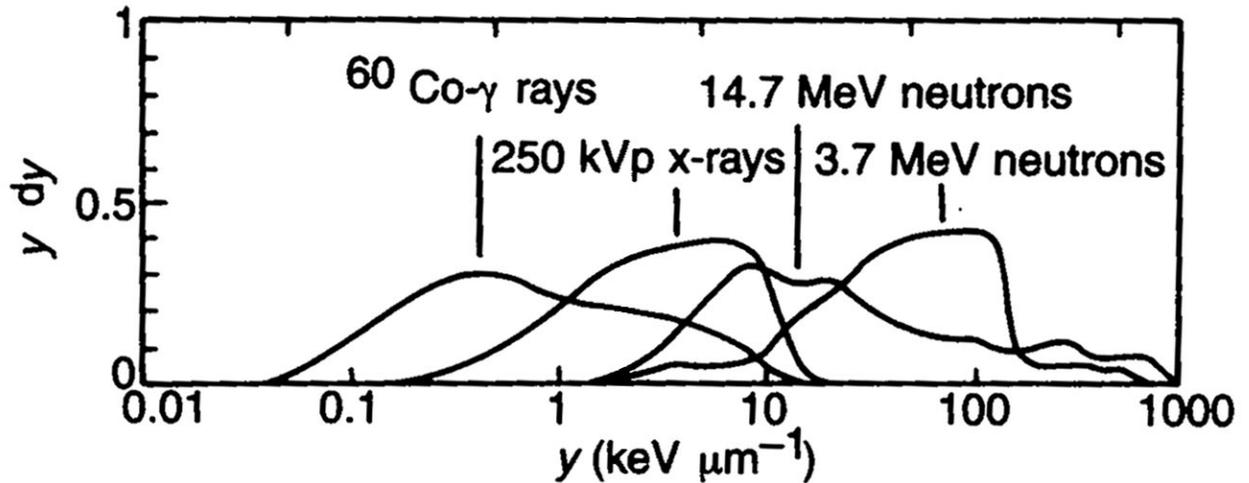


Figure 2.4. Measured probability distributions of dose vs lineal energy (y) in 1- μm -diameter sphere of tissue-equivalent material for different types of incident radiation (Kellerer and Rossi 1974; NCRP 2001). Points of note include (1) the large differences in energy deposition patterns of high- and low-LET radiations, (2) the tendency for a higher lineal energy for 250 kVp x rays compared with ^{60}Co gamma rays, (3) the inclusion of a small component at higher lineal energies ($>10 \text{ keV } \mu\text{m}^{-1}$) in distributions for the two low-LET radiations, and (4) the larger contribution of higher lineal energies to the distribution for x rays compared with gamma rays.

2.4.2.2 Significance

Most epidemiological data used in cancer risk assessments, other than data in the LSS cohort, were obtained in studies of medical patients exposed to x rays, while most of the data on tumor induction in laboratory animals were obtained in studies using high-energy gamma radiation. Effects of dose fractionation or protraction in studies in which subjects were exposed to x rays may have been obscured by the effects of a higher biological effectiveness of x rays relative to high-energy gamma rays. Thus, the effects of variations in biological effectiveness and DDREF with photon energy on estimates of risk need to be considered. However, recent information discussed in Section 2.4.2.4 suggests that variations in DDREF with energy may be much less than suggested by data on dose-responses for dicentric chromosome aberrations discussed by Trabalka and Kocher (2007) and may not be a major concern.

Equally importantly, in some studies of radiation carcinogenesis in animals, one type of low-LET radiation (orthovoltage x rays¹⁵) was used in acute exposures and another (e.g., high-energy gamma rays) was used in chronic exposures, which potentially biases estimates of DDREF. Consequently, the effects of

¹⁵ Orthovoltage x rays typically are generated at peak tube voltages of about 180–300 kV.

possible differences in biological effectiveness of different types of low-LET radiation (Hill 2004; Kocher et al. 2002, 2005; Heyes et al. 2009) on comparisons of dose-responses in animals that have been used to estimate a DDREF need to be considered. This concern also applies when DDREFs are estimated by comparing cancer risks in medically exposed persons and the LSS cohort.

2.4.2.3 Summary of efforts to quantify energy dependence of RBE

Gamma rays from ^{60}Co decay are a commonly used reference radiation in radiobiological studies to estimate RBEs for other radiation types because their mean energy (1.25 MeV) is similar to the mean energy of gamma rays produced by the atomic bombs in Japan of about 3 MeV (Straume 1995). The possibility that orthovoltage x rays and other lower-energy photons are 2–3 times more effective in inducing cancer in humans at low doses than high-energy photons has been noted by the BEIR VII committee (NRC 2006), ICRU (1986), ICRP (2003, 2007), and UNSCEAR (2008). ICRP (2003) also recommended that such an increase in biological effectiveness should be noted in cancer risk assessments whenever risk estimates derived from exposures to high-energy gamma rays are applied to x rays. However, an increase in biological effectiveness of lower-energy photons is not incorporated in cancer risk models preferred by the BEIR VII committee (NRC 2006) or UNSCEAR (2008). ICRP and the other organizations based their conclusions about a possible difference in the effectiveness of orthovoltage x rays and high-energy gamma rays in inducing cancer in humans at low doses mainly on data on induction of chromosome aberrations, such as the central estimates of RBE_M summarized in Table 2.1.

Table 2.1. Medians and ranges of central estimates of dose-response parameters, LDEFs, and maximum RBEs at low doses (RBE_M) for induction of dicentric chromosome aberrations in human lymphocytes by 220–250 kVp x rays relative to ^{60}Co gamma rays^a

Radiation type	Mean energy (keV)	Linear α -coefficient $\times 10^{-2}$ (Gy^{-1})	β/α (Gy^{-1})	LDEF at 1 Gy	RBE_M
220–250 kVp x rays	≈90	4.4 (3.6–9.1)	1.4 (0.66–1.9)	2.4 (1.7–2.9)	2.7 (1.5–3.8)
^{60}Co gamma rays	1250	1.6 (1.1–3.9)	3.4 (1.4–5.4)	4.4 (2.4–6.4)	≡1.0

^a Estimates are based on LQ dose-response model applied to six paired sets of data for x rays and ^{60}Co gamma rays in studies of acute exposures of human lymphocytes given in Table 8 in Kocher et al. (2002, 2005), which cites original data sources. Doses ranged from 0.05 to 8 Gy depending on the study.

As summarized in Table 2.2, a comparison of a dose-response for induction of dicentric chromosome aberrations in human lymphocytes exposed to low doses of 250 kVp x rays (Lloyd et al. 1992) with the dose-response for chromosome aberrations induced by acute exposure to ⁶⁰Co gamma rays summarized in Table 2.1 suggests a slightly lower RBE_M for the x rays. Such a reduction might be due to the higher mean energy of the x rays in Table 2.2 compared with the mean energy in Table 2.1. However, estimates of RBE_M in Tables 2.1 and 2.2 do not differ significantly when uncertainties in the central estimates, which are summarized by Kocher et al. (2002, 2005), are taken into account.

An energy dependence of the biological effectiveness of photons is incorporated in cancer risk models in IREP in the form of probability distributions of radiation effectiveness factors at low doses or low dose rates, denoted by REF_L (Land et al. 2003a). REF_Ls for photons were derived by Kocher et al. (2002, 2005) from an analysis of estimates of RBE_M obtained from radiobiological and epidemiological data on the effectiveness of photons of various energies in inducing stochastic effects at low doses or low dose rates relative to high-energy photons (e.g., ⁶⁰Co gamma rays).¹⁶ The REF_L for 30–250 keV photons in IREP, which covers most energies in spectra of orthovoltage x rays, is a subjective probability distribution with a median and 95% CI of 1.9 (1.0, 4.7) (Kocher et al. 2002, 2005, 2008; Land et al. 2003a).

Table 2.2. Dose-response parameters and median and range of central estimates of maximum RBEs at low doses (RBE_M) for induction of dicentric chromosome aberrations in human lymphocytes by 250 kVp x rays delivered at doses ≤0.3 Gy relative to ⁶⁰Co gamma rays^a

Radiation type	Mean energy (keV)	Linear α-coefficient × 10 ⁻² (Gy ⁻¹) ± 1 SE ^b	β/α (Gy ⁻¹)	RBE _M (range)
250 kVp x rays ^c	169	2.9 ± 1.0	β coefficient not statistically significant ^d	1.7 (0.7–2.6)

^a Estimates are based on data for x rays from analysis of pooled results from irradiation of lymphocytes from 20 donors by Lloyd et al. (1992) and six sets of data for ⁶⁰Co gamma rays from Table 8 in Kocher et al. (2002, 2005).

^b Standard error.

^c Filtered by 4.3 mm Cu.

^d Since β coefficient was not determined, LDEF at 1 Gy could not be estimated.

¹⁶ Kocher et al. (2002, 2005) used the term “radiation effectiveness factor” (REF) to distinguish a quantity that represents biological effectiveness for purposes of estimating cancer risks in humans from “relative biological effectiveness” (RBE), which strictly applies only to results of specific radiobiological studies conducted under controlled conditions (NCRP 1990).

Although the probability distribution of REF_L for 30–250 keV photons used in IREP was based in large part on data summarized in Table 2.1 and uncertainties in those estimates of RBE_M , that distribution gives a weight of 25% to the value 1.0 to take into account the lack of a clear difference in the biological effectiveness of orthovoltage x rays and high-energy gamma rays when cancer risks in medical patients exposed to x rays were compared with risks in the LSS cohort (Kocher et al. 2002, 2005). The BEIR VII committee (NRC 2006) cited the absence of adequate epidemiological information to support its decision not to make a specific recommendation about a difference in the effectiveness of x rays and radiations from the atomic bombs in estimating cancer risks in humans. The committee also noted that differences in exposures of medical patients to x rays and exposures of the LSS cohort, including the much higher doses in many medical exposures and dose fractionation or protraction in those exposures, may affect comparisons of estimated risks.¹⁷ Citing evidence based on data on chromosomal aberrations, such as the data summarized in Table 2.1, and biophysical considerations of the type taken into account by ICRU (1986), the BEIR VII committee stated that “it may be desirable to increase risk estimates in [our] report by a factor of two or three for the purpose of estimating risks from low-dose x-ray exposure” (NRC 2006). Sasaki et al. (2008) cited this recommendation and a similar recommendation by ICRP (2003) in support of their decision to use an RBE_M of 2.5 for orthovoltage x rays relative to high-energy gamma rays in their analysis of data on cancer in animals for the purpose of estimating an RBE_M for neutrons that was used in estimating cancer risks in the LSS cohort.

2.4.2.4 Recent challenges to data on energy dependence of RBE and DDREF

As discussed in Section 2.3 and by Goodhead (2009b), it is now questionable whether estimates of RBE_M or DDREF derived from analyses of dose-responses for induction of dicentric chromosome aberrations by low-LET radiation that were scored using conventional assays are meaningful. Thus, judgments by ICRU (1986), ICRP (2003, 2007), the BEIR VII committee (NRC 2006), UNSCEAR (2008), and Kocher et al. (2002, 2005) about the biological effectiveness of photons of energy less than about 250 keV are compromised by uncertainties in the nature of dose-responses for dicentric chromosome aberrations that were scored using conventional assays.

¹⁷ The BEIR VII committee’s comparisons of epidemiological data were problematic in that estimated risks in different populations were not adjusted to account for differences among the cohorts, including the ranges of doses to exposed individuals, the degree of dose fractionation or protraction, x-ray energies in exposures of medical patients, baseline risks of specific cancers and their impact on transfer of risks between populations, and other important modifiers of risk, such as sex, age at exposure, and attained age. These issues also affected comparisons of epidemiological data by Kocher et al. (2002, 2005). Valid comparisons would require a pooled analysis in which such factors are fully considered.

Previous suggestions of a substantial dependence of DDREF on photon energy (Trabalka and Kocher 2007) are similarly called into question. As indicated in Table 2.3, dose-responses for simple chromosome exchanges in human lymphocytes and fibroblasts at acute doses of high-energy photons obtained in studies using mFISH (Loucas and Cornforth 2001; Loucas et al. 2004) are consistent with a DDREF (an LDEF) at 1 Gy of no more than about 1.3. A DDREF of this magnitude is considerably lower than estimates for high-energy photons based on an assumption that an LQ model represents the acute dose-response for induction of simple and complex exchanges combined in studies of dicentric chromosome aberrations that were scored using conventional assays, as indicated in Table 2.1 and reported elsewhere (NCRP 1990; Guerrero-Carbajal et al. 2003). If a DDREF for high-energy photons (e.g., ^{60}Co gamma rays) were close to 1, there should be little reduction with decreasing energy unless a DDREF substantially less than 1 is possible.

Similar concerns apply to the use of data on induction of dicentric chromosome aberrations that were scored using conventional assays to investigate the energy dependence of RBE_M for photons. Studies using mFISH cast doubt on the validity of estimates of RBE_M derived from linear (α) coefficients in an assumed LQ dose-response model for simple and complex exchanges combined. We reiterate that the data on induction of dicentric chromosome aberrations in human lymphocytes by ^{60}Co gamma rays and 220 or 250 kVp x rays summarized in Table 2.1 were the primary basis for the probability distributions of REF_L s at photon energies less than 250 keV used in IREP (Kocher et al. 2002, 2005). Since DDREF and RBE_M are estimated by assuming an LQ dose-response model, estimates of REF_L for lower-energy photons that are based on estimates of RBE_M from conventional studies of dicentric chromosome aberrations would be too high if DDREFs for high-energy photons obtained in those studies are too high.

Table 2.3. Dose-response parameters and LDEFs for induction of exchange aberrations in human lymphocytes and fibroblasts by acute exposure to ^{137}Cs gamma rays from studies using mFISH^a

Cell type	Dose range (Gy)	Type of exchange aberrations	Linear α -coefficient $\times 10^{-2}$ (Gy^{-1})	β/α (Gy^{-1})	LDEF at 1 Gy ^b
Lymphocytes ^c	1–4	Total simple	22 ± 7	0.28	1.3
Fibroblasts ^d	0.8–3.6	Total simple	18 ± 4	0.23	1.2

^a mFISH: multicolor fluorescence *in situ* hybridization.

^b LDEF calculated as $1 + (\beta/\alpha)$.

^c Loucas and Cornforth (2001).

^d Loucas et al. (2004).

These concerns are reinforced by recent results summarized in Table 2.4 on induction of apparently simple translocations¹⁸ that were scored using FISH (Mestres et al. 2008). The DDREF for photons does not vary significantly over a wide range of energies, and the curvature in the dose-responses (mean β/α of 0.65 Gy^{-1}) is consistent with a DDREF (LDEF) at 1 Gy of about 1.7 at all energies. These results also suggest that RBE_M is significantly greater than 1 at the lowest energies and may increase with decreasing energy. The energy dependence of RBE_M may conform to expectations based on microdosimetric considerations (ICRP 2003; Hill 2004). If these results are confirmed and are supported by data for other biological endpoints relevant to carcinogenesis, concerns about a potential effect of a decrease in DDREF with decreasing photon energy (Trabalka and Kocher 2007) would be allayed.

Data shown in Figure 2.5 that would allow direct estimation of an RBE for induction of cancer in animals by orthovoltage or lower-energy x rays relative to high-energy gamma rays are sparse and not altogether consistent. The apparently higher effectiveness of acute exposures to 250 kVp x rays for induction of myeloid leukemia in RF mice, as indicated by a comparison of the slopes of curves 1 and 2 at doses up to about 3 Gy, is not seen in a comparison of the slopes of curves 3 and 4 in CBA/H mice.

Table 2.4. Dose-response parameters, LDEFs, and maximum RBEs at low doses (RBE_M) for induction of apparently simple translocations in human lymphocytes by x rays relative to ^{60}Co gamma rays from studies using FISH^a

Radiation type	Beam half-value layer thickness (mm Al)	Linear α -coefficient $\times 10^{-2} (\text{Gy}^{-1})$	$\beta/\alpha (\text{Gy}^{-1})$	LDEF at 1 Gy	RBE_M
30 kVp x rays	0.53	2.98 ± 0.56	0.67	1.67	2.1 ± 0.65
80 kVp x rays	2.27	2.48 ± 0.52	0.62	1.62	1.7 ± 0.63
120 kVp x rays	8.52	1.97 ± 0.48	0.63	1.63	1.4 ± 0.60
180 kVp x rays	Not provided	2.09 ± 0.34	0.63	1.63	1.5 ± 0.50
^{60}Co gamma rays	Not applicable	1.43 ± 0.36	0.71	1.71	$\equiv 1.0$

^a Data obtained by Mestres et al. (2008). Blood obtained from same donor in studies at three lowest x-ray energies was acutely irradiated as whole blood at doses of 0.05–3 Gy. Dose-responses for 180 kVp x rays and ^{60}Co gamma rays were obtained previously; see Mestres et al. (2008) for references. Uncertainties are standard errors.

¹⁸ Dose-responses for total dicentrics reported by Mestres et al. (2008) are not directly comparable to data for apparently simple translocations. Dicentrics that affected painted or counterstained portions of chromosomes were recorded, even when the painted portion showed no aberrations. Those results also were somewhat equivocal, in that RBE_M exhibited only a weak tendency to increase with decreasing energy, and there was no tendency for LDEF to decrease with decreasing energy. The curvature in the dose-response for dicentrics also was about four times greater than the curvature in the dose-response for apparently simple translocations.

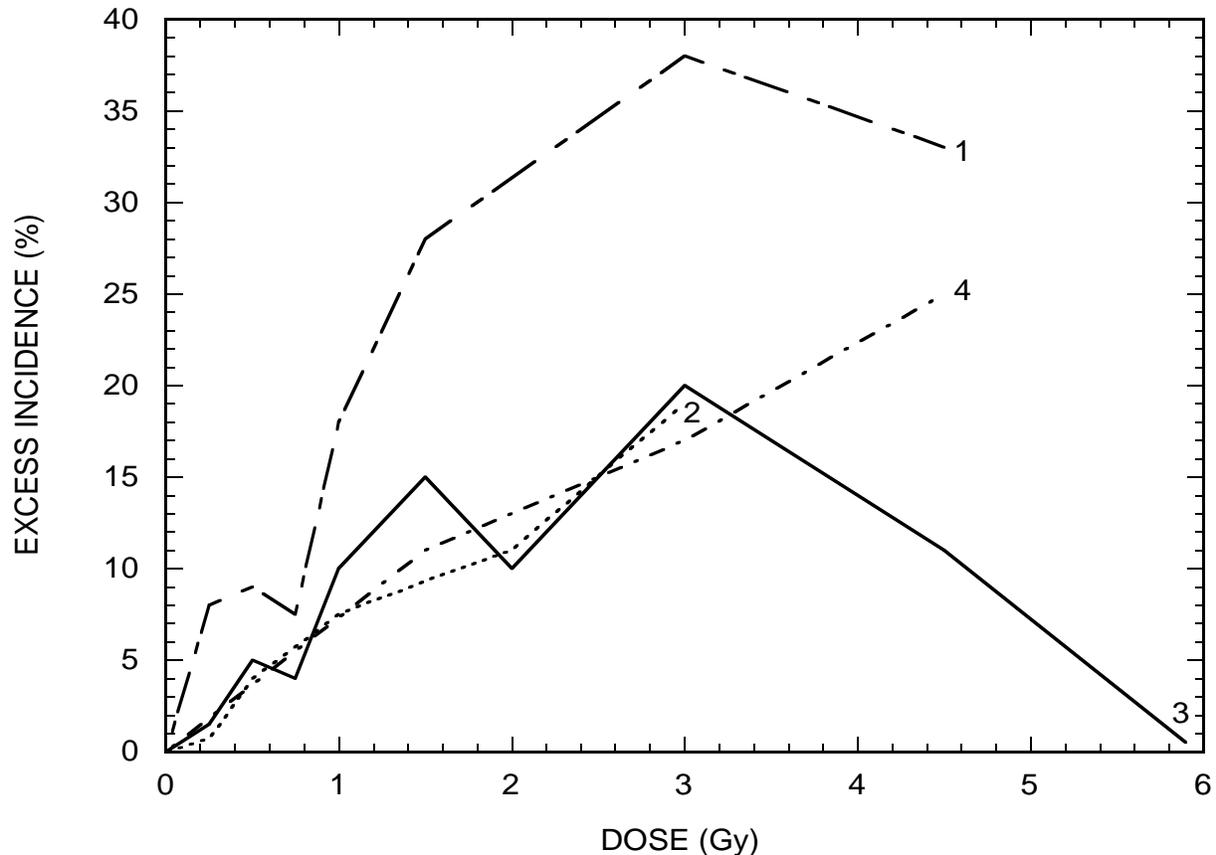


Figure 2.5. Dose-responses for lifetime incidence of myeloid leukemia in two strains of male mice from acute exposure to different low-LET radiations: data in RF mice exposed to 250 kVp x rays (curve 1; Upton et al. 1970) or ^{137}Cs gamma rays (curve 2; Ullrich et al. 1987); data in CBA/H mice exposed to 250 kVp x rays (curve 3; Mole et al. 1983) or ^{60}Co gamma rays (curve 4; Mole and Major 1983) [modified from NRC (1990)].

Increases in the biological effectiveness of low-energy beta particles emitted in decay of tritium relative to 180–250 kVp x rays and high-energy ^{137}Cs or ^{60}Co gamma rays were observed in many radiobiological studies of various endpoints, including induction of cancer in rats and mice (Straume and Carsten 1993; Little and Lambert 2008). A subjective probability distribution of an REF_L for electrons of energy <15 keV with a median of 2.4 and 95% CI of (1.2, 5.0) relative to high-energy photons, which is intended to represent data on RBE at low doses or low dose rates (RBE_M), is used in IREP (Kocher et al. 2002, 2005, 2008; Land et al. 2003a). An increase in the biological effectiveness of tritium beta particles by a factor of 1.7 was included in early ICRP recommendations on radiation protection (ICRP 1960), but no such increase has been included in subsequent recommendations (ICRP 1977, 1991, 2003, 2007).

The Independent Advisory Group on Ionising Radiation of the U.K.’s Health Protection Agency (HPA 2007) reviewed radiobiological data and biophysical considerations that support an RBE for tritium

beta particles greater than 1. The advisory group concluded that this information supports an RBE of 1–2 relative to orthovoltage x rays and 2–3 relative to ^{60}Co gamma rays (the recommended reference radiation) for induction of stochastic effects in humans at low doses or low dose rates. A rounded RBE of 2 for the latter was recommended for use in epidemiological studies and retrospective risk assessments. The advisory group also recommended that ICRP consider adopting a radiation weighting factor (w_R) of 2 for tritium beta particles (HPA 2007; Bridges 2008), a recommendation since supported by Goodhead (2009a) but opposed by ICRP (Cox et al. 2008) and Paquet and Métivier (2009).

Data on incidence of mammary tumors in female Sprague-Dawley rats (Gragtmans et al. 1984) or myeloid leukemia in CBA/H mice (Johnson et al. 1995) that were reviewed in the HPA report (HPA 2007) indicate that the effectiveness of tritium beta particles in inducing cancer is about 20% higher than the effectiveness of 200 kVp x rays delivered chronically. Little and Lambert (2008) reached a similar conclusion by developing a probability distribution of an RBE for tritium beta particles relative to orthovoltage x rays with a central estimate of 1.17 and 95% CI of (0.96, 1.39) based on an analysis of selected studies, including the studies by Gragtmans et al. (1984) and Johnson et al. (1995).

Little and Lambert (2008) also developed a probability distribution of an RBE for tritium beta particles relative to high-energy gamma rays with a central estimate of 2.19 and 95% CI of (2.04, 2.33) based on an analysis of selected studies. If we accept the conclusions of Little and Lambert (2008) and HPA (2007) about the biological effectiveness of tritium beta particles, orthovoltage x rays with a mean energy of about 100 keV are about twice as effective as high-energy photons in inducing cancer.

2.4.2.5 Current status and conclusions

The information discussed above presents a dilemma. Studies in cells using FISH and mFISH call into question the validity of estimates of RBE_M for lower-energy photons that were the primary basis for the probability distributions of REF_L for photons of energy <250 keV (including orthovoltage x rays) used in IREP. However, estimates of RBE_M in this energy range are needed to assess the potential effect of a higher biological effectiveness of orthovoltage x rays on estimates of cancer risks in animals and humans for the purpose of evaluating the effect of dose fractionation and protraction on dose-responses, i.e., estimating a DDREF.

The primary support for the possibility of an $\text{REF}_L >3$ in the distribution in IREP that applies to orthovoltage x rays (the distribution at photon energies of 30–250 keV) came from estimates of RBE_M for induction of dicentric chromosome aberrations that probably are invalid. Indirect estimates of REF_L obtained from data on cancer induction in mice and rats suggested values for orthovoltage x rays in the

range of less than 2 to about 3 (Kocher et al. 2002, 2005).¹⁹ Similar estimates derived from data on cell transformation in mouse or hamster cells, life-span shortening in mice, or tumor induction in rats indicated values of about 3 or less (Kocher et al. 2002, 2005). Thus, if the questionable data from studies of induction of chromosome aberrations are eliminated, the width of the probability distribution of REF_L used in IREP would be narrowed from about 1–5 to about 1–3. Results from studies of simple translocations in cells or cancer in animals discussed above and the indirect comparisons based on the reviews by HPA (2007) and Little and Lambert (2008) suggest a central estimate of REF_L of about 2 for orthovoltage x rays relative to ^{60}Co gamma rays.

On the basis of available information, we propose to use a modified probability distribution of REF_L for 30–250 keV photons relative to high-energy gamma rays with a median of 2 and 95% CI of (1, 3) for purposes of estimating a DDREF from analyses of dose-responses in animals and humans. To represent this uncertainty, we assume a discrete probability distribution that gives 25% weight to the value 1.0, 50% weight to the value 2.0, and 25% weight to the value 3.0. The weight given to the value 1.0 is consistent with the assumption in the probability distribution in IREP described in Section 2.4.2.3. We do not think that current information supports a conclusion that DDREF also varies with photon energy.

2.4.3 Effect of Uncertainty in RBE for Neutrons on Dose-Responses in LSS Cohort

In an analysis of data in the LSS cohort, Kellerer et al. (2006) concluded that the RBE for neutrons from the atomic bombings in Japan could have been >100 at a dose of 1 Gy, rather than 10 as usually assumed (NRC 2006; Preston et al. 2007). This possibility reinforces our concern about an over-reliance on dose-responses from acute exposure in the LSS cohort to estimate a DDREF. If risks in that cohort were influenced by greater contributions from neutrons than usually assumed (i.e., a greater risk per unit absorbed dose), dose-responses from gamma rays and neutrons combined in the LSS cohort should be biased toward linearity as a consequence of the presumably linear dose-response for neutrons (high-LET radiation). Such a bias would lead to underestimates of an LDEF in dose-responses from gamma rays. Dose-responses for cancer induction in lightly shielded tissues, such as the female breast and thyroid, would be expected to show the largest effect of higher RBEs for neutrons (Walsh et al. 2004a; Kellerer et al. 2006).

If the conclusion by Kellerer et al. (2006) is correct, risks of breast and thyroid cancer in the LSS cohort from exposure to gamma rays would be reduced by about a factor of two. This effect could reduce differences in the biological effectiveness of x rays and high-energy gamma rays that are inferred based on

¹⁹ These estimates of REF_L were based on comparisons of RBE_M for fission neutrons or tritium beta particles obtained from studies in which x rays and high-energy gamma rays were used as reference radiations.

comparisons of epidemiological data, and it could increase estimates of LDEF that are based on an analysis of the curvature in acute dose-responses in the LSS cohort.

Given the preliminary nature of findings by Kellerer et al. (2006) and the uncertainty in the effect of their correction on the curvature in dose-responses from high-energy gamma rays in the LSS cohort, we have not taken those findings into account in our analysis. However, that analysis and similar conclusions from an analysis by Sasaki et al. (2008) provide evidence of substantially greater uncertainties in RBE_M for neutrons and DDREF for gamma rays in exposures at Hiroshima and Nagasaki and, thus, greater uncertainties in estimates of cancer risks from gamma rays in the LSS cohort than previously considered.

Estimates of RBE_M for induction of leukemia in laboratory animals by fission neutrons are more than an order of magnitude lower than estimates of RBE_M for induction of solid cancers (Sasaki et al. 2008). A similar reduction in RBE_M is seen in data on induction of leukemia in humans by alpha particles (Harrison and Muirhead 2003; ICRP 2003). This reduction suggests that the greater degree of curvature in the dose-response for leukemia in the LSS cohort, which should not have been influenced greatly by the dose from neutrons, could be a better representation of the expected curvature in the dose-response for solid cancers in the LSS cohort and, hence, could provide a better estimate of LDEF for the latter. However, data discussed in Section 5.8.2 indicate that this hypothesis is not valid.

2.5 OVERALL SUMMARY AND CONCLUSIONS

For purposes of estimating cancer risks from exposure to low-LET radiation, a dose and dose-rate effectiveness factor (DDREF) can be defined as a factor by which the risk per unit dose at low doses or low dose rates differs from the risk per unit dose at high doses and high dose rates. For example, if the dose-response from acute exposure is assumed to be linear-quadratic (LQ)—i.e., the response, \mathcal{R} , as a function of an acute dose, D , is modeled as $\mathcal{R} = \alpha D + \beta D^2$ —as is often assumed in cancer risk assessments, then DDREF is a dose-dependent quantity calculated as $1 + (\beta/\alpha)D$. Although an LQ dose-response is often assumed, it is important to note that a DDREF can be calculated for any form of the dose-response.

A DDREF embodies two concepts: (1) a low-dose effectiveness factor (LDEF), which can be estimated from an analysis of a possible non-linearity in a dose-response from acute exposure, and (2) a dose-rate effectiveness factor (DREF), which can be estimated by comparing a dose-response from an acute exposure at a high dose with the dose-response from chronic or highly fractionated acute exposures at a similar or lower total dose. With reference to Figure 2.3, LDEFs and DREFs are estimated as follows:

- An LDEF is estimated from a dose-response for acute exposure as the ratio of the slope of a linear, no-threshold extrapolation of the response at a high acute dose (slope α_L in Figure 2.3) to the slope of the dose-response at low doses (slope α_1); $LDEF = \alpha_L/\alpha_1$.

An LDEF generally depends on dose when the acute dose-response is non-linear. If an LQ dose-response relationship is assumed, an LDEF also can be calculated as $1 + (\beta/\alpha)D$.

- A DREF is estimated as the ratio of the slope of a linear, no-threshold extrapolation of the response at a high acute dose (slope α_L in Figure 2.3) to the slope of the dose-response, which presumably is linear, from chronic or highly fractionated acute exposure (slope α_{EX}); $DREF = \alpha_L/\alpha_{EX}$.

If the slopes α_1 and α_{EX} in Figure 2.3 are equal, LDEF and DREF are the same at any dose.

Estimation of a DDREF for low-LET radiations is not a simple process, even if concerns about the effects of a possible dependence of DDREF on the energy or biological effectiveness of those radiations are ignored. Recent developments in radiation cytogenetics research (e.g., mFISH studies) called into question the original basis for a DDREF, which is an assumption that an LQ dose-response model applies to cancer induction in whole animals. In particular, the large effects of dose rate on dose-responses in a study of exchange aberrations using mFISH by Loucas et al. (2004) and in many studies of radiation carcinogenesis in laboratory animals indicate that an adjustment similar to a DREF may need to be applied to estimates of cancer risks from acute exposure based on a dose-response that appears to be linear (or nearly so), despite what the LQ model implies. Thus, dose-responses for such endpoints as chromosomal aberrations that underpin standard paradigms to translate radiation effects observed at the cellular level to cancer in whole animals or humans should be interpreted with caution. In addition, derivation of an LDEF from data on acute dose-responses for induction of cancers in animals or humans can be strongly influenced by effects of cell sterilization at higher doses, even if those effects are superimposed on an inherently LQ (or linear) dose-response.

Because of concerns raised by studies using mFISH and a variety of other information that indicates that induction of cancer by ionizing radiation is too complex a process to be modeled effectively by simple extrapolations from acute dose-responses in individual cells, it appears that DDREFs cannot be estimated reliably from data in animals and humans without considering data on effects of exposures at low dose rates or highly fractionated exposures (many acute exposures at low doses per fraction). We therefore think that a distinction should be made between LDEFs based on analyses of non-linearities in dose-responses from acute exposure and DREFs based on comparisons of dose-responses from acute and

chronic exposures, and that estimates of DREF should be given at least as great a weight in defining a DDREF and its uncertainty as estimates of LDEF.

We also think that further investigation of the energy dependence of the biological effectiveness and DDREF for low-LET radiations is important. There is a need for further investigations of DDREFs and RBEs in studies of single endpoints of relevance to cancer induction in humans (e.g., tumor induction in animals). In the interim, the uncertainty introduced by the potential effects of variations in biological effectiveness with photon (or electron) energy on estimates of cancer risks and DDREF needs to be considered in evaluating data from animal and epidemiological studies.

The significance of a higher biological effectiveness of 30–250 keV photons relative to high-energy gamma rays in estimating cancer risks and DDREFs is evaluated in analyses of data in animals and humans presented in Sections 4 and 5. For purposes of estimating a DDREF based on the data in animals and humans, a modified probability distribution of REF_L with a median of 2 and 95% CI of (1, 3) is assumed to represent differences in cancer risks per unit dose from exposure to orthovoltage x rays of energies comparable to 30–250 keV photons and exposure to high-energy gamma rays.

Another potentially important concern is the biological effectiveness of neutrons in exposures of the LSS cohort. If the biological effectiveness of neutrons was substantially higher than generally assumed in estimating risks of solid cancers in the LSS cohort, estimates of DDREF for high-energy gamma rays based on an analysis of the curvature in dose-responses for solid cancers could be too low (i.e., biased toward a DDREF of 1). Studies of the effect on estimates of DDREF of an underestimate of the biological effectiveness of neutrons in exposures of the LSS cohort are taken into account in our analysis. Given that the biological effectiveness of fission neutrons in inducing leukemia should be much less than the biological effectiveness in inducing solid cancers, an analysis of the curvature in the dose-response for leukemia in the LSS cohort should be affected to a lesser extent by the biological effectiveness of neutrons. However, data discussed in Section 5.8.2 indicate that the curvature in the dose-response for all leukemias in the LSS cohort probably cannot be used to represent the curvature in the dose-response for all solid cancers from exposure to high-energy gamma rays.

3. STATUS OF LNT DOSE-RESPONSE MODEL AND POSSIBLE ALTERNATIVES

3.1 INTRODUCTION

In recent years, the debate over the validity of the LNT dose-response model for radiation-induced cancer in humans has mainly revolved around the differing views expressed in major reports by committees representing the French and U.S. National Academies of Science (Aurengo et al. 2005; NRC 2006). The differing views were discussed at major symposia and in a series of publications (Brenner and Sachs 2006; Tubiana et al. 2006; Averbeck 2009; Brenner 2009).

In 2005, David Brenner of Columbia University presented his views on why reviews of the effects of ionizing radiation at low doses by the U.S. and French committees led to different and contradictory conclusions. His conclusions, which were presented at the Fourth Annual Gilbert W. Beebe Symposium,²⁰ include the following:

- “The biophysical arguments for a linear no-threshold model at doses below those amenable to epidemiology are plausible, but rely on assumptions about single cells acting autonomously, which we know are not fully correct.”
- “At this time, we don’t know if deviations from the predictions of this linear approach will be large or small, or even whether they will increase or decrease low-dose cancer [risk] estimates.”
- “The issue is how to extrapolate cancer risks from low doses to very low doses.”
- “The real battleground is over the validity and utility of the biophysical argument—that’s all we have at very low doses.”
- “BEIR VII [NRC 2006] accepts [the biophysical argument] rather uncritically, though stressing uncertainty.”
- “The French report [Aurengo et al. 2005] rejects [the biophysical argument] because it does not accept that there is a cancer risk at [about] 10 mSv [and] it argues that there are different biological mechanisms active at extremely low doses.”

The biophysical underpinning of the LNT model is discussed in Sections 1.1 and 2.1 and in Appendix A, Section A.2.2. In this section, we consider whether current information supports Brenner’s

²⁰ From presentation on “Cancer Risks at Very Low Doses: Why Did the US and French National Academies Come to Directly Opposite Conclusions?,” Fourth Annual Gilbert W. Beebe Symposium, December 5, 2005, National Academy of Sciences, Washington, DC; see also Brenner and Sachs (2006), Hei (2006), and Brenner (2009).

conclusions, which would indicate a need to increase the uncertainty in DDREF at low doses (<30 mGy) and low dose rates (<0.1 mGy min⁻¹), or whether current information warrants abandoning the LNT hypothesis and replacing it with an alternative model. We do this by summarizing information obtained largely from radiobiological studies that addresses the question of whether the biophysical arguments are still valid.

Our review considered information on biophysical, molecular, and cellular phenomena that determine the biological effects of ionizing radiation and recent information on epigenetic, intercellular, and homeostatic mechanisms that appear to play a much larger role in radiation carcinogenesis than formerly considered. This information, which is discussed in Section 3.2, indicates that the nature and expression of the genome and maintenance of its integrity in response to mutagens and clastogens (agents that can damage chromosomes), which determine the link between initial radiation damage and induction of cancer, are far more complex than previously thought. Phenomena that are thought by some to call for alternatives to the LNT model are discussed in Section 3.3. Section 3.4 presents an evaluation of the current status of the LNT model as the default assumption for radiation carcinogenesis at low doses or low dose rates in light of the new information thought by some to support alternative models.

Our review indicates that the uncertainty in linear low-dose extrapolations of cancer risks is at least as great as the uncertainty suggested by Brenner. However, it also raises serious questions about whether any alternative model (e.g., threshold, adaptive response, or hormesis) is an appropriate substitute for the LNT approach, despite its uncertainty.

3.2 REVIEW OF PHENOMENA INVOLVED IN RADIATION CARCINOGENESIS

3.2.1 Initial Radiation Damage and Cellular Responses

The rapid and extensive increase in knowledge resulting from the genomics revolution and the development of new tools for elucidating the effects of ionizing radiation on biological systems (such as x-ray and ion microbeams and exquisitely sensitive markers and assays for DNA damage and mutagenesis) has not only expanded our understanding of the kinetics of radiation damage and repair but also demonstrated the complexities and interrelationships of the cellular systems that maintain genomic (DNA and chromosomal) integrity.

Figure 3.1 illustrates the two interconnected chains of events and processes that take place in the cell nucleus in response to exposure to ionizing radiation. Those on the left are dedicated to repair of DNA damage, and those on the right involve signaling that leads to an expression of genes necessary for executing the programs of cellular recovery, cell cycle control, or cell death. In addition, production of

reactive oxygen species in the cytoplasm (or external to the cell) sets off a chain of events that can modulate DNA damage fixation and repair, cell cycle arrest, and apoptosis. Such processes may play a role in signaling that leads to bystander effects²¹ in unirradiated cells. Figure 3.1 does not include effects on mitochondria, which play a major role in apoptosis and also may play an important role in regulation of bystander effects.

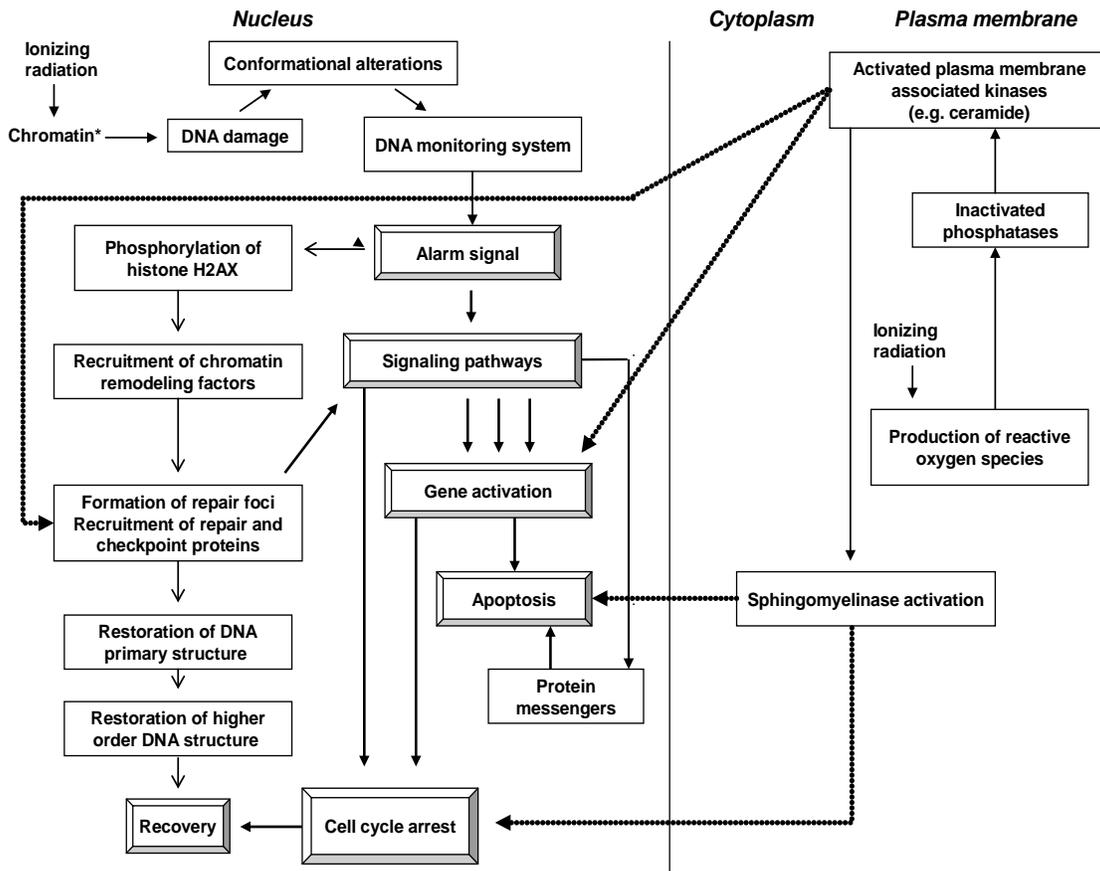


Figure 3.1. Events initiated by DNA damage-monitoring system (left) and DNA-damage-independent processes involving plasma membrane (right) in response to exposure to ionizing radiation [modified from Szumiel (2008)]. *DNA is never found in isolation in cell nucleus but is surrounded by histone and nonhistone proteins in dynamic polymer called chromatin, which is the main constituent of chromosomes.

²¹ Bystander effects occur in nuclei of cells not traversed by a radiation track. They are thought to be triggered by chemical signals released by directly irradiated cells and to contribute to the overall tissue response.

As described in Section 2.1, the LQ dose-response model, from which the LNT relationship is derived, was based in large part on data obtained from studies of the kinetics of production and rejoining of DNA DSBs. A considerable body of evidence discussed in Appendix A, Section A.1.1, suggests that production of DNA DSBs in mammalian cell systems is linear with dose and that biological mechanisms for dealing with DSBs or even more complex clustered damage²² that can be produced, even at the lowest doses, by a single track of low-LET radiation, as indicated in Figure 3.2, may not be 100% effective. On this basis, there would not be a dose at which all radiation-induced damage could be repaired with fidelity.

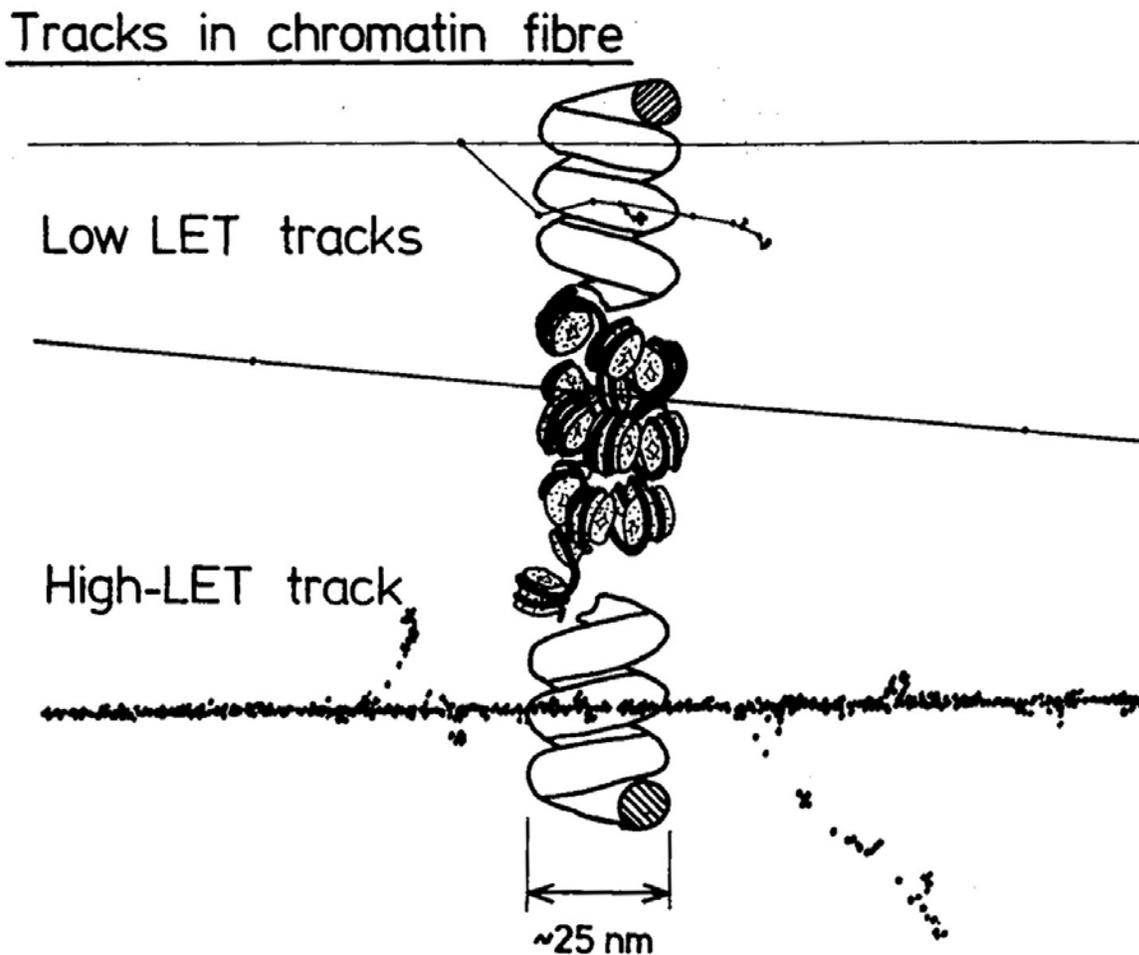


Figure 3.2. Diagram of high- and low-LET radiation tracks in section of chromatin (ICRP 1991).

²² Clustered damage is affected by the chemical environment surrounding DNA (Sutherland et al. 2002), which is highly folded, constrained, and compacted by histone and nonhistone proteins in chromatin that consists of fibers of DNA wound around histone protein core particles (nucleosomes) linked together by other histones.

Figure 3.2 illustrates that low-LET radiation causes relatively sparse ionizations except at the ends of tracks, whereas high-LET radiation causes dense ionizations along an entire track. A significant fraction of the dose from low-LET radiation is delivered at track ends by low-energy secondary electrons with LETs that approach those of high-LET radiation. This fraction of the dose from low-LET radiation is thought to produce clustered DNA damage. The diameter of the condensed chromatin shown at the center of the depicted fiber is about 30 nm (about 20% greater than shown in the figure). In comparison, the diameter of double-stranded DNA is about 2 nm and the diameter of the linear “beads on a string” euchromatin fiber (not shown), on which active transcription takes place, is about 10 nm.

The extent to which DNA repair is error-prone *in vivo* is not known with certainty. In recent years, it also became apparent that chromatin context and architecture affect the fate of damaged DNA by altering the initial level of damage and its repair,²³ and that cellular signaling is an important determinant of recovery from, or expression of, radiation damage. Damaged DNA or chromatin is the major site of signal generation, although alternative signaling at the plasma membrane may be triggered by reactive oxygen species, as indicated in Figure 3.1. Cells with deficiencies in specific enzymes essential to repair activation and cell-cycle checkpoint control may be compromised even if they have a functional DNA repair system. Other signals may affect proneness to apoptosis (programmed cell death), the balance between DNA damage fixation and repair, and translocation of proteins that participate in the response to ionizing radiation. The interplay between the various signals determines the extent to which repair of radiation damage is supported or limited. In some cell types, this interplay includes processes independent of DNA damage that are guided by plasma membrane-generated signaling. Irradiated cells may die as a result of apoptosis triggered by signals generated solely at the plasma membrane. Sphingolipid signaling can control growth or survival through biochemical changes initiated by binding to cell-surface receptors or by epigenetic²⁴ changes in gene expression that are triggered by binding to histone deacetylases, which

²³ The nature, repair, and expression of radiation damage to DNA in chromatin can be affected significantly by (1) variations in the structure of the basic chromatin fiber, (2) the higher-order folding of chromatin into complex, highly condensed forms, such as transcriptionally inactive heterochromatin, which increase stability by covalent modifications to histones but limit accessibility of repair factors, (3) movements of chromatin within the nucleus during the cell cycle and while repair processes are operating, which increase the likelihood that separated DSBs will interact to form chromosomal rearrangements, and (4) nonrandom spatial associations of chromatin, which influence the spectrum of aberrations produced. Competition between different types of reactive chromosome breaks is a major factor that affects the expression of radiation damage and interpretation of the resulting dose-responses. The net effects are complex, but as yet poorly understood, and the influence of the histone protein component of chromatin has not yet been incorporated formally into biophysical models of DNA-damage formation.

²⁴ Epigenetic changes are (1) heritable changes in gene expression that occur without a change in DNA sequence or (2) non-mutational but stable changes to cellular genomes. They are produced by such mechanisms as DNA cytosine methylation, covalent modifications of histones, physical alterations in nucleosome positioning, and certain aspects of RNA interference (Jones and Baylin 2007) that direct a “structural adaptation of chromosomal regions so as to register, signal, or perpetuate altered activity states” (Bird 2007).

alter the structure of chromatin in the nucleus (Hait et al. 2009). Thus, competence in DNA repair is necessary, but not sufficient, for successful recovery from radiation-induced damage (Szumiel 2008).

However, it has been proposed that a low-dose threshold (or even hormesis) could result from the absence of repair, not from the absence of DSBs and complex lesions at very low doses; i.e., damaged cells that are unable to replicate are removed from the cell cycle or killed via apoptosis and, therefore, cannot contribute to carcinogenesis (ICRP 2005; Jeggo and Löbrich 2006). The affected organ or tissue might be genetically programmed to accommodate a certain amount of cell loss as a means of minimizing the risk of mutation and cancer due to misrepair, and, if cellular response mechanisms are primed by a low dose of ionizing radiation to “over-respond” to DNA damage (ICRP 2005), beneficial effects (i.e., hormesis) conceivably could result from a lessening of endogenous non-radiation-induced DNA damage in exposed cells.

The crux of the problem is whether the phenomena described above, which sometimes are observed *in vitro*, also occur *in vivo* and generally affect radiation carcinogenesis at low doses or low dose rates. These matters are discussed further in Section 3.2.5.

3.2.2 Importance of Epigenetic Phenomena

The existence of an epigenetic “histone code” in chromatin may extend the information potential of the genetic code considerably,²⁵ and there is clear evidence of a link between alterations in the structure of chromatin and cell-cycle progression, DNA replication, DNA damage and repair, and overall genomic stability. Chromatin-based epigenetics plays a major role in developmental reprogramming of cell lineages, as well as normal functioning and progression through the cell cycle in an adult, and also can contribute to genomic instability and the development of tumors. Chromatin remodeling factors control self-renewal of stem cells that are considered to be important cellular targets for initiation of cancer by ionizing radiation.

Normal development and differentiation of cells requires stable repression of genes that are not required in specific cell types; this is accomplished via epigenetic mechanisms. In mammals, methylation of DNA partners with DNA-histone interactions to organize the genome into transcriptionally active and inactive zones. Chromatin architecture and epigenetic memory also are regulated by RNA-directed

²⁵ Chromatin *in toto*, rather than DNA alone, is the true physiological template of genetic information and is subject to a diverse array of covalent modifications that regulate access to the underlying DNA. These modifications alter chromatin structure, which leads to inherited differences in transcriptional “on-off” states or to the stable propagation of chromosomes. The combinatorial nature of these modifications reveals a “histone code” that considerably extends the information potential of the genetic code. This epigenetic marking system represents a fundamental regulatory system with far-reaching consequences for cell fate decisions and normal and pathological development (Jenuwein and Allis 2001), e.g., development of a cancer in response to exposure to ionizing radiation.

processes that involve recruitment of histone-modifying complexes and DNA methyltransferases. Long non-coding RNAs (ncRNAs)²⁶ play a broad role in epigenetic controls. For example, they interact with chromatin and mediate recruitment of histone methyltransferases that epigenetically silence DNA transcription. In addition, small ncRNAs and their associated proteins act in distinct but related RNA silencing pathways that regulate DNA transcription, chromatin structure, genomic integrity, and messenger RNA stability.

Accumulating evidence of the critical role of ncRNAs has led to the conclusion that the nature of genetic programming in higher organisms may have been misunderstood by assuming that most genetic information is expressed and transacted by proteins, as it is in bacteria. Essential for normal development, such epigenetic controls can become misdirected in cancer cells and in other human disease syndromes. Epigenetic changes can promote cell proliferation, inhibit apoptosis, and induce angiogenesis during tumor development by activating proto-oncogenes²⁷ and silencing tumor suppressor genes.

The emerging complexity of systems for information packaging, storage, and recall in chromosomes suggests that our understanding of the formation, repair, and expression of damage by ionizing radiation may be considerably more rudimentary than previously believed.

3.2.3 Effect of Ionizing Radiation on Carcinogenesis

Biophysical arguments for the LNT hypothesis were developed originally without knowledge of the importance of epigenetic factors, as well as intercellular interactions and homeostatic mechanisms described in the following section, that appear to play a much larger role in radiation carcinogenesis than formerly considered. As Brenner pointed out in his discussion summarized in Section 3.1, biophysical arguments for a linear response at low doses are plausible only if single cells, when genetically altered by radiation, act autonomously to produce a cancer. However, cancer represents the failure of a system of checks and balances that control cell numbers. The aberrant functioning of genes that promote or inhibit cell growth or survival can be caused by errors introduced into DNA or by faulty epigenetic mechanisms that control gene expression and are mitotically heritable. Genetic alterations and epigenetic lesions can work individually or in concert to cause a loss of control over cell growth and subsequent development of a cancer (Jones and Baylin 2007).

The formation of a cancer thus is accompanied by epigenetic changes and genetic alterations of the genome. Because radiation damage can have a genetic and an epigenetic component, the two cannot be

²⁶ Long non-coding RNAs are RNAs that are transcribed from relatively short DNA sequences once thought to be “junk” DNA because they do not code for protein sequences.

²⁷ Proto-oncogenes are normal genes which, when mutated, can contribute to cancer development.

considered in isolation, even though it generally is not clear which are causes and which are consequences with respect to carcinogenesis. Are effects of ionizing radiation that are manifested as changes in protein expression produced primarily by mutations in genes that code for critical proteins or groups of proteins, changes in DNA or DNA expression associated with small noncoding RNAs, changes in the level of DNA methylation of affected genes, or covalent modifications to histone proteins in chromatin—or some combination of these? It appears that definitive answers to such questions cannot be provided in many cases, and evidence for epigenetic effects of radiation exposure is too extensive to be ignored.

Carcinogenesis also is an evolutionary process that requires and selects for multiple genetic and epigenetic changes that result in an evasion of anti-proliferative and cell-death-inducing mechanisms that limit clonal expansion of somatic cells in normal tissues (Lowe et al. 2004; Bartkova et al. 2005). There are indications that an individual tumor is a heterogeneous population of cells with differing carcinogenic and metastatic potentials (Jones and Baylin 2007; Bartkova et al. 2005; Gorgoulis et al. 2005; Halazonetis et al. 2008), rather than a homogeneous clone derived from a mutation or chromosome aberration induced in a single cell as implied by biophysical arguments for a linear dose-response (NCRP 2001). For example, a recent analysis indicated that the particular mutated genes and the types of mutations were different in breast and colon cancers (Wood et al. 2007). In addition, there was no substantial overlap in the assemblages of mutated genes in different tumor specimens in the same tissue type that were obtained from different individuals (Sjoblöm et al. 2006; Shibata 2012).

Genes affected by exposure to ionizing radiation include those involved in transcription, cell signaling and growth regulation, cell-cycle checkpoint control, apoptosis, DNA damage response and repair, differentiation, angiogenesis, cellular adhesion and motility, escape from immune control, and tissue invasion and metastasis. The number of mutations required appears to be incompatible with the simple paradigms and epidemiological models currently applied to induction of cancer by ionizing radiation, because mutation of individual genes is an inefficient, slow process (Hanahan and Weinberg 2000; Sjoblöm et al. 2006; Wood et al. 2007). The analysis of breast and colon cancers by Wood et al. (2007) indicated that these tumors had each accumulated approximately 80 mutant genes.

Thus, some investigators concluded that acquisition of genomic instability,²⁸ which conceivably could include an epigenetic component, is an enabling characteristic that is needed to generate the increased mutability required for tumor formation (Hanahan and Weinberg 2000; Baverstock and Belyakov 2005). However, the role of induced genomic instability in radiation-induced cancer is

²⁸ Genomic instability is a condition in which the rate of introduction of genomic changes, either point mutations, chromosomal structural aberrations, aneuploidies (abnormal numbers of chromosomes), amplifications of genes, or other permanent alterations, is elevated (usually grossly) compared with the normal condition (Bedford and Dewey 2002). It has been suggested that genomic instability is a hallmark of premalignant and malignant cells, as well as a precondition for development of a malignancy.

controversial (UNSCEAR 2009). In addition, research on carcinogenesis indicates that activation of the DNA-damage-response network, particularly DNA-damage-checkpoint genes, typically precedes genomic instability and conversion to a malignancy.

3.2.4 Modulation of Carcinogenesis by Integrated Cellular and Multicellular Responses

The cellular response to radiation damage also is part of a multi-cellular response to a perturbation of the homeostatic state of the affected organ or tissue that is directed toward restoring that state. As illustrated in Figure 3.3, cells in intact tissues exist in a three-dimensional configuration in which they interact with each other, the extracellular matrix, other cells that form the microenvironment, and, in some cases, elements of the immune system. Such multicellular responses are mediated largely through epigenetic mechanisms. Exposure to radiation can induce changes that impede this restoration, which could lead to survival and expression of genomically unstable cells and, ultimately, to cancer.

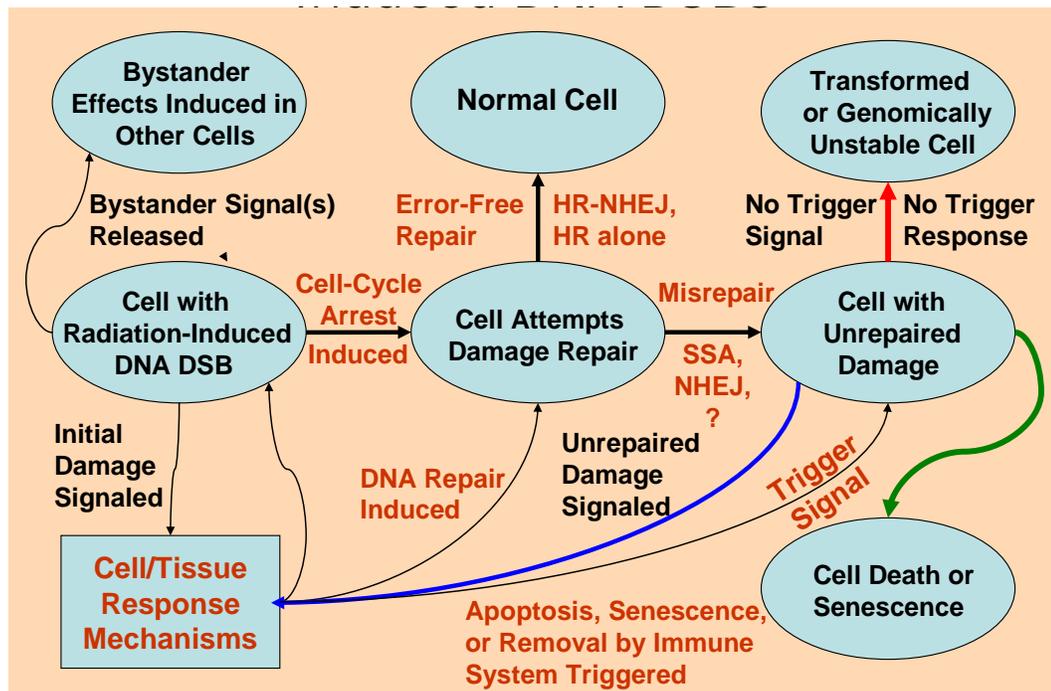


Figure 3.3. Representation of cellular and tissue-level response mechanisms to deal with DNA DSBs induced by ionizing radiation. HR = homologous recombination; NHEJ = non-homologous end-joining; SSA = single-strand annealing.

The importance of the extra-cellular environment is demonstrated by “the remarkable difference in mutation spectra of breast and colorectal cancers” (Sjoblöm et al. 2006), which indicates that the phenomena that lead to cancer are likely to be highly organ- or tissue-specific. Organ-specific differences in gene expression in mice after exposure to low doses of gamma radiation (Lee et al. 2006) also suggest the importance of epigenetic factors in determining responses.

Irradiated cells may die as a result of apoptosis triggered by signals that are generated solely at the plasma membrane. However, as illustrated in Figure 3.3, apoptosis also may be triggered as a bystander effect in an unirradiated cell (e.g., via signals received from an irradiated cell), which is generated either as a result of damage to DNA or chromatin or via DNA-damage-independent processes. Intercellular signaling also can produce mutations, chromosome aberrations, or even genomic instability in unirradiated cells as bystander effects.

Genetic alterations and epigenetic lesions accumulate with aging (Jones and Baylin 2007), with or without exposure to ionizing radiation. The process of aging also can produce changes in the homeostatic state of an affected organ or tissue that could increase the rate of accumulation of mutations or epigenetic lesions. That increase may be accelerated by an accumulation of dysfunctional senescent cells to numbers sufficient to alter the tissue microenvironment, with the result that normal homeostatic mechanisms are compromised, thus enhancing the potential for the development of neoplasms.

Because carcinogenesis is a complex, multistage process that is heavily influenced by the nature of epigenetic factors and homeostatic mechanisms, models of radiation carcinogenesis that do not take such phenomena into account appear to be overly simplistic. Thus, the link between initial radiation damage and cancer induction appears to be much more complex than previously thought.

3.2.5 Effects of Differences in Gene Expression at Low Doses

The foregoing discussions raise the question of whether such concepts as LNT represent an oversimplified genomic-proteomic model and, thus, need rethinking. Evidence obtained *in vitro* that shows that gene expression is significantly different, both qualitatively and quantitatively, at low doses of low-LET radiation than at high doses (Coleman et al. 2005; Ding et al. 2005; Fachin et al. 2007; Ulsh 2010) also has been used to support alternative dose-response models. It has been argued that those differences show that dose-responses at low doses (and low dose rates) are unlikely to conform to an LNT model, because an observed linearity in responses at high doses or dose rates (e.g., in the LSS cohort) indicates that a single response mechanism (such as DNA repair, perhaps suggested by the pattern of gene expression) determines the final outcome. It is then argued that a superposition of responses that depend on dose or dose rate and involve a wider variety of mechanisms (e.g., repair, cell-cycle controls, apoptosis,

senescence, triggering of stress or immune responses) leads to a completely different outcome at low doses or low dose rates. Observations of differential gene expression have been advanced as an explanation for putative adaptive responses that could result in potential thresholds or hormetic responses.

Such arguments do not unequivocally support the existence of the low-dose phenomena noted above, however. Differences in gene expression at low doses compared with high doses do indicate that responses at low doses or low dose rates may be quite complex and, therefore, might not conform to an LNT model. However, those responses also may be quite variable and, thus, may be unpredictable, and they could vary significantly as the dose and dose rate changes.

These conclusions are supported by *in vitro* and *in vivo* studies that reported apparent thresholds or hormesis over one range of low doses or dose rates but detrimental effects, including supralinear responses, over a lower range of doses or dose rates. Patterns of chromosomal aberrations in transgenic mice irradiated *in vivo* (Hooker et al. 2004; Zeng et al. 2006) and tumor induction in C57Bl/6 mice (Mitchel et al. 2008) suggested that hormetic or threshold responses occurred within a restricted range of doses or dose rates, but that enhanced deleterious effects occurred at the lowest doses and dose rates studied. In another study, a proposed hormetic effect (i.e., an adaptive response leading to suppression of neoplastic transformation in human cells in tissue culture) was not seen when the dose rate was reduced below about 1 mGy d⁻¹ (Elmore et al. 2008). Earlier studies of fatal cancers in beagle dogs from continuous exposure to ⁶⁰Co gamma radiation at dose rates of 3–128 mGy d⁻¹ (0.002–0.09 mGy min⁻¹) gave similar results. The occurrence of solid tumors in those studies was highest at the lowest dose rate and decreased to zero at the highest dose rate (Seed et al. 2002). However, the occurrence of myeloid leukemias was highest at an intermediate dose rate of 37.5 mGy d⁻¹ (0.026 mGy min⁻¹), and the occurrence of those leukemias decreased to zero at the lowest dose rate and was supplanted successively at higher dose rates by aplastic anemias and septicemia (Fritz et al. 1986; Seed et al. 2002). Such data not only challenge the validity of the LNT model but also indicate why general application of specific alternative models, such as hormesis, to estimation of risks at low doses is difficult to justify.

3.2.6 Conclusions

Maintenance and expression of the human genome in the presence of damage from ionizing radiation involves a variety of incompletely understood processes and feedbacks, both internal and external to an irradiated cell. The relative importance of cellular and tissue- or organ-level responses to radiation *in vivo* and the extent to which those responses are different at low doses than at high doses continues to be widely debated and intensively researched. At the present time, “it is clear that no current animal or *in vitro* model of cancer recapitulates the genetic landscape of an actual human tumor” (Sjoblöm

et al. 2006). It is apparent that genetic and epigenetic effects, along with multicellular interactions and homeostatic mechanisms, are involved in determining biological outcomes from exposure to ionizing radiation, and that models of radiation carcinogenesis used to estimate health risks need to incorporate both direct and indirect effects (Baverstock and Belyakov 2005; Sachs et al. 2005; UNSCEAR 2009).

Given the complexity of genetic and epigenetic modifications of the genome that are produced by exposure to ionizing radiation and the potential influence of homeostatic mechanisms, which can trigger major epigenetic changes, it is difficult to evaluate the relative importance of radiation-induced direct or indirect changes at the level of the cell or the intact organ or tissue and to estimate the likelihood that such changes at low doses or low dose rates will lead to cancer. An LNT model for radiation carcinogenesis would be inappropriate if indirect changes or homeostatic responses are induced in a non-linear manner at low doses or low dose rates, unless the superposition of all responses fortuitously yields an overall linear response (Breckow 2006).

The apparent complexity of systems for information packaging, storage, and recall in chromosomes and for maintaining the integrity of that information in the presence of damage from mutagens and clastogens suggests that our understanding of the formation, repair, and expression of radiation damage may be considerably more rudimentary than previously believed. This conclusion is supported by the demonstration discussed in Section 2.3 that the formation of apparently simple chromosomal aberrations is more complex than formerly appreciated. In addition, the cellular response to radiation damage is part of a multicellular response to a perturbation of the homeostatic state of the affected organ or tissue that is directed toward restoring that state. Both the system in which biological damage from ionizing radiation is initiated and the process of cancer induction, which appears to require much more than the single genetic change usually attributed to radiation exposure (Hanahan and Weinberg 2000), are far more complex and, thus, much more uncertain than formerly realized. This raises the question of whether concepts such as LNT, which apparently represents an oversimplified model of the effects of damage from radiation exposure, also needs rethinking.

3.3 ALTERNATIVE MODELS OF LOW-DOSE RESPONSES

Use of a DDREF is thought by some to represent an external correction to the LNT model because it is a divisor of a risk coefficient (risk per unit dose) that does not alter the shape of the dose-response at low doses or low dose rates (Mossman 2001). However, the situation is more involved than that because DDREFs often are derived by analyzing the curvature in acute dose-responses. Nonetheless, application of a DDREF to estimates of risk that are based on an assumed LNT dose-response relationship results in

simple risk coefficients that can be applied at any dose or dose rate, in contrast to use of an LQ or even more complex dose-response relationship that incorporates a dose-dependent DDREF implicitly.

Given the high degree of variability in the shapes of dose-responses for cancer induction in animals and humans and information from recent biological and radiobiological research, use of the LNT model modified by a DDREF in radiation protection and risk assessment has been subjected to considerable criticism. Some think that the LNT model without a DDREF should be used in estimating cancer risks (Breckow 2006; UNSCEAR 2008; Richardson 2009) or that the DDREF of two recommended by ICRP for use in radiation protection may be too high (Goodhead 2000; Pierce and Preston 2000; Richardson 2002; NRC 2006). Others argue that the LNT relationship does not apply at low doses (Hooker et al. 2004; Aurengo et al. 2005; Zeng et al. 2006; Ulsh 2010), at least for some types of cancer, such as leukemia for which a quadratic dose-response over the entire dose range or a threshold at low doses was suggested (Little et al. 1999; UNSCEAR 2000; Mossman 2001). Proponents of hormesis cite evidence from various studies in plants and animals and some epidemiological studies that suggests that there may be beneficial effects at low doses or low dose rates (Figure 1.1, curve e), including a reduction of adverse health effects in humans (Feinendegen and Pollycove 2001; Feinendegen 2002, 2005; Pollycove and Feinendegen 1999, 2001, 2003; Luckey 1992; Mossman 2001; NCRP 2001; Upton 2001; Calabrese and Baldwin 2003). Still others believe that health risks at low doses are underestimated by the LNT model and have proposed supralinear dose-response models at low doses or low dose rates of low-LET radiation (Figure 1.1, curve d) based, for example, on observations of some bystander effects, inverse dose-rate effects (Crompton et al. 1990; NCRP 2001; Snyder 2003; Hooker et al. 2004; Zeng et al. 2006), and limited evidence from epidemiological studies, including data in the LSS cohort at doses <0.3 Sv.

Most biological explanations for radiation hormesis and some threshold responses that could be applied to humans are based on the existence of cellular mechanisms, such as DNA repair and adaptive responses, that might lessen the occurrence of radiation-induced cancer (Mossman 2001; Upton 2001). More recently, low-dose hyper-radiosensitivity, along with cell-cycle checkpoint controls and programmed cell death (apoptosis), have been invoked as mechanisms that deplete the population of cells that are most likely to be transformed by a subsequent dose, or transformed spontaneously. It also has been hypothesized that a hormetic response results from a lessening of endogenous non-radiation-induced DNA damage in exposed cells by detoxification of reactive oxygen species, DNA repair, or cell removal by apoptosis and immune responses following low-dose stimulation of the DNA-damage control system.

Perhaps the greatest challenge to the validity of the LNT model, and to a lesser extent to hormesis or threshold dose-responses, comes from the extensive body of information reviewed by UNSCEAR (2009) on non-targeted and delayed effects of radiation exposure obtained primarily *in vitro*, such as bystander effects and delayed genomic instability. Those phenomena are thought to have the potential to produce

elevated effects at low doses as a result of an increase in target size, supralinear responses, and inverse dose-rate effects compared with predictions using an LNT model with a DDREF ≥ 1 . However, bystander effects and delayed genomic instability also could reduce the effectiveness of low doses of radiation by induction of apoptosis or cellular senescence following incomplete repair of radiation damage, as evidenced in some studies by the presence of micronuclei, which are DNA fragments that appear within the cytoplasm. An understanding of those phenomena appears to require more research on the roles of epigenetic and tissue-level (multicellular) mechanisms in radiation responses.

Section 3.1 summarizes the debate over the relevance of the LNT model and the differing views of the committees that represented the U.S. and French National Academies (NRC 2006; Aurengo et al. 2005). The BEIR VII committee (NRC 2006) strongly supported the LNT model on the basis of biophysical arguments, including the likelihood of incompletely repaired radiation damage to DNA, even at low doses or low dose rates. However, the committee did not address the role of such phenomena as cell-cycle checkpoint controls, apoptosis, senescence, or triggering of stress or immune responses that could offset or perhaps even outweigh the effects of damage to DNA. The committee of the French National Academies (Aurengo et al. 2005) was strongly critical of biophysical arguments and cited the influence of alternative biological mechanisms that could lead to thresholds, adaptive responses, and hormesis as more credible at doses <10 – 100 mSv.

On the basis of our review, we think that the strong stance of the BEIR VII committee in favor of the LNT model and the equally firm contrarian position of the committee of the French National Academies both represent unwarranted certainty about the response to radiation exposure at low doses or low dose rates. There clearly is not a consensus among experts about the relevance to cancer risks at low doses or low dose rates of phenomena that might support major alternatives to the LNT model, and which have been studied largely *in vitro*. A sampling of the views of experts is given below.

- Johansson (2003) concluded that “current epidemiological data do not supply enough evidence to justify a belief that radiation hormesis is a common phenomenon for a wide spectrum of irradiation situations or for a population composed of persons of all ages ... If a hormetic effect of radiation exists, it seems to be rather weak and inconsistent, and in such a situation the precautionary principle requires a pessimistic assumption for safety reasons.” However, Johansson (2003) also noted that “[d]ata for leukemia, bone cancer, and lung cancer offer weak evidence pointing to a threshold or even to a hormetic model of dose response.”
- Brooks (2003) concluded that genomic instability provides a mechanism for a linear relationship between dose and induction of cancer, because only a single radiation-induced change may be required.

- In contrast, Goodhead (2000) suggested that radiation-induced genomic instability could lead to a true threshold for damage from low-LET radiation, with the risk approaching zero at sufficiently low doses or dose rates and DDREF tending to infinity, provided a threshold level of simultaneous damage at several locations in a cell is needed to trigger the process.
- Brooks (2003, 2005) also suggested that differential genetic susceptibility or differences in gene expression and bystander effects could influence the shape of the dose-response curve to either increase or decrease the risk at very low doses. Brooks (2005) concluded that “[u]nderstanding the balance between protective and harmful effects must be an important part of future research.”
- Coates et al. (2004) concluded that “[a]t present it is not known to what extent [radiation-induced genomic instability and bystander effects] contribute to overall cellular radiation responses, especially *in vivo*, but clearly they may be of particular significance at low doses of radiation and may increase or decrease risk depending on the nature of the response.”
- Kadhim et al. (2004) observed that “[l]ittle is understood as to the likely interactions between bystander responses and direct effects, or their relevance to understanding risk after radiation exposure at low doses where predominantly single cells are exposed within populations.”
- Mothersill and Seymour (2004) argued that adaptive responses, bystander effects, and genomic instability are part of the cellular homeostatic response and, as such, modulate the low-dose response to radiation. However, while their effects at low doses can be detected, it is very difficult to classify them as harmful or beneficial, as suggested previously by Barcellos-Hoff and Brooks (2001). The potential for operational thresholds for harmful radiation damage may be tied to the level of “protective” cell death induced, which is judged to be genotype-specific. “For genotypes where the bystander response, if there is one, does not involve coordinated cell death, it is likely that there is no operational threshold and that stochastic effects such as carcinogenesis have some very small probability of occurring at low doses.”
- UNSCEAR (2009) noted that “[a] bystander effect induced by low-LET radiation is less well established and ... has only been demonstrated after medium transfer experiments [of the type conducted by Mothersill and colleagues] ... Low-LET bystander effects appear to be a low-dose phenomenon, and reconciling low-dose bystander cytotoxicity with the lack of directly induced cell killing at these same doses is perplexing.”
- Mitchel (2004) observed that “[t]he data suggest that beneficial bystander effects outweigh detrimental effects at doses below about 100 mGy, but that the reverse is true [for adaptive responses] above this threshold.”
- Mitchel et al. (2008) reached a different conclusion: “[C]urrent work on cancer risk in C57BL/6 mice and [previous work] on a non-cancer disease ... both indicate that lower dose thresholds for

protective adaptive responses exist *in vivo*. Chronic occupation-like exposures that were below this threshold did not induce protective responses for either measure of risk. Furthermore, detrimental effects from the exposures that were below the adaptive threshold could be observed for some tumor types.”

- Although Aurengo et al. (2005) expressed support for the existence of biological mechanisms that could produce a threshold response, they also acknowledged that “it is not possible to define the threshold level ... or to provide the evidence for it.”
- ICRP (2005) concluded that “[w]hile the 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 favour 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 at low doses and dose rates.”
- The BEIR VII committee (NRC 2006) concluded that “[m]echanistic uncertainties remain, but the weight of available evidence would argue against the presence of a low dose threshold for tumor induction based upon error-free repair of initial DNA damage.” However, the committee did not address the possibility of contributions from other mechanisms, such as cell-cycle checkpoint controls and apoptosis.
- UNSCEAR (2009) noted that “[a]t low doses and dose rates, the effects of ionizing radiation on the immune system may be suppressive or stimulatory. The long-term impact of low radiation doses on the immune function in relation to human health needs to be further evaluated.”
- Feinendegen (2005) contended that “[t]he probability of radiation induced adaptive protection measurably outweighs that of damage from doses well below 200 mGy [of] low-LET radiation.”
- Prise (2006) noted that “[a]daptive responses appear to be highly variable and depending on the [cell] system and endpoint used. Mechanistically, it has been suggested that stimulation of repair processes and antioxidant activity play a role, but the precise molecular mechanisms are still poorly characterized.” Prise also noted that further studies on the role of bystander effects *in vivo* were needed to determine the relative importance of effects that could be damaging or protective: “What will be critical is the relative role of these effects in tissues and individuals in determining overall cancer risk.” With regard to radiation-induced genomic instability, Prise pointed out that “little is understood of the processes involved in initiation of inducible instabilities and in maintenance and transmission of phenotype over many generations of cell replication. It is becoming evident that expression of inducible instability has a strong dependence on the type of radiation exposure, cell type irradiated, and genetic predisposition of the irradiated cell.”

- Schöllnberger et al. (2007) developed a multistage model for induction of chromosome aberrations and *in vitro* neoplastic transformation that incorporates detrimental and protective (i.e., apoptosis-mediated) bystander effects. However, those investigators noted that the magnitude of the protective effect in their model was strongly dependent on the duration of the effect, and that “experiments are needed to investigate the potential of low doses (<200 mGy) of low-LET radiation to induce apoptosis [and] the time dependence of [its] induction.”
- The need for further research on protective effects was supported by Bauer (2007), who noted that findings by Portess et al. (2007) “allow a mechanistic explanation for the suppression of observable transformation events by low dose radiation, but they do not allow [us] to conclude that this potential [beneficial] effect of low dose radiation occurs under all conditions ... These specific conditions, the determination of the frequency of their occurrence and the understanding of their consequences require further experimental approaches.”
- Ulsh (2010) noted that “a large and rapidly growing body of radiobiological evidence indicates that cell and tissue level responses to [radiation] damage, particularly at low doses and/or low dose-rates, are non-linear and may exhibit thresholds. To the extent that responses observed at lower levels of biological organization *in vitro* are predictive of carcinogenesis observed *in vivo*, this evidence directly contradicts the assumptions upon which the microdosimetric argument [which implies a linear no-threshold response] is based.”
- Morgan and Sowa (2007) concluded “that despite a large body of information, there continues to be uncertainty regarding any causal relationship between bystander effects and the observed health consequences to ionizing radiation. The available information provides some support for disease associations but not a causal relationship ...”
- With regard to induction of genomic instability, adaptation, and bystander effects at low doses, Schwartz (2007) pointed out that “[each] of the responses is also highly variable; not all cell and tissue models show the same response and there is much interindividual variation in response. Most of these studies have employed *in vitro* or tissue explant models, and understanding underlying mechanisms and the biological significance of these low-dose responses will require study of tissue-specific *in vivo* endpoints. The *in vitro* studies strongly suggest that modeling low dose radiation effects will be a complex process ...”
- UNSCEAR (2009) noted that “[i]n spite of the ... new information available, considerable disagreement remains concerning any definitive relationship between ... non-targeted [and delayed] effects and the observed health effects attributable to radiation ... [D]irect epidemiological observations and associated quantification of the health effects of radiation

incorporate all mechanistic elements, including the targeted (direct) effects of irradiation as well as the non-targeted and delayed effects ...”

- Aurengo et al. (2005) and Tubiana et al. (2006) expressed the view that “[i]t appears that in most cases, low-dose ionizing radiation doses tend to elicit protective mechanisms in normal cells which are not compatible with the LNT concept.” However, Auerbeck (2010) argued that “the actual impact on health risk assessments of non-targeted effects are not yet clear enough to define a new paradigm.”
- Wright (2010) noted that “[n]on-targeted mechanisms have significant implications for understanding mechanisms of radiation action but the current state of knowledge does not permit definitive statements about whether these phenomena have implications for assessing radiation risk.”
- Thomassen and Metting (2003) pointed out that “[j]ust as our understanding of high dose radiation exposure provides us with an admittedly limited understanding of the critical events that occur at low dose[s] of radiation, so too *in vitro* experiments only provide a limited view of the critical events that occur *in vivo* following exposure to low doses of radiation.”
- The CERRIE (2004) report concluded that “[t]here was general agreement that whilst much has been learned from studying the individual responses of cells irradiated *in vitro*, studying isolated cells cannot reveal the complexity of tissue responses in which complex cell-cell interactions and microenvironmental factors contribute to the overall *in vivo* response.”

On the whole, emerging results on thresholds, adaptive responses, genomic instability, bystander effects, and such related phenomena as hormesis raise the possibility that the dose-response at low doses or low dose rates of ionizing radiation is highly uncertain, and that a simple linear extrapolation from higher acute doses, even with a DDREF, may be inappropriate. However, a better understanding of the mechanisms of these phenomena, the extent to which they are active *in vivo*, and how they are interrelated is needed before they can be factored into methods of estimating risks to humans from exposure to low levels of ionizing radiation (e.g., Cox et al. 2005; ICRP 2005; Jacob et al. 2010; NRC 2006; EPRI 2009; Dauer et al. 2010; UNSCEAR 2009; Ulsh 2010).

Although existing information, including the views of experts given above, does not allow us to draw firm conclusions, it appears that non-targeted and delayed effects could impact all stages of cancer development and serve to modulate the dose-response to the initial genetic damage. While fundamental knowledge of these phenomena is increasing rapidly, the extent to which such processes specifically influence low-dose carcinogenic responses remains largely a matter of speculation (e.g., Goodhead 2000; UNSCEAR 2000; NCRP 2001; Brooks 2003, 2005; Hall 2003; Johansson 2003; Little 2010; Morgan

2003a, 2003b; Schwartz 2004a, 2004b, 2007; Cox et al. 2005; ICRP 2005; Brenner and Sachs 2006; NRC 2006; Morgan and Sowa 2007, 2009; Preston 2008; EPRI 2009; Dauer et al. 2010; UNSCEAR 2009; Ulsh 2010). Potential modifiers of low-dose cellular responses (thresholds, hormesis, adaptation, bystander effects, and genomic instability) have not been shown conclusively to be associated with cancer development in humans. However, it is interesting that while Little (2010) concluded that there is little evidence of non-targeted effects in data on dose-responses in humans, Jacob et al. (2010) maintained that biological models of carcinogenesis indicate that such data show the expression of radiation-induced genomic instability and a bystander effect with a dose threshold.

UNSCEAR (2009) concluded that “it cannot be excluded that the increasing knowledge basis for *in vivo* bystander effects at low doses and dose rates in specific organs may affect current organ risk estimates in humans.” Further, the observation of a strong genetic component in genomic instability induced *in vivo* in animals strongly suggests that instability and cancer induction are mechanistically linked. UNSCEAR (2009) also concluded that (1) “it would be prudent to consider the implications of non-targeted [and] delayed effects of radiation exposure when considering models of radiation carcinogenesis, particularly at low doses,” and (2) “models of radiation-induced carcinogenesis should incorporate both direct and indirect effects when evaluating radiation risks.”

Preston (2003) contended that adaptive responses, bystander effects, and genomic instability tend to influence the slope of the dose-response curve for cellular responses at low doses but not the shape, which results in a quantitative rather than a qualitative modification of the dose-response. However, existing information on the bystander effect and genomic instability, including the apparent “binary” nature of the majority of responses (i.e., once triggered, a response appears to be little affected by increases in dose over a fairly wide range), is inconsistent with this conclusion (UNSCEAR 2009). For example, a net elimination of transformed cells by bystander mechanisms or genomic instability (e.g., via induced apoptosis) could reduce the low-dose slope and alter the shape of the dose-response in an organ or tissue.

Morgan (2003a, 2003b) and UNSCEAR (2009) concluded that non-targeted effects may serve to “amplify” the biological effectiveness of a given radiation dose by increasing the number of cells that experience effects over those directly exposed; see also Morgan and Sowa (2007). It has been suggested that this indicates that the target for genetic effects is larger than either the nucleus or the cell (which are the focus of biophysical arguments based on microdosimetry) and, based on *in vivo* studies cited above, could be considered to be the entire tissue or organ, particularly in studies of internal exposure to radionuclides. On this basis, a reconsideration of the concepts of radiation dose and target size and incorporation of direct and indirect effects in models of radiation carcinogenesis was recommended.

It is not clear that the conclusion with respect to “amplification” of the biological effect would apply at all doses or under all conditions. Because of the apparent “binary” nature of the dose-response for most

bystander effects, for example, it reasonably can be argued that once the response has been triggered (i.e., by hits on a small percentage of the cells in a population), much of the remaining energy deposited by a low dose of radiation should be much less effective because the response plateaus and is not proportional to dose (Sawant et al. 2001a; Morgan 2003a).

Although information on thresholds, adaptive responses, hyper-radiosensitivity and induced radioresistance, hormesis, and non-targeted and delayed effects clearly is intriguing, we agree with the view of Waldren (2004) that unresolved issues and the sometimes contradictory nature of information make it difficult to develop a quantitative basis for revising risk estimates, abandoning the LNT approach, or defining DDREFs, particularly for low-LET radiation. Additional research to resolve uncertainties clearly is warranted (e.g., Averbeck 2010; Baverstock and Belyakov 2005; Jacob et al. 2010; Morgan and Sowa 2007, 2009; Schwartz 2007; Preston 2008; EPRI 2009; Dauer et al. 2010).

3.4 LNT MODEL—STILL THE DEFAULT?

Models of genetic programming, epigenetic phenomena, and homeostatic mechanisms and their interactions in maintaining genomic stability in response to damage from ionizing radiation are being modified or replaced as results from new research begin to resolve questions about how such phenomena operate. Although current knowledge is incomplete, it is apparent that some change at the level of the genome itself, in the form of mutations, chromosomal aberrations, configurational changes to chromatin, or some combination of those effects, is responsible for the long-term sequelae that lead to cancer.

The intriguing questions raised by recent research notwithstanding, it is generally recognized that damage to DNA or chromatin is the main initiating event that leads to long-term effects of radiation in organs and tissues of the body, with or without modification by non-targeted and delayed effects, such as bystander effects. Although a radiation track does not need to traverse the cell nucleus for damage to DNA or chromatin to occur [e.g., because effects are produced by cytoplasmic irradiation (Wu et al. 1999) or intercellular signaling], studies in which the nucleus was targeted in only 10% of cells showed that the extent of bystander-induced cell sterilization is proportional to the extent of irradiation of nuclei (Sawant et al. 2001a, 2001b; Morgan 2003a). In addition, chromosomal instability was reduced in irradiated cells by the presence of free radical scavengers (Limoli et al. 2001) and was transmitted by transfer of an irradiated chromosome to an unirradiated cell (Mukaida et al. 2007). Thus, direct damage to DNA or chromatin appears to be the primary trigger for bystander phenomena or induced genomic instability and the other phenomena discussed in Section 3.3. Absent some form of primary direct damage to initiate the signaling cascade (e.g., of cytokines or reactive oxygen species) and release of cytotoxic products that lead to non-targeted and delayed effects, it is difficult to see how those phenomena could be induced.

Given the evidence that single tracks of all types of radiation can produce a broad spectrum of complex DNA or chromosomal damage, for which DNA repair mechanisms may not be fully effective and other cellular response mechanisms (e.g., cell-cycle checkpoint controls, apoptosis) are not foolproof (UNSCEAR 2000; NCRP 2001; ICRP 2005), long-term damage leading to cancer should be possible even at the lowest doses, albeit with a low probability. Such damage occurs because low-LET radiations have a densely ionizing component at the ends of tracks that could affect cells in a manner similar to high-LET radiation, for which the dose-response is expected to be linear.

Limitations involved in applying the LNT model, with or without a DDREF, as a generalization to describe the multi-factorial process of carcinogenesis in humans at low doses or low dose rates are generally appreciated. However, with one exception (Aurengo et al. 2005), national and international expert committees appear reluctant to abandon use of a simple proportionate relationship between increments of dose and risk in the absence of a consistent body of information, particularly on carcinogenesis *in vivo*, that would justify substitution of an alternative model. Thus, most expert groups have concluded that, given appropriate adjustments to account for differences in dose, dose rate, and radiation quality, the weight of evidence supports the continued use of the LNT model for assessing the risk of mutations, chromosome aberrations, and most types of cancer in populations exposed to low levels of ionizing radiation, until new information is developed to indicate that the LNT model needs to be modified (Brenner et al. 2003; CERRIE 2004; Cox et al. 1995, 2005; Dendy and Brugmans 2003; ICRP 2005; Little 2010; Mossman 2001; NCRP 1997, 2001; NRC 2006; Preston 2003, 2008; UNSCEAR 1993, 1994, 2000, 2008; Upton 2001, 2003).

The current situation is summarized by several groups of experts in the following ways:

- “Although other dose-response relationships for the mutagenic and carcinogenic effects of low-level radiation cannot be excluded, no alternate dose-response relationship appears to be more plausible than the linear-nonthreshold model on the basis of present scientific knowledge” (NCRP 2001).
- “At present, we cannot be sure of the appropriate dose-response relation to use for risk estimation at very low doses ... Given that it is supported by experimentally grounded, quantifiable, biophysical arguments, a linear extrapolation of cancer risks from intermediate to very low doses currently appears to be the most appropriate methodology” (Brenner et al. 2003).
- “The [LNT] theory is not universally accepted as biological truth. However, because it is not actually known what level of risk is associated with very low-dose exposure, [it] is considered by many as a prudent rule of thumb for public policy aimed at avoiding risk from unnecessary exposure” (ICRP 2005).

- The report of the BEIR VII committee (NRC 2006) concluded that “the current scientific evidence is consistent with the hypothesis that there is a linear, no threshold dose-response relationship between exposure to ionizing radiation and the development of cancer in humans ... [T]he committee judges that the balance of scientific evidence tends to weigh in favor of a simple proportionate relationship at low doses between radiation dose and cancer risk.”
- The report of a joint committee of the French Academy of Sciences and National Academy of Medicine (Aurengo et al. 2005) raised doubts about the validity of the LNT model to estimate cancer risks of low doses (<100 mSv) and even more so at very low doses (<10 mSv). The committee cited the potential influence of biological mechanisms that could lead to thresholds, adaptive responses, and hormesis.

The dissenting view of Aurengo et al. (2005), as also summarized by Tubiana et al. (2006), is based on mechanistic arguments for alternative models. The French Academies also cited evidence and opinions we think are inconclusive, as did ICRP (2005), Brenner and Sachs (2006), and Brenner (2009). More importantly, as discussed in Section 3.3, there is a lack of consensus among experts on the important question of whether results from ongoing research on the mechanistic basis for the phenomena the French Academies cited as invalidating the use of the LNT model are applicable to cancer risk assessments. We believe this is a strong argument against acceptance of their contrarian view.

Land (2002, 2009) and ICRP (2005) examined the effects of a possible existence of a threshold at low doses on uncertainties in estimated risks. Land (2002) showed that the probability of such a threshold had to exceed 80% before a significant effect on the upper 95% confidence limit of an uncertain estimate of risk was seen. ICRP (2005) then showed that unless the existence of a threshold was virtually certain, the effect of introducing the uncertain possibility of a threshold was equivalent to the effect of an uncertain increase in a DDREF to be applied to an LNT dose-response. This effect is a variation on the result obtained by ignoring the possibility of a threshold.

The views of NCRP (2001), Brenner et al. (2003), and ICRP (2005) also indicate that there is considerable uncertainty about the appropriate dose-response relationship to be used in estimating cancer risks at very low doses. Brenner et al. (2003) concluded that it was likely that a linear extrapolation “will result in an underestimate of some radiation risks and an overestimate of others.” An underestimate implies that a DDREF applied to an LNT model would be <1, as suggested by some of the information reviewed in the preceding sections. An overestimate of risk could result from “practical thresholds,” as well as the biological characteristics of certain types of tissues. Brenner et al. (2003) supported their conclusions by citing results from a wide range of animal (including cell-culture) and human epidemiological studies of relevance to estimation of a DDREF. Those types of data are reviewed in

Sections 4 and 5, which presents an assessment of the suitability of data in animals and humans for the purpose of estimating a DDREF and also examines the question of how well the observed dose-responses conform to the expectations of standard paradigms.

It seems unlikely that the opinions of most experts on the importance of thresholds, adaptive responses, hormesis, and related phenomena in estimating risks from exposure to ionizing radiation will be altered in the absence of a consistent body of information on carcinogenesis *in vivo* that would justify substitution of an alternative model, particularly in view of the apparent linearity in the dose-response for incidence of all solid cancers in Japanese atomic-bomb survivors (UNSCEAR 2008). Given that mechanistic studies are the primary focus of recent radiobiological research, and the proposed focus of toxicology in general (Collins et al. 2008), and that facilities for conducting studies in large numbers of animals no longer exist, it would appear that concrete evidence in support of alternate dose-response models may have to come from a marriage of new technologies for detection of biological responses and long-term epidemiological studies of chronically exposed populations, such as radiation workers.

Breckow (2006) concluded that the uncertainty in the dose-risk relationship in the low-dose range based on current mechanistic and epidemiological information is such that no specific model, including LNT, can be justified on scientific grounds alone. Thus, the acceptance of the LNT concept, and by inference a DDREF, should be based on the need to estimate risks for purposes of radiation protection. Breckow (2006) further argued that the rationale for a DDREF is so weak that if it had not been “defined earlier, it probably would not be introduced today.” For reasons of practicality and transparency, he concluded that the simplest and most straightforward approach was to assume the validity of the LNT model and a DDREF of 1, given the uncertainties in the latter. That view was supported by Richardson (2009), based in large part on a study by Jacob et al. (2009) that compared cancer risks in nuclear workers (chronic exposure) and the LSS cohort (acute exposure).

In contrast, Gilbert (2009) concluded that the value of a DDREF and whether it is even needed are both uncertain. She pointed out that while results from epidemiological studies with well characterized estimates of dose are compatible with a linear dose-response at doses up to 2–3 Gy, the possibility of curvature in the dose-response or a low threshold dose cannot be ruled out. With respect to studies of nuclear workers and other groups exposed at lower doses and dose rates, Gilbert (2009) cautioned that imprecise dose estimates and the potential effects of other factors (e.g., smoking and exposure to chemical carcinogens) on estimates of risk from radiation exposure limit what can be learned from such studies. These issues and their implications for estimation of a DDREF based on estimates of cancer risks in nuclear workers and persons exposed to environmental radiation are discussed in Section 5.2.2.

Although the suggestions by Breckow (2006) and Richardson (2009) could be useful in the context of radiation protection, we do not agree that a default DDREF of 1 should be assumed for purposes of

estimating cancer risks from actual exposures of identified individuals. Use of such a default is tantamount to saying that we know with certainty that the DDREF to be used in estimating cancer risks is 1. If an LNT model is assumed, the uncertainty in a DDREF should take into account uncertainties associated with the model and uncertainties in the data used to develop estimates of DDREF.

Given the current state of knowledge, we think that firm conclusions about the magnitude or direction of possible deviations from predictions of an LNT model at the low doses or low dose rates at which a DDREF for solid cancers is applied in IREP are premature. We agree with the conclusion by Brenner noted in Section 3.1 that “[a]t this time we don’t know if deviations from the predictions of this linear approach will be large or small, or even whether they will increase or decrease low-dose cancer risk estimates.” Results of research on non-targeted and delayed effects, although not yet conclusive, support Brenner’s judgment. We think that this lack of knowledge should be represented by a full accounting of uncertainty in DDREF for solid cancers based on the current state of knowledge.

4. RADIOBIOLOGICAL STUDIES TO ESTIMATE DDREF

4.1 INTRODUCTION

This section presents a review of radiobiological data obtained from studies in cells and whole animals that could be used for the purpose of estimating DDREFs. Relevant data from epidemiological studies are reviewed in Section 5.

In developing probability distributions of DDREFs based on radiobiological and epidemiological data, critical questions that need to be addressed include the following:

- Do available data indicate that a distinction should be made between an LDEF based on analyses of possible non-linearities in dose-responses for acute exposure (e.g., an analysis of the curvature in a dose-response assuming an LQ model) and a DREF based on comparisons of dose-responses from acute and chronic exposure?
- Over what ranges of doses and dose rates should DDREFs be applied?
- What are the appropriate sources of data for defining probability distributions of DDREFs?
- Is the distinction in IREP between a DDREF for breast and thyroid cancer and a DDREF for all other solid cancers appropriate? Do available data support the development of DDREFs for other specific cancers? Or, is the use of a single DDREF for all solid cancers more appropriate?

It clearly would be preferable to rely on epidemiological data to develop DDREFs. However, epidemiological data may be too limited to be used as the sole source of information on the effects of dose or dose rate on risks of radiation-induced cancer in humans. Consequently, results from studies of cancer induction in laboratory animals may be useful in developing DDREFs in humans.

Although data in laboratory animals are potentially relevant, caution is warranted in evaluating those data for the purpose of defining DDREFs for use in estimating cancer risks in humans at low doses or low dose rates (NCRP 1980; Fry 1992). There are important questions about the relevance of data on cancer induction in animals to humans, given the differences in cellular origins and etiology of tumors and the critical influence of the genetic background of laboratory animals, which varies widely among different species and among different strains of the same species. Does the wide variety of dose-responses in animals reflect differences among tumor types, or is it an artifact of the experimental design, technique, or influence of selection and inbreeding on genetic background? These issues may complicate the interpretation of data that could be used to estimate a DDREF.

In evaluating available data for purposes of radiation protection, ICRP (1991) expressed reservations about what they believed was an overly broad range of DDREFs derived from studies of cancer in animals (i.e., a range of 2–10).²⁹ Nonetheless, given the limitations in epidemiological data, information from studies in laboratory animals and other radiobiological studies should be considered in developing DDREFs. For example, the BEIR VII committee used human and animal data to develop a probability distribution of DDREF (NRC 2006).

The following section presents a review of data obtained from studies of genetic and cytogenetic endpoints, including somatic mutations, cell transformation, and chromosomal aberrations, that could be used in developing a DDREF. Section 4.3 then presents a review of data on radiation-induced cancer in laboratory animals.

4.2 STUDIES OF GENETIC AND CYTOGENETIC ENDPOINTS

Data on dose-responses for three types of genetic and cytogenetic endpoints—mutagenesis, chromosomal aberrations, and cell transformation—obtained mainly *in vitro* (i.e., in cultured cells) were used to derive estimates of LDEF and DREF summarized in Table 4.1. Concerns about the applicability of *in vitro* data to *in vivo* responses to radiation are discussed in Section 3.³⁰

Reviews by NCRP (1980, 2001), UNSCEAR (1993, 1994, 2000), and the BEIR VII committee (NRC 2006) provide little evidence that dose-responses for genetic and cytogenetic endpoints obtained *in vitro* or *in vivo* can be used to narrow the limits on credible estimates of DDREF based on studies of cancer in animals or humans. However, the genetic and cytogenetic data are consistent with the animal and human data in that, with one exception, the ranges of LDEFs or DREFs are similar.

Estimates summarized in Table 4.1 and discussed below indicate that LDEFs or DREFs derived from dose-responses for genetic and cytogenetic endpoints range from much less than 1 to much greater than 10, and that the ranges of estimates for particular endpoints vary substantially. For those endpoints of potential relevance to cancer (i.e., mutagenesis and chromosomal aberrations), estimates of DDREF range from relatively low values within a narrow range (e.g., DREFs for somatic cell mutagenesis *in vitro*) to relatively large values within a much wider range (LDEFs for dicentric chromosome aberrations).

²⁹ The range cited by ICRP (1991) is greatly extended when uncertainties in central estimates within that range and more recent information on DDREFs are taken into account. However, animal studies do provide information on effects of dose rate that is otherwise unavailable, and the reasons given by ICRP for their concerns about the wide range of DDREFs from animal studies may not be significant (see Section 4.3).

³⁰ We also note that estimates of the oncogenic transformation frequency Gy^{-1} in immortalized human cells, which are otherwise not transformable in cell culture, are about $10^{-5} - 10^{-7} \text{Gy}^{-1}$, or about two orders of magnitude less than the transformation frequency in cultured rodent cells. However, the incidence of radiation-induced breast cancer in the LSS cohort translates to a transformation frequency per cell of only 10^{-15}Gy^{-1} (NCRP 2001).

Table 4.1. Estimates of DREF and LDEF based on dose-responses for genetic and cytogenetic endpoints obtained mainly from *in vitro* studies of mutagenesis, cell transformation, and chromosome aberrations induced by low-LET radiation

Endpoint	Effects of dose/dose rate	Comments
<u>Mutagenesis and Cell Transformation</u>		
Somatic cell mutagenesis <i>in vitro</i> (NCRP 1980, 2001; Lorenz et al. 1993; UNSCEAR 1993, 2000; ICRP 2005; Kumar et al. 2006; NRC 2006)	DREFs \approx 0.2–4	Effects of dose rate are complex and difficult to interpret; reports of no effect or inverse effect of dose rate are common (NCRP 2001).
Induction of hprt mutations (Rothkamm et al. 2008) in mouse spleen T-lymphocytes <i>in vivo</i> by ^{137}Cs gamma rays at dose rates of 0.5 Gy min^{-1} and $0.09 \text{ mGy min}^{-1}$ and total doses of 0.5–6 Gy	DREF: 6.9 at 6–10 weeks after irradiation; 9.7 after 7–10 months DREF: 1.5 ± 0.6 (1 SE ^a) at 1 Gy, increasing to ≈ 3 at 3 Gy and ≈ 5 at 6 Gy, 8–10 weeks after irradiation	Lorenz et al. (1993). Data appear to have been reanalyzed by Lorentz et al. (1994). Lorenz et al. (1994). Frequency of mutations reduced by 65% at 30–40 weeks after irradiation.
Cell transformation <i>in vitro</i> (NCRP 2001; UNSCEAR 1993, 2000; Brooks 2003; NRC 2006; Elmore et al. 2006, 2008)	DREFs or LDEFs typically 1.5–4.5, but also <1 and ∞	Dose-responses are complex and difficult to interpret. Some results show reduction of transformation frequency below level in controls at acute doses of gamma radiation $<100 \text{ mGy}$; i.e., $\text{LDEF} = \infty^b$ (Azzam et al. 1996; Redpath and Antoniono 1998; Redpath et al. 2001, 2003; Ko et al. 2004), while other results show enhancement of frequency with dose fractionation (Miller et al. 1979) or dose-rate dependent effect of dose protraction (Elmore et al. 2006, 2008).
Neoplastic transformation in human hybrid cells <i>in vitro</i> (Frankenburg et al. 2002; GöggeImann et al. 2003; Heyes and Mill 2004)	DDREFs at 1 Gy \pm 1 SE range from 1.02 ± 0.05 to 1.9 ± 0.6 for various low-LET radiations	Dose-responses are complex and difficult to interpret; relevance of data in already transformed cell lines to transformation of normal non-immortalized cells <i>in vivo</i> not established (NCRP 2001; NRC 2006)

Table 4.1 (continued)

Endpoint	Effects of dose/dose rate	Comments
<u>Chromosome aberrations</u>		
Dicentrics in human lymphocytes Acute exposure to: 220–250 kVp x rays ⁶⁰ Co gamma rays Doses of 0.05–8 Gy	LDEFs: 1.7–2.9 at 1 Gy; 2.1–3.9 at 1.5 Gy 2.4–6.4 at 1 Gy; 3.1–9.1 at 1.5 Gy	Aberrations scored using conventional Giemsa staining. LDEFs calculated from equation (1) in Section 2.2 using central estimates of β and α from six studies in Table 8 of Kocher et al. (2005).
Dicentrics in human lymphocytes Acute exposure to: 29 kVp x rays 60 kVp x rays 220 kVp x rays ¹³⁷ Cs gamma rays ⁶⁰ Co gamma rays Doses of 0.05–3 Gy	LDEFs at 1 Gy \pm 1 SE: 1.55 \pm 0.15 1.48 \pm 0.19 2.50 \pm 0.12, 3.1 \pm 0.4 ^c 4.5 \pm 1.2; 6.9 \pm 2.3	Aberrations scored using conventional Giemsa staining. LDEFs calculated by Trabalka and Kocher (2007) from equation (1) in Section 2.2 using estimates of β and α and uncertainties from Schmid et al. (2002). ^d LDEFs at 1.5 Gy are 20% higher for 29 kVp x rays and increase with increasing energy to about 40% higher for high-energy gamma rays
Total simple exchanges in human lymphocytes: acute exposure to ¹³⁷ Cs gamma rays at 1–4 Gy (Loucas and Cornforth 2001)	LDEF: 1.3 at 1 Gy; 1.5 at 1.5 Gy	Aberrations scored using mFISH techniques.
Apparently simple translocations in human lymphocytes: acute exposure to 30–180 kVp x rays or ⁶⁰ Co gamma rays (Mestres et al. 2008)	LDEFs: 1.6–1.7 at 1 Gy; 1.9–2.1 at 1.5 Gy	Aberrations scored by FISH painting of chromosomes 1, 4, and 11. No apparent dependence of LDEF on photon energy.
Total aberrations in human fibroblasts: exposure to ¹³⁷ Cs gamma rays at 1–6 Gy (Cornforth et al. 2002)	LDEF: 1.5 at 1 Gy; 1.8 at 1.5 Gy DREF: 1.8 at 1 Gy; 2.3 at 1.5 Gy	Aberrations scored using conventional Giemsa staining. DREF estimated from curvature in dose-response based on pooled results from exposures at 0.47 and 1.05 mGy min ⁻¹
Total simple exchanges in human fibroblasts: acute exposure to ¹³⁷ Cs gamma rays at 0.8–3.6 Gy (Loucas et al. 2004)	LDEF: 1.2 at 1 Gy; 1.3 at 1.5 Gy	Aberrations scored using mFISH techniques.
Total simple exchanges in human fibroblasts: exposure to ¹³⁷ Cs gamma rays at 1.2–4.6 Gy (Loucas et al. 2004)	DREF: 5.7	Aberrations scored using mFISH techniques. DREF estimated based on comparison of slopes of linear dose-responses at dose rates of 1.1 Gy min ⁻¹ and 0.8 mGy min ⁻¹

Table 4.1 (continued)

Endpoint	Effects of dose/dose rate	Comments
<u>Chromosome aberrations</u> (continued)		
Translocations in mouse lymphocytes <i>in vivo</i> : acute, fractionated acute, or chronic exposure to ¹³⁷ Cs gamma rays at 0.08–0.67 mGy min ⁻¹ and 0.15–3.6 Gy (Sorensen et al. 2000)	DREF for fractionated exposures: 3.1 at 1 Gy; 4.0 at 1.5 Gy DREF for chronic exposures: 5.8 at 1 Gy; 7.4 at 1.5 Gy	Aberrations scored using mFISH techniques, but simple and complex aberrations not distinguished. Estimates based on comparisons of LQ fit to response from acute exposure and linear responses from fractionated acute and chronic exposures.
Dicentrics in mouse splenocytes ^e <i>in vivo</i> : acute (0.89 Gy min ⁻¹) or chronic (0.014 mGy min ⁻¹) exposure to ¹³⁷ Cs gamma rays (Tanaka et al. 2009)	DREF for dicentrics using FISH: 17.8 at 1 Gy; 4.5 at 0.1 Gy DREF for dicentrics plus centric rings using Giemsa staining: 24.5 at 1 Gy; 5.2 at 0.1 Gy	Estimates based on comparisons of LQ fits to responses from acute exposure and linear fits to responses from chronic exposure. Simple and complex aberrations not distinguished in FISH analysis.
Inversions in PKZ1 transgenic mouse spleen cells <i>in vivo</i> : exposure to 250 kVp x rays at dose of 1 μGy–2 Gy; dose rates decreased from 180 mGy min ⁻¹ at 2 Gy to 0.0017 mGy min ⁻¹ at 1 μGy (Hooker et al. 2004)	LDEFs: ∞ at 1–10 mGy; ^b ≤5 × 10 ⁻⁵ at 1–10 μGy	“U-shaped” dose-response with maximum at 100 mGy, decreasing to level below response in controls at 1–10 mGy, increasing to approximate level in controls at 20–100 μGy, and increasing to levels well above responses at high doses at 1–10 μGy.
Inversions in PKZ1 transgenic mouse prostate cells <i>in vivo</i> : exposure to 250 kVp x rays at dose of 1 μGy–1 Gy; dose rates decreased from 180 mGy min ⁻¹ at 2 Gy to 0.0014 mGy min ⁻¹ at 1 μGy (Zeng et al. 2006)	LDEFs: ∞ at 1–10 mGy; ^b <2 × 10 ⁻² at 5–10 μGy	“U-shaped” dose-response with maximum at 1 Gy, decreasing to level below response in controls at 1–10 mGy, increasing to approximate level in controls at 20 μGy, increasing to levels above controls at 5–10 μGy, and decreasing to level slightly below controls at 1 μGy.

^a Standard error.

^b DDREFs for hormetic responses should have finite, negative values. However, when risk coefficients in humans are constrained to values ≥0, DDREFs for hormetic or threshold dose-responses are assigned the value ∞. An apparent threshold in a dose-response may not mean that there is a dose below which there is no response.

^c LDEFs apply at mean x-ray energies of 96 and 135 keV, respectively.

^d DDREFs (LDEFs) at 1 Gy for acentric chromosome aberrations based on data from Schmid et al. (2002) range from 1.18 ± 0.11 for 29 kVp x rays to 2.87 ± 0.25 for ⁶⁰Co gamma rays (Trabalka and Kocher 2007).

^e Lymphocytes residing in spleen.

Estimates of DREFs based on dose-responses for somatic cell mutations *in vitro* include values as low as 0.2, more typically about 1, and up to about 4. Effects of dose rate on dose-responses are complex and often difficult to interpret. Observations of no effect (DREF ≈ 1) or an inverse dose-rate effect (DREF < 1) are common (NCRP 2001). However, inverse dose-rate effects have not been reported in *in vivo* studies, and a wider range of values, all > 1 , is observed.

DDREFs (mostly LDEFs) inferred from cell transformation assays typically are about 1.5–4.5 but also include values < 1 and ∞ . However, the validity of such results has been questioned (NRC, 2006). The cell lines are abnormal and aneuploid (i.e., cells have an abnormal balance or number of chromosomes), and they exhibit aberrant growth patterns. These cell lines sometimes are derived from cancer cell lines or are considered well on the way to becoming cancer clones prior to radiation exposure (i.e., the process of cancer induction has already been initiated). In addition, dose-responses are complex and sometimes difficult to interpret. Responses are muted compared with induction of chromosomal aberrations, and some results indicate a significant lowering of the transformation frequency Gy^{-1} at doses < 100 mGy, while other results have shown an enhancement with dose fractionation.

In studies of induction of dicentric chromosome aberrations in human lymphocytes that were scored using conventional assays (Giemsa staining), LDEFs from acute exposure to high-energy gamma rays were in the range of about 3–9 at 1.5 Gy.³¹ Lower values typically were obtained in studies of acute exposure of human fibroblasts. Estimates of LDEF were about a factor of two lower for both cell types when simple aberrations were scored using FISH or mFISH techniques. Estimates of DREF for simple transmissible aberrations in human fibroblasts based on mFISH assays and translocations in mouse lymphocytes irradiated *in vivo* are within the same range as LDEFs based on data from acute exposures of lymphocytes obtained using conventional assays. One study of dicentrics in mouse splenocytes yielded a DREF of about 18 at 1 Gy (Tanaka et al. 2009). However, a wide variation in dose-responses for induction of chromosome aberrations in lymphocytes of different species has been reported, with the linear coefficient, α , in the modeled dose-response ranging from nearly zero to about twice the value of α in the dose-response in humans (NCRP 2001). Thus, mouse data may not be fully representative of the situation in humans.

Studies using a highly sensitive assay for radiation-induced inversions in spleen or prostate cells in transgenic mice produced “U-shaped” dose-responses with DREFs ranging from $< 10^{-5}$ to ∞ , depending on the range of doses and dose rates. However, an abnormally high background rate of aberrations in the transgenic mice could have contributed to the observed responses. Similar depressions in “U-shaped”

³¹ A dose of 1.5 Gy is the approximate midpoint of the dose range in the LSS cohort that was used to derive most cancer risk coefficients in IREP (Land et al. 2003a). Members of the LSS cohort with colon doses greater than about 4 Gy were not included in dose-response analyses to estimate risk coefficients in IREP.

dose-responses at 1–10 mGy were observed in prostate cells of transgenic PKZ1 mice (Day et al. 2006). However, this response did not occur in non-transgenic mice, and the frequency of inversions in transgenic controls was much higher than in non-transgenic controls. Although low priming doses between 1 μ Gy and 10 mGy induced an adaptive response in transgenic mice exposed to a challenge dose of 1 Gy, an adaptive response was not observed in non-transgenic mice. Rather, the effects of the two doses were additive. These differences suggest that abnormalities in the transgenic mice could have contributed to the dose-responses seen by Hooker et al. (2004) and Zeng et al. (2006).

LDEFs based on dose-responses for chromosome aberrations that were scored using conventional assays exhibit a pronounced energy dependence when the data are analyzed by assuming an LQ model of the dose-response (Trabalka and Kocher 2007). However, interpretation of those data may be compromised by the effects on dose-responses of complex (likely non-transmissible) aberrations. As discussed in Section 2.4.2, more recent data obtained using mFISH techniques suggest that the apparent energy dependence of LDEFs was an artifact of the use of conventional assays and the influence of complex aberrations on the dose-responses at high doses.

The combined effects of cell type, genetic background, interspecies variation, radiation type, and range of doses or dose rates studied complicate the interpretation of the data summarized in Table 4.1. The frequent finding that there is relatively little effect of dose-rate, or an inverse dose-rate effect, on mutagenesis in some somatic cell lines may indicate that activation of the full repair capacity of a cell requires a minimum level of damage (UNSCEAR 2000). In contrast, data on mutagenesis *in vivo* typically do not exhibit an inverse dose-rate effect, although the dose-response for the chromosomal inversion assay reported by Hooker et al. (2004) appears to exhibit such an effect.

Most LDEFs and DREFs based on dose-responses for genetic and cytogenetic endpoints are in the range of 1–10. However, some data suggest values <1 or >10 including ∞ from potentially hormetic or apparently threshold responses. A central estimate suggested by these data is in the range of about 2–6. An uncertain dependence of DDREF on photon energy, as indicated by the data for cell transformation and chromosome aberrations, adds to the concerns about the validity of DREFs or LDEFs derived from data on genetic or cytogenetic endpoints for the purpose of developing a DDREF distribution in humans. Recent results from studies of chromosome aberrations using mFISH serve to reinforce the concern that the LQ dose-response model, which was based largely on earlier studies of chromosome aberrations and was often used to interpret dose-responses in the studies summarized in Table 4.1, may not be a suitable representation of the dose-response for cancer induction in humans.

All the genetic and cytogenetic effects for which data are summarized in Table 4.1 reflect only one of the many steps in radiation carcinogenesis, and they do not account for the influence of epigenetic factors and homeostatic phenomena (e.g., including tissue-level coordination of cell function) that should

be considered in developing realistic models of dose-responses for cancer in humans. Use of data for these endpoints is based on biophysical (e.g., microdosimetric) arguments for the validity of an LNT model at doses below those at which dose-responses for cancer have been evaluated in human epidemiological studies and studies in laboratory animals. Although these arguments are considered plausible by most expert groups, they depend on assumptions about the ability of single cells to act autonomously in producing a cancer, i.e., in ways that are not completely plausible based on the current state of knowledge. Thus, our review focuses on information obtained in studies of radiation-induced cancer in humans or whole animals.

4.3 STUDIES IN WHOLE ANIMALS

4.3.1 Overview of Studies to Estimate DDREFs

DDREFs have been estimated based on data from many studies of radiation-induced cancer in laboratory animals; most estimates were based on comparisons of responses at high and low dose rates and, therefore, are DREFs. ICRP (1991) was reluctant to rely on those data on the grounds that the range of estimates of DDREF at that time of 2–10 (NCRP 1980) might include values that were too high, given that the ranges of doses in those studies included doses much higher than those experienced by the LSS cohort. However, ICRP's concerns about the effects of high doses on estimates of DDREF were justifiable only for the DREF of 10 derived by NCRP (1980) from data on induction of thyroid cancer in rats. The remaining estimates were based on data from studies in animals in which the maximum doses typically were 2 Gy and in no case more than 3.3 Gy.

Thus, the dose ranges in studies from which most of the DREFs derived by NCRP (1980) were obtained are compatible with organ doses in the LSS cohort of about 0–4 Gy or higher, depending on the cancer type, that were included in deriving the cancer risk coefficients used in IREP (Land et al. 2003a) and with organ doses of 0–2 Gy that were included in some recent studies (ICRP 2005; Preston et al. 2004, 2007). Most of the DREFs that were based on studies in animals were derived by comparing the effects of acute or high-dose-rate exposures with the effects of chronic exposure at dose rates <0.1 mGy min^{-1} , a dose rate which is used to define chronic exposures in IREP (Land et al. 2003a). Exceptions are noted in tables of data and the following discussions.

UNSCEAR (1993) concluded that studies in animals gave DDREFs of 1–10 or more, with a median value of 4. However, statistical and methodological uncertainties associated with those estimates are substantially larger than the ranges of central values cited by NCRP (1980) or UNSCEAR (1993). DDREFs cited by ICRP (1991) were estimates of DREF derived by NCRP (1980).

Our evaluation of data in animals was based in large part on a review by UNSCEAR (1993). However, we independently evaluated the data UNSCEAR used to estimate DDREFs, which led us to select other central values and uncertainties in some cases. We also developed independent estimates based on data from a number of studies published after the UNSCEAR (1993) report was completed.

A compilation of DREFs and their uncertainties that were based on studies of cancer induction in laboratory animals is presented in Table 4.2; our modifications of published estimates also are described. Section 4.3.2 discusses the suitability and limitations of applying DREFs derived from studies in animals to cancer induction in humans. DREFs based on dose-responses for specific cancer types, including leukemia, all solid tumors combined, and mammary cancers only, are discussed in Sections 4.3.3–4.3.5. Estimates of DREF based on data on life-span shortening in animals, which is attributable primarily to cancer, are evaluated in Section 4.3.6.

Probability distributions of DDREF also were derived by the BEIR VII committee using selected data on tumor induction and life-span shortening in animals under conditions of acute exposure (NRC 2006). However, for reasons discussed in Section 4.3.4, the BEIR VII committee's estimate of a DDREF based on the selected animal data is not directly comparable to DDREFs developed previously by others using the same data. In addition, as discussed in Appendix B, our review indicates that the approach used by the BEIR VII committee does not result in an estimate of DDREF and its uncertainty that represents the full range of credible values based on available data in animals.

When statistical uncertainties, differences in the ranges of doses and dose rates, and an assumption of a higher biological effectiveness of orthovoltage x rays relative to ^{60}Co gamma rays and beta particles from decay of ^{131}I and its uncertainty are taken into account in analyzing data on tumor incidence and results from studies of fractionated exposures are included, the range of credible values of DDREF based on all the data in Table 4.2, as defined by 95% CIs, is about 0.2– ∞ . Some of this variation is explainable by differences in experimental techniques, including fractionated vs protracted exposures and the time interval between dose fractions, in addition to differences in the ranges of doses and dose rates. The highest value (∞) cited by UNSCEAR (1993) was associated with incidence of myeloid leukemia in female RFM mice and was based on the suggestion of a threshold in the dose-response. The lowest DDREFs (about 1 or less) for lung carcinomas in female BALB/c mice at a dose of 2 Gy, thyroid tumors in female Long-Evans rats, and mammary tumors in WAG/Rij rats that did not receive estrogen supplements after irradiation are indicative of little or no effect of dose or dose rate or, perhaps, an inverse dose-rate effect. However, the low DREF for lung carcinomas (0.46) appears to be an artifact of data selection and the method of calculation and is inconsistent with other data on fractionated and chronic exposures in female BALB/c mice.

Table 4.2. Estimates of DREF based on dose-responses for cancer induction in laboratory animals by high-energy gamma radiation (except as noted)

Cancer type	Animal	DREF	Reference
Myeloid leukemia	RF mice (male)	2.7 [95% CI: (1.2, 7.9)] ^a	Our estimate calculated as ratio of linear slopes derived by Edwards (1992) from data in Upton et al. (1970) at doses of 0 – ≈3.2 Gy cited in Annex F, Table 9, in UNSCEAR (1993)
	RF mice (female)	5.8 [95% CI: (2.2, 10)] ^b	Our estimate calculated as ratio of linear slopes derived by Edwards (1992) from data in Upton et al. (1970) at doses of 0–3.1 Gy cited in Annex F, Table 9, in UNSCEAR (1993)
	RFM mice (female)	95% CI: (9.7, ∞)	Annex F, Table 8, in UNSCEAR (1993); derived from data in Ullrich and Storer (1979c)
	CBA/H mice (male)	Range: 2.2–5	Annex F, Table 8, in UNSCEAR (1993); derived from data in Mole and Major (1983); estimates are LDEFs
Mammary carcinomas	BALB/c mice	12 (upper limit: ∞) ^c	Annex F, Table 15, in UNSCEAR (1993); derived from data in Ullrich (1983) and Ullrich et al. (1987) at doses up to 0.25 Gy
		1.9	NCRP (1980) and Annex F, Table 8, in UNSCEAR (1993); derived from data in Ullrich and Storer (1979c) at doses of 0–2 Gy
		1.8 (1.1–2.4) ^d	Arnish and Groer (2000); based on analysis of data at dose of 2 Gy in Ullrich and Storer (1979c) and Storer et al. (1988)
	Sprague-Dawley rats	3 ^e	Vogel and Dickson (1982)
	WAG/Rij rats	1.1 [95% CI: (0.6, 2.0)] ^f	Our estimate based on data in rats that did not receive estrogen supplements from Bartstra et al. (1998a, 2000)
		10 (range: 6.4–15) ^g	Our estimate based on data in rats that received estrogen supplements from Bartstra et al. (1998b, 2000)
Mammary tumors	Sprague-Dawley rats	1.4–1.8 ^h	Gragtmans et al. (1984); based on comparison of effects of acute exposure to x rays and chronic exposure to tritium beta particles
Pituitary gland	RFM mice (female)	3.1 [95% CI: (0.7, 56)]	Our estimate based on DDREF derived by Edwards (1992) from data in Ullrich and Storer (1979c) at doses of 0–2 Gy cited in Annex F, Table 9, in UNSCEAR (1993)

Table 4.2 (continued)

Cancer type	Animal	DREF	Reference
Lung carcinomas	BALB/c mice (female)	2.8	NCRP (1980) and Annex F, Table 8, in UNSCEAR (1993); derived from data at doses up to 2 Gy in Ullrich and Storer (1979c)
		3.2 at 2 Gy; 4.2 at 3 Gy	Annex F, Tables 8 and 13, in UNSCEAR (1993); derived from data in Ullrich et al. (1987)
		3 [95% CI: (1, 5)]	Our estimate based on DDREF derived by Edwards (1992) from data in Ullrich and Storer (1979c), Ullrich (1983), and Ullrich et al. (1987) at doses up to 2 Gy
	0.46 (0.26–0.74) ^d	NCRP (2005); based on data at dose from chronic or acute exposure of 2 Gy from Ullrich and Storer (1979c) and Storer et al. (1988)	
	B6CF ₁ mice (male and female)	2.5 ⁱ	Estimate based on comparison of effects of acute and 60 once-weekly exposures (Heidenreich et al. 2006)
Beagle dogs		≈1, ≈3, ≈8–10 ^j	Estimates derived by comparing dose-responses from administered ⁹⁰ Sr or ⁹⁰ Y and ⁹⁰ Sr or ⁹¹ Y (Boecker et al. 1997) ^k
		1.2, 2.3, 4.5; ∞	Estimates of 1.2–4.5 based on relative carcinogenic potency ratios from administered ⁹⁰ Sr, ⁹⁰ Y, ⁹¹ Y, and ¹⁴⁴ Ce; estimate of ∞ based on lifespan virtual dose threshold at cumulative doses <5 Gy or higher, depending on radionuclide (Raabe 2010)
Thyroid carcinomas	Pre-pubescent Long-Evans rats (female)	0.53 [95% CI: (0.18, 1.84)] ^m	Our estimates derived from data in Lee et al. (1982) comparing effects of acute exposure to 250 kVp x rays and chronic exposure to administered ¹³¹ I
Thyroid carcinomas and adenomas		0.63 [95% CI: (0.19, 2.40)] ^m	
Bone sarcomas	Beagle dogs	95% CI: (11, ∞) ⁿ	Our estimate derived from data in White et al. (1993)
		95% CI: (7, ∞) ^o	Our estimate derived from data in Miller and Buster (1986), NCRP (1990), and Boecker et al. (1994)
		>18 or 19	Our estimates of lower limit derived from analyses of data in Miller and Buster (1986) by Lloyd et al. (1994) and Bijwaard et al. (2004)
	CF ₁ mice (female)	95% CI: (15, ∞) ^p	Our estimate derived from data in Finkel et al. (1959), Mays and Finkel (1980), and NCRP (1990)

Table 4.2 (continued)

Cancer type	Animal	DREF	Reference
Harderian gland	RFM mice (female)	3.8 [95% CI: (1.8, 11)]	Our estimate based on DDREF derived by Edwards (1992) from data in Ullrich and Storer (1979c) at doses of 0–2 Gy cited in Annex F, Table 9, in UNSCEAR (1993)
Skin tumors	ICR mice (female)	>30	Our estimate of lower limit derived from data in Ootsuyama and Tanooka (1991, 1993) and Tanooka and Ootsuyama (1991) ^g
Total tumors	Sprague-Dawley rats (male)	≈3	Annex F in UNSCEAR (1993); derived from data in Morin et al. (1991)
Carcinomas		≈6	
Sarcomas		≈1	

^a Median and CI estimated using Monte Carlo uncertainty propagation techniques; ratio of linear slopes was divided by REF_L of 2 [95% CI: (1, 3)] described in Section 2.4.2.5 to account for assumption of higher biological effectiveness of x rays used in acute exposures relative to ⁶⁰Co gamma rays used in chronic exposures.

^b Median and CI estimated using Monte Carlo uncertainty propagation techniques.

^c Same result was obtained when mice were given dose of 0.25 Gy at dose rate of 0.069 mGy min⁻¹ or in 25 daily fractions of 10 mGy each; see Section 4.3.5.1 and data from Ullrich et al. (1987) in Table 4.3. Upper limit is ∞ when responses were not significantly different from controls.

^d Approximate range of values in reported probability distribution over which DREF exceeds 5% of its central value.

^e Estimate based on dose-responses from chronic exposure at dose rates of 0.067–0.22 mGy min⁻¹.

^f Estimate based on dose-responses from fractionated exposures (2.5 or 10 mGy per fraction at 12-hour intervals) and single acute exposure to ¹³⁷Cs gamma rays at total doses of 1 or 2 Gy.

^g Estimates based on excess relative risks (ERRs) from fractionated exposure (2.5 or 10 mGy per fraction at 12- or 24-hour intervals) and single acute exposure to ¹³⁷Cs gamma rays at total doses of 1 or 2 Gy. Dose-responses from fractionated and acute exposures were linear at doses up to about 1.5 Gy. Narrower range of DREF of 8–11 is obtained if comparisons are restricted to ERRs at 1 Gy. DREF was reduced by factor of 4 when dose per fraction was increased to 40 mGy (value not shown in table; see Section 4.3.4).

^h Estimate based on dose-responses from chronic exposure to tritiated water over about 20 days and acute exposure to 200 kVp x rays, adjusted for a 20% higher biological effectiveness of tritium beta particles relative to x rays (Kocher et al. 2002, 2005). DREFs of 1.6–1.7 were estimated from dose-responses from acute exposure to 200 kVp x rays and chronic exposure to x rays at dose rates of 0.02–0.14 mGy min⁻¹ over 10 days.

ⁱ Data from JANUS study were analyzed using two-stage cancer induction model. Exposure duration was 20 minutes for most fractionated exposures, and dose rate for single acute exposures was more than three orders of magnitude lower than dose rate from atomic bombs in Japan and varied with total dose for fractionated exposures.

^j DREFs derived by comparing dose-responses from inhaled insoluble particles containing ⁹⁰Sr or shorter-lived ⁹⁰Y or ⁹¹Y. Because effective half-lives in lung were 900 days (⁹⁰Sr), 2.5 days (⁹⁰Y), and 75 days (⁹¹Y), dose rates to lung tissue delivered by different radionuclides differed greatly (e.g., by several orders of magnitude for ⁹⁰Sr compared with ⁹⁰Y); average dose rate from ⁹⁰Sr was <0.1 mGy min⁻¹.

^k See also Hahn et al. (1983), UNSCEAR (1993), Boecker et al. (1994), Cox et al. (1995), and Brooks et al. (2009).

^m DREFs derived by Lee et al. (1982) based on dose-responses from chronic exposure to ¹³¹I at doses ≤3.3 Gy and highly localized acute exposure to x rays at doses ≤4.1 Gy were divided by REF_L of 2 [95% CI: (1, 3)] described in Section 2.4.2.5 to account for assumption of higher biological effectiveness of x rays relative to ¹³¹I beta particles. Initial dose rates from ¹³¹I were 0.17–0.69 mGy min⁻¹, and mean dose rates were <0.1 mGy min⁻¹.

ⁿ DREF derived based on dose-responses from chronic exposure to ⁹⁰Sr at dose rates of 0.001–0.003 mGy min⁻¹ that show apparent threshold for induction of bone sarcomas at doses of 7.7–31 Gy.

^o DREF derived based on dose-responses from chronic exposure to ⁹⁰Sr at dose rates of 0.001–0.003 mGy min⁻¹ that show apparent threshold for induction of bone sarcomas at total doses of 5.97–21.7 Gy.

Table 4.2 (continued)

^p DREF derived based on dose-responses from chronic exposure to ⁹⁰Sr at dose rates of 0.002–0.02 mGy min⁻¹ that show apparent threshold for induction of bone sarcomas at doses of 1.72–20.9 Gy.

^q DREF derived based on dose-response from three weekly exposures to ⁹⁰Sr/⁹⁰Y over period ≥117 weeks that show apparent threshold for induction of skin tumors at doses of 0.5, 0.75, or 1 Gy. See NCRP (2001) for discussion of other studies of radiation-induced skin tumors in animals.

4.3.2 Influence of Biological Factors

There are biological reasons why DDREFs derived from studies in animals are so variable and difficult to relate to cancer induction in humans, even when an analysis is restricted tumor types relevant to humans. One reason is that dose-responses for a given tumor in one strain of an animal are of uncertain predictive significance in other strains of the same animal or in other species, including humans (NCRP 2001). The following examples illustrate this point. The dominant hematopoietic neoplasm in mice is of lymphocytic origin, whereas those neoplasms in humans are frequently of myelocytic origin. Two-thirds of all malignant tumors in uniformly irradiated beagle dogs occurred in the mammary gland or genital organs (Carnes et al. 2003), whereas the most prominent radiation-induced solid tumors in the LSS cohort have occurred in the stomach, lung, and female breast (Preston et al. 2007). For sarcomas that are poorly inducible in the rat (including leukemias) but frequent in humans, no dependence on dose or dose rate was observed, but for a second group of tumors that are infrequent in humans but common in the rat, incidence increased with increasing dose but was independent of dose rate (Morin et al. 1991; UNSCEAR 1993).

Fry (1992) questioned whether DREFs for seven mouse tumors and two types of mammary and thyroid tumors in rats estimated by NCRP (1980) could be applied to humans under any conditions, even when the tumors were homologous. He concluded that DREFs based on dose-responses for tumors of the Harderian gland,³² ovarian and pituitary tumors, and thymic lymphoma in mice probably have little or no relevance to humans, except to contribute to the general picture concerning the effects of dose rate. In regard to lung cancers, he noted that the cell of origin in mice is not the same as in bronchogenic cancer in humans,³³ and that there are differences in hormonal factors involved in carcinogenesis in breast tissue in mice and humans, as discussed in Section 4.3.5.1. Fry (1992) noted that for each tumor type for which DREFs had been estimated in animals, there were special features that raise questions about its

³² The Harderian gland is found only in animals with a third eyelid.

³³ This conclusion may not be valid, based on recent work which suggests that lung tumors other than small-cell carcinoma arise from a common stem/progenitor cell (Kim et al. 2005; Tonon et al. 2005).

applicability to humans.³⁴ He questioned whether the mechanisms that determined the effects of dose rate were not only species dependent but also differed quantitatively. Given that different DREFs have been obtained for different tissues in the same animal, different DREFs for the same tissue in different species are not unexpected. NCRP (1980) reached a similar conclusion by noting that “there can be no single [DREF] to apply to all organisms, and each tumor type must be considered individually.” Despite these pessimistic conclusions, animal data have been used to estimate DDREFs for cancer induction in humans (ICRP 2005; NCRP 2005; NRC 2006).

Some of the variability in DDREFs can be explained by effects on dose-responses associated with differences in animal species (mice vs rats or dogs), genetic factors that result in major differences between strains of the same species,³⁵ differential responses between different sexes of the same animal, variations in rates of turnover of cells and in life span, the involvement of cell sterilization or hormonal influences on the development of some tumors, and differences in the physiological condition and, in some cases, the environment in which animals were maintained.

Goodhead (2000) and NCRP (2001) concluded that data from studies in animals permitted few generalizations about the shapes of dose-response curves and, thus, would not support a general pattern of LQ responses at high dose rates or linear responses at low dose rates. Bedford and Dewey (2002) noted that if there are complicating factors or important differences that rule out any broad generalizations, they need to be known for practical reasons and for what they may reveal about the biological factors involved in radiation carcinogenesis. For example, the shapes of dose-responses in studies in animals appear to include threshold responses, which may not mean that there is a true threshold in the response, potentially hormetic responses, negligible dependencies on dose rate, or possible effects of other modifying factors

³⁴ See NCRP (2005) for a recent review of disparities and similarities between humans and laboratory animals with respect to target cells and hormonal factors involved in radiation-induced cancer at specific sites.

³⁵ Inter-strain comparisons of radiation effects in the same species often show marked differences. For example, BALB/c mice are sensitive to the development of mammary tumors when exposed to single or highly fractionated doses of gamma radiation (Ullrich et al. 1987), but no significant effects on the development of mammary tumors were observed in similarly exposed RFM mice (Ullrich et al. 1976). However, RFM mice are more sensitive than BALB/c mice to the development of radiation-induced hematopoietic cancers (Storer et al. 1979). The CBA strain is much more radiosensitive than the RFM strain for induction of myeloid leukemia, even though the CBA strain exhibits a spontaneous incidence 70 times lower (UNSCEAR 2000). Both the radiosensitivity for induction of myeloid leukemia and the spontaneous incidence in the BC3F1 strain are intermediate between those in the RFM and CBA strains (Covelli et al. 1989). In addition, the RFM, BC3F1, and AKR/J strains are unusually susceptible to development of lymphomas, with a 52%, 57%, and 81% incidence, respectively, in unirradiated males (Ullrich and Storer 1979a; Covelli et al. 1989; Ishii et al. 1996). Induction of thymic lymphomas and mammary tumors by abscopal mechanisms also has been reported in some strains of mice (Kaplan 1949; Kaplan and Brown 1951, 1952a, 1952b; Shellabarger et al. 1986). Sprague-Dawley and Long-Evans rats are the most radiosensitive rat strains for induction of mammary tumors (Vogel and Turner 1982; UNSCEAR 1993), whereas WAG/Rij rats used in studies by Bartstra et al. (2000) and Broerse et al. (1983) are the most sensitive strain to induction of carcinomas (UNSCEAR 2000). Fischer F344 rats (26% tumor incidence after one year) exhibit a sensitivity intermediate between that of Sprague-Dawley and Long-Evans rats (56% tumor incidence in both strains) and Wistar-Lewis rats (5.5% incidence) when exposed to a single dose of fission neutrons of 0.5 Gy (Vogel and Turner 1982).

reviewed in Section 3 that would call into question the use of a DREF. Potential hormetic effects on life span in laboratory animals exposed at low doses or dose rates are discussed in Section 4.3.6.

Although we concluded that hormesis should not be the default response at low doses,³⁶ apparently threshold responses may be a reasonable expectation for cancers of certain tissues. This is particularly the case when exposures are chronic at very low dose rates (ICRP 2005; see also Section 3.2).³⁷ Apparent thresholds in dose-responses typically (but not exclusively) occur when certain organs or tissues are targeted (e.g., bone, lung, or skin).

A few studies in animals reported apparent thresholds for induction of bone, lung, or skin cancer. In most cases, we estimated lower limits on CIs of DREFs from such data on the basis of uncertainties in dose-responses in exposed and control groups. The lower 95% confidence limits range from 7 to 19 based on data for bone tumors in beagle dogs and mice, whereas a DREF estimated from the lower limit of an apparent threshold in the dose-response for non-melanoma skin cancers in a study of the effects of highly fractionated exposures in mice is about 30.

4.3.3 Analyses of Data for Leukemia

We devote considerable attention to an evaluation of dose-responses and DDREFs for leukemia, specifically myeloid leukemia, in animals, because this information has been used to support the general applicability of an LQ dose-response for carcinogenesis in humans. DDREFs are not used in risk models for leukemias in IREP because risks are estimated assuming an LQ dose-response from acute exposure. However, since only the linear (α) coefficients in the LQ models for acute exposure are used to estimate risks of leukemia from chronic exposure, we evaluated data for leukemia in animals in case an adjustment similar to a DREF needs to be applied to risk coefficients in the chronic exposure models for leukemias, which were derived from data on dose-responses from acute exposure in the LSS cohort.³⁸

³⁶ Calabrese and Baldwin (2003) cited evidence of hormesis in induction of certain malignancies in mice and rats at acute doses of low-LET radiation of 0.1–2 Gy, but they did not mention a greater body of evidence from other studies that showed significant increases in other malignancies at the same doses (NCRP 1980, 2001; Edwards 1992; UNSCEAR 1993, 2000; NRC 2006). For example, they cited evidence from a study by Ullrich and Storer (1979b) of a lower incidence of lung adenomas in RFM mice exposed to gamma radiation at doses of 0.1–1.5 Gy, but they did not acknowledge that significant increases in other malignancies were observed at the same doses.

³⁷ Several studies reported apparent threshold responses for radiation-induced cancer in animals, including studies of skin and mammary cancer and a study of myeloid leukemia from which DREFs were derived, along with all studies of bone cancer we reviewed (Table 4.2). It may be significant that apparent thresholds for induction of bone sarcomas were observed at total doses of 10–20 Gy from chronic internal exposure at dose rates that were one to two orders of magnitude lower than dose rates in most studies of chronic external exposure in animals, which were about 0.06 mGy min⁻¹.

³⁸ In IREP, risks are estimated for all leukemias as a group, excluding chronic lymphocytic leukemia (CLL), and for acute myelogenous leukemia (AML), acute lymphocytic leukemia (ALL), and chronic myelogenous leukemia (CML) separately (Land et al. 2003a).

Fry (1992) and ICRP (2005) concluded that studies of myeloid leukemia in mice could be used to estimate a DDREF for leukemia in humans. ICRP (2005) further concluded that data on myeloid leukemia in CBA and RFM mice were the most suitable and yielded estimates of DDREF of about 2–6. However, ICRP's estimates differ from the central estimates ranging from 2.2 to ∞ given by UNSCEAR (1993), which used data from studies in both mouse strains identified by ICRP (2005). Estimates of DDREF derived by UNSCEAR (1993) from data in the two studies cited by ICRP (2005) are as follows:

- 2.2–5 [male CBA/H mice; data from Mole and Major (1983); included in Table 4.2];
- 5.1 (3.8–7.0) [mean \pm 1 standard error (SE)] [male RF mice that received high-dose-rate exposures up to 1 Gy and protracted exposures up to 3.08 Gy; original data from Upton et al. (1970)];
- about 8 (5–15) (mean \pm 1 SE) [female RF mice that received high-dose-rate exposures up to 3 Gy and protracted exposures up to 5.8–6.1 Gy; original data from Upton et al. (1970)].

The last two estimates came from analyses performed by Edwards (1992) for the UNSCEAR (1993) report. The weak dose-response for leukemia in female RF mice, even at total doses of about 6 Gy, made it difficult to assess the effects of dose rate. One reason for this may be that females in the study by Upton et al. (1970) were exposed at lower dose rates than males (0.07 vs 0.8 Gy min⁻¹ in exposures at high dose rates and 0.004–0.7 vs 0.04–0.6 mGy min⁻¹ in protracted exposures). In addition, a different radiation type (250 kVp x rays) was used in acute exposures of males than in exposures of the other groups. Calculations based on data from a third study (Ullrich and Storer 1979a, 1979c), in which leukemia incidence in female RFM mice from protracted exposures to ¹³⁷Cs gamma rays at a dose rate of 0.069 mGy min⁻¹ and total doses of 0.5, 1, and 2 Gy was not significantly different from the incidence in controls, gave a DREF of ∞ with a lower 95% confidence limit of 9.7 (UNSCEAR 1993).

NCRP (1980) did not use the data described in the previous paragraph to calculate a DREF, possibly because of the lack of an elevated dose-response in animals exposed at a low dose rate and the apparent linearity in the dose-response from acute exposure at doses up to 3 Gy in male and female mice (Ullrich and Storer 1979a, 1979c; Ullrich and Preston 1987). Rather, NCRP (1980) derived DREFs of 6.7 and 2.3 in male and female RF mice, respectively, using selected data from Upton et al. (1970). The data in females used by NCRP were limited to exposures that were terminated before appreciable mortality in the exposed animals occurred. Had NCRP (1980) used data from exposures that were terminated later, the total doses and DREF (about 18) would have been higher (Upton et al. 1970). This higher DREF could be an overestimate because radiation injury induced late in life might not have been fully expressed.

Our examination of dose-responses in female RF mice reported by Upton et al. (1970) indicated that the low central estimate of a DREF of 2.3 derived by NCRP (1980) in that case probably was not indicative of the difference in dose-responses from acute and protracted exposures. Rather, we think that DREFs we estimated from regression-based estimates of the linear (α) coefficients derived by Edwards (1992), as given in Annex F, Table 9, in UNSCEAR (1993), are more representative. NCRP (1980) also did not provide estimates of uncertainty, which are large in the dose-responses for acute and protracted exposures of female RF mice.

Using the data reported by Edwards (1992) based on the study by Upton et al. (1970) that used common dose intervals for acute and chronic exposures in male and female RF mice, as given in Annex F, Table 9, in UNSCEAR (1993), we estimated DREFs using Monte Carlo uncertainty propagation techniques. The following estimates of median values and 95% CIs were obtained:

- 5.1 [95% CI: (3.3, 12)] – males that received acute exposures at doses up to 3 Gy and protracted exposures at doses up to 3.08 Gy;
- 5.5 [95% CI: (3.6, 12)] – males that received acute exposures at doses up to 3 Gy and protracted exposures at doses up to 3.29 Gy;
- 5.8 [95% CI: (2.2, 10)] – females that received acute exposures at doses up to 3 Gy and protracted exposures at doses up to 3.1 Gy.

Given the similarity in the two estimates in males, we averaged the results to give a DREF with a median of 5.3 and 95% CI of (3.5, 12).

However, DREFs based on data for myeloid leukemia in male RF mice that are derived by any of these approaches should be adjusted for the following reasons:

- Female mice in the study by Upton et al. (1970) were exposed to ^{60}Co gamma rays only, whereas the high-dose-rate groups of male mice were exposed to 250 kVp x rays (mean energy about 100 keV) and the low-dose-rate groups of males were exposed to ^{60}Co gamma rays.
- As shown in Figure 2.5, differences in the slopes of acute dose-responses for incidence of myeloid leukemia in mice exposed to x rays (Upton et al. 1970) or ^{137}Cs gamma rays (Ullrich and Storer 1979a, 1979c; Ullrich and Preston 1987) indicate that the x rays were more effective than the higher-energy gamma rays by a factor of about 2 at doses of 2–3 Gy.

Thus, DREFs for myeloid leukemia in male mice may have been overestimated by a factor of about 2, irrespective of any differences in the slopes of dose-responses due to differences in dose rate.

If we had used DREFs of 6.7 and 2.3 in male and female RF mice, respectively, estimated by NCRP (1980), the correction for a difference in biological effectiveness of x rays and high-energy gamma rays would have brought the DREFs in the two sexes closer together and would suggest a range of central estimates in RF mice of about 2–4. However, those estimates still differ greatly from the range of 9.7–∞ for myeloid leukemia in female RFM mice derived from the study by Ullrich and Storer (1979a, 1979c). Furthermore, as indicated in Table 4.2, correcting our estimate of DREF in male RF mice to account for an assumed REF_L for x rays of 2 [95% CI: (1, 3)] has the opposite effect: the DREF in males decreases to 2.7 [95% CI: (1.2, 7.9)] compared with the DREF in females of 5.8 [95% CI: (2.2, 10)].

Uncertainties in a DREF for myeloid leukemia in RFM female mice that we estimated based on data reported by Upton et al. (1970) encompass the lower limit of 9.7 derived by UNSCEAR (1993) based on data reported by Ullrich and Storer (1979a, 1979c). We do not think that results from the latter two studies can be ignored because (1) this DREF was based on a study that used more than four times as many chronically exposed mice than the study by Upton et al. (1970) and, thus, had a higher statistical power; (2) the study by Ullrich and Storer (1979a, 1979c) used specific-pathogen-free mice housed in a barrier facility with a rigidly controlled microbial environment, whereas Upton et al. used conventional animals housed in conventional facilities; (3) risks estimated by Upton et al. were not adjusted for competing causes of death; (4) males in the study by Upton et al. were exposed at dose rates an order of magnitude higher than females; and (5) some groups in the study by Upton et al. received protracted exposures at dose rates that exceeded the 0.1 mGy min⁻¹ threshold used to define chronic exposures in IREP (Land et al. 2003a) by a considerable margin, whereas mice in the study by Ullrich and Storer were exposed at a uniform dose rate (0.069 mGy min⁻¹) below that threshold.

Given the wide variation in DDREFs from the three studies of myeloid leukemia in mice, UNSCEAR (1993) concluded that there was no consistent trend with dose rate. In addition, Mole and Major (1983) observed a low, flat dose-response at doses of 1.5–4.5 Gy in male CBA/H mice that received protracted exposures at 0.044–0.11 mGy min⁻¹ over a 4-week period or 20 equal fractions at a high dose rate of 0.25 Gy min⁻¹ for five days each week over the same time period (UNSCEAR 1993). Incidence of leukemia in the two groups was the same and appeared to be independent of total dose. Thus, in this case, similar estimates of DREF in the range of 2.2–5 are derived by comparing these results with dose-responses for leukemia incidence in CBA/H mice from acute exposure to the same type of radiation (⁶⁰Co gamma rays) at a dose rate of 0.25 Gy min⁻¹ (Table 4.2).

Studies of fatal cancers in beagle dogs that received continuous, duration-of-life exposures to ⁶⁰Co gamma rays at dose rates of 3–128 mGy d⁻¹ (0.002–0.09 mGy min⁻¹) also suggest that the dose-response for leukemia at low dose rates may be highly uncertain. The occurrence of myeloid leukemias was highest (46%) at an intermediate dose rate of 37.5 mGy d⁻¹ (0.026 mGy h⁻¹), was supplanted successively at

higher dose rates by the occurrence of aplastic anemias and septicemia, and decreased to zero at the lowest dose rate (Fritz et al. 1986; Seed et al. 2002). In contrast, the occurrence of fatal solid tumors was highest (about 50%) at the lowest dose rate and decreased to zero at the highest dose rate (Seed et al. 2002). These data also show why accounting for competing causes of death can be an important consideration.

4.3.4 Consideration of Data for All Solid Tumors Combined

ICRP (2005) considered that data on induction of Harderian gland and pituitary tumors in female RFM mice, lung and mammary cancers in female BALB/c mice, and mammary tumors in female Sprague-Dawley rats provided the best animal models for induction of solid cancers in humans because of the sensitivity of those tissues to radiation-induced cancer and the dose ranges over which data had been obtained. ICRP (2005) concluded that those data showed that a reduction in dose rate or fractionation of the dose at low doses per fraction generally reduced the risk of cancer predicted by an LQ model at doses of 0.1–2 Gy. Alternative interpretations of those data are discussed in Section 4.3.1 and Appendix B.

NCRP (2001) noted that when an analysis of data for specific tumors was restricted to cases where the dose-response from acute exposure was described by an LQ model, doses accumulated as small fractions or at very low dose rates produced tumors at a frequency predicted by the linear portion of the LQ relationship. In such cases, which appear to be more exceptional than general (Goodhead 2000; see Section 4.3.1 and Appendix B),³⁹ central estimates of a DREF recommended by NCRP (2001)⁴⁰ ranged from 2 to 10, as estimated previously (NCRP 1980). However, those estimates were based on comparisons of purely linear, not LQ, fits to dose-responses from acute and chronic exposure.

The BEIR VII committee (NRC 2006) focused on an analysis of data from acute exposure on induction of Harderian gland and lung tumors in male and female RFM mice, mammary, pituitary, and uterine tumors in female RFM mice, and lung and mammary tumors in female BALB/c mice combined. For unknown reasons, data from acute exposure on induction of myeloid leukemia in male and female

³⁹ For example, the occurrence of lung tumors in female BALB/c mice at doses from ¹³⁷Cs gamma rays of 2 Gy given in daily fractions of 100 mGy, a dose which was expected to be in the linear region of an LQ dose-response, was essentially identical to the occurrence following protracted exposure at a dose rate of 0.06 mGy min⁻¹. At the lowest dose (100 mGy in both cases), the linear term dominated and the occurrence of tumors was largely independent of dose rate (DDREF ≈ 1.1), as expected if an LQ dose-response applied to the entire data set. At higher doses, the quadratic term increased in importance, and DDREFs were about 2–4 at doses of 1–3 Gy, as summarized in Table 4.2. Unfortunately, other data suggest that the dose-responses for lung tumors may be exceptional. For example, in the same mice, the dose-response from acute exposure could not be distinguished from a linear response at doses of 0–2 Gy (Ullrich 1983; Ullrich et al. 1987); data for lung tumors in CBA/H mice exposed to 200 kVp x rays at doses of 0.25–7.5 Gy were best fit by a quadratic-exponential model (Coggle 1988); and dose-responses for mammary tumors in BALB/c mice were not similar to those for lung tumors (Section 4.3.5.1).

⁴⁰ NCRP's characterization of the modifying factor as a DREF appears appropriate based on the studies reviewed for their 1980 and 2001 reports, which were concerned mainly with the effects of dose rate.

RFM mice also were included in the committee's analysis of a DDREF for solid tumors. Contrary to conclusions by previous investigators, the committee concluded that a single DDREF could be applied to all tumors and that the variability in dose-responses for cancer in animals could be attributed to statistical uncertainties. In addition, the DDREF derived by the committee from data in animals is not comparable to other estimates, because it also was based in part on data from acute exposure on life-span shortening, presumably because the objective was to develop a DDREF that could be applied to risk estimates for cancer incidence and cancer mortality in the LSS cohort.

To summarize its analysis, the BEIR VII committee presented a probability distribution of the pooled estimate of the curvature parameter (β/α) in the dose-response from acute exposure that was derived from the data on cancer in animals (NRC 2006, Figure 10B-4). We estimated a central value of the curvature parameter of about 0.4 Gy^{-1} , with a range of about -0.2 to 6 Gy^{-1} . Using these estimates in equation (1) in Section 2.2, we estimated an LDEF at 1.5 Gy of about 1.6, with a range of about 0.7–10. Our concerns about the approach used by the BEIR VII committee to estimate a DDREF from the data in animals and our rationale for not accepting their estimate of a DDREF based on data on leukemia, solid tumors, and life-span shortening combined are discussed in Appendix B.

ICRP (2005) suggested a narrower range of central estimates of DDREF from <2 to about 3 if the evaluation is restricted to data on the limited set of solid tumors identified at the beginning of this section. However, estimates of about 1–12 for the same set of tumors given by UNSCEAR (1993) are similar to the estimates of about 2–10 cited by NCRP (1980, 2001) and summarized in Table 4.2. UNSCEAR (1993) and ICRP (2005) based their estimates on extrapolations to low doses of responses at doses ≤ 3 Gy for the limited set of solid tumors, thus eliminating the concern expressed previously by ICRP (1991) about the effect of high doses in studies in animals.

The difference between the ranges of a DDREF developed by ICRP (2005) and UNSCEAR (1993) appears to result from the omission by ICRP (2005) of estimates derived from data on induction of pituitary tumors in RFM mice (Ullrich and Storer 1979b, 1979c)—a DREF in the range of 4.6–8.1 derived by UNSCEAR (1993)—and data on induction of mammary adenocarcinomas in BALB/c mice (Ullrich 1983; Ullrich et al. 1987)—a DREF of 12 derived by UNSCEAR (1993). The omission of those data by ICRP (2005) was not explained but is somewhat surprising because, as noted above, ICRP (2005) cited data on those tumor types as providing evidence for the applicability of an LQ dose-response model for cancer incidence at doses of 0.1–2 Gy. We suspect that the results for mammary tumors were omitted by ICRP (2005) because of differences in the ranges of doses over which those data were obtained compared with the data for other cancer types.

When the DREF of 12 described above is included in the range of DDREFs for mammary tumors in laboratory animals, the overall range is about 1–12 (Table 4.2). This range is the same as the range of

DDREFs for all types of tumors estimated by UNSCEAR (1993). If the DREF of 12 is excluded, the range of DDREFs for mammary tumors in rats and mice is not appreciably narrowed, and the impact on the overall range of DDREFs for solid tumors given in UNSCEAR (1993) is small; i.e., the range is reduced to about 1–10 (UNSCEAR 1993, Annex F, Table 8). However, the highest values in the range of 1–10 were based on data not summarized in Table 4.2 from studies of induction of thyroid tumors in CBA mice and several strains of rats at acute doses of x rays of 10 Gy or greater or doses from administered ^{131}I of 100 Gy or greater. Those studies may have other problems, including dosimetric uncertainties in animals exposed to ^{131}I (UNSCEAR 1993; Lee et al. 1979), particularly when results are compared with results from the study in pre-pubescent rats by Lee et al. (1982) summarized in Table 4.2. One concern about the study by Lee et al. (1982) is that it was terminated at two years, when nearly two-thirds of the animals were still alive, which may have prevented the appearance of some late tumors (UNSCEAR 1993). The first carcinoma was not observed until 16 months after exposure (Lee et al. 1982).

If we assume that the exclusion of DDREFs derived from the high-dose studies of thyroid tumors noted above is justified, the range of central estimates of DDREFs for all types of solid tumors is not appreciably narrowed unless data on mammary carcinomas in estrogen-treated rats and data in BALB/c mice at low doses of 0.25 Gy or less summarized in Table 4.2 also are excluded. If those data are excluded, the highest DDREF in the compilation by UNSCEAR (1993) is the mean DREF for pituitary tumors of 8.1 (range of 3.3–20, as defined by ± 1 SE) derived by Edwards (1992) but not included in Table 4.2. A higher mean DREF for pituitary tumors of 14 (range of 3– ∞ , as defined by ± 1 SE) was derived by Edwards (1992) using a different approach to uncertainty analysis. That estimate is not considered here because it was based on a more approximate method. Our central estimate of the DREF for induction of pituitary tumors of 3.1 given in Table 4.2 is the median, rather than the mean, of a distribution we derived from data reported by Edwards (1992). The mean of that distribution of 13 is higher than the mean of 8.1 derived by Edwards (1992).

4.3.5 Analysis of Data for Mammary Tumors

4.3.5.1 Review of data

Data on dose-responses for mammary tumors in laboratory animals have been used to support a lower DDREF for this tumor type than for other solid tumors. DDREFs for mammary cancer in laboratory animals summarized in Table 4.2 fall into two categories:

- DREFs of about 10 that were derived by comparing dose-responses in female WAG/Rij rats given estrogen supplements that received acute and highly fractionated exposures at doses of 1–2 Gy with dose-responses in BALB/c mice that received acute, chronic, and fractionated exposures at doses up to 0.25 Gy, above which the effects of acute exposure on the ovary and ovarian function (a reduction in hormone levels) reduced the incidence of mammary cancers; the dose-responses in BALB/c mice are shown in Figures 4.1 and 4.2 and summarized in Table 4.3.
- DREFs of about 1–3 that were derived by comparing dose-responses in mice and rats not given estrogen supplements that received acute exposures at doses of about 1–3 Gy with dose-responses from highly fractionated or chronic exposures (Table 4.2).

The DDREF of 12 for mammary cancer in BALB/c mice at a dose of 0.25 Gy estimated by UNSCEAR (1993) was based on data from acute, fractionated, or chronic exposures at doses of 0.1, 0.2, and 0.25 Gy (Ullrich 1983; Ullrich et al. 1987) given in Table 4.3 and an LQ dose-response model for acute exposure (Ullrich 1983) described in Table 4.3, footnote *b*, and shown in Figure 4.2.⁴¹ However, UNSCEAR (1993) did not consider uncertainties in the data in estimating a DDREF of 12 at 0.25 Gy. Since incidence rates of mammary tumors at 0.25 Gy in mice that received fractionated exposures of 10 mGy d⁻¹ or protracted exposures at a dose rate of 0.069 mGy min⁻¹ did not differ significantly from incidence rates in the control groups given in Table 4.3, the upper limit of a DDREF is ∞ . Nonetheless, the similarity in the shapes of the acute dose-responses for fission neutrons and ¹³⁷Cs gamma rays in Figure 4.1, combined with the results obtained by Ullrich et al. (1987) for fractionated exposures of 50 mGy d⁻¹ and protracted exposures given in Table 4.3, indicate that the occurrences of mammary tumors in BALB/c mice at low doses cannot be dismissed as statistical artifacts.

⁴¹ The contrast between dose-responses for induction of genomic instability and mammary carcinomas in BALB/c mice and the effects of fractionation on dose-responses for both endpoints provide important information on the nature of dose-responses for radiation carcinogenesis. Although the rate of increase in both responses is maximal at doses of 0–0.25 Gy, the dose-response for genomic instability exhibits downward curvature at low doses similar to curve *d* in Figure 1.1 (Section 1.1), whereas the dose-response for tumor induction shows an upward curvature, as expected when a dose-response has a significant quadratic component (Figure 4.1). In addition, the yield of chromosomal aberrations at 0.25 Gy was halved when mice were given 25 equal fractions of 10 mGy (Ullrich and Davis 1999), whereas the occurrence of tumors was reduced by a factor of about 12. These results suggest that extrapolation of dose-responses for such endpoints as genomic instability and bystander effects to carcinogenesis is problematic. However, the magnitude of the effect of dose fractionation on the occurrence of mammary tumors also is remarkable in view of the unique genetic characteristics of BALB/c mice, and it suggests that processes other than genomic instability and compromised DNA-DSB repair play a major role in determining the response.

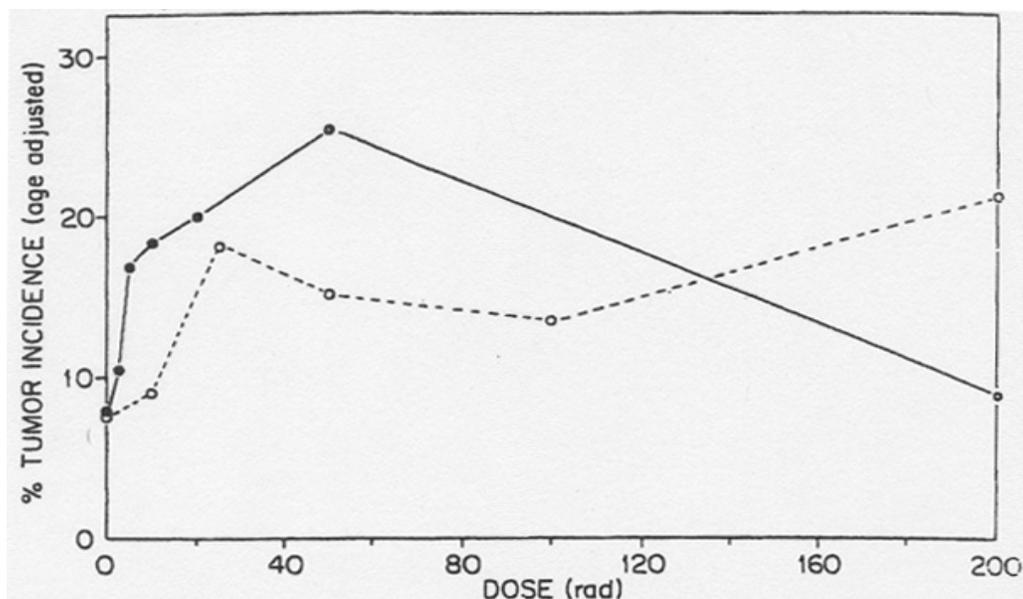


Figure 4.1. Incidence of mammary adenocarcinomas in female BALB/c mice from acute exposure to fission neutrons (●) or ¹³⁷Cs gamma rays (○) (Ullrich 1983). Curves can be compared with generalized dose-response that includes cell-sterilization term in Figure 2.3, curve A.

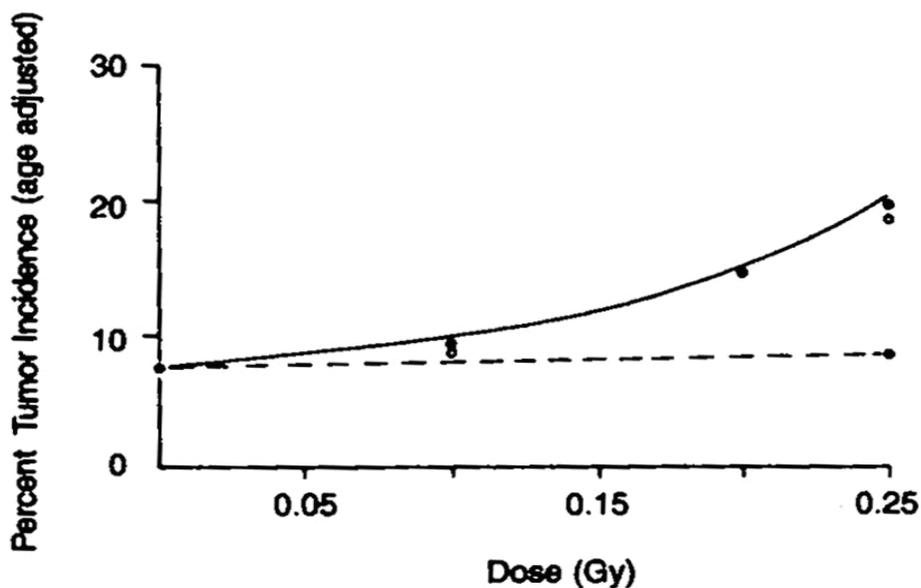


Figure 4.2. Effect of dose rate and dose fractionation on incidence of mammary carcinomas in female BALB/c mice exposed to ¹³⁷Cs gamma rays. Solid line is LQ fit at high dose rate (0.4 Gy min⁻¹); dashed line is linear term in LQ regression at low dose rate (0.069 mGy min⁻¹). Solid circles near solid line are incidence rates from acute exposure at high dose rate; open circle at 0.25 Gy next to solid line is incidence rate from five daily doses of 50 mGy; solid circle at 0.25 Gy next to dashed line is incidence rate from 25 daily doses of 10 mGy. Modified from Ullrich et al. (1987); see also NCRP (2001).

Table 4.3. Incidence rate (% \pm 1 SE) of mammary adenocarcinomas in BALB/c mice from acute, fractionated, or protracted exposure to ^{137}Cs gamma rays

Dose (Gy)	Cancer incidence rate by exposure regimen: dose rate						
	Acute ^a : 0.40 Gy min ⁻¹	Acute ^b : 0.40 Gy min ⁻¹	Acute ^c : 0.35 Gy min ⁻¹	Fractionated: 50 mGy d ⁻¹ (50 mGy min ⁻¹)	Fractionated ^d : 10 mGy d ⁻¹ (50 mGy min ⁻¹)	Protracted ^e : 0.069 mGy min ⁻¹	Protracted ^d : 0.069 mGy min ⁻¹
0	7.6 \pm 0.9	7.5 \pm 2.5	—	—	—	7.6 \pm 0.9	—
0	—	7.9 \pm 1.7	—	—	—	—	—
0.1	—	9.1 \pm 2.7	9 \pm 3	—	—	—	—
0.2	—	—	15 \pm 5	—	—	—	—
0.25	—	18 \pm 4	20 \pm 5	17 \pm 4	7.5 \pm 2.3	—	7.9 \pm 2.1
0.5	12.1 \pm 1.4	16 \pm 4	—	—	—	9.0 \pm 0.9	—
1	—	14 \pm 4	—	—	—	13.2 \pm 1.2	—
2	20.5 \pm 2.5	22 \pm 4	—	—	—	13.9 \pm 1.3	—
Source	Ullrich and Storer (1979c)	Ullrich (1983)	Ullrich et al. (1987)	Ullrich et al. (1987)	Ullrich et al. (1987)	Ullrich and Storer (1979c)	Ullrich et al. (1987)

^a Linear dose-response; slope = 6.7% Gy⁻¹.

^b Linear-quadratic dose-response at doses up to 0.25 Gy. Incidence rate (%) = 7.7 + 3.5D + 150D²; D = dose in Gy.

^c Dose-response consistent with LQ relationship in footnote b.

^d Dose-response consistent with linear slope indicated by data for protracted exposures from Ullrich and Storer (1979b) and linear slope at low doses from LQ relationship in footnote b.

^e Linear dose-response; slope = 3.5% Gy⁻¹. DREF of 1.9 is estimated when slope is compared with dose-response for acute exposure from Ullrich and Storer (1979c), but DREF of about 12 is estimated when slope is compared with dose-response for acute exposure up to 0.25 Gy from Ullrich (1983) and Ullrich et al. (1987).

In contrast to the incidence rate of mammary cancers in BALB/c mice that received daily fractions of 10 mGy in Table 4.3, which was not elevated significantly compared with incidence rates in the control groups, the effects of daily fractions of 50 mGy delivered at 50 mGy min⁻¹ appear to be almost additive, as indicated in Figure 4.2. This result suggests that the higher dose fractions (and associated higher dose rates) are not “low” in the context of protection against induction of mammary cancer in this animal model. However, the five-fold higher degree of dose fractionation in mice that received daily fractions of 10 mGy should have been a major contributing factor to the observed difference in responses. Similarly, the flattening of the acute dose-response for mammary carcinomas at doses above 0.25 Gy reported by Ullrich (1983) and indicated in Table 4.3 and Figure 4.1 contrasts with dose-responses from acute and

protracted exposures reported by Ullrich and Storer (1979c), which showed increases in incidence rates at doses of 1 or 2 Gy compared with incidence rates at 0.5 Gy.⁴²

Should data on mammary carcinomas in estrogen-treated rats and in BALB/c mice at low doses be excluded in estimating a DDREF? Prior to the study by Ullrich et al. (1987), NCRP (1980) concluded that “in general the influence of dose rate seems to be least for the induction of mammary tumors.” Cox et al. (1995) agreed but also pointed out that the effect of dose fractionation or protraction reported by Ullrich et al. (1987) “would suggest DDREFs in excess of 10.” A DREF for induction of mammary tumors in the same strain of mouse estimated by NCRP (1980) was 1.9 (Table 4.2), or about a factor of six lower; that DREF was derived based on data from the early study by Ullrich and Storer (1979b), which lacked data at doses of 0–0.5 Gy. UNSCEAR (1993) cited both estimates of DREF but noted that “interpretation of the [higher value of about 12] is limited by the lack of information at higher doses”; that estimate was derived from data on incidence of mammary tumors at doses of 0–0.25 Gy.

However, if the acute dose-response was linear-quadratic at doses of 0–2 Gy, a DREF based on data at doses of 0–0.25 or 0–0.5 Gy should have been lower, not higher, than an estimate based on data at doses of 0–2 Gy. In addition, data that would allow a comparison of incidence of mammary tumors in BALB/c mice from acute or protracted exposures at doses of 0–2 Gy are available (Table 4.2). Estimates of cancer incidence from acute exposure in Table 4.3 show a flattening at doses >0.25–0.5 Gy, as indicated by the dashed curve in Figure 4.1, which probably is associated with a 99% loss of oocytes at 0.5 Gy (NCRP 1980) that resulted in ovarian dysfunction and hormonal imbalances. However, estimates of cancer incidence from exposures in 10 mGy d⁻¹ fractions over 25 days or from protracted exposure in Table 4.3 are consistent with either a linear dose-response based on an LQ fit to the dose-response from acute exposure at doses of 0–0.25 Gy or no response at doses up to 0.25 Gy (DREF = ∞; Table 4.2). Restricting the analysis to doses of 0–0.25 Gy over which the LQ dose-response from acute exposure applies, without considering uncertainties in the responses, yields the DREF of 12 (UNSCEAR 1993). DREF decreases at higher doses as a consequence of a flattening of the acute dose-response (Figure 4.1), in a manner similar to the effect of cell sterilization on the generalized dose-response described in Section 2.4.1, leading to the DREF of about 2 at 2 Gy cited by NCRP (1980) and given in Table 4.2.

Although carcinogenesis is too complex a process to attribute all the variation in dose-responses for induction of mammary adenocarcinomas in laboratory animals to the influence of a single factor, the literature on radiation effects on the mammary gland indicates that the maximum neoplastic response to ionizing radiation occurs only when the ovary is functioning normally (Bond et al. 1960; Cronkite et al.

⁴² Ullrich (1983) noted that the flattening of the dose-response in the later data was unexpected, but that the previous conclusion was based on limited data.

1960).⁴³ At an acute dose of 0.5 Gy, no mammary tumors were induced in female BALB/c mice in which the ovaries were removed. However, the incidence of mammary adenocarcinomas in the same strain at an acute dose of 2 Gy was about twice the incidence in mice with no ovaries or in mice that were chronically exposed at a dose rate of about 0.06 mGy min⁻¹ (Ullrich and Storer 1979c; Storer et al. 1982). Because the lower DREF of 1.9 based on the dose-response at 0–2 Gy obtained by Ullrich and Storer (1979b) probably reflects an effect of suppression of ovulation at higher doses, which leads to a reduced secretion of estrogens and, thus, to an underestimation of the risk from irradiation of the mammary gland (Bartstra et al. 1998b), the higher DREF of 12 based on data from Ullrich et al. (1987) cannot be excluded.

Dose-responses for incidence of breast cancer in humans from uniform whole-body irradiation are influenced by cell sterilization in the ovaries only at doses well above 2 Gy (Preston et al. 2002; NRC 2006; UNSCEAR 2008). One reason is that the ovary is much less radiosensitive in humans than in laboratory mice (NCRP 1980; ICRP 2005; NRC 2006) and, in contrast to laboratory animals, radiosensitivity in humans increases with increasing age (Mettler and Upton 1995).

Although there are other biological differences between humans and mice that complicate comparisons, estimated DREFs obtained at lower doses in mice appear to be relevant to extrapolations of radiation effects to low doses and low dose rates. Unless it is certain that there is no analogy between dose-responses in mice at 0–0.25 Gy and dose-responses in humans up to about 4 Gy, we think that the higher estimate of DREF obtained from studies in BALB/c mice indicates that the range of credible DREFs for breast cancer in humans should be expanded to include values of about 10 or higher.

Our conclusion is supported by epidemiological studies of breast cancer in females reviewed by the BEIR VII committee (NRC 2006) and UNSCEAR (2008), which showed either an absence of risk or significant reductions in risk associated with cessation or reduction of ovarian function in women who received 5 Gy or more of x rays to the ovaries or whose therapy advanced the onset of menopause. For example, ovarian ablation associated with radiation or chemotherapy substantially reduced the risk of breast cancer in patients treated for Hodgkin's disease (UNSCEAR 2008).

The BEIR VII committee (NRC 2006) expressed concern about the dose-response for mammary adenocarcinomas in BALB/c mice because of the lack of a similar dose-response in data in humans. Rather than rejecting the results in mice, the committee recommended that research on the dose-response for mammary cancer from exposure to low-LET radiation be continued.

Recent research on radiation-induced mammary cancer in estrogen-treated rats has reinforced the possible significance of the high DREF of about 12 derived from studies in mice at low doses. In studies

⁴³ Incidence of mammary cancer in unexposed female BALB/c mice is reduced by a factor of 13 in mice with their ovaries removed (Storer et al. 1982), and incidence of ovarian tumors is about 70% in acutely exposed mice at doses ≥ 0.5 Gy (Ullrich and Storer 1979c; Storer et al. 1988). There is a similar steep rise in incidence of ovarian tumors in RFM and BALB/c mice at doses up to 0.5 Gy (Ullrich and Storer 1979b; Ullrich 1983).

by Bartstra et al. (1998a, 1998b, 2000), DREF increased by about an order of magnitude in WAG/Rij rats that were treated with estrogen compared with untreated rats at doses of ^{137}Cs gamma radiation of 2.5 or 10 mGy administered at 12- or 24-hour intervals at total doses up to 1 or 2 Gy (Table 4.2). Those data are consistent with data from studies of BALB/c mice because rat oocytes are much less radiosensitive ($\text{LD}_{50} \approx 1$ Gy; Mole and Papworth 1966) and, thus, reinforce the idea that the elevated DREF obtained from the study by Ullrich et al. (1987) was strongly influenced by normal hormonal effects.

Because hormonal factors are crucial to the development of mammary tumors in humans and animals, administered estrogen is used to study the influence of sex hormones in animals and to eliminate possible effects of natural or radiation-induced variations of plasma estrogen levels (Bartstra et al. 2000). Hormonal promotion increases the incidence of mammary cancer in irradiated rats and decreases latency (NCRP 2005). Estrogens control growth of hormone-sensitive cells by inducing the expression of genes of importance to cell-cycle progression and apoptosis. Studies have shown that controlled DNA damage and repair is required for estrogen-induced transcription of estrogen-responsive genes to occur (Appendix B, Section B.2.2). This finding may explain the role of estrogen in cancer induction. Suppression of ovulation at higher doses leads to a reduced secretion of estrogens and an underestimation of the risk from irradiation of the mammary gland (Bartstra et al. 1998b).

Risk coefficients for induction of mammary carcinomas in estrogen-treated WAG/Rij rats were reduced by a factor of four when the dose per fraction was reduced from 40 to 10 mGy; there was no further reduction when the dose per fraction was reduced to 2.5 mGy (Bartstra et al. 2000). Viewed in the context of the effects of dose fractionation in BALB/c mice, including the data for lung cancer discussed in Section 4.3.4, these results suggest that full additivity of the effects of dose fractions may occur at doses of 10–100 mGy and that the effects of multiple dose fractions of 10 mGy or less are not fully additive, which is in accord with studies of breast cancer in humans discussed in Section 5.3.

Although the effects of dose fractionation and dose rate observed in animal models appear to be consistent with data on breast cancer in humans, the conventional interpretation of the animal and human data is that the effects of dose fractionation are negligible and the effects of a reduced dose rate are quite limited. With respect to the animal data, the conventional interpretation appears to be based on reviews of studies in which acute doses to mice and rats were sufficiently high to compromise ovarian function and potentially affect hormone levels.

In addition to the studies of mammary tumors in BALB/c mice by Ullrich and Storer (1979b, 1979c), UNSCEAR (1993) and NCRP (2001) reviewed several studies in Sprague-Dawley rats in which the effects of dose rate or dose fractionation were evaluated. In one study of induction of adenocarcinomas by ^{60}Co gamma rays (Shellabarger and Brown 1972) summarized in Table 4.4, a statistically significant DREF of 4 was observed at a dose of 2.7 Gy, but not at a lower dose of 0.9 Gy, when compared with data

at the same doses delivered chronically over several days at a dose rate of 0.3 mGy min⁻¹, and there was no effect of dose rate on the incidence of fibroadenomas at either dose. In an earlier study in rats that received doses from ⁶⁰Co gamma rays of 5 Gy (Shellabarger et al. 1966), incidence of carcinomas increased with dose fractionation, while incidence of fibroadenomas tended to decrease with dose fractionation such that the overall change in tumor incidence was not significant. A study by Broerse et al. (1983) summarized in Table 4.4 showed little or no effect of dose fractionation on the incidence of fibroadenomas or adenocarcinomas in WAG/Rij rats given total doses of x rays of 2 Gy.

4.3.5.2 Relevance of data in animals to breast cancer in humans

The relevance of data on induction of mammary cancers in laboratory animals to humans should be considered in the context of caveats discussed by NRC (1990) and Fry (1992) concerning uncertainties in cross-species extrapolation. These concerns are reinforced by the rapid rise in tumor incidence at low doses in DNA-repair deficient BALB/c mice, which is contrary to an expectation of a reduction, rather than an increase, in the sparing effect of reduced doses in such animals and, hence, in the extent of upward curvature in an LQ dose-response. NRC (1990) concluded that results of studies involving rats were “somewhat difficult to relate to human data. The designs of rat experiments have differed from laboratory to laboratory, hormonal manipulations were often used, experimental groups were often small, and benign fibroadenomas were often grouped with adenocarcinomas. The promotional effects of hormones on the induction of fibroadenomas differ from those for the induction of adenocarcinomas.”

Table 4.4. DREFs for mammary carcinomas in rats induced by low-LET radiation

Animal	DREF	Reference
Sprague-Dawley rats	≈1; 4 ^a	Derived from data in Shellabarger and Brown (1972); see Annex F, Table 8, in UNSCEAR (1993) and NCRP (2001)
WAG/Rij rats	≈1 ^b	Derived from data in Broerse et al. (1983); see Annex F, Table 8, in UNSCEAR (1993)

^a Derived from data for chronic exposures over a few days at dose rate of 0.3 mGy min⁻¹ and single acute exposures; lower value estimated at acute dose of 0.9 Gy, higher value at acute dose of 2.7 Gy.

^b Derived from data for fractionated exposures to x rays at acute doses of 0.2 Gy administered monthly for 10 months and single acute dose of 2 Gy.

Additional concerns include the possibility of an increased response and a bias toward linearity in the dose-response for x rays in several studies, e.g., the study in WAG/Rij rats by Broerse et al. (1983). The latter effect is consistent with a finding of no effect of fractionation in rats exposed to x rays (Bartstra et al. 2000). These results also reinforce concerns that studies that did not distinguish between different types of mammary tumors, such as the study by Gragtmans et al. (1984) summarized in Table 4.2, may not be as useful as studies that made a such a distinction (NRC 1990; Shellabarger et al. 1986). Another drawback of the study by Gragtmans et al. (1984) is that tumor incidence was estimated at 450 days after irradiation, so that results are not based on the lifetime incidence of tumors. Although a follow-up study distinguished between adenocarcinomas and fibroadenomas (Johnson et al. 1989), a doubling of the incidence of carcinomas to about 60% of all tumors and a much earlier appearance of tumors in controls in the second study than in the first, which required that the data be analyzed at 300 days after irradiation, may compromise the results and limit the usefulness of the data.⁴⁴ This is unfortunate when results from the follow-up study showed a significant effect of dose rate in animals that were chronically exposed to gamma rays, particularly at doses <2 Gy, while the effects of x rays were less dependent on dose rate.

In regard to the apparent linearity in the dose-response for mammary neoplasia in rats, Shellabarger et al. (1986) noted that (1) rigorous statistical analyses to exclude other types of dose-responses were not performed and (2) data on the effects of dose fractionation and dose protraction are difficult to interpret due to differences in experimental design, even though most studies showed little effect of a spreading of the dose over time. Bartstra et al. (2000) noted that in studies of rats and mice that provided a statistical evaluation, dose protraction or fractionation reduced the incidence of mammary tumors by a factor of two or more. This conclusion was in agreement with results from their own studies of estrogen-treated rats, but it did not agree with the results of studies of untreated rats (Table 4.2).

Bartstra et al. (2000) also found that the excess relative risk (ERR) for radiation-induced mammary cancer in studies in which doses were given in 2.5- or 10-mGy fractions was about the same in normal and estrogen-treated animals. Despite the elevated baseline rate of mammary cancers in estrogen-treated rats, the excess incidence of carcinomas was proportional to the baseline rate.⁴⁵ These results suggested that

⁴⁴ Sprague-Dawley rats used in the study by Gragtmans et al. (1984) have a high spontaneous incidence of mammary tumors (mainly fibroadenomas) at ages beyond about 15 months. Near the end of their life, the total tumor incidence in unirradiated Sprague-Dawley rats is about the same as in irradiated animals, an observation that led some investigators to conclude that the primary effect of irradiation is to accelerate the appearance of tumors, rather than to increase the overall incidence (Ullrich and Storer 1979b; Vogel 1982; UNSCEAR 1993). However, the appearance of adenocarcinomas is different (Shellabarger et al. 1986). Those types of tumors appear relatively soon after irradiation, but they appear relatively late in life and with a relatively low frequency in unirradiated rats.

⁴⁵ A high spontaneous incidence of cancers also is seen in laboratory animals and humans that carry mutations that disrupt the functions of components of DNA repair pathways (Khanna and Jackson 2001; van Gent et al. 2001; Daniels et al. 2004). The baseline incidence of mammary carcinomas in WAG/Rij rats is higher than the average incidence of breast cancer in women but lower than the incidence in some subpopulations of women who are at increased risk for developing breast cancer, which is as high as 50–80% (Bartstra et al. 2000).

use of an ERR model may be the most appropriate for comparing epidemiological data on radiation-induced breast cancer.⁴⁶ Bartstra et al. (2000) then noted that a comparison of the excess incidence of breast cancer in the LSS cohort with the excess incidence in the Massachusetts and Canadian tuberculosis fluoroscopy cohorts suggested that fractionation reduced the incidence in humans by a factor of 3–6. If we apply another factor of two to account for a possible increase in the biological effectiveness of x rays in exposures in the fluoroscopy cohorts, the effect of dose fractionation increases to a factor of about 6–12. These estimates are comparable to DREFs based on data in estrogen-treated rats obtained by Bartstra et al. (2000) and a DREF based on the study in mice by Ullrich et al. (1987).

Data on radiation-induced mammary cancer in laboratory animals raise several questions. First, are dose-responses for any solid tumors in any strain of laboratory animal relevant to normal human populations? The existence of a cancer-resistant SR/CR mouse provides a caution that results from studies of highly inbred strains of laboratory animals, despite their utility as models of many human diseases, may not be relevant to an assessment of dose-responses in humans. Second, can high estimates of DDREF derived from data in animals be excluded on the grounds that lower values are more compatible with the apparently linear dose-responses for female breast cancer in humans? If those DDREFs can be excluded, do the data in humans and animals, considered together, indicate that there is a radiosensitive subpopulation of women (e.g., women with an inherited DNA-repair deficiency) whose collective response dominates the dose-response for breast cancer in humans? Or, has the meaning of the apparent linearity in dose-responses in epidemiological data been misinterpreted to exclude significant effects of dose fractionation or protraction? Finally, can an increase in the risk of breast cancer or a bias toward linearity in the dose-response in humans be excluded in studies of cohorts exposed exclusively to x rays? If an adjustment to account for a possibly higher biological effectiveness of x rays is applied to estimated risks in those cohorts, do the adjusted risks lead to a conclusion that the higher DDREFs from data in animals are reasonable?

Although we think it is reasonable to account for the possibility of a higher biological effectiveness of x rays in evaluating dose-responses in cohorts exposed to those radiations, we also think that, at the very least, animal and human data for mammary cancer indicate that the uncertainty in a DDREF for breast cancer in humans is much greater than considered previously.

⁴⁶ Storer et al. (1988) reached similar conclusions with respect to tumors of the lung, breast, liver, ovary, and adrenals in four strains of mice, whereas absolute and relative risk models both fit data for myeloid leukemia and tumors of the Harderian gland.

4.3.6 Analysis of Data on Life Shortening

4.3.6.1 Review of data

Difficulties in evaluating uncertain dose-responses for individual cancer types in laboratory animals led to the suggestion that a DDREF that represents dose-responses for all cancers combined should be considered. For example, some investigators argued that life shortening in animals, which is mainly attributable to an accumulation of malignancies at low-to-intermediate doses (<3 Gy) and low dose rates (ICRP 2003), could provide an appropriate measure of the deleterious effects of ionizing radiation (Fry 1992; NCRP 2001; ICRP 2005; NRC 2006) and, thus, could be used to estimate a DREF (Fry 1992).

Analyses of mortality from all solid tumors due to acute exposure in B6CF₁ mice, beagle dogs, and the LSS cohort indicated that the cumulative survival vs age at death in the dogs and humans could be predicted using a simple dose-response model that fit the data in mice when differences in lifespans of the animals and humans were taken into account (Carnes et al. 2003; NCRP 2005). Data in B6CF₁ mice also were predictive of cumulative survival in beagle dogs under conditions of chronic exposure at different dose rates when adjusted for the difference in lifespan (Carnes et al. 1998; NCRP 2005). Similarly, data on induction of bone tumors in humans, beagle dogs, and B6CF₁ mice from exposure to ²²⁶Ra indicated that when time is normalized with respect to lifespan, the three species have nearly identical risks of bone cancer as a function of dose rate and time (UNSCEAR 2000). Such evidence supports the existence of a dose or dose-rate effect on overall tumorigenesis in animals (UNSCEAR 1993; NCRP 2001), and it suggests that data on life-span shortening in animals could be used to estimate a DDREF in humans.

Data on the fractional mortality rate from all causes except leukemia and lymphoma vs dose rate in two strains of mice exposed daily over a lifetime (Sacher 1976) are shown in Figure 4.3. At dose rates less than about 0.20 Gy d⁻¹ (0.1 mGy min⁻¹), the value of Slope 1 of about 1.0 in the log-log plot means that the fractional mortality per Gy, calculated as the fractional mortality rate per unit dose rate, is independent of dose rate and, thus, that DDREF is about 1. At higher dose rates, the dose-response in Figure 4.3 becomes approximately quadratic and the fractional mortality per Gy is nearly proportional to the dose rate. NCRP (1980) estimated a DREF (termed a protraction factor) of 10 from the same data using the number of days of life lost per unit dose as the endpoint and taking into account the response at dose rates up to 0.56 Gy d⁻¹, which is in the range covered by Slope 2 in Figure 4.3.

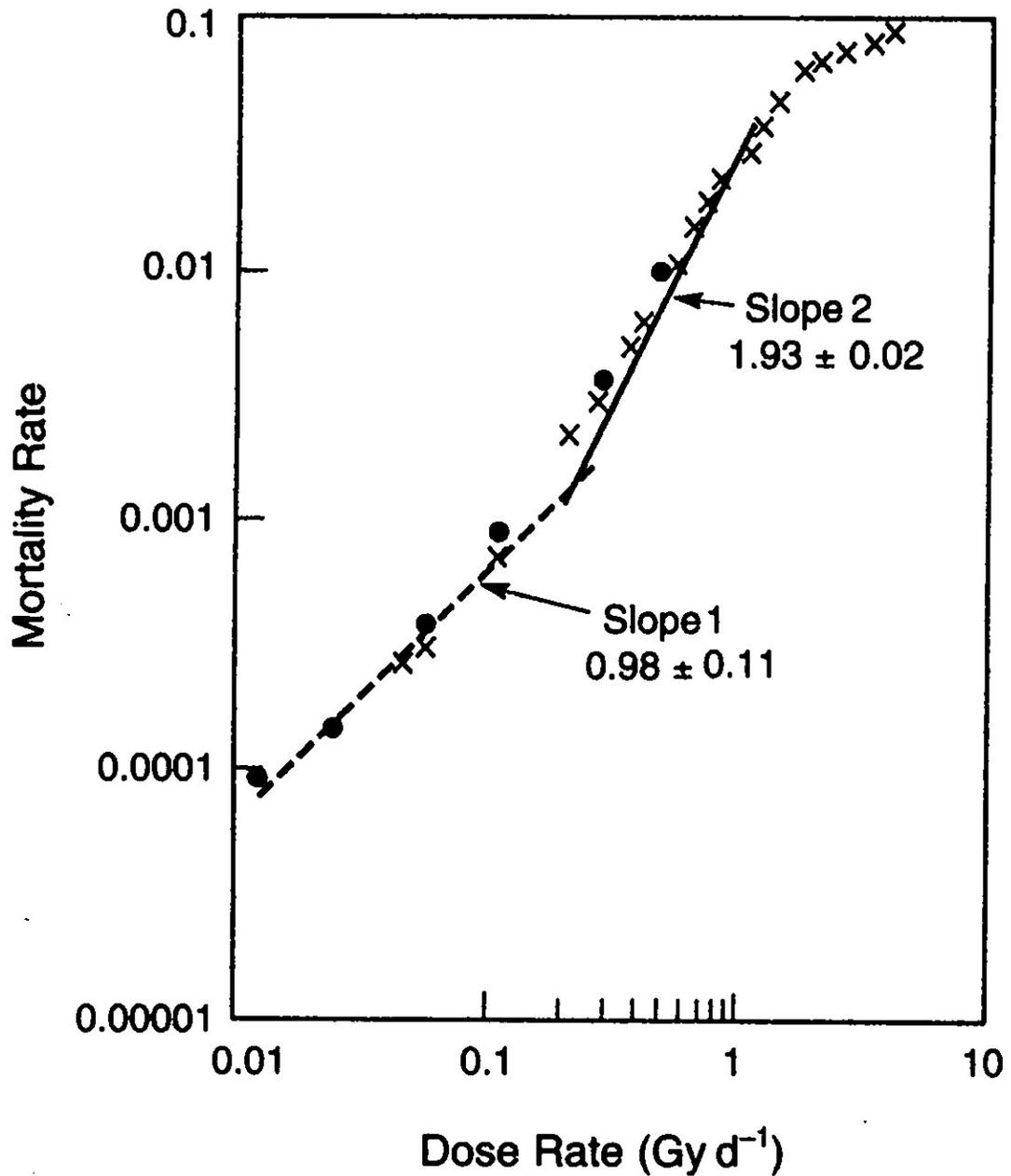


Figure 4.3. Effect of dose rate on fractional mortality rate (d⁻¹) from all causes except leukemia and lymphoma in B6CF₁ (●) and LAF₁ (×) mice exposed daily over a lifetime to ⁶⁰Co gamma rays (Grahn 1970; Sacher 1973; NCRP 2001). Response was linear at dose rates from 0.003 Gy d⁻¹ (data not shown) to about 0.20 Gy d⁻¹. Quadratic component of dose-response was more important than linear component at dose rates above about 0.24 Gy d⁻¹, until flattening occurred at highest dose rates (Sacher 1976).

In studies of excess mortality in chronically exposed beagle dogs, the dose-response at higher dose rates exhibited the same slope as in the data in mice at higher dose rates (Slope 2) in Figure 4.3, but a significant quadratic component of the response extended to a much lower dose rate of 0.038 Gy d^{-1} ($0.026 \text{ mGy min}^{-1}$) (Fritz et al. 1986; Grahn and Fritz 1986). The studies in dogs were terminated before it could be determined whether the lack of dependence on dose rate at dose rates down to $0.002 \text{ mGy min}^{-1}$ (0.003 Gy d^{-1}) in mice (Sacher 1976) not shown in Figure 4.3 also occurred in dogs (R.J.M. Fry, personal communication, August 17, 2009). In a study in guinea pigs, a significant quadratic component in the dose-response was seen at dose rates as low as 0.01 Gy d^{-1} with no evidence of a transition to a linear response (Sacher 1976), in contrast to the data in mice in Figure 4.3 for which the transition occurred at a dose rate of about 0.24 Gy d^{-1} . Thus, data in different animals do not present a consistent view of the dependence of DDREF on dose rate in dose-responses for life shortening at the lower dose rates studied.

Most of the data on life shortening in animals have drawbacks at least as important as drawbacks in studies of tumorigenesis. For example, DDREFs based on studies in which exposures were protracted over the entire life span, as in Figure 4.3, were poorly constrained when radiation injury induced late in life was not fully expressed at the time of death, particularly at low dose rates. Exposures continued after tumorigenic processes had been initiated, but a greater proportion of tumors should have occurred earlier in animals exposed at higher dose rates, which makes it difficult to relate doses and effects. This situation could result in an overestimate of the dose required to produce a specific degree of life shortening and, thus, a DDREF derived from such data (NCRP 1980, 2001; ICRP 2005).

Because the sensitivity of laboratory animals to radiation-induced life shortening decreases with age (NCRP 1980; Grahn et al. 1992), the concern about a possible overestimation of a DDREF would be lessened if acute exposures used in most studies were not given to the youngest animals only. This situation does not apply to the data in Figure 4.3, because all animals were exposed over their entire life spans, but the concern about the influence of an incomplete expression of tumorigenesis still applies.

DREFs of 6.6 and 10 were estimated from studies of life shortening in female and male mice, respectively, by Upton et al. (1967) when exposures were limited to about half the normal life span (NCRP 1980; Fry 1992). Because males were acutely exposed to 250 kVp x rays but were chronically exposed to ^{60}Co gamma rays (Upton et al. 1967), the DREF in males probably should be reduced by a factor of about two to account for a possibly higher biological effectiveness of the x rays.

ICRP (2005) concluded that studies in which exposure durations were even shorter (i.e., about one month or less) were more appropriate, and that such studies yielded DREFs of no more than about 2. These conclusions presumably referred to results from part of a study by Storer et al. (1979) in which animals received total doses of ^{137}Cs gamma rays of 0.5–2 Gy at dose rates of 0.40 Gy min^{-1} (two exposure groups) or $0.069 \text{ mGy min}^{-1}$ (three exposure groups). When uncertainties are considered, those

dose-responses indicate DREFs for life shortening of about 2–3 in female RFM mice and about 2–4 in female BALB/c mice. NCRP (1980) calculated DREFs of 2.1 and 2.0, respectively, from those data by comparing the linear slopes of dose-responses in acutely and chronically exposed animals.

We think that data from studies of either lifetime or terminated exposures should be considered, because dose rates in the lifetime exposures were an order of magnitude lower than in the terminated exposures and are more comparable to dose rates experienced by most nuclear energy workers. In addition, NCRP (1980) noted that terminated exposures at low dose rates might be less effective in inducing life shortening than an equal dose administered over the entire life span, given the possibility that repair processes could reverse pre-malignant conditions following termination of exposures.

Data from studies of shorter-term exposures may be more relevant to estimating a DDREF for effects of most external exposures of radiation workers, which were non-continuous. However, data from longer, continuous exposures should be more relevant to internal exposures to long-lived, beta-gamma emitters with long retention half-times in the body, especially in younger workers. In addition, protracted exposures of laboratory animals were never continuous, due to the need to check on the condition of the animals and perform maintenance activities (Ullrich and Storer 1979a; Carnes et al. 1989; Fritz 2002; Seed et al. 2002). Animals in other life-span studies, such as the studies summarized in Figure 4.3, were exposed for either 10 minutes or 8 hours each day and, in some studies in beagle dogs described below, only five days each week. These exposure conditions should be more relevant to occupational exposures, and they could allow time for repair of a significant fraction of radiation damage at low doses prior to succeeding exposures (Ullrich et al. 1987; Sachs et al. 1997; Bartstra et al. 2000; NRC 2006).

By taking such factors into account, NCRP (1980) concluded that the range of a DREF from studies of life shortening was extended to 5–10 on the basis of comparisons of the effects in mice of (1) high acute doses and fractionated acute doses of <0.05 Gy each and (2) acute exposures and protracted exposures delivered over $7\text{--}10$ h d^{-1} . A somewhat higher DREF of about 13 was derived from data for single exposures in beagle dogs at a high dose rate and lifetime exposures to fractionated doses of 0.6, 1.2, and 6.0 mGy d^{-1} given during a 10-minute period for five days week.

DREFs estimated based on data from the JANUS study on life shortening in B6CF₁ mice that received single weekly doses of ⁶⁰Co gamma rays for 60 weeks were 2.9 in males and 3.5 in females (Carnes et al. 1989). DREF decreased to about 2 in males and females when exposures were terminated after 24 weeks, but there was a wide variation in dose rates to groups with terminated exposures (Heidenreich et al. 2006). When B6CF₁ mice were chronically exposed for 5 days each week (22 h d^{-1}) for 59 weeks, a higher DREF of 5.1 in males was estimated. DREF was reduced by half when exposures were terminated after 23 weeks.

An estimate of DREF based on data for lifetime mortality from the JANUS study was reported for lung cancer only; this is the estimate based on data in B6CF₁ mice given in Table 4.2. Comparisons of the average slopes of linear dose-responses for four broad groupings of tumor sites and five additional analyses, principally of mortality from tumors that occurred in two intervals at 600–999 days after irradiation (Grahn et al. 1992), gave estimates of DREF similar to those for life shortening. However, because thymic lymphomas and leukemias contributed significantly to tumor mortality and life shortening, those results may have major limitations, as discussed in the following section.

Carnes and Gavrilova (2001) analyzed dose-responses for solid tumors from the JANUS study using proportional hazard models. Preliminary results indicated that dose protraction produced the same pattern of risk reduction as observed in studies of life shortening by Carnes et al. (1989). However, differences in doses to mice in the different exposure groups and between sexes within exposure groups made it difficult to draw definitive conclusions. As discussed above, Heidenreich et al. (2006) also noted that there were wide variations in dose rates within the groups that received single weekly doses for 24 weeks.

4.3.6.2 Influence of other biological factors

A major factor that complicates the use of data on life shortening described in the previous section to develop a DDREF in humans is that the spectrum of tumor types induced by protracted exposures at low dose rates in laboratory animals differs from the spectrum of tumor types induced by acute exposures. In mice, for example, high acute doses induce more thymic lymphomas and myeloid leukemias, which result in mortality at a relatively young age, whereas lymphomas and ovarian tumors induced by protracted exposures at low dose rates occur late in life, with a much lower reduction in life span (Fry 1992). Fritz (2002) also suggested that leukemia was the earliest neoplastic disease in beagle dogs given continuous, duration-of-life exposures at dose rates ≥ 0.019 Gy d⁻¹, but Seed et al. (2002) reported that the highest incidence of fatal solid cancers (about 50%) occurred in animals exposed at the lowest dose rate of 0.003 Gy d⁻¹, at which no leukemias were observed. Consequently, use of data on life shortening that could be influenced appreciably by the occurrence of hematopoietic cancers could result in an overestimate of DDREF for solid tumors.

Data in Figure 4.3 on the effects of dose rate that were observed in earlier studies of mortality are not compromised by the occurrence of hematopoietic cancers, because deaths from leukemias and thymic lymphomas were excluded from the two data sets. There also is good agreement in the data from studies in two different strains of mice. In addition, the dose-response in Figure 4.3, which suggests a DDREF of about one, is supported by data from studies of terminated and continuous exposures of beagle dogs at comparable dose rates (Carnes and Fritz 1991; Fritz 2002). In studies of terminated exposures, deaths

from solid tumors did not depend on dose rate. In studies of duration-of-life exposures, once an animal had lived long enough to die from cancer, the incidence of fatal cancers (including leukemias) depended on the total dose only. However, Carnes and Fritz (1991) also noted that using data on induction of fatal tumors, which are a composite of neoplasms that may not respond equally to radiation, could lead to misinterpretation of the influences of dose and dose rate. There are similar concerns about use of data on all solid cancers combined in analyses of the dose-response in the LSS cohort.

Studies of life shortening in rats also revealed an inverse relationship between radiation dose and the latency of mammary neoplasms (NRC 1990). In addition, not all tumors are a cause of life shortening in animals or humans (NCRP 1993a; Ron et al. 1994; UNSCEAR 2000), and non-cancer effects contribute to life shortening (Carnes and Fritz 1991, Carnes et al. 2002; Fritz 2002). NCRP (1990) and ICRP (2003) provide additional discussion of life shortening as a meaningful biological endpoint for purposes of radiation protection and risk estimation.

Another complication is that some studies found no detectable shortening of the average life span of laboratory animals at low doses or low dose rates, and even increases of about 10–30% that suggest a DDREF of ∞ (NCRP 1980, 2001; Calabrese and Baldwin 2000; NRC 2006). Results from most of those studies are not inconsistent with the dose-response relationships in Figure 4.3 and other data described above, due to the small numbers of animals involved, and may represent no more than expected random variations at low doses or low dose rates (UNSCEAR 1993; NCRP 2001). An increase in life span following radiation exposure was reported in studies involving three strains of mice and one strain each of rats and guinea pigs (Calabrese and Baldwin 2000). One of those studies (Caratero et al. 1998) gave questionable results when life spans in the control group were 100–150 days shorter than in any other published study of C57BL/6 mice (NRC 2006). Aberrant findings usually result when excessive mortality is observed in controls.

Mechanisms that could cause an increased longevity due to radiation exposure are unknown but could involve stimulation of the hematopoietic or immune system (UNSCEAR 1994; Calabrese and Baldwin 2000). Information reviewed in Section 3 suggests that a variety of other mechanisms could be involved, such as a combined effect of enhanced DNA repair and apoptosis. However, Brenner et al. (2003) concluded that observed increases in life span, if they are real, were more likely to be associated with an enhancement of the immune system than a stimulation of DNA-repair mechanisms (see also Ina et al. 2005; Lacoste-Collin et al. 2007; Mitchel et al. 2007; UNSCEAR 2009).

In studies in which an increase in longevity was observed, the increase generally was attributable to a radiation-induced reduction in the rate of mortality from intercurrent infectious or other nonmalignant diseases (e.g., ulcerative dermatitis) early in adult life (Lorenz et al. 1955; Mitchel et al. 2007), rather than a radiation-induced protection against tumor development and prolongation of the life span (UNSCEAR

1994; NCRP 2001; Brenner et al. 2003; NRC 2006). Since infectious diseases contributed significantly to overall mortality in studies that reported an increase in longevity, caution is warranted in interpreting the results with respect to radiation-induced cancer in humans (NRC 2006).

In studies in animals that were maintained under conditions conducive to long-term survival, e.g., in a barrier facility with a rigidly controlled microbial environment (Storer et al. 1979), sensitivity to radiation-induced life shortening at low doses increased (Storer et al. 1979; NCRP 1980), and irradiation at low levels under such conditions did not consistently confer protection against the development of tumors associated with normal aging (NCRP 2001). Those results suggest that increases in life span observed in some studies of laboratory animals have little relevance to radiation-induced cancer in otherwise healthy adult radiation workers, in whom an enhancement of the baseline health status (“healthy worker effect”) is often observed (NRC 2006; Rothman et al. 2008).

The study by Storer et al. (1979) discussed previously was the largest of its kind, involving about 26,000 RFM and 7,600 BALB/c mice. However, a significant difference in mean life span of 35 days, which is comparable to the average days of life shortening Gy^{-1} in a wide variety of studies in which animals were acutely exposed (UNSCEAR 2000), also was observed in two large control groups of female BALB/c mice used in that study (Storer et al. 1979). This result indicates the difficulties in generating reproducible results in animal experiments, even under the most carefully controlled conditions. It also provides a useful caution about the potential for overinterpretation of results from animal studies that appear to show beneficial effects of radiation exposure at low doses.⁴⁷

4.3.6.3 Summary and conclusions on use of data on life shortening to estimate DDREF

Radiation-induced life shortening in laboratory animals at low-to-intermediate doses (<3 Gy) and low dose rates is mainly attributable to an accumulation of malignancies. The range of central estimates of DDREF of about 1–13 obtained from analyses of dose-responses for life shortening in laboratory animals is similar to the range of estimates obtained from studies of specific tumors in animals summarized in Table 4.2. However, the spectrum of tumor types induced by protracted exposures of laboratory animals at low dose rates often is different from the spectrum of tumor types induced by acute exposures. More hematopoietic cancers, which occur sooner and exhibit a higher level of lethality than solid tumors, are induced by acute exposures. In mice, protracted exposure at low dose rates yields more lymphomas and

⁴⁷ A significant reduction in life span was observed in a study in specific-pathogen-free B6CF3F1 mice of both sexes irradiated with ^{137}Cs gamma rays at a dose rate of $0.015 \text{ mGy min}^{-1}$ and in females irradiated at a dose rate $0.00076 \text{ mGy min}^{-1}$ (Tanaka et al. 2003). Results from that study provide no evidence of an increased life span in normal mice exposed continuously at very low dose rates. Life shortening was due to an earlier occurrence of malignant lymphomas and soft tissue neoplasms (Tanaka et al. 2007).

ovarian tumors late in life, with much less reduction in life span. In addition, not all tumors are a cause of life shortening in animals or humans. On the basis of these considerations, we think that estimates of DDREF derived from dose-responses for life shortening in animals have limited relevance to the development of a probability distribution of DDREF for solid tumors in humans, despite the apparent similarities with DDREFs derived from data for specific tumors in animals.

4.4 SUMMARY AND CONCLUSIONS ON USE OF RADIOBIOLOGICAL DATA TO ESTIMATE DDREF

We think that the most useful information on a DDREF from radiobiological studies is represented by estimates of DREF based on dose-responses for various solid tumors and hematopoietic cancers in laboratory rodents, mainly mice. In agreement with conclusions by Edwards (1992) and UNSCEAR (1993), a consideration of the effects of dose rate and dose fractionation on dose-responses greatly expands the range of DDREFs compared with the range based only on analyses of acute dose-responses. We think that estimates of DDREF obtained from data on genetic and cytogenetic effects in cells are less informative, due primarily to concerns about whether dose-responses for those endpoints are indicative of cancer in humans.

Estimates of DREF for solid tumors in laboratory animals summarized in Table 4.2 include values <1 , more commonly in the range of 1–15, and ∞ in cases of threshold or potentially hormetic responses. A central estimate to represent this data set is in the range of about 2–4. Lower limits of DREFs based on apparent threshold responses in studies of the effects of protracted internal exposures of bone are in the range of 7–19. We also estimated a lower limit of a DREF of about 30 based on a threshold response for induction of non-melanoma skin cancers in mice. DDREFs for life shortening due to solid tumors are in the range of about 1–13.

Although DREFs for a few types of solid tumors (e.g., lung carcinomas in beagle dogs, osteosarcomas in beagle dogs or mice) can be estimated from studies of protracted internal exposures, those dose-responses often exhibit a threshold, which limits their usefulness compared with most of the other data on DREFs from animal studies for which the central values and CIs are finite (Table 4.2). Lack of statistical power is an issue with some apparent threshold responses, given that the dose rates and numbers of animals exposed probably were too low to produce observable effects at doses <3 Gy within the relatively short lifetimes of the animals.

Unlike LDEFs derived from an analysis of the curvature in modeled acute dose-responses for solid tumors in the LSS cohort, DREFs estimated from studies of fractionated doses are based on direct comparisons of tumor incidence in animals irradiated under differing dose and dose-rate regimes.

However, the range of ages at exposure in studies of animals is limited, and there are concerns about extrapolating responses in laboratory animals to humans due, for example, to genetic differences between animals and humans and the genetic uniqueness of highly inbred animal strains. As with genetic and cytogenetic endpoints, dose-responses in some studies in animals are complex and difficult to interpret. In particular, effects of cell sterilization and hormonal influences on observed dose-responses should be considered. These effects cannot be addressed just by restricting the dose range in an attempt to minimize their importance. In some cases, such as induction of mammary cancers in female rodents, effects of cell sterilization and hormonal influences at low doses are more significant than at higher doses.

DDREFs are not used in risk models for leukemias in IREP, because risks are estimated by assuming an LQ dose-response for acute or fractionated acute exposures that incorporates a DDREF implicitly. Only the linear term (i.e., the risk coefficient α) in the LQ dose-response for acute exposures is used to estimate risks of leukemias in cases of chronic exposure. Thus, we also evaluated data on induction of leukemia in animals, which could be useful if an adjustment similar to a DREF might need to be applied to the linear risk coefficients for leukemias in IREP in cases of chronic exposure.

With one exception, dose-responses for induction of myeloid leukemia in mice suggest that central estimates of DREF are in the range of about 2–6. The one exception involved a study of female RFM mice in which the dose-response in the chronically exposed group was reduced to the level of controls and the 95% CI of a DREF was (9.7, ∞). Taken as a whole, data from studies in animals do not provide support for an LQ dose-response for leukemia from acute exposure and, thus, cannot be used to derive a DDREF for leukemia in humans.

Although radiation-induced life shortening in animals is mainly attributable to an accumulation of malignancies at low-to-intermediate doses (<3 Gy) and low dose rates and estimates of DREF for life shortening are similar to estimates for induction of specific cancers, we concluded that the use of available data for life shortening to estimate a DDREF for incidence of solid tumors in humans is questionable. The principal reason is that the spectrum of tumor types induced by protracted exposures at low dose rates in laboratory animals is different from the spectrum of tumor types induced by acute exposures at high doses. In addition, not all tumors are a cause of life shortening in animals or humans.

5. EPIDEMIOLOGICAL STUDIES TO ESTIMATE DDREF

Epidemiological data on radiation-induced cancer incidence or mortality in several organs or tissues of humans could be used to estimate DDREFs. The types of cancers considered in our analysis include:

- All solid cancers (Sections 5.1 and 5.2);
- Female breast cancer (Section 5.3);
- Thyroid cancer (Section 5.4);
- Lung cancer (Section 5.5);
- Skin cancer (Section 5.6);
- Bone cancer (Section 5.7);
- Leukemia (Section 5.8).

Limited information on other radiation-induced cancers, such as stomach and esophageal cancers (Little and Muirhead 2000, 2004), also is available.

There are some cancer types for which there is only weak evidence of an association with radiation exposure in humans, such as pancreatic cancer, cervical cancer, cutaneous malignant melanoma, prostate cancer, testicular cancer, uterine cancer, Hodgkin's lymphoma, and multiple myeloma. For other cancer types, such as cancers of the small intestine, rectum, uterus, and kidney, excess risks have been seen only at very high doses, such as occur in radiotherapy (UNSCEAR 2008; Boice 2011). ICRP (2005) concluded that evidence from epidemiological and radiobiological data indicated that radiation carcinogenesis at some sites (e.g., the small intestine and rectum in addition to bone and skin) is markedly and disproportionately less likely to occur at low doses than at high doses and may even have a threshold. UNSCEAR (2008) identified bone cancer, non-melanoma skin cancers, and leukemia as examples of such outcomes on the basis of the more substantial upward curvature in their modeled dose-responses in the LSS cohort.

5.1 ADVANTAGES AND DISADVANTAGES OF VARIOUS EPIDEMIOLOGICAL DATA: IMPLICATIONS FOR ESTIMATING DDREF

A number of factors should be considered when attempting to estimate DDREFs by analyzing possible non-linearities in dose-responses in the LSS cohort or by comparing risks in the LSS cohort with risks in other study populations that received highly fractionated or protracted exposures. Given the

limitations in epidemiological data for many cancers, as well as the observed variations in dose-responses for specific cancers, some investigators have focused on estimating a DDREF based on data for all solid cancers or all cancers combined. In many cases, comparisons of estimated risks are limited to data for cancer mortality, rather than data for cancer incidence that provide the basis for risk models in IREP. Our review of epidemiological studies begins with an overview of advantages and disadvantages of different approaches and types of data.

5.1.1 Total Cancer vs Cancer-Specific Risks

There are two issues to be considered in judging whether data on dose-responses for all cancers combined or dose-responses for specific cancers should be used in developing DDREFs for solid cancers: (1) whether data for all cancers combined represent DDREFs for specific cancers; and (2) the importance of risk transfer in estimating DDREFs by comparing risks in the LSS cohort with risks in other populations that received chronic or protracted exposures.

5.1.1.1 Use of data for all cancers to represent DDREFs for specific cancers

Estimation of total cancer risks or DDREFs based on dose-responses for all solid cancers combined should be easier than estimation of risks or DDREFs based on data for specific cancers, because the larger number of cancers should increase the statistical precision of such estimates, unless there is substantial heterogeneity in dose-responses for different cancer types, and should increase prospects for extrapolating dose-response relationships to lower doses. Failure to detect a significant dose-response for a specific cancer type may reflect a lack of statistical power, rather than an absence of a true dose-response.

As discussed by Pierce et al. (1996a) and Preston et al. (2003b) and illustrated by estimates of ERR/Gy for major causes of mortality in the LSS cohort reported by Ozasa et al. (2012) and shown in Figure 5.1, the observed variability in estimates of the excess relative risk (ERR) of mortality due to solid cancers at specific sites in the LSS cohort is comparable to the expected variability under a hypothesis that there is a common ERR for all types of solid cancers. Preston et al. (2003a) concluded that real but small variations in site-specific ERRs are difficult to assess, and Preston et al. (2003b) recommended that care should be taken to avoid overinterpretation of differences in site-specific ERRs. By inference, this recommendation also applies to interpretations of DDREFs for specific cancer types.

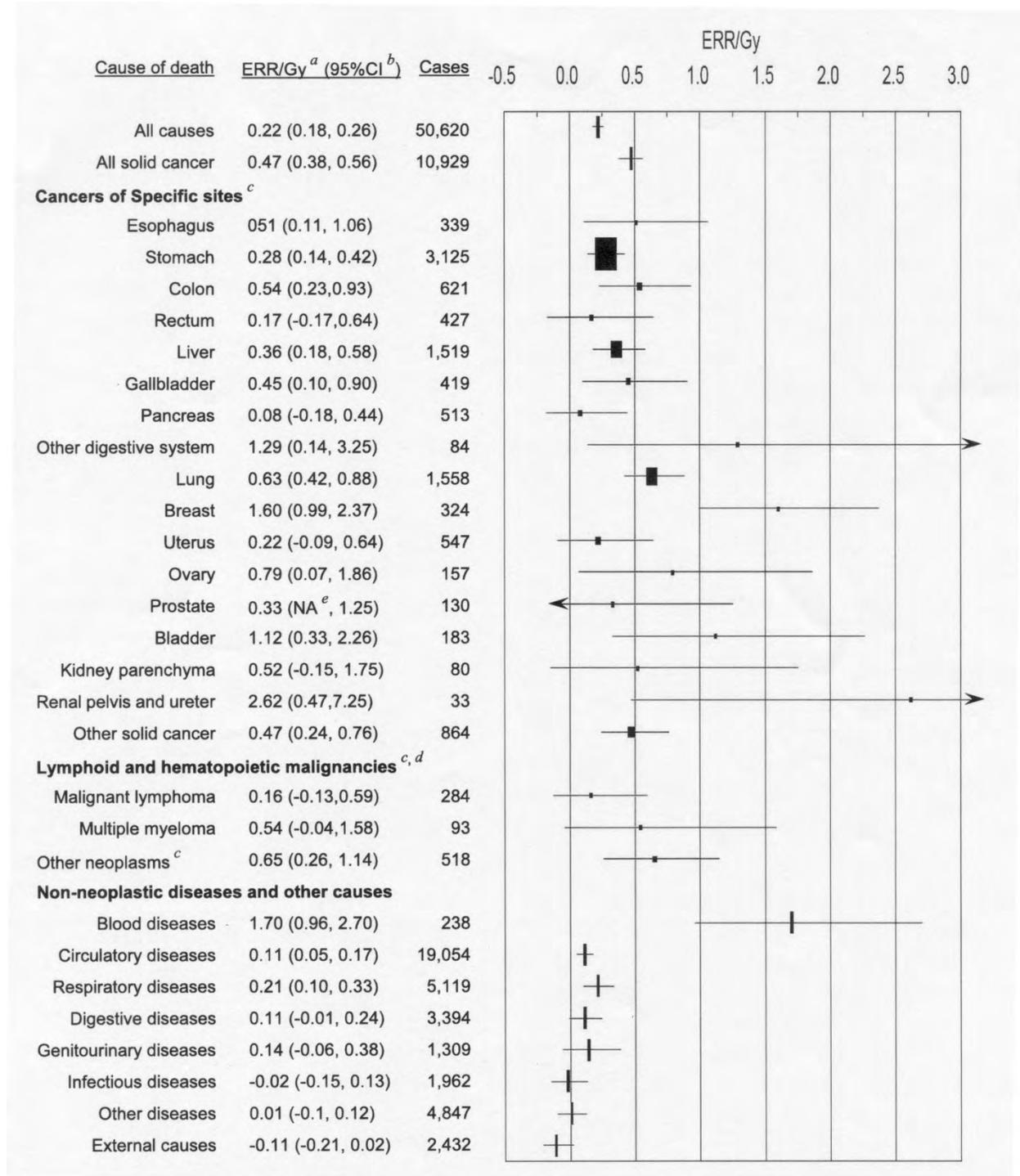


Figure 5.1. Estimates of ERR/Gy for major causes of death in LSS cohort based on DS02 dosimetry (Ozasa et al. 2012). ^a ERRs were estimated using linear dose-response models in which city, age at exposure, and attained age were taken into account in estimating baseline rates but were not assumed to modify effects of radiation. ^b Horizontal bars indicate 95% CIs. ^c Sizes of symbols are proportional to number of cases. ^d ERR (95% CI) for leukemia not shown is 3.1 (1.8, 4.3) at neutron-weighted dose to bone marrow of 1 Gy and 0.15 (-0.01, 0.31) at 0.1 Gy based on LQ dose-response model. ^e Lower limit of 95% CI not specified is <0.

Although it appears to be advantageous to group all solid cancers for the purpose of developing a DDREF based on data in the LSS cohort, a consensus on whether that approach is justifiable, when it could conceal real cancer-specific differences in dose-responses and DDREFs, is lacking. The benefit of an increased precision in a DDREF estimated from data for all solid cancers should be weighed against the possibility that the DDREF for a specific cancer type would be over- or underestimated. The analysis of data on incidence of solid cancers in the LSS cohort through 1998 by Preston et al. (2007) suggests that there are real differences in dose-responses, age-related modifiers, and the effects of sex on risks of specific cancers when compared with the corresponding estimates for all solid cancers combined.

Pawel et al. (2008) used empirical Bayesian methods to narrow the range of estimated ERRs for incidence of specific solid cancers by combining estimates of the means and variances of ERRs for specific cancers with the mean and variance of the ERR for all solid cancers as a group. As expected, the tendency for a cancer-specific ERR to merge toward a common value was greater when its variance was larger. A controversial aspect of this approach is the assumption that the variability in ERRs is due primarily to statistical fluctuations in the data (i.e., ERRs vary at random) and that differences in biological and other influences on induction of specific cancers are unimportant. Indeed, Pawel et al. (2008) excluded thyroid cancer from their analysis because they judged that it was “different from other cancers.” The BEIR VII committee (NRC 2006) excluded thyroid cancer and non-melanoma skin cancers from their analysis of ERRs for combined solid cancers for the same reason. UNSCEAR (2008) did not develop a risk model for incidence of all solid cancers as a group, probably because of the heterogeneity in dose-responses for specific cancers that they and Preston et al. (2007) observed. If the approach used by Pawel et al. (2008) is valid, it would seem to argue for a single DDREF for all solid cancers, provided the ratio of risks from acute and chronic exposures also does not depend on the cancer site.

The increased precision in estimating total cancer risks makes it possible to detect variations in risk with such factors as age, time, and dose that may not be apparent in data for individual cancers, and it also may prevent the appearance of trends in risks that reflect chance variations (UNSCEAR 2000). On the other hand, data on cancer in animals and the heterogeneity in dose-responses for specific cancers in the LSS cohort indicate that combining data on individual cancer types with differing etiologies, minimum latencies, and baseline rates may introduce artifacts into an analysis. This concern is reinforced by the weak evidence of an association with radiation exposure for many cancer types.

5.1.1.2 Importance of risk transfer for all solid cancers vs specific cancers

Another advantage of combining data for different cancer types in the LSS cohort is that differences in total cancer risks due to radiation in other populations that are estimated based on risks in the LSS

cohort using a multiplicative or an additive risk-transfer model usually are much smaller than differences in estimates for specific cancer types, because there is less variation across populations in baseline rates for all cancers combined than for specific cancers. Baseline rates of cancer incidence at specific sites in other populations may differ greatly from those in the LSS cohort. This is an important concern when neither risk-transfer model is likely to be correct for specific cancers or groups of cancers, and the true effect of factors that contribute to differences in baseline cancer rates is likely to be more complicated than implied by any current model (UNSCEAR 2000). UNSCEAR (2008) concluded that it was “not clear in terms of mechanisms and biology how data for excess risks from one population should be transported to another” and “there [was] no simple solution to the [risk transport] problem ... There does not appear to be an obvious, consistent relationship between underlying and radiation-related cancer risk, either across all cancer sites within a single population or across populations for a single cancer site.”

Concerns about uncertainties in transferring estimated cancer risks in the LSS cohort to other populations can be addressed using mixture models that assign non-zero weights to additive and multiplicative risk-transfer models and combine estimated risks based on the two models on a linear or logarithmic scale (UNSCEAR 2008). In IREP, a probability distribution around an arithmetic mean of estimates based on additive and multiplicative models is calculated for each cancer type, with relative weights assigned to each model and mixtures of the two based on the weight of evidence from available data (Land et al. 2003a; Kocher et al. 2008). A multiplicative risk-transfer model alone was used for thyroid cancer in IREP to reflect the use of estimated risks in populations of several nationalities with different baseline rates of thyroid cancer reported by Ron et al. (1995) to estimate risks in the U.S. population (Land et al. 2003a). However, much of the multi-national basis for estimated risks of thyroid cancer used in IREP was provided by data in the Israeli tinea capitis cohort, in which differences between exposed and unexposed members or an increased genetic susceptibility in part of the study population could have influenced the estimated risks significantly.

In general, it is important to address concerns about risk transfer and its uncertainty when DDREFs are estimated by comparing estimated risks in the LSS cohort with estimated risks in other study populations that received highly fractionated or chronic exposures and had baseline rates of cancer incidence substantially different from those in the LSS cohort.

5.1.2 Analysis of Cancer Incidence vs Mortality

Based on an analysis of data from studies of cancer mortality in animals, ICRP (1991) recommended a DDREF of 2 for all cancers for purposes of radiation protection, a value which was judged to be consistent with human (mainly LSS) data on cancer mortality. In particular, a DDREF of 2

was consistent with a dose-response for mortality from leukemia, which has a relatively short minimum latency period and a high lethality in adults (ICRP 1991; NCRP 1993a) and has contributed significantly to the estimated number of radiation-induced cancer deaths in the LSS cohort (Preston et al. 2004).⁴⁸

However, estimated risks incorporated in IREP, which are cancer-specific or apply to groupings of cancers with fewer cases in the LSS cohort, were derived on the basis of data on cancer incidence (Land et al. 2003a). Given the significant differences in the curvature of dose-responses (e.g., non-melanoma skin cancers vs female breast cancer), minimum latency, and lethality for specific cancers in the LSS data, it is not expected that DDREFs derived from an evaluation of dose-responses for cancer incidence or cancer mortality would be the same,⁴⁹ even if data for all cancers were used. For example, Little and Muirhead (2000) suggested that the greater degree of linearity in a modeled dose-response for incidence of all solid cancers in the LSS cohort than in a modeled dose-response for cancer mortality may reflect the data for breast and thyroid cancer, which contribute more to cancer incidence than to mortality and for which there was little evidence of curvature in the acute dose-responses.⁵⁰

Data on cancer incidence in the LSS cohort provide estimated risks of the type required in IREP and are based on more accurate disease diagnoses. However, mortality data are advantageous because they cover a longer time period (1950–2000) than the incidence data (1958–1998) and they include members of the cohort who migrated from Hiroshima or Nagasaki to other cities (NRC 2006). The later start date for compiling incidence data undoubtedly caused some early-onset cancers to be missed, a point that has become more important in light of recent indications that the minimum latency period for induction of solid cancers by radiation is about 3–4 years (UNSCEAR 2008; Ivanov et al. 2009; D. Preston, personal communication, June 2, 2011), rather than 10 years as often assumed in epidemiological studies (e.g., Cardis et al. 2007; Muirhead et al. 2009). Limited information on cancer incidence suggests that if early follow-up in the LSS cohort had been conducted, risks of some childhood cancers would have been very high (Preston et al. 2007).

Tumor registries for incidence and mortality in the LSS cohort are not entirely independent, since 9.3% of the diagnoses of cancer incidence used in recent dose-response analyses (NRC 2006; Preston et al. 2007; UNSCEAR 2008) were based on information on death certificates and some diagnoses (<4%) were based on autopsy records. Diagnoses based on death certificates alone exceeded 15% of all recorded cases of cancers of the liver, lung, pancreas, and uterus (Preston et al. 2007).

⁴⁸ ICRP now uses data on cancer incidence, rather than mortality, as the basis for its estimates of risk (ICRP 2007).

⁴⁹ Data on cancer mortality influenced probability distributions of DDREFs currently used in IREP to some extent (Section 1.1.1).

⁵⁰ We note, however, that a significant neutron contribution to the cancer risk in lightly shielded organs, such as the breast and thyroid, could have influenced these results significantly (Section 2.4.3).

5.1.3 Conclusions

Weighing all the information discussed above, our assumption is that we should give greater weight to data on cancer incidence in estimating a DDREF, whenever practicable, and that we should emphasize data for all solid cancers combined. We also concluded that the effect of risk transfer and its uncertainty should be taken into account whenever DDREFs are estimated by comparing risks of specific cancers in the LSS cohort with risks of those cancers in other study populations.

5.2 DDREFS DERIVED FROM DOSE-RESPONSES FOR ALL SOLID CANCERS

Data on dose-responses for all solid cancers combined in the LSS cohort can be used to estimate a DDREF in two ways. First, the curvature in a modeled non-linear dose-response can be analyzed to assess the degree to which risks at low acute doses are overestimated, or possibly underestimated, by fitting the data with a linear model; this approach gives an LDEF. Alternatively, estimated risks of all solid cancers in the LSS cohort can be compared with estimated risks in cohorts that received protracted (chronic) or highly fractionated acute exposures to estimate a DREF.

5.2.1 Analyses of Dose-Responses in LSS Cohort

Analyses of dose-responses (excess relative risks, ERRs, or excess absolute rates, EARs) for incidence of or mortality from all solid cancers combined in the LSS cohort to estimate an LDEF are summarized in Tables 5.1–5.4. Doses to members of the LSS cohort were estimated using either Dosimetry System 86 (DS86) (RERF 1987, 1988) or DS02 (RERF 2005). Recent estimates of a possible threshold in dose-responses in the LSS cohort, at which $LDEF = \infty$, are neutron-weighted doses, assuming a neutron RBE of 10, of 0.04 Gy, with an upper limit of a 90% CI of 0.085 Gy, for solid cancer incidence (Preston et al. 2007) and 0.0 Gy, with an upper limit of a 95% CI of 0.15 Gy, for solid cancer mortality (Ozasa et al. (2012)). However, threshold dose-response models did not fit the data for solid cancer incidence or mortality better than linear models.

In presenting LDEFs in Tables 5.1–5.4, we assumed that reported central values of LDEFs or central values of risk coefficients or ratios of risk coefficients that we used to estimate an LDEF are maximum likelihood estimates (MLEs). We then estimated 50th percentiles and 90% CIs of LDEFs by assuming that reported LDEFs, risk coefficients, or ratios of risk coefficients and their CIs are described by Weibull distributions with modes at the reported central values. Weibull distributions were chosen for their flexibility, especially in allowing values <0 .

Table 5.1. LDEFs derived from analyses of curvature in modeled dose-responses (ERRs) for incidence of all solid cancers in LSS cohort based on DS86 dosimetry^a

Dose range (Gy)	Follow-up period	Members of cohort	Method of calculation ^b	LDEF			Source
				Central estimate	Lower confidence limit	Upper confidence limit	
0–3 ^c	1958–1994	Proximal survivors ^d	α_L/α_{LQ}	—	—	1.5	Pierce and Preston (2000)
0–2 ^c		Proximal survivors ^d		—	—	1.9	
0–2 ^c		Proximal and distal survivors		—	—	2.4	
0–4 ^e	1958–1987	All suitable survivors	α_L/α_{LQ}^g	1.06 ^h	0.78 ^h	1.62 ^h	Little and Muirhead (2000, 2004)
0–2 ^f				(1.1) ⁱ	(0.8) ⁱ	(1.5) ⁱ	
				1.21 ^h	0.81 ^h	2.45 ^h	
				(1.4) ^j	(0.9) ^j	(2.3) ^j	
0–2 ^f	1958–1987	All suitable survivors	$[1 + (\beta/\alpha)D]$ at 1 Gy ^k	—	—	1.7	Kellerer et al. (2002)
0–>5 ^m	1958–1987	All suitable survivors	α_L/α_{LQE}^n	1.1 ^o	0.7 ^o	3.4 ^o	ICRP (2005)
0–2 ^m							
				1.1 ^p	0.8 ^p	1.9 ^p	

^a ERRs are sex-averaged and, except as noted, were modified by age at exposure and attained age. Analyses were based on linear-quadratic (LQ) dose-response models, except as noted, and neutron-weighted doses to colon.

^b See Sections 2.2 and 2.4.1 for details of dose-response models and methods of calculating LDEF; α_L is linear risk coefficient (ERR/Gy) based on linear fit to data over indicated dose range; α_{LQ} is linear risk coefficient based on LQ fit to data; α_{LQE} is linear risk coefficient based on linear-quadratic-exponential fit (LQE) to data; β/α is curvature parameter; D is neutron-weighted dose in Gy.

^c Neutron-weighted doses to colon calculated assuming variable neutron RBE increasing from 40 at dose of 5 mGy to 10 at highest doses.

^d Proximal survivors were located at distances ≤ 3 km from hypocenter of a detonation.

^e Shielded kerma free-in-air from photons and neutrons. Neutron-weighted doses to colon were calculated assuming neutron RBE of 20. Members of LSS cohort with shielded kerma >4 Gy were omitted.

^f Neutron-weighted doses to colon calculated assuming neutron RBE of 20.

^g Modeled ERRs were modified by time since exposure, rather than age at exposure, and attained age.

^h Reported MLE and 95% CI. Estimates of LDEF obtained by Little and Muirhead (2000, 2004) assuming neutron RBEs other than 20 are given in Table 5.5.

ⁱ 50th percentile and 90% CI we estimated from reported MLE and 95% CI of α_L/α_{LQ} . MLE of LDEF is at 41st percentile of assumed Weibull distribution.

^j 50th percentile and 90% CI we estimated from reported MLE and 95% CI of α_L/α_{LQ} . MLE of LDEF is at 35th percentile of assumed Weibull distribution.

^k Modeled ERRs were modified by age at exposure only. ERR/Gy for gamma-ray component of dose was derived assuming LQ dose-response for gamma rays and linear dose-response for neutrons (LQ-L model).

^m Neutron-weighted doses to colon calculated assuming neutron RBE of 10.

Table 5.1 (continued)

ⁿ LQE denotes linear-quadratic-exponential dose-response model.

^o 50th percentile and 90% CI we estimated from reported MLEs and 90% CIs of α_L [0.57 (0.48, 0.68)] and α_{LQE} [0.52 (0.16, 0.83)] and assumption that α_L and α_{LQE} are uncorrelated. MLEs of α_L and α_{LQE} are at 50th and 53rd percentiles, respectively, of assumed Weibull distributions.

^p 50th percentile and 90% CI we estimated from reported MLEs and 90% CIs of α_L [0.64 (0.54, 0.74)] and α_{LQ} [0.61 (0.35, 0.76)] and assumption that α_L and α_{LQ} are uncorrelated. MLEs of α_L and α_{LQ} are at 50th and 57th percentiles, respectively, of assumed Weibull distributions.

Table 5.2. LDEFs derived from analyses of curvature in modeled dose-responses (ERRs) for incidence of all solid cancers in LSS cohort based on DS02 dosimetry^a

Dose range (Gy)	Follow-up period	Method of calculation ^b	LDEF			Source
			Central estimate	Lower confidence limit	Upper confidence limit	
0–1.5 ^c	1958–1998	α_L/α_{LQ} ^d	1.3 ^e	0.8 (95% CI)	2.6 (95% CI)	NRC (2006)
			(1.5) ^f	0.9 ^f (90% CI)	2.4 ^f (90% CI)	
			[1 + (β/α) D] at 1 Gy [$\beta/\alpha = 0.3 \text{ Gy}^{-1}$; 95% CI: (-0.1, 1.5)]	1.3 ^g	0.9 (95% CI)	
			(1.5) ^h	1.0 ^h (90% CI)	2.3 ^h (90% CI)	
0–2 ^c	1958–1998	[1 + (β/α) D] at 1 Gy [$\beta/\alpha = 0.3 \text{ Gy}^{-1}$; 90% CI: (0.01, 0.90)]	1.3 ^g (1.4) ⁱ	1.0 (90% CI)	1.9 (90% CI)	Preston et al. (2007)

^a ERRs are sex-averaged and modified by age at exposure and attained age. Analyses were based on linear-quadratic (LQ) dose-response models and neutron-weighted doses to colon.

^b See Section 2.2 for details of dose-response models and methods of calculating LDEF; α_L is linear risk coefficient (ERR/Gy) based on linear fit to data over indicated dose range; α_{LQ} is linear risk coefficient based on LQ fit to data; β/α is curvature parameter; D is neutron-weighted dose in Gy.

^c Neutron-weighted doses to colon calculated assuming neutron RBE of 10.

^d Method of calculation preferred by NRC (2006).

^e Reported central value is MLE.

^f 50th percentile and 90% CI we estimated from reported MLE and 95% CI of α_L/α_{LQ} . MLE of LDEF is at 37th percentile of assumed Weibull distribution.

^g MLE based on reported central value of β/α .

^h 50th percentile and 90% CI we estimated from reported MLE and 95% CI of β/α . MLE of β/α is at 35th percentile of assumed Weibull distribution.

ⁱ 50th percentile we estimated from reported MLE and 90% CI of β/α . MLE of β/α is at 39th percentile of assumed Weibull distribution.

Table 5.3. LDEFs derived from analyses of curvature in modeled dose-responses (ERRs) for mortality from all solid cancers in LSS cohort based on DS86 dosimetry^a

Dose range (Gy)	Follow-up period	Method of calculation ^b	Age-related modifiers	LDEF			Source
				Central estimate	Lower confidence limit	Upper confidence limit	
0–2 ^c	1950–1990	[1 + (β/α)D] at 1 Gy ^d	Age at exposure	—	—	3.2 (95% CI)	Kellerer et al. (2002)
			Attained age	—	—	6.4 (95% CI)	
0–2 ^e	1950–1997	[1 + (β/α)D] at 1 Gy ^d	Age at exposure	1.55 ^f	—	4.4 (95% CI)	Walsh et al. (2004a)
			Attained age	1.82 ^f	—	8.1 (95% CI)	
0–2 ^e	1950–2000	α _L /α _{LQ}	Age at exposure; attained age	1.8 ^g	1.0 ^g (90% CI)	5.1 ^g (90% CI)	Preston et al. (2004)
		[1 + (β/α)D] at 1 Gy [(β/α = 0.61 Gy ⁻¹ ; 90% CI: (0.07, 3.0)]		1.6 ^h (2.1) ⁱ	1.1 (90% CI)	4.0 (90% CI)	

^a ERRs are sex-averaged. Analyses were based on linear-quadratic (LQ) dose-response models and neutron-weighted doses to colon.

^b See Sections 2.2 and 2.4.1 for details of dose-response models and methods of calculating LDEF; α_L is linear risk coefficient (ERR/Gy) based on linear fit to data over indicated dose range; α_{LQ} is linear risk coefficient based on LQ fit to data; β/α is curvature parameter; D is neutron-weighted dose in Gy.

^c Neutron-weighted doses to colon calculated assuming neutron RBE of 20.

^d ERR/Gy for gamma-ray component of dose was derived assuming LQ dose-response for gamma rays and linear dose-response for neutrons (LQ-L model).

^e Neutron-weighted doses to colon calculated assuming neutron RBE of 10.

^f Reported central value is MLE.

^g 50th percentile and 90% CI we estimated from reported MLEs and 90% CIs of α_L [0.46 (0.36, 0.57)] and α_{LQ} [0.26 (0.09, 0.44)] and assumption that α_L and α_{LQ} are uncorrelated. MLEs of α_L and α_{LQ} are at 49th and 50th percentiles, respectively, of assumed Weibull distributions.

^h MLE based on reported central value of β/α.

ⁱ 50th percentile we estimated from reported MLE and 90% CI of β/α. MLE of β/α is at 29th percentile of assumed Weibull distribution.

Table 5.4. LDEFs derived from analyses of curvature in modeled dose-responses (ERRs or EARs) for mortality from all solid cancers in LSS cohort based on DS02 dosimetry^a

Dose range (Gy)	Follow-up period	Method of calculation ^b	Age-related modifiers	LDEF			Source
				Central estimate	Lower confidence limit	Upper confidence limit	
0–2 ^c	1950–2000	α_L/α_{LQ} (ERR model)	Age at exposure; attained age	2.1 ^d	1.0 ^d (90% CI)	9.4 ^d (90% CI)	Preston et al. (2004)
		$[1 + (\beta/\alpha)D]$ at 1 Gy (ERR model) [($\beta/\alpha = 0.94 \text{ Gy}^{-1}$; 90% CI: (0.16, 8.4)]		1.9 ^e (3.6) ^f	1.2 (90% CI)	9.4 (90% CI)	
0–1.5 ^c	1950–2000	$[1 + (\beta/\alpha)D]$ at 1 Gy (ERR model)	Age at exposure; attained age	2.1 ^g	—	—	Pierce et al. (2008)
		$[1 + (\beta/\alpha)D]$ at 1 Gy (ERR model)		2.3 ^h	—	—	
0–4 ⁱ	1950–2000	$[1 + (\beta/\alpha)D]$ at 1 Gy (ERR model)	Time since exposure; attained age	1.34 ^j	1.01 ^j (90% CI)	2.53 ^j (90% CI)	Little et al. (2008)
		$[1 + (\beta/\alpha)D]$ at 1 Gy (EAR model)		1.51 ^k	1.07 ^k (90% CI)	3.26 ^k (90% CI)	
		$[(1 + (\beta/\alpha)D) \exp(-\gamma D)]$ at 1 Gy (LQE ERR model)	Time since exposure; attained age	2.1 ^m	–13 ^m (90% CI)	19 ^m (90% CI)	Little et al. (2008)
		$[(1 + (\beta/\alpha)D) \exp(-\gamma D)]$ at 1 Gy (LQE EAR model)		2.3 ⁿ	–15 ⁿ (90% CI)	25 ⁿ (90% CI)	
0–2 ^c	1950–2003	$[1 + (\beta/\alpha)D]$ at 1 Gy (ERR model) [($\beta/\alpha = 0.81 \text{ Gy}^{-1}$; 95% CI: (0.08, 8.6)]	Age at exposure; attained age	1.8 ^e (3.2) ^o	1.1 (95% CI) 1.2 ^o (90% CI)	9.6 (95% CI) 8.3 ^o (90% CI)	Ozasa et al. (2012)
		α_L/α_{LQ} (ERR model)		2.0 ^p	1.0 ^p (90% CI)	6.8 ^p (90% CI)	

Table 5.4. (continued)

Dose range (Gy)	Follow-up period	Method of calculation ^b	Age-related modifiers	LDEF			Source
				Central estimate	Lower confidence limit	Upper confidence limit	
0–4 ^g	1950–2003	[1 + (β/α)D] at 1 Gy (ERR model)	Age at exposure; attained age	1.11 ^r	0.94 ^r (90% CI)	1.48 ^r (90% CI)	Ozasa et al. (2012)
		α _L /α _{LQ} (ERR model)		1.16 ^s	0.77 ^s (90% CI)	1.90 ^s (90% CI)	

^a Risks are sex-averaged. Analyses were based on linear-quadratic (LQ) dose-response models, except as noted, and neutron-weighted doses to colon.

^b See Sections 2.2 and 2.4.1 for details of dose-response models and methods of calculating LDEF; α_L is linear risk coefficient (ERR/Gy) based on linear fit to data over indicated dose range; α_{LQ} is linear risk coefficient based on LQ fit to data; β/α is curvature parameter; LQE denotes linear-quadratic-exponential dose-response; γ is linear coefficient in exponential term to represent cell sterilization in LQE model; D is neutron-weighted dose in Gy.

^c Neutron-weighted doses to colon calculated assuming neutron RBE of 10.

^d 50th percentile and 90% CI we estimated from reported MLEs and 90% CIs of α_L [0.43 (0.33, 0.53)] and α_{LQ} [0.19 (0.03, 0.37)] and assumption that α_L and α_{LQ} are uncorrelated. MLEs of α_L and α_{LQ} are at 50th and 48th percentiles, respectively, of assumed Weibull distributions.

^e MLE based on reported central value of β/α.

^f 50th percentile we estimated from reported MLE and 90% CI of β/α. MLE of β/α is at 20th percentile of assumed Weibull distribution.

^g MLE based on β/α derived by assuming 35% measurement error and 35% averaging error in estimated doses.

^h MLE based on preferred β/α derived by assuming 40% measurement (classical) error and 20% averaging (Berkson) error in estimated doses. Classical and Berkson errors are described in UNSCEAR (2012).

ⁱ Shielded kerma free-in-air from photons and neutrons. Neutron-weighted doses to colon were calculated assuming neutron RBE of 10. Members of LSS cohort with shielded kerma >4 Gy were omitted.

^j 50th percentile and 90% CI we estimated from reported MLEs and 90% CIs of α [0.347 (0.161, 0.566)] and β [0.121 (0.004, 0.246)] and assumption that α and β are negatively correlated (correlation coefficient of -1). MLEs of α and β are at 48th and 50th percentiles, respectively, of assumed Weibull distributions. Assumed parameter correlation should result in slight overestimate of uncertainty in LDEF.

^k 50th percentile and 90% CI we estimated from reported MLEs and 90% CIs of α [5.58 (2.31, 9.40)] and β [2.86 (0.66, 5.22)] and assumption that α and β are negatively correlated (correlation coefficient of -1). MLEs of α and β are at 48th and 49th percentiles, respectively, of assumed Weibull distributions. Assumed parameter correlation should result in slight overestimate of uncertainty in LDEF.

^m 50th percentile and 90% CI we estimated from reported MLEs and 90% CIs of α [0.16 (-0.17, 0.50)], β [0.68 (-0.079, 1.55)], and γ [-0.41 (-0.86, 0.40)] and assumption that α, β, and γ are uncorrelated. MLEs of α, β, and γ are at 50th, 49th, and 42nd percentiles, respectively, of assumed Weibull distributions. Assumption that parameters are uncorrelated should result large overestimate of uncertainty in LDEF.

ⁿ 50th percentile and 90% CI we estimated from reported MLEs and 90% CIs of α [2.44 (-3.49, 7.60)], β [11.5 (-1.82, 25.4)], and γ [-0.32 (-0.80, 0.85)] and assumption that α, β, and γ are uncorrelated. MLEs of α, β, and γ are at 52nd, 50th, and 37th percentiles, respectively, of assumed Weibull distributions. Assumption that parameters are uncorrelated should result large overestimate of uncertainty in LDEF.

^o 50th percentile and 90% CI we estimated from reported MLE and 95% CI of β/α. MLE of β/α is at 19th percentile of assumed Weibull distribution.

Table 5.4. (continued)

^p 50th percentile and 90% CI we estimated from reported MLEs of α_L (0.44) and α_{LQ} (0.22), estimated 95% CIs of α_L (0.33, 0.56) and α_{LQ} (0.036, 0.43) (D. Preston, personal communication, November 6, 2016), and assumption that α_L and α_{LQ} are uncorrelated. MLEs of α_L and α_{LQ} are at 50th and 49th percentiles, respectively, of assumed Weibull distributions. MLE of α_L/α_{LQ} is 2.0.

^q Shielded kerma free-in-air from photons and neutrons, with estimates of shielded kerma >4 Gy truncated to 4 Gy. Neutron-weighted doses to colon were calculated assuming neutron RBE of 10.

^r 50th percentile and 90% CI we estimated from reported MLEs of α (0.36) and β (0.038), estimated 95% CIs of α (0.21, 0.53) and β (-0.043, 0.123) (D. Preston, personal communication, November 6, 2016), and assumption that α and β are negatively correlated (correlation coefficient of -1). MLEs of α and β are at 49th and 50th percentiles, respectively, of assumed Weibull distributions. Assumed parameter correlation should result in slight overestimate of uncertainty in LDEF. MLE of β/α is 0.106.

^s 50th percentile and 90% CI we estimated from reported MLE and 95% CI of α_L [0.42 (0.32, 0.53)], reported MLE of α_{LQ} (0.36), estimated 95% CI of α_{LQ} (0.21, 0.53) (D. Preston, personal communication, November 6, 2016), and assumption that α_L and α_{LQ} are uncorrelated. MLEs of α_L and α_{LQ} are at 50th and 49th percentiles, respectively, of assumed Weibull distributions. MLE of α_L/α_{LQ} is 1.17.

In several cases, we estimated 50th percentiles and 90% CIs of LDEFs from reported central values (MLEs) and CIs of two or three risk coefficients. For example, when the coefficients α and β in a fit to a dose-response assuming an LQ model were reported separately, we estimated the 50th percentile and 90% CI of β/α , with LDEF calculated as $[1 + (\beta/\alpha)]$, using Monte Carlo uncertainty propagation techniques with 10,000 iterations of stratified (Latin hypercube) random sampling from an assumed Weibull distribution of each coefficient with mode at the reported MLE. A similar procedure was used when the coefficients α_L and α_{LQ} from a fit assuming an LQ model or the coefficients α , β , and γ from a fit assuming an LQE model were reported separately.

In the recent analysis of solid cancer mortality in the LSS cohort by Ozasa et al. (2012) summarized in Table 5.4, only an estimate of LDEF and its uncertainty based on an estimate of β/α at colon doses of 0–2 Gy could be obtained from reported parameters and their uncertainties; this β/α is the estimated curvature in the dose-response preferred by Ozasa et al. (2012). However, we also used reported MLEs of other parameters, the reported uncertainty in the risk coefficient α_L from an analysis at a shielded kerma of 0–4 Gy using a linear model, and uncertainties in the other parameters estimated by D. Preston (personal communication, November 6, 2016), to estimate LDEFs and their uncertainties based on an estimate of α_L/α_{LQ} at colon doses of 0–2 Gy and estimates of β/α and α_L/α_{LQ} at a shielded kerma of 0–4 Gy.

Analyses of dose-responses for solid cancer incidence in the LSS cohort summarized in Tables 5.1 and 5.2 do not provide strong support for a DDREF >2. Despite differences in the length of follow-up and dosimetry system, approaches to data selection (i.e., differences in dose ranges analyzed or locations of survivors), modeling of a dose-response, or approaches to calculating an LDEF, all central estimates (MLEs and 50th percentiles) are <2, upper limits of CIs are <3 except in the one case in Table 5.1 where

an LQE dose-response model was assumed, and lower limits of most CIs are <1 , indicating that a linear model may underestimate the risk at low acute doses. However, analyses of data on mortality from all solid cancers in the LSS cohort discussed below indicate that responses at low doses are more uncertain than suggested by the range of these LDEFs.

In analyses of dose-responses for solid cancer mortality summarized in Tables 5.3 and 5.4, central estimates of LDEFs tend to be higher than central estimates of LDEFs for solid cancer incidence in Tables 5.1 and 5.2. Except for upper limits of CIs we estimated from LQ dose-response models developed by Little et al. (2008) and from an analysis by Ozasa et al. (2012) at a shielded kerma of 0–4 Gy, upper limits of CIs of LDEFs in Tables 5.3 and 5.4 are higher than those in Tables 5.1 and 5.2.

In most analyses summarized in Tables 5.1–5.4, an error (uncertainty) of 35% was assigned to estimated doses. However, Pierce et al. (2008) recommended that two components of random error should be assigned: a 40% “classical” measurement error and a 20% Berkson averaging error, which result in an overall coefficient of variation of 45%. Estimated LDEFs from Pierce et al. (2008) in Table 5.4 indicate an effect of the different assumptions about uncertainties in estimated doses. Classical errors in estimated doses produce a flattening of a modeled dose-response (e.g., a reduction in the ERR/Gy in a linear model), while Berkson errors lead to underestimates of CIs but do not affect central values of estimated risks.

Correlations between uncertain risk coefficients were taken into account in our analyses of curvature parameters (β/α) based on estimates of β and α assuming LQ dose-response models reported by Little et al. (2008) and estimates of β and α from Ozasa et al. (2012) at a shielded kerma of 0–4 Gy (Table 5.4). Since β and α should be negatively correlated, we estimated 90% CIs of LDEFs in those cases by assuming a correlation coefficient of -1 , which gives the largest uncertainty. However, those LDEFs were not strongly sensitive to the assumed correlation coefficient. For example, using estimates of β and α reported by Little et al. (2008), an assumption of no correlation gave 50th percentiles and 90% CIs of LDEFs of 1.3 (1.0, 2.0) when ERR was modeled and 1.5 (1.1, 2.5) when EAR was modeled.

No parameter correlations were assumed in our analyses of results from ICRP (2005), Preston et al. (2004), and Ozasa et al. (2012) in which an LDEF was estimated as α_L/α_{LQ} (Tables 5.1, 5.3, and 5.4) and in our analyses of results from Little et al. (2008) based on LQE dose-response models (Table 5.4). A possible correlation of α_L and α_{LQ} should not result in a substantial increase in 90% CIs of estimated LDEFs. In analyzing results from Little et al. (2008) based on LQE dose-response models, we did not know the nature and extent of correlations between β and α when the parameter γ also is uncertain and its correlations with the other two parameters were not reported. In those cases, our assumption of no parameter correlations should result in large overestimates of uncertainty in LDEFs.

In the analyses of dose-responses for solid cancer mortality based on DS02 dosimetry summarized in Table 5.4, Little et al. (2008) omitted data for survivors with a shielded kerma >4 Gy, whereas Preston

et al. (2004) and Ozasa et al. (2012) used the data at high doses by truncating estimates of shielded kerma to 4 Gy. Preston et al. (2004), Pierce et al. (2008), and Ozasa et al. (2012) used the same age-related modifiers, but the curvature in dose-responses was estimated based on data over a more restricted range of doses than in the full analyses (colon doses of 0–2 Gy, 0–1.5 Gy, and 0–2 Gy in preferred analysis, respectively). In addition, Little et al. (2008) used models in which ERRs or EARs were modified by time since exposure, rather than age at exposure. Little et al. (2008) also estimated CIs of model parameters using Bayesian methods, which resulted in smaller uncertainties in LDEFs than those obtained in other studies. These comparisons indicate that differences in data selection, model structure, model parameters, and estimates of dosimetric errors can lead to differences in estimates of LDEF and their uncertainties.⁵¹

The BEIR VII committee (NRC 2006) noted that the analysis of data on cancer mortality at colon doses of 0–2 Gy by Preston et al. (2004) gave a larger estimate of the curvature parameter (β/α) of 0.94 Gy^{-1} [90% CI: (0.16, 8.4)] than the committee estimated from an analysis of data on cancer incidence at colon doses of 0–1.5 Gy [$\beta/\alpha = 0.3 \text{ Gy}^{-1}$; 95% CI: (–0.1, 1.5)]. Nonetheless, the BEIR VII committee concluded that the two estimates were consistent, given the imprecision in the estimate by Preston et al. (2004). However, one can also question whether the BEIR VII committee’s estimate is overly precise, particularly when the committee recognized the limitations of the data and the uncertainties in estimating a DDREF (NRC 2006). The committee’s approach to estimation of DDREF discussed in Appendix B suggests that uncertainties were not fully addressed.

On the whole, analyses of data for all solid cancers combined in the LSS cohort summarized in Tables 5.1–5.4 give central estimates (MLEs or 50th percentiles) of LDEF <4, differences in the endpoint (incidence or mortality) and differences in assumptions used in modeling and substantial differences in estimated uncertainties notwithstanding. This conclusion is particularly apparent in central estimates of LDEF based on DS02 dosimetry in Tables 5.2 and 5.4, which are of greater interest to this report.

In the analyses by Little et al. (2008) summarized in Table 5.4, the LQE model provided the best fit to the data, even though the uncertainty in LDEF is much higher than the uncertainty assuming an LQ model when the parameters α and β are poorly constrained in the three-parameter LQE model. However, although the LQ and LQE models were considered to be biologically plausible and the coefficients in the cell-sterilization term in the LQE models were not inconsistent with estimates derived from radiobiological data, Little et al. (2008) preferred the simpler LQ model. They also noted that risks at low doses obtained using an LQE model were lower than risks obtained using an LQ model.

In results from analyses by Ozasa et al. (2012) summarized in Table 5.4, estimated 50th percentiles of LDEFs at a shielded kerma of 0–4 Gy were less than at colon doses of 0–2 Gy, and uncertainties in the

⁵¹ Interpretation of dose-responses also can be influenced by the number of dose categories specified for analysis; see Chomentowski et al. (2000) and discussion of possible threshold responses for leukemia in Section 5.8.2.

LDEFs at a shielded kerma of 0–4 Gy were much smaller, with upper limits of 90% CIs <2. These comparisons indicate the sensitivity of estimated LDEFs to the dose range over which dose-responses in the LSS cohort are analyzed. The ERR/Gy of 0.42 [95% CI: (0.32, 0.53)] preferred by Ozasa et al. (2012) was based on a linear fit to the dose-response at a shielded kerma of 0–4 Gy, whereas the preferred curvature parameter, β/α , of 0.81 [95% CI (0.08, 8.6)] was based on a fit at colon doses of 0–2 Gy assuming an LQ model. This analysis is discussed further in Section 5.2.1.4.

Before accepting estimates of LDEF based on a particular dose-response model for solid cancer incidence or mortality, we should consider whether an LDEF derived from an analysis of the curvature in the dose-response for acute exposure in the LSS cohort is a suitable representation of a DDREF at low doses or low dose rates. In large part, this question hinges on whether an LDEF derived from an LQ or LQE model of an acute dose-response also can be considered to represent a DREF. The question is whether a valid estimate of LDEF can be derived from a model of solid cancer incidence or mortality in the LSS cohort that is driven largely by responses at organ doses ≥ 0.5 Gy. A modeled dose-response in the LSS cohort is greatly influenced by data at higher doses and, thus, appears to require confirmation using independent data sets at low doses or low dose rates, as suggested by Leenhouts and Chadwick (2011).

An argument against the need for independent data sets at low doses or low dose rates is that the large number of members in the LSS cohort with low doses provides adequate statistical power to make direct inferences about cancer risks at low doses, albeit at a high dose rate (Preston et al. 2007). The LSS is often referred to as a high-dose study, but this characterization is somewhat misleading (Pierce and Preston 2000). Although estimates of cancer risks are largely driven by responses at organ doses >0.5 Gy, about 75% of the exposed survivors were assigned doses of 0.5–200 mGy.

We would agree that data in the LSS cohort alone might be sufficient to estimate a DDREF if doses to survivors who were lightly exposed or were not exposed to direct radiation from the detonations were well characterized. However, many of those survivors were exposed to fallout and neutron-activation products, which have not been fully characterized (Section 5.2.1.2). As a result, doses to those survivors may be substantially greater and, at a minimum, are more uncertain than currently estimated.

Contributions from those exposures have not yet been taken into account “because they are generally believed to have been small and the area that received fallout in Nagasaki was very sparsely populated while in Hiroshima people living in fallout-affected areas constitute only a small proportion of the distal survivors. Defining who could have received fallout is also problematic since many people moved around in the immediate aftermath of the bombs making it essentially impossible to determine who might have received these doses” (D. Preston, personal communication, February 13, 2008). Finally, the slope of the dose-response at doses to the colon <200–250 mGy is not significantly different from zero, which further compromises the applicability of the LSS data for the purpose of estimating risks at low doses.

In the following sections, we examine these questions by focusing mainly on the approach taken by the BEIR VII committee to estimate a DDREF using data on incidence of all solid cancers based on DS02 dosimetry (NRC 2006). However, our concerns also apply to most of the other studies summarized in Tables 5.1–5.4, and we also cover relevant observations and results from those studies. Data in the LSS cohort used by the BEIR VII committee, and by Preston et al. (2007), were based on follow-up through 1998, whereas the follow-up period was 4 years shorter in the analysis by Pierce and Preston (2000) and 11 years shorter in the analysis by Little and Muirhead (2000, 2004). We consider the effects on estimated risks at low doses in the LSS cohort of uncertainties associated with the following:

- definition of the cohort, including exposed and unexposed groups;
- contributions to doses from exposure to fallout and neutron-activation products;
- uncertainty in the RBE for neutrons;
- effects of the dose range analyzed and model structure;
- LSS data and applicability of parameter choices; and
- aggregation of data for individual solid cancers.

5.2.1.1 Influence of definition of LSS cohort

An analysis of the dose-response for solid cancer incidence at low doses by Pierce and Preston (2000) focused primarily on members of the LSS cohort who were located within 3 km of the hypocenter at the time of a bombing, referred to as proximal survivors, and included data for the period 1958–1994. Exclusion of distal survivors at locations beyond 3 km at the time of a bombing was justified on the basis of differences in baseline cancer rates associated with living in an urban vs a rural environment and, hence, differences in lifestyle factors. Baseline cancer rates were about 5% higher in the distal group but, as noted by Pierce and Preston (2000), “[a] bias of this size has very little effect for analyses over the full dose range, but it does substantially affect assessment of low-dose risks.” This effect is discussed below.

As indicated in Figure 5.2, Pierce and Preston (2000) reported a marginally significant ($P = 0.06$) increase in the dose-response for incidence of all solid cancers at doses to the colon of 0.1–0.3 Sv⁵² compared with the best linear fit at doses of 0–2 Gy when distal survivors were omitted from the analysis. The maximum slope in the data occurred at colon doses of 0–0.2 Sv. The ratio of the slope of the linear dose-response at colon doses of 0–2 Sv to the maximum slope suggests an LDEF of 0.75 (i.e., <1).

⁵² These are neutron-weighted doses that should be given in Gy, not Sv, because the assumed RBE for neutrons was not the same as the radiation weighting factor (w_R) of 20 for neutrons recommended by ICRP (Preston et al. 2007). In this report, we usually present doses to members of the LSS cohort as neutron-weighted doses in Gy.

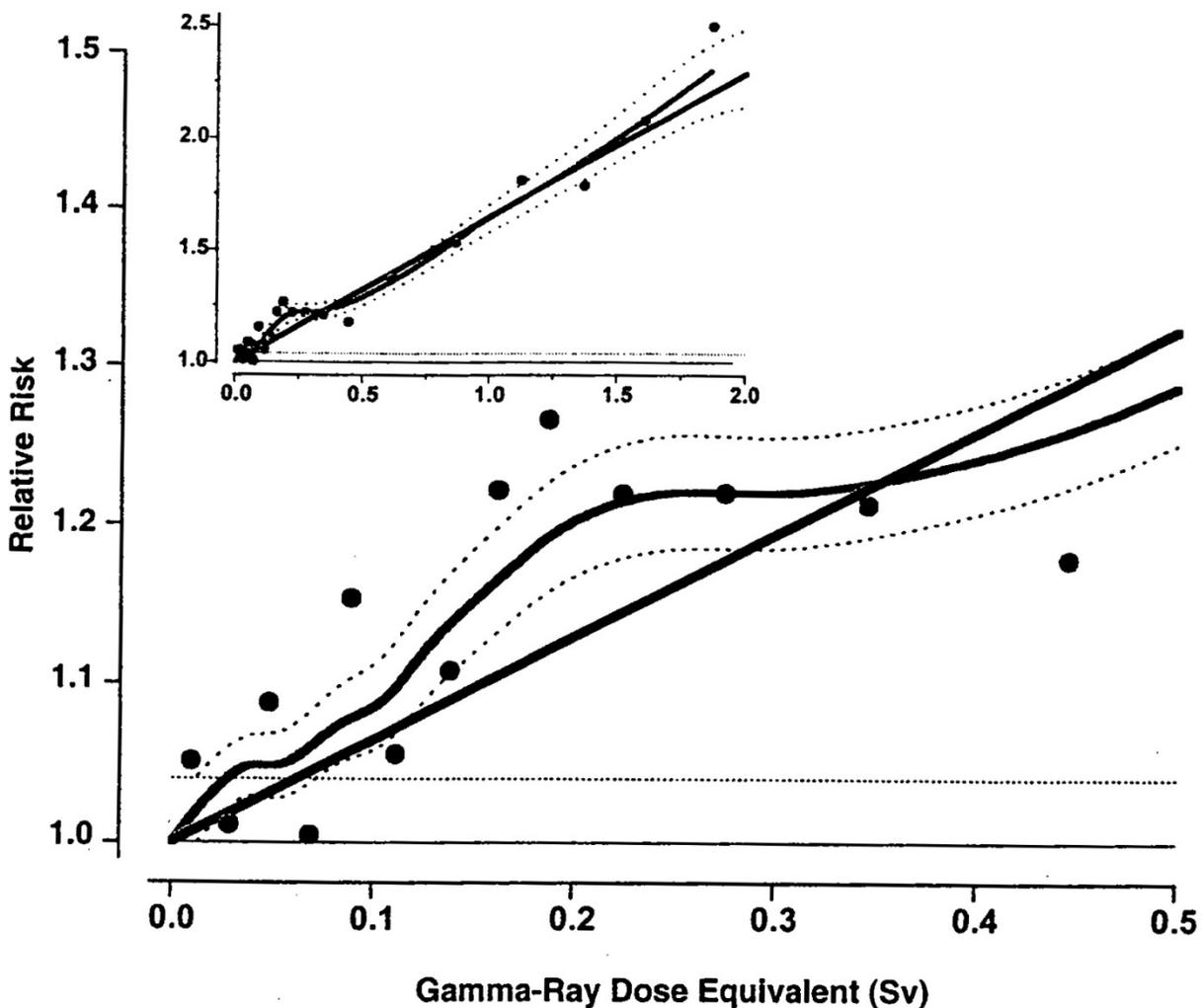


Figure 5.2. Estimates of relative risks of incidence of all solid cancers in LSS cohort at neutron-weighted colon doses <2 Sv based on DS86 dosimetry with distal survivors beyond 3 km omitted (Pierce and Preston 2000). Neutron RBE was assumed to decrease from 40 at colon dose of 5 mGy to 10 at highest doses. Dotted curves with non-linear fit represent ± 1 standard error (SE), and horizontal dotted line reflects baseline risk if distal survivors are included. Straight line is linear fit to data at doses of 0–2 Sv.

Suggestions of supralinearity in dose-responses at low doses in the LSS cohort also appear in earlier analyses that included distal survivors. Analyses of data on mortality from all solid cancers based on follow-up to 1990 by Pierce et al. (1996a, 1997) and Little (1997) indicated a statistically significant risk and a suggestion of supralinearity in groups of survivors with neutron-weighted colon doses ≤ 0.05 Gy. Those analyses were used in defining lower limits of the probability distributions of DDREFs used in IREP (Section 1.1.1). However, Pierce et al. (1996a, 1997) were cautious in interpreting these findings,

which differed from results from the 1994 analysis of data on incidence of all solid cancers by Thompson et al. (1994).⁵³

As shown in Figure 5.3, when distal survivors in the LSS cohort were included, similar elevations in risks were suggested by an analysis of dose-responses for cancer mortality based on DS86 and DS02 dosimetry at neutron-weighted colon doses ≤ 0.3 Sv (i.e., 0.3 Gy) (Preston et al. 2004). However, the slope of the dose-response for solid cancer incidence at doses of 0–0.15 Gy based on DS02 dosimetry (Preston et al. 2007) was consistent with the slope at 0–2.5 Gy, which suggests no elevation of risks at the lower doses. Similarly, an analysis of the same data by UNSCEAR (2008) yielded statistically significant estimates of ERR/Gy for solid cancer incidence or mortality only at doses of about 0–0.25 Gy or higher, and a tendency for estimates of ERR/Gy to increase at doses of 0–0.06 Gy or less was not significant.

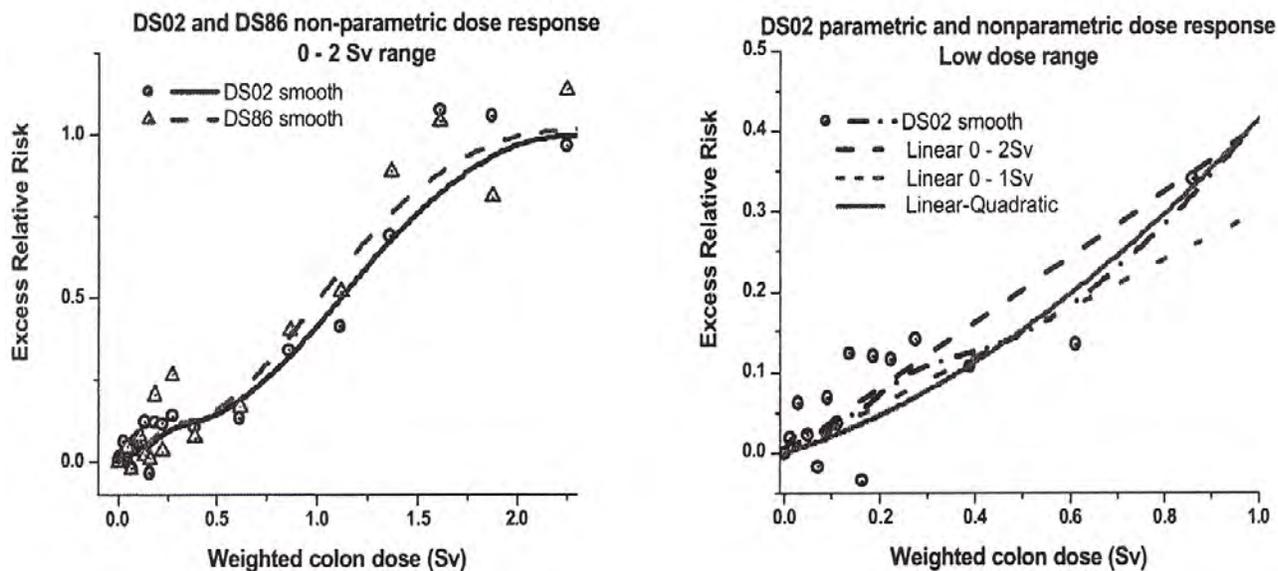


Figure 5.3. Dose-responses (ERRs) for mortality from all solid cancers in LSS cohort from reanalyses of data at neutron-weighted colon doses of 0–2.5 Sv based on DS02 (circles) and DS86 (triangles) dosimetry (Preston et al. 2004).

⁵³ The 1996 analyses of data on cancer mortality were challenged by Rossi and Zaider (1996, 1997) and Baker and Hoel (2003), who contended that underestimation of neutron doses at Hiroshima and an assumption of a constant neutron RBE, rather than an RBE that decreases with increasing dose, resulted in non-linearities in the dose-response at low doses that would indicate a decrease in risks and, in the analysis by Baker and Hoel (2003), threshold doses for incidence of solid cancers and leukemia of about 0.1–0.15 Gy. However, Pierce et al. (1996b) showed that when DS86 doses included a neutron contribution that was weighted using the dependence of RBE on dose suggested by Rossi and Zaider (1996) and used by Baker and Hoel (2003), estimated doses and risks changed by no more than 5%. Furthermore, the neutron-to-gamma dose ratio decreased substantially in the DS02 dosimetry system, particularly at distances beyond 1.5 km from the hypocenters, which would eliminate concerns about a dose-dependent RBE for neutrons unless the higher RBEs estimated by Kellerer et al. (2006) and discussed in Section 5.2.1.3 are valid.

Fits to dose-responses in the LSS cohort assuming a linear model are determined primarily by data at doses >0.5 Gy (Land et al. 2003a; NRC 2006). Although risk coefficients assuming a linear model can be estimated based only on data at lower doses, statistical uncertainties in those coefficients are substantially greater than when survivors with higher doses are included (ICRP 2005; NRC 2006). As indicated in Figures 5.4 and 5.5, estimates of ERR/Gy are statistically unstable when linear fits are restricted to neutron-weighted colon doses less than about 0.3 Gy, where the fits are influenced by the inclusion or exclusion of distal survivors with low doses. If distal survivors are excluded (Figure 5.4), estimates of ERR/Gy based on data in survivors with doses ≤ 0.3 Gy appear to exceed estimates based on data over the entire dose range, but if distal survivors are included (Figure 5.5), the pattern appears to be reversed; i.e., estimates of ERR/Gy decrease with decreasing dose at doses ≤ 0.3 Gy. Estimates of ERR/Gy at the lowest doses in Figure 5.4 suggest an LDEF of about 0.5 or less, whereas estimates at the lowest doses in Figure 5.5 suggest an LDEF as high as 7 or more. However, uncertainties in the data are too large to conclude that either interpretation is valid (i.e., that LDEF differs from 1).

Given the different patterns of estimates of ERR/Gy at low doses in Figures 5.4 and 5.5, it is reasonable to question whether a dose-response model for the LSS cohort can be used to select either alternative, let alone define an LDEF <2 as in the analysis by the BEIR VII committee (NRC 2006).

In the analysis of solid cancer incidence by Preston et al. (2007), the LSS cohort was redefined to include three major groups of Hiroshima and Nagasaki residents: (1) survivors who were located within 2.5 km of the hypocenters at the time of the bombings (ATB), (2) survivors who were located between 2.5 and 10 km of the hypocenters ATB (low- or no-dose group); and (3) residents who were temporarily away from Hiroshima or Nagasaki or were located more than 10 km from either hypocenter ATB (not-in-city or no-exposure group). Since results from the more recent analysis were based on a redefined LSS cohort, it may be difficult to compare those results with results from earlier studies. It could be instructive to investigate whether the expansion of the cohort to include more survivors with low or no doses has affected the dose-response at low doses significantly.

Estimates of risk coefficients based on analyses of data over selected dose ranges in Figures 5.4 and 5.6 suggest a supralinearity in the dose-response, although uncertainties are large. In the data in Figure 5.6, which are based on DS02 dosimetry and data in the three groups of survivors defined by Preston et al. (2007) described above, increases in ERR/Gy are suggested at neutron-weighted colon doses of about 0.1 Gy or less. Ozasa et al. (2012) did not explain the patterns of dose-responses in Figure 5.6, but they noted that there was insufficient information about additional doses from exposure to fallout or other residual radiation from neutron-activation products to rule out those sources as a possible explanation. The potential impacts of those sources are discussed in the following section.

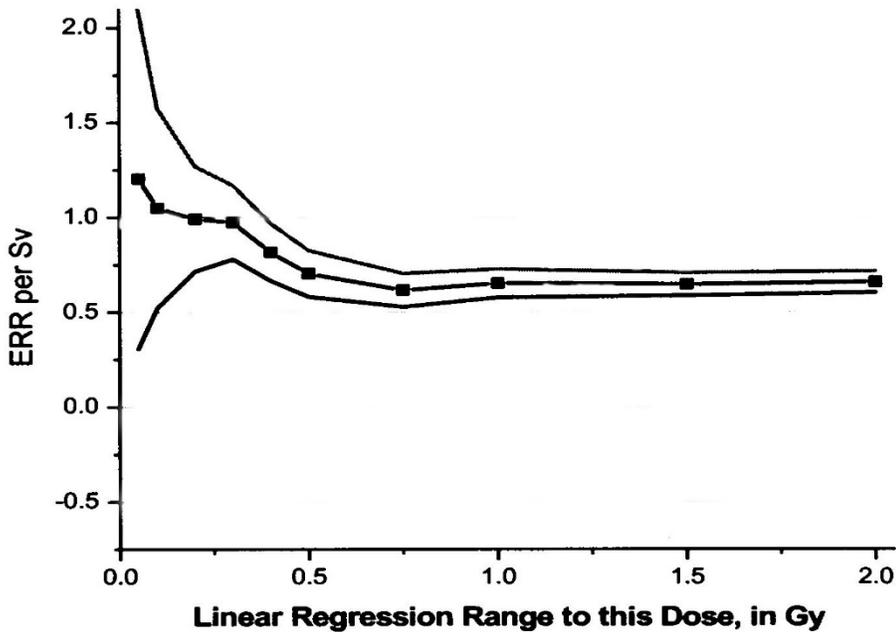


Figure 5.4. ERR/Gy \pm 1 SE for incidence of all solid cancers in proximal survivors in LSS cohort with neutron-weighted colon doses <2 Gy based on DS86 dosimetry, follow-up for period 1958–1994, and linear regression of responses over dose intervals from zero to selected dose (ICRP 2005). Proximal survivors were exposed at distances <3 km from hypocenters of bombings.

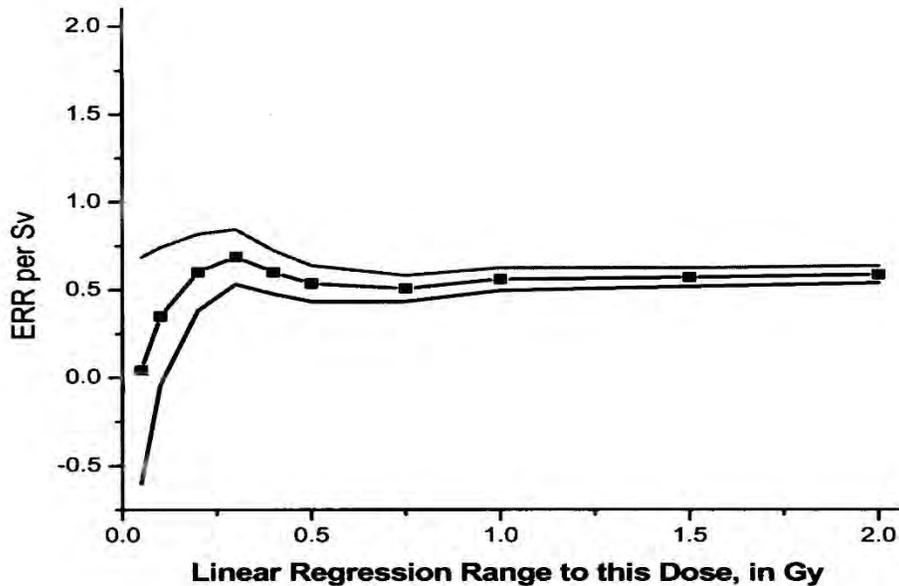


Figure 5.5. ERR/Gy \pm 1 SE for incidence of all solid cancers in LSS cohort, including distal survivors, with neutron-weighted colon doses <2 Gy based on DS86 dosimetry, follow-up for period 1958–1994, and linear regression of responses over dose intervals from zero to selected dose (ICRP 2005).

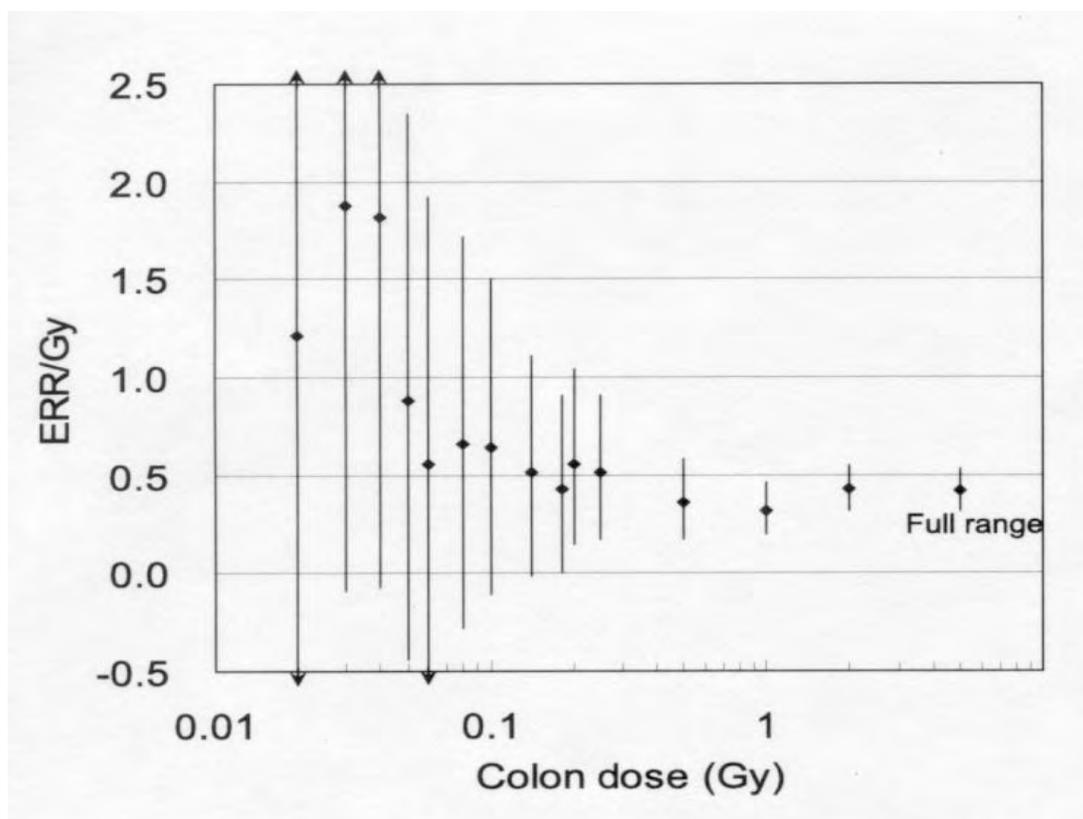


Figure 5.6. ERR/Gy and 95% CIs for mortality from all solid cancers in LSS cohort, including distal survivors, with neutron-weighted colon doses <2 Gy based on DS02 dosimetry, follow-up through 2003, and analyses over selected dose ranges based on a linear dose-response model (Ozasa et al. 2012).

5.2.1.2 Influence of doses from exposure to fallout and neutron activation products

In analyses of dose-responses in the LSS cohort performed to date, doses assigned to survivors in Group 2 (the low- or no-dose group at distances of 2.5–10 km) or Group 3 (the no-exposure or not-in-city group at distances >10 km), as redefined by Preston et al. (2007), were not adjusted to account for contributions from exposure to fallout or exposure to neutron-activation products in building materials or soil. Although omitting those doses may not have a significant effect on estimated risks, which are based primarily on data at higher doses, there could be an effect on estimated risks at the lowest doses, as suggested by the possible differences in dose-responses at the lowest doses in Figures 5.4 and 5.5. For several reasons, contributions to doses from exposure to fallout and neutron-activation products at Hiroshima and Nagasaki need to be estimated accurately. The observation of a higher baseline cancer rate in the low- and no-dose survivors in Group 2 and the possible influence of their inclusion or exclusion on

estimated risks at the lowest doses, as suggested by calculations in Figures 5.4 and 5.5, indicates the need for an evaluation of whether an adjustment of estimated risks to account for a greater uncertainty in estimated doses is warranted, and, if so, what the impact of neglecting such exposures on current estimates of risk might be. If the higher baseline cancer risks in distal survivors in which the dose-response was analyzed by Pierce and Preston (2000) were not associated with differences in lifestyle factors but, rather, were due to additional exposures that were not taken into account, estimates of risks at low doses based on analyses of the shapes of dose-responses could be compromised.

The main group of survivors who received little exposure or were included in the control group (i.e., survivors with doses <0.005 Gy) were located within 2.5–10 km of the hypocenters of the bombs ATB. The control group in that region was based on a sample of the population chosen to match the age and sex distributions in the exposed group at locations ≤ 2.5 km from the hypocenters (Preston et al. 2007).

At 2.5 km from the hypocenter at Hiroshima, the total free-field kerma was about 0.01 Gy. However, some of the more distant survivors who received lower doses from bomb-produced radiation entered the devastated areas after the explosion. Gritzner and Woolson (1986) concluded that early entrants at Hiroshima could have received doses from exposure to neutron-activation products similar to doses received by survivors at 2.5 km from the hypocenter ATB. For example, they estimated that a person who spent days 2 and 3 after the bombing at a distance of 0.5 km from the hypocenter at Hiroshima could have received a dose of about 0.03 Gy. They then concluded that there was substantial uncertainty in the doses to those persons that should be understood before they were included in a control group. However, contrary to expectations based on the low doses estimated by Gritzner and Woolson (1986), some early entrants reportedly exhibited symptoms of acute radiation syndrome, including petechia and epilation (Watanabe 1974).

Such reports and other reports of symptoms of acute radiation syndrome, such as hemorrhage and diarrhea, led to additional studies of doses from neutron-induced radionuclides in soil. RERF (2007) cited results from studies that indicated that doses as high as 0.16 Gy and 0.08 Gy could have been received by a person who spent days 2 and 3 near the hypocenter of either bomb, respectively. However, an analysis by Imanaka et al. (2008) suggested that those estimates may be too high by about a factor of three. Higher doses could have been received by individuals who entered the area around the hypocenters on the first day, but this scenario was considered unlikely by RERF (2007). Nonetheless, some individuals presumably were involved in fighting fires that broke out immediately after the explosions (Watanabe 1974). It also is conceivable that the area in which higher exposures to neutron-activated materials could have occurred was increased due to spreading of activated materials by the fires. However, since doses to skin from exposure to neutron-activated soil in Hiroshima estimated by Tanaka et al. (2008) were much lower than an estimated threshold of about 1 Gy for epilation, even if exposure at the hypocenter for the

first week is assumed, we conclude that a source of exposure other than neutron-activated materials in soils is required to explain reports of acute radiation effects.

We do not know how many survivors in Group 2, who were located at a distance of 2.5–10 km from the hypocenters ATB, entered the cities soon after the bombings, but nearly 26,000 persons who were located ≥ 5 km from the hypocenter ATB are known to have entered Hiroshima within 3 days (Hirose 1968; Watanabe 1974). Seventy-five persons who entered the city within 14 days were diagnosed with leukemia by 1972; 62 of those cases occurred in persons who entered during the first 3 days. The incidence of leukemia in this group was significantly higher than in the non-exposed group as a whole as defined in 1974, which included more than 250,000 persons who were located ≥ 5 km from the hypocenter ATB, and the distribution of acute and chronic forms of leukemia was similar to the distribution in persons who were located within 2 km of the hypocenter ATB (Watanabe 1974).

We do not have comparable information at Nagasaki, but about 4,500 of the 26,580 persons who were not in either city ATB entered the cities within 3 days after the bombings (Schmitz-Feuerhake and Carbonell 1983). Thus, it is possible that persons who received little or no direct exposure to the bombs received significantly higher doses from fallout or neutron-activation products, as described below.

Some distant survivors at Hiroshima and Nagasaki were exposed to fallout in the so-called “black rain” areas, and some survivors also could have been exposed to neutron-activated materials. Survivors in the Nishiyama district in Nagasaki reportedly received the highest doses from fallout of 0.2–0.4 Gy (Okajima 1986; RERF 2007). Although a recent analysis suggests that the highest doses from fallout in Hiroshima were about 0.01–0.03 Gy (RERF 2007), previous analyses suggested that some doses from fallout could have been an order of magnitude higher (e.g., Takeshita 1975). In addition, a map of the area in Hiroshima that received the heaviest rainfall following the bombings and the accompanying reconstructed doses based on areal surveys of radiation levels provided by Takeshita (1975) suggest that the area affected by fallout and the upper end of the range of doses of about 0.4 Gy could have been much greater than reported by RERF (2007). Yamada and Jones (1972) reached similar conclusions based on observations of symptoms of acute radiation syndrome (i.e., epilation) outside the “black rain” areas. The highest doses in Hiroshima estimated by Takeshita (1975) are comparable to the maximum doses in the Nishiyama area in Nagasaki estimated by Okajima (1986); see also Okajima (1975).

Gritzner and Woolson (1986) concluded that “while the kermas calculated ... here are relatively small, they are nonetheless non-negligible, especially as it concerns possible exposures to control survivors used in radiation risk analysis.” We would agree. We also think that uncertainties in doses from exposure to fallout at Hiroshima may be much larger than considered by RERF (2007), and we would add lightly exposed survivors to the group in which dose-responses are modeled.

Estimated doses from exposure to fallout noted above were based on interpretations of areal radiation survey data using various approaches to account for the redistribution of fallout by about 90 cm of precipitation that fell within 60–90 days after the bombings, including the impacts of a typhoon with heavy precipitation on September 17, 1945. The potential for exposure to neutron-activation products adds another layer of complexity to an assessment of uncertainties in doses to lightly exposed survivors or survivors assigned to the control group. Thus, a reexamination of existing information to address such questions seems warranted, if for no other reason than to understand the importance of exposures to residual radioactive material. Until such issues are resolved, we think that the magnitude and uncertainty in doses to “low-dose” and “unexposed” survivors and, thus, in the dose-response at low doses in the LSS cohort could be substantially greater than reported in recent studies, such as the BEIR VII report (NRC 2006) and the study by Preston et al. (2007). The need for further work to estimate doses from exposure to residual radioactive material was discussed at a recent workshop (Kerr et al. 2015).

Neglect of doses from exposure to fallout and neutron activation products results in a bias in estimated doses in the LSS cohort. Since those doses should be much less than the highest doses to survivors (organ doses >2 Gy), possible underestimates of dose should be more important in survivors with low doses and should be unimportant at the highest doses. Consequently, neglect of doses from fallout and neutron activation products should result in an estimate of the curvature in the dose-response assuming an LQ model that is less than the true curvature and, therefore, an underestimate of an LDEF.

5.2.1.3 Effects of uncertainty in RBE for neutrons

This section discusses analyses of data on cancer incidence and mortality in the LSS cohort that indicate that assumptions about an RBE for neutrons can impact the curvature in the dose-response for all solid cancers and, thus, the magnitude of an LDEF for photons and its uncertainty. Use of estimates of dose to the colon in analyses of the dose-response results in underestimates of the contribution from neutrons to doses to the least shielded tissues, such as the female breast, bladder, esophagus, and thyroid. Consequently, estimated risks in those tissues are the most sensitive to assumptions about a neutron RBE (Walsh et al. 2004b; Kellerer et al. 2006).

Most analyses of the dose-response for solid cancers in the LSS cohort assumed a neutron RBE of 10 (e.g., Preston et al. 2007). As shown in Table 5.5, when RBE was assumed to increase to 100 and the dose-response from photons and neutrons combined was analyzed [i.e., ERR was modeled as $(\alpha D + \beta D^2)$, where $D = D_\gamma + \text{RBE}_n D_n$], central estimates of LDEF for photons decreased with increasing RBE (Little and Muirhead 2000, 2004). This is an expected result when the dose-response from neutrons (high-LET radiation) presumably is linear and any curvature in the dose-response should be due to the curvature in

the dose-response for photons, which would increasingly be suppressed as the weighted neutron dose increases. As shown in Tables 5.6 and 5.7, however, when dose-responses from photons and neutrons were analyzed separately and a linear dose-response for neutrons was assumed [i.e., ERR was modeled as $(\alpha D_\gamma + \beta D_\gamma^2 + \delta \text{RBE}_n D_n)$], central estimates of LDEF for photons were higher and there was little dependence on the assumed neutron RBE in the range of 10–50 (Walsh et al. 2004a). These results also are expected when dose-responses from photons and neutrons should be independent. Results in Tables 5.6 and 5.7 were obtained using models that included a dependence of ERR on age at exposure or attained age, respectively. Upper limits of 95% CIs in Table 5.5 are about 3 or less and are largely independent of RBE, whereas upper limits in Tables 5.6 and 5.7 are higher (including ∞) and, in Table 5.6, increase with increasing RBE. Central estimates and upper limits of 95% CIs of LDEFs in these tables indicate that differences in specification of the dose-response model could affect estimates of DDREF and its uncertainty derived from analyses of data on solid cancers in the LSS cohort.

Table 5.5. LDEFs derived from analyses of curvature in modeled dose-response (ERRs) for incidence of all solid cancers in LSS cohort based on DS86 dosimetry and different assumptions about neutron RBE^a

Dose range (Gy)	Neutron RBE	LDEF ^b		
		Central estimate	Lower limit of 95% CI	Upper limit of 95% CI
0–4 ^c	10	1.10	0.82	1.70
	20	1.06	0.78	1.67
	50	0.96 ^d	0.65	1.62
	100	0.83	0.47	1.64
0–2 ^e	10	1.31	0.83	2.65
	20	1.26	0.78	2.63
	50	1.16 ^f	0.65	2.65
	100	1.08	0.47	2.91

^a Little and Muirhead (2000, 2004). Modeled ERRs were modified by time since exposure and attained age.

^b Calculated as $[1 + (\beta/\alpha)D]$ at 1 Gy, where β/α is the curvature parameter and D is dose to colon in Gy from photons and neutrons combined estimated as $D_\gamma + \text{RBE}_n D_n$. Reported central values are MLEs. Preferred estimates of LDEF calculated as $\alpha_1/\alpha_{1,Q}$ assuming neutron RBE of 20 are given in Table 5.1.

^c Shielded kerma free-in-air from photons and neutrons, with members of LSS cohort with shielded kerma >4 Gy omitted.

^d 50th percentile and 90% CI of LDEF we estimated from reported MLE and 95% CI is 1.0 (0.7, 1.5). MLE is at 40th percentile of assumed Weibull distribution. Estimate is included in summary Table 5.26 (Section 5.9).

^e Neutron-weighted doses to colon.

^f 50th percentile and 90% CI of LDEF we estimated from reported MLE and 95% CI is 1.4 (0.7, 2.4). MLE is at 35th percentile of assumed Weibull distribution. Estimate is included in summary Table 5.26 (Section 5.9).

Table 5.6. LDEFs derived from analyses of curvature in modeled dose-response (ERRs) with dependence on age at exposure for mortality from all solid cancers in LSS cohort based on DS86 dosimetry and different assumptions about dose specification and neutron RBE^a

Doses calculated ^b	Neutron RBE	LDEF ^c	
		Central estimate	Upper limit of 95% CI
Colon dose	10	1.55	4.4
Organ-averaged dose	20	1.52	7.2
	35	1.54	11
	50	1.5	32
Organ-specific doses for organs with >100 tumors	20	1.67	8.4
	35	1.58	12
	50	1.54	23

^a Walsh et al. (2004a).

^b Analysis restricted to neutron-weighted organ doses < 2 Gy.

^c Calculated as $(\alpha + \beta D \text{ at } 1 \text{ Gy})/\alpha$ for photon component of dose-response using sex-averaged model. ERR/Gy for photons was derived assuming LQ dose-response from photons and linear dose-response from neutrons. Reported central values are MLEs; lower limits of CIs not reported.

Table 5.7. LDEFs derived from analyses of curvature in modeled dose-response (ERRs) with dependence on attained age for mortality from all solid cancers in LSS cohort based on DS86 dosimetry and different assumptions about dose specification and neutron RBE^a

Dose calculated ^b	Neutron RBE	LDEF ^c	
		Central estimate	Upper limit of 95% CI
Colon dose	10	1.82	8.1
Organ-averaged dose	20	1.85	55
	35	1.83	∞
	50	1.85	∞
Organ-specific doses for organs with >100 tumors	20	1.96	∞
	35	1.96	∞
	50	1.95	∞

^a Walsh et al. (2004a).

^b Analysis restricted to neutron-weighted organ doses < 2 Gy.

^c Calculated as $(\alpha + \beta D \text{ at } 1 \text{ Gy})/\alpha$ for photon component of dose-response using sex-averaged model. ERR/Gy for photons was derived assuming LQ dose-response from photons and linear dose-response from neutrons. Reported central values are MLEs; lower limits of CIs not reported.

Estimates of LDEF and their uncertainties that we derived from an analysis by Sasaki et al. (2008) of the dose-response for mortality from all solid cancers in the LSS cohort based on DS02 dosimetry and neutron-weighted colon doses are given in Table 5.8. Sasaki et al. (2008) used data on induction of various solid tumors in animals to derive an RBE for neutrons that increases with decreasing dose, with a central estimate at low doses (RBE_M) of about 87. The derived relationship between neutron RBE and dose was used to generate neutron-weighted doses in an analysis of the dose-response in the LSS cohort based on an LQ model. In developing a dose-dependent RBE, estimated risks in animals exposed to orthovoltage x rays were converted to high-energy gamma-ray equivalents by dividing by 2.5 to account for an increased biological effectiveness of the x rays.

The central estimate of LDEF of 1.88 we derived from results of the analysis by Sasaki et al. (2008) by assuming a dose-dependent RBE for neutrons is similar to the central estimate based on a fixed RBE of 10 and central estimates reported by Little and Muirhead (2000, 2004), Preston et al. (2004), and Walsh et al. (2004a) given in Tables 5.4–5.7. However, the CIs in Table 5.8 are much narrower. No uncertainty was assigned to the dose-dependent RBE, even though the data in animals on which it was based indicated an uncertainty in RBE_M of about $\pm 50\%$. No uncertainty was assigned to estimates of neutron RBE assumed by the other investigators, either. Because there were other differences in the approaches taken in the various analyses, we could not determine why the uncertainties in estimates of LDEF based on the analysis by Sasaki et al. (2008) are so small. Nonetheless, we believe that the uncertainties in LDEFs in Table 5.8 are not credible, and these estimates are not considered in our analysis.

Table 5.8. LDEFs derived from analyses of curvature in modeled dose-response (ERRs) for mortality from all solid cancers in LSS cohort based on DS02 dosimetry and different assumptions about neutron RBE^a

Dose range (Gy) ^b	Neutron RBE	Method of calculation ^c	LDEF ^d		
			Central estimate	Lower limit of 95% CI	Upper limit of 95% CI
0–3	RBE = 10	$[1 + (\beta/\alpha)D]$ at 1 Gy	1.92	1.83	2.02
0–3	RBE increases with decreasing dose	$[1 + (\beta/\alpha)D]$ at 1 Gy	1.88	1.79	1.97

^a Sasaki et al. (2008). Modeled ERRs based on follow-up period of 1950–1997 are sex-averaged and modified by age at exposure and attained age.

^b Neutron-weighted doses to colon.

^c β/α is curvature parameter assuming LQ dose-response model.

^d 50th percentiles and 95% CIs we estimated from reported MLEs and 95% CIs of α [0.220 (0.127, 0.313) at neutron RBE of 10 and 0.179 (0.172, 0.187) at dose-dependent RBE] and β [0.202 (0.196, 0.209) and 0.157 (0.153, 0.162) at same neutron RBEs], except uncertainty in α at neutron RBE of 10 was assumed to be factor of 10 too high, and assumption that α and β are uncorrelated. MLEs of α and β are at 50th percentiles of assumed Weibull distributions.

The analysis by Kellerer et al. (2006), which suggested that RBEs for neutrons from the atomic bombings at a dose of 1 Gy could have exceeded 100 (Section 2.4.3), indicates that the issue of uncertainties in RBEs for neutrons at Hiroshima and Nagasaki is unresolved. Dose-responses for female breast and thyroid cancers, which contribute significantly to the linearity in dose-responses for all solid cancers, should show the largest effect (Walsh et al. 2004a; Kellerer et al. 2006). Such effects could introduce additional errors in estimates of LDEF for photons produced by the atomic bombs.

As noted in Section 2.4.3, estimates of RBE_M for induction of leukemias in laboratory animals by fission neutrons are more than an order of magnitude lower than estimates of RBE_M for induction of solid cancers (see also Sasaki et al. 2008). On this basis, it could be argued that the curvature in the dose-response for leukemia in the LSS cohort, which should be less affected by contributions to doses from neutrons, should provide a better representation of the expected curvature in the dose-response for solid cancers from exposure to photons and, thus, a better estimate of an LDEF for photons.⁵⁴

5.2.1.4 Effects of dose range analyzed and formulation of dose-response model

The analysis by the BEIR VII committee (NRC 2006) of data in the LSS cohort on incidence of solid cancers for the purpose of estimating a DDREF (an LDEF) was based on estimates of ERR and their uncertainty as a function of dose and the fitted curves shown in Figure 5.7. An LDEF was derived by analyzing the curvature in this dose-response at doses of 0–1.5 Sv (neutron-weighted doses of 0–1.5 Gy; Table 5.2). A central estimate of LDEF was calculated as $\alpha_L/\alpha_{LQ} = 0.56/0.43 = 1.3$, where α_L is the risk coefficient in the best fit to the data assuming a linear dose-response and α_{LQ} is the coefficient of the linear term assuming an LQ dose-response; the latter fit is the dotted curve in Figure 5.7 with curvature parameter (β/α) constrained to 0.3 Sv^{-1} . As indicated in the Figure 5.7, an LQ model with curvature parameter constrained to 0.7 Sv^{-1} , which gives a higher LDEF calculated as α_L/α_{LQ} of 1.8, also is consistent with the data. When calculated as $[1 + (\beta/\alpha)]$, similar estimates of LDEF of 1.3 and 1.7, respectively, are obtained.

Selection of a different dose range for analysis might have resulted in a different estimate of LDEF. For example, an examination of Figure 5.7 indicates that fits to the data at doses of 0–1.2 Sv would be compatible with a larger slope with a greater uncertainty when a linear dose-response is assumed and a

⁵⁴ Sasaki et al. (2008) also performed an analysis of data on mortality from leukemia in the LSS cohort. However, lymphomas and multiple myeloma were included inappropriately in the analysis, and the dose-dependent RBE for neutrons that was developed for solid cancers also was used in the analysis of the dose-response for leukemia based on the conclusion that the dose-dependent RBE indicated by data on induction of myeloid leukemia in mice should not apply to the atomic-bomb survivors. On the basis of these considerations, we have not included the results from Sasaki et al. (2008) in our compilation of DDREFs for leukemia in Section 5.8.

greater degree of curvature when an LQ dose-response is assumed, resulting in a higher LDEF. A purely quadratic dose-response model also could be compatible with those data. Indeed, we concluded that the relationship $ERR = 0.75D^2$ provides a reasonable fit at doses of 0–1.2 Sv.⁵⁵

Uncertainties in estimated ERRs are not important in understanding discussions in text.

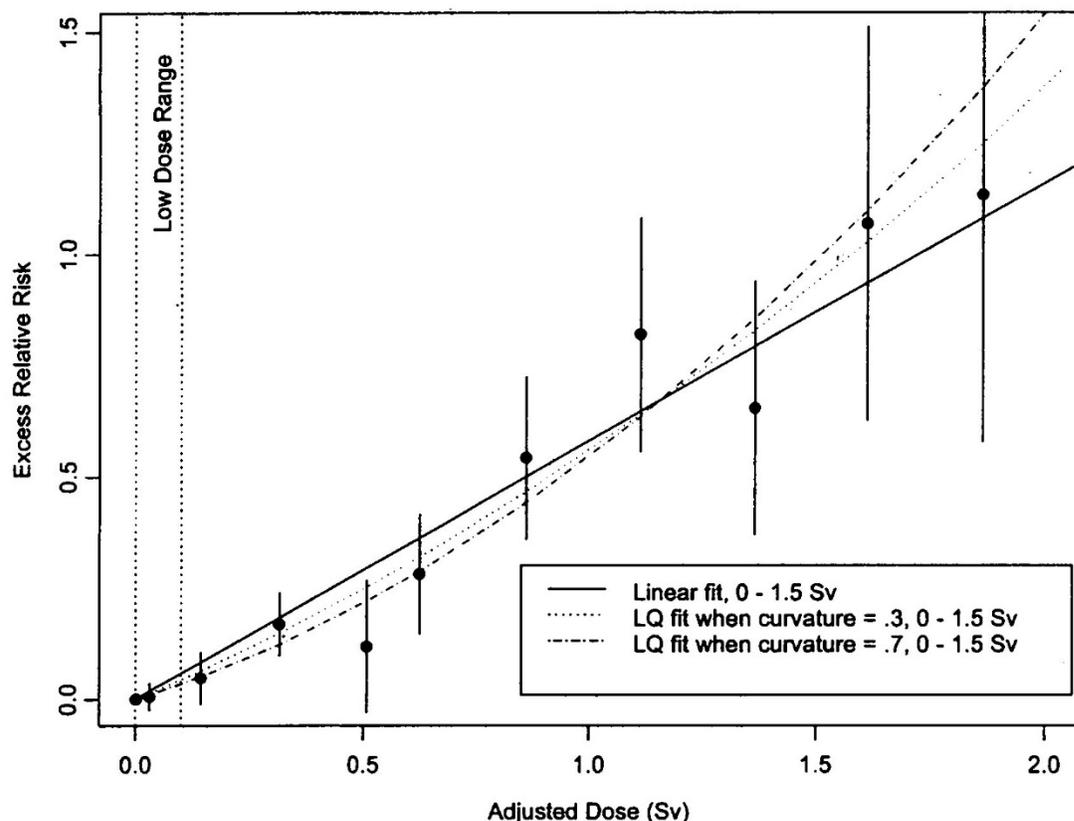


Figure 5.7. Illustration of approach by BEIR VII committee (NRC 2006) to estimating DDREF (LDEF) based on data for solid cancer incidence in LSS cohort. Data points are estimated ERRs (± 2 SE), averaged over sex, in individuals of age 60 exposed at age 30 in 11 dose categories based on DS02 dosimetry. Adjusted dose (Sv) is neutron-weighted dose in Gy calculated assuming neutron RBE of 10. Solid line is linear fit at doses of 0–1.5 Sv, with slope $\alpha_L = 0.56$, and other two curves are fits assuming LQ model over the same dose range with curvature parameter (β/α) constrained to 0.3 Sv^{-1} ($\alpha_{LQ} = 0.43$) or 0.7 Sv^{-1} ($\alpha_{LQ} = 0.32$). Resulting DDREFs (LDEFs) calculated as α_L/α_{LQ} are $0.56/0.43 = 1.3$ and $0.56/0.32 = 1.8$. When calculated as $[1 + (\beta/\alpha)]$, LDEFs are 1.3 and 1.7, respectively.

⁵⁵ The BEIR VII committee acknowledged the possibility of a quadratic dose-response for low-LET radiation at low doses based on radiobiological considerations (NRC 2006). Implications of differences between purely quadratic and linear or LQ dose-responses also were discussed by Rossi and Kellerer (1972) and Land (1980). A quadratic model implies that the response approaches zero at very low doses and dose rates; i.e., $DDREF \rightarrow \infty$. A dose-response with a large quadratic component could be consistent with the effects of dose rate suggested by data on chromosome aberrations obtained using mFISH and dose-responses in other biological systems that are linear when exposures are acute but show greatly reduced responses at lower dose rates. Thus, we believe that uncertainty in the form of the dose-response is a potentially important but poorly constrained contribution to uncertainty in estimated risks at low doses in the LSS cohort.

Because the BEIR VII committee's preferred risk coefficients for specific solid cancers were derived from linear fits to dose-responses for cancer incidence in the LSS cohort at neutron-weighted organ doses corresponding to a shielded kerma of 0–4 Gy (NRC 2006), not at organ doses of 0–1.5 Gy, a DDREF to be applied to those risk coefficients ideally should be based on an analysis of dose-responses over the higher dose range. Inclusion of data at the higher doses in the LSS cohort is problematic, however, because those data include the potential effects of cell sterilization, as illustrated in Figure 5.8 and discussed below, that the simple linear and LQ models used by the committee to estimate a DDREF do not accommodate. Inclusion of a term to represent cell sterilization in the dose-response model can have a significant effect on an analysis of curvature at low-to-intermediate doses where that term does not contribute significantly to modeled risks (Leenhouts and Chadwick 2011).

By not considering the impact of cell sterilization at high doses on the dose-response over the entire range of doses in the LSS cohort, and by not considering restricted dose ranges other than 0–1.5 Gy, could the BEIR VII committee have underestimated a DDREF? Could the use of data over the lower dose range conceal a higher degree of curvature in the dose-response that was offset to some extent by the effects of cell sterilization? The committee noted that “[i]t could be that a linear relationship is the result of some cancellation of inward curvature and high-dose leveling off” but then stated that “[i]t is not obvious that the linear relationship resulting from such cancellation overestimates low-dose risk” (NRC 2006).⁵⁶

As noted above, the BEIR VII committee applied its DDREF to cancer-specific risk coefficients that were derived by assuming linear dose-responses in the LSS cohort at neutron-weighted organ doses corresponding to a shielded kerma of 0–4 Gy (NRC 2006). The slopes of those dose-responses are less than the slopes of fitted linear dose-responses over the more restricted dose range of 0–1.5 Gy that was assumed in deriving a DDREF, due to the effect of a leveling of dose-responses at the higher doses and the greater degree of curvature that is consistent with those dose-responses when the effect of that leveling is taken into account. On the basis of these considerations, it seems to us that the committee's DDREF is likely to be an underestimate, which leads to overestimates of risks at low doses.

Figure 5.8 shows an earlier model fit to a dose-response for solid cancer incidence in the LSS cohort given by $ERR = (0.52D + 0.94D^2) \exp(-0.84D)$ (ICRP 2005). However, the more complex model did not provide a better fit to the dose-response over the full dose range (0–5 Gy) than a linear model when the fits were assessed on a statistical basis, even though the more complex model represented the overall pattern of curvature quite well. The reason for the similarity in the quality of the fits is that uncertainties in parameters in the more complex model were greater to reflect that wide ranges of values were consistent with the data when the number of parameters was increased (ICRP 2005; Little et al. 2008).

⁵⁶ Pierce and Preston (2000) also argued that even though it was potentially artifactual, the resulting “linear risk estimate” obtained by restricting the dose range could still apply to humans at low doses in other exposure settings.

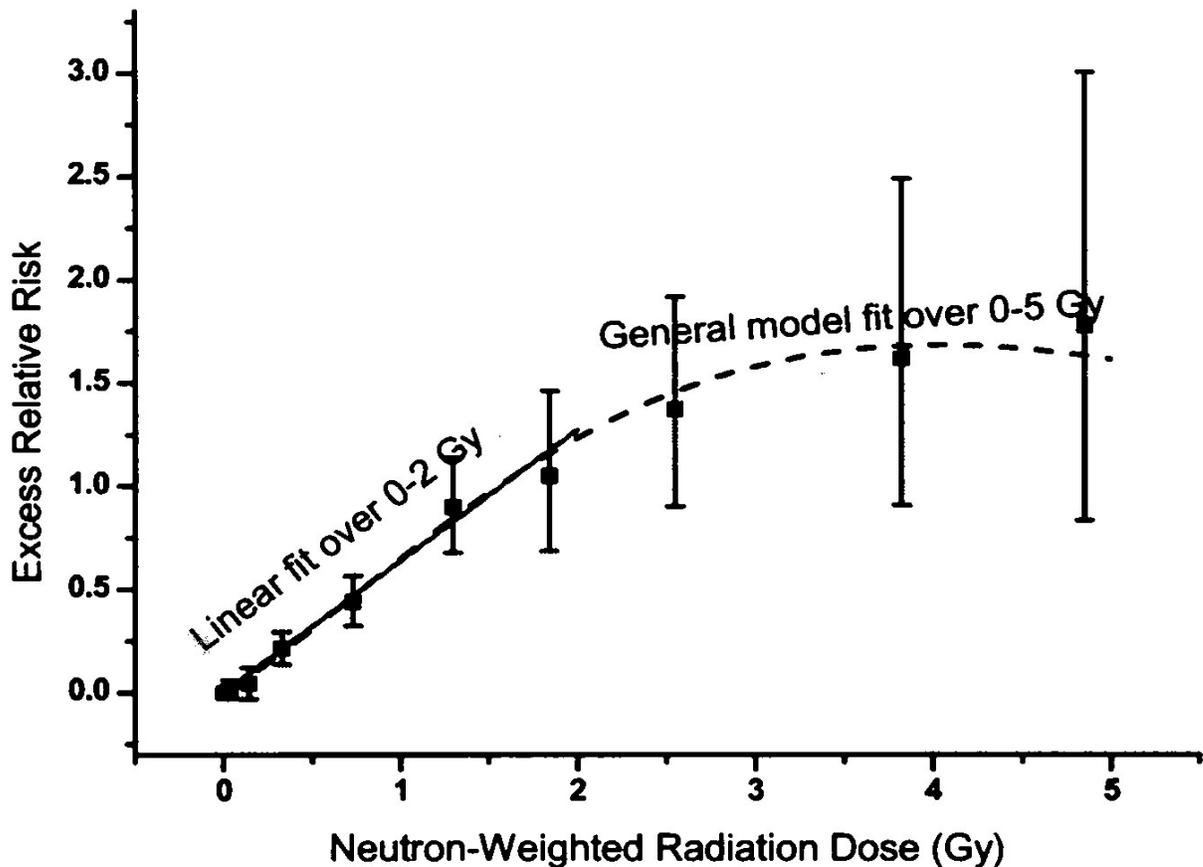


Figure 5.8. Dose-response (ERRs) and 90% CIs for solid cancer incidence in LSS cohort based on data for period 1958–1987, neutron-weighted colon doses of 0–5 Gy, and DS86 dosimetry (ICRP 2005). Dashed line is fit assuming LQ model modified by exponential cell-sterilization term [Section 2.4.1.1, equation (2)], and solid line is fit at doses of 0–2 Gy assuming linear model with no cell-sterilization term.

However, this observation does not invalidate the more complex LQE dose-response model. Rather, it means that the LSS data lacked the power to test the full range of plausible models and, thus, to estimate a DDREF independently of other radiobiological and epidemiological information. As discussed in Section 5.2.1, Little et al. (2008) showed that an LQE model provided the best fit to the dose-response for mortality from all solid cancers in the LSS cohort based on data through the year 2000; an LQE model also provided the best fit to the data on mortality from leukemias. As discussed in Section 5.8.2, a quadratic-exponential model also is consistent with the dose-response for mortality from leukemia.

An effect of the dose range over which the curvature in dose-responses in the LSS cohort was analyzed assuming an LQ model also is seen in the recent analysis of solid cancer mortality by Ozasa et al. (2012). As shown in Figure 5.9, the curvature in a fitted LQ dose-response at neutron-weighted colon

doses of 0–2 Gy—an estimated β/α of 0.81 [95% CI: (0.08, 8.6)] (Table 5.4)—is more pronounced than the curvature in a fitted LQ dose-response over the full dose range corresponding to a shielded kerma of 0–4 Gy—an estimated β/α of 0.11 (Ozasa et al. 2012), with a 95% CI of (–0.08, 0.58) estimated by D. Preston (personal communication, November 6, 2016). Over the full dose range, the LQ fit is nearly indistinguishable from the best linear fit. However, the best linear fit was much less dependent on the dose range; the estimated ERR/Gy was 0.42 over the full dose range and 0.44 over the more restricted dose range (Ozasa et al. 2012). Similar to the analysis of solid cancer incidence in the LSS cohort by the BEIR VII committee (NRC 2006), Ozasa et al. (2012) preferred an estimate of ERR/Gy from a linear fit to the dose-response for solid cancer mortality over the full dose range but preferred an estimate of the curvature in the dose-response based on an LQ fit at doses of 0–2 Gy. The effect on β/α of the dose range selected calls into question whether an LDEF based on an LQ fit to a dose-response over a restricted dose range should be used to adjust estimated risks based on a linear fit to a dose-response over a wider dose range.

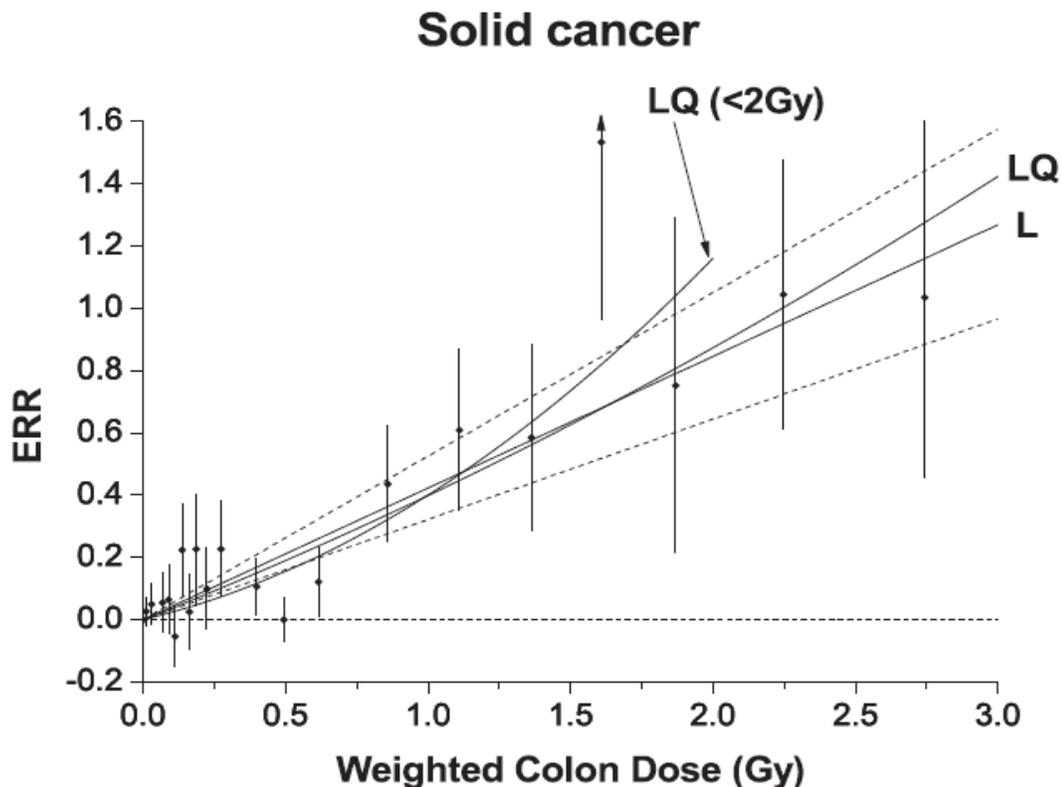


Figure 5.9. Dose-response (ERRs) and 95% CIs for mortality from all solid cancers in LSS cohort based on data for period 1950–2003 and DS02 dosimetry with linear-quadratic (LQ) and linear (L) fits over full range of neutron-weighted colon doses corresponding to shielded kerma <4 Gy and LQ fit at colon doses of 0–2 Gy (Ozasa et al. 2012).

Ozasa et al. (2012) also noted that the curvature in the dose-response for solid cancer mortality in the LSS cohort at colon doses of 0–2 Gy assuming an LQ model tended to increase as the period of follow-up of the cohort increased. Estimates of β/α were 0.20 [95% CI: (–0.23, 3.2)] for follow-up through 1985 and 0.40 [95% CI: (–0.09, 3.2)] for follow-up through 1995, compared with the statistically significant estimate of 0.81 [95% CI: (0.08, 8.6)] in Table 5.4 for follow-up through 2003. This trend presumably is a consequence of the greater statistical precision in estimated risks with increasing period of follow-up. However, the uncertainty in the curvature, especially the upper limit of a 95% CI, was greatest in the most recent analysis.

If the apparent near-linearity in the dose-response for incidence of all solid cancers in the LSS cohort is significantly influenced by dose-responses for female breast and thyroid cancers, as suggested by Little and Muirhead (2000), if the RBE for neutrons is much higher than usually assumed, if uncertainties in estimated doses to the LSS cohort are greater than suggested by Pierce et al. (2008) (Section 5.2.1.2), and if selection of the dose range for analysis can significantly influence modeled dose-responses at low doses, the curvature in the dose-response for solid cancer incidence or mortality and, thus, an LDEF may be substantially greater than estimated using current models. Such effects could result in substantial errors in estimates of LDEF for the photon component of radiations produced by the atomic bombs.

5.2.1.5 Effects of uncertainties in LSS data and applicability of model parameters

Uncertainties in ERRs estimated by the BEIR VII committee (NRC 2006) are larger than shown in Figure 5.7, because those CIs do not account for the effects of (1) uncertainties in data in the LSS cohort, such as those associated with diagnostic misclassification, (2) the choice of parameters in a dose-response model, such as a possible relationship between the effects of age at exposure and birth cohort (NRC 2006; Preston et al. 2007), (3) using colon doses rather than doses to individual organs in analyzing the data for all solid cancers (Section 5.2.1.3), and (4) combining data for all solid cancers (Section 5.2.1.6). Schafer and Gilbert (2006) noted that the effect of multiple uncertainties is difficult to generalize when multiplicative Berkson-type dose uncertainties can exaggerate an upward curvature in a dose-response, whereas multiplicative classical uncertainties can introduce a downward curvature and mask the presence of an underlying true upward curvature. The overall effect depends on the degree of skewness of unknown true doses about assigned central estimates of doses in the LSS cohort in relation to the curvature in the dose-response introduced by other factors.

Many assumptions have been made in analyzing data in the LSS cohort to account for the dependence of risks on such factors as age at exposure, attained age (or time since exposure), sex, and minimum latency of radiation-induced cancers. Those assumptions may be appropriate, but as

acknowledged by the BEIR VII committee: “Models for the dependence of risk on variables such as age at exposure, attained age, and time since exposure are often empirical and are justified more by epidemiologic and statistical principles than by radiobiologic theory” (NRC 2006). The approach to parameterization of dose-response models could introduce errors not accounted for and an artificial degree of linearity in modeled dose-responses. The possible variability in modeled dose-responses is indicated, for example, by the ranges of alternative parameter values and model specifications considered by the BEIR VII committee (NRC 2006) and UNSCEAR (2008).

Models used by the BEIR VII committee (NRC 2006), Preston et al. (2007), and Land et al. (2003a) to estimate risks of solid cancers in the LSS cohort include exponential modifiers to represent the effects of age at exposure, attained age, and sex. However, UNSCEAR (2008) used power functions to represent those effect modifiers. In addition, many cancer-specific models developed by UNSCEAR (2008) include only a single effect modifier or, in some cases (e.g., ERRs for bladder and liver cancer), no effect modifiers. Some of the UNSCEAR models also used time since exposure (attained age minus age at exposure), either in place of age at exposure or as a single effect modifier.

UNSCEAR (2008) considered the approach taken by the BEIR VII committee to account for the effects of age at exposure to be “unusual” and pointed out that “[t]here is no evidence for changes in the modifying effect of age at exposure on ERR or EAR at age 30.” Unless UNSCEAR erred in its conclusion, potentially significant uncertainties may have been introduced into the BEIR VII committee’s analysis of DDREF by its assumptions about model structure and parameter selection.

Preston et al. (2007) reported a wide variation in the shapes of non-parametric dose-responses and effect modifications by age at exposure and attained age for different cancer sites. They also reported large differences in the effects of birth cohort on estimated cancer risks at different sites. Statistical tests for heterogeneity revealed significant differences between models for seven individual sites, one grouping of sites, and all solid cancers combined in regard to the magnitude of ERRs and their dependence on age at exposure, attained age, and sex. Differences in site-specific dose-responses and birth cohort effects reported by Preston et al. (2007) and confirmed by independent modeling apparently dissuaded UNSCEAR (2008) from using a model for all solid cancers in its risk projections.

Pierce and Preston (2000) noted that differences among groups of atomic-bomb survivors and differences in intervening events over the years between exposure and follow-up, in addition to biological or dosimetric factors, have the potential to “linearize” the dose-response in that population. For example, the effects of age at exposure are complicated by differences in factors that affect subgroups born in different years (birth cohort effects) (NRC 2006). Baseline rates for many specific cancers in Japan show strong secular trends, which probably resulted in part from changes in lifestyle that accompanied the partial westernization of the population. If the assumed dose-response model is not correct, estimated

effects of age at exposure may be influenced by secular trends in baseline cancer rates in Japan and may not be directly applicable to populations other than the LSS cohort.

Preston et al. (2007) reported significant increases over time in age-specific baseline rates for all solid cancers in the LSS cohort. Baseline rates for specific cancers showed much greater variation, with striking declines for cervical and stomach cancer and increases at most other sites, especially colon, lung, liver, female breast, prostate, and bladder. These temporal patterns led Preston et al. (2007) to conduct formal analyses to assess the impacts of birth cohort effects on estimated cancer risks. Even though baseline rates changed significantly over time, there were no discernable effects of age at exposure on the EAR for stomach cancer or on ERRs for colon, liver, and breast cancer, which suggested that the risk of stomach cancer due to radiation is additive to the baseline risk (i.e., independent of the baseline) and that risks of the other three cancer types are multiples of the baseline risks (i.e., proportional to the baseline). Baseline risks used by the BEIR VII committee (NRC 2006) and UNSCEAR (2008) also were based on birth cohort data, but analyses of birth cohort effects on ERRs or EARs were not conducted.

Some aspects of the observed effects of age at exposure in the LSS data, such as the higher ERRs and EARs for all solid cancers in the oldest age groups described below, were not incorporated in risk models developed by the BEIR VII committee (NRC 2006). Estimated risks of stomach and liver cancers showed the largest increases in the oldest age groups; those cancer types were far more prevalent in Japan than in the U.S. The dependence on age at exposure in the committee's assumed dose-response models, which does not include an increase in risks in the oldest age groups, was based on the conclusion that this effect was unlikely to generalize to a modern U.S. population, even though the committee admitted that the reasons for the observed dependencies on age at exposure were not understood (NRC 2006).

As shown in Figure 5.10, an analysis of dose-responses for incidence of all solid cancers combined in the LSS cohort by Preston et al. (2007) indicated that ERR and EAR increase with increasing age at exposure at ages >50, in contrast to the decrease in risk at older ages commonly assumed in other analyses, e.g., by the BEIR VII committee (NRC 2006). An alternative parameterization of the effects of age at exposure to represent the dashed curves in Figure 5.10 was not incorporated in risk models developed by Preston et al. (2007) but was suggested as a topic for further investigation. An analysis of the same data by Little (2009) showed that the alternative parameterization of the effect of age at exposure on ERRs was statistically significant. However, Walsh (2009) downplayed the significance of those findings based on the large uncertainty in the estimated risk at age at exposure 65 and the lack of a similar dose-response in the data for mortality from all solid cancers.

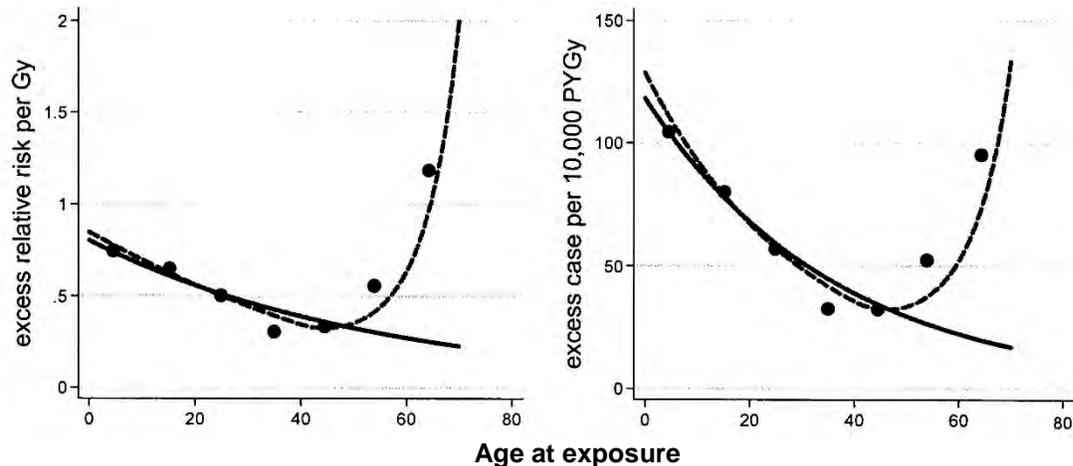


Figure 5.10. Alternative representations of effects of age at exposure on excess risks (ERRs and EARs) of incidence of all solid cancers in LSS cohort based on DS02 dosimetry (Preston et al. 2007). Points are non-parametric estimates of sex-averaged excess risks at age 70 at neutron-weighted colon dose of 1 Gy. Solid lines are simple log-linear trends commonly used to represent effects of age at exposure. Dashed lines are fitted log-quadratic splines with single knot at age 40 that describe effects of age at exposure significantly better.

Similarly, the highest risks of mortality from all solid cancers or leukemia in the 15-country study of radiation workers were seen in workers of attained age ≥ 70 , and analyses of the effects of age at exposure indicated that doses received later in life might pose a higher risk than doses received earlier (Cardis et al. 2007). Although an analysis of data at all ages did not show a statistically significant increase in leukemia mortality (Section 5.2.2.2), a statistically significant increase in risk was observed in workers exposed at ages >50 (Cardis et al. 2007). Although Cardis et al. (2007) concluded that their findings were not incompatible with the effects of age at exposure and time since exposure in the BEIR VII committee’s risk model for leukemia (NRC 2006), they also noted that “[age-related/temporal] patterns of cancer risk after low-dose protracted exposures may not necessarily be the same as those observed in the A-bomb study.”

The observations by the BEIR VII committee (NRC 2006), Cardis et al. (2007), and Preston et al. (2007) and the concerns about the dependence of risks on age at exposure assumed by the BEIR VII committee (UNSCEAR 2008) indicate that the uncertainty in modeled dose-responses introduced by current approaches to parameterizing the effects of age at exposure deserves further examination. This uncertainty could result in a greater uncertainty in estimates of LDEF based on data in the LSS cohort.

5.2.1.6 Effects of combining data for individual solid cancers

Effects of age at exposure on modeled dose-responses for all solid cancers combined in the LSS cohort are determined primarily by data for a few cancers (e.g., stomach, colon, liver, lung, female breast). This observation leads to a concern that combining data for all solid cancers, as in analyses to estimate an LDEF discussed previously, may mask significant differences in dose-responses and DDREFs for different cancer types similar to observed differences in studies in the same strain of laboratory animal (Edwards 1992; Fry 1992; UNSCEAR 1993, Appendix C). In addition, an analysis of dose-responses for all solid cancers based on estimated doses to the colon may not account for significant variations in neutron doses to specific organs and the neutron RBE (Kellerer et al. 2006). Thus, combining data for all solid cancers could introduce artifacts into a modeled dose-response and generate an overly simplified dose-response relationship that may not be justified (e.g., Leenhouts and Chadwick 2011).

One justification for combining data for specific solid cancers in the LSS cohort is that baseline rates for all solid cancers in U.S. and Japanese populations are similar. However, this similarity is due in part to the much higher baseline rates of certain cancer types in the U.S. population (e.g., female breast, colon, lung, and prostate) that are compensated by the much higher baseline rates of other cancer types in the Japanese population (e.g., stomach and liver) (NRC 2006). When specific cancer types were considered individually, dose-responses for incidence of cancers of the lung, female breast, bladder, and liver in the LSS cohort could not be fit satisfactorily using a common set of model parameters estimated from an analysis of the dose-response for all solid cancers combined (NRC 2006).

Given the significant differences in dose-response models that best fit the data for specific solid cancers in the LSS cohort, UNSCEAR (2008) did not develop a model for incidence of all solid cancers combined for use in risk assessment. That decision is supported by differences in dose-response models for specific solid cancers and a grouping of other solid cancers developed by Preston et al. (2007), as shown in Figure 5.11, and by tests for heterogeneity between dose-response models for combined and site-specific solid cancers. Preston et al. (2007) observed statistically significant differences in ERRs for stomach, rectum, gallbladder, lung, non-melanoma skin, female breast and uterine cancers, and a grouping of other cancers not included in site-specific analyses compared with the ERR for all solid cancers. There also were significant differences in effect modifiers of ERRs for colon, lung, non-melanoma skin, renal cell, and brain and central nervous system cancers and effect modifiers of EARs for cancers of the esophagus, colon, lung, female breast, bladder, brain and central nervous system, and thyroid.

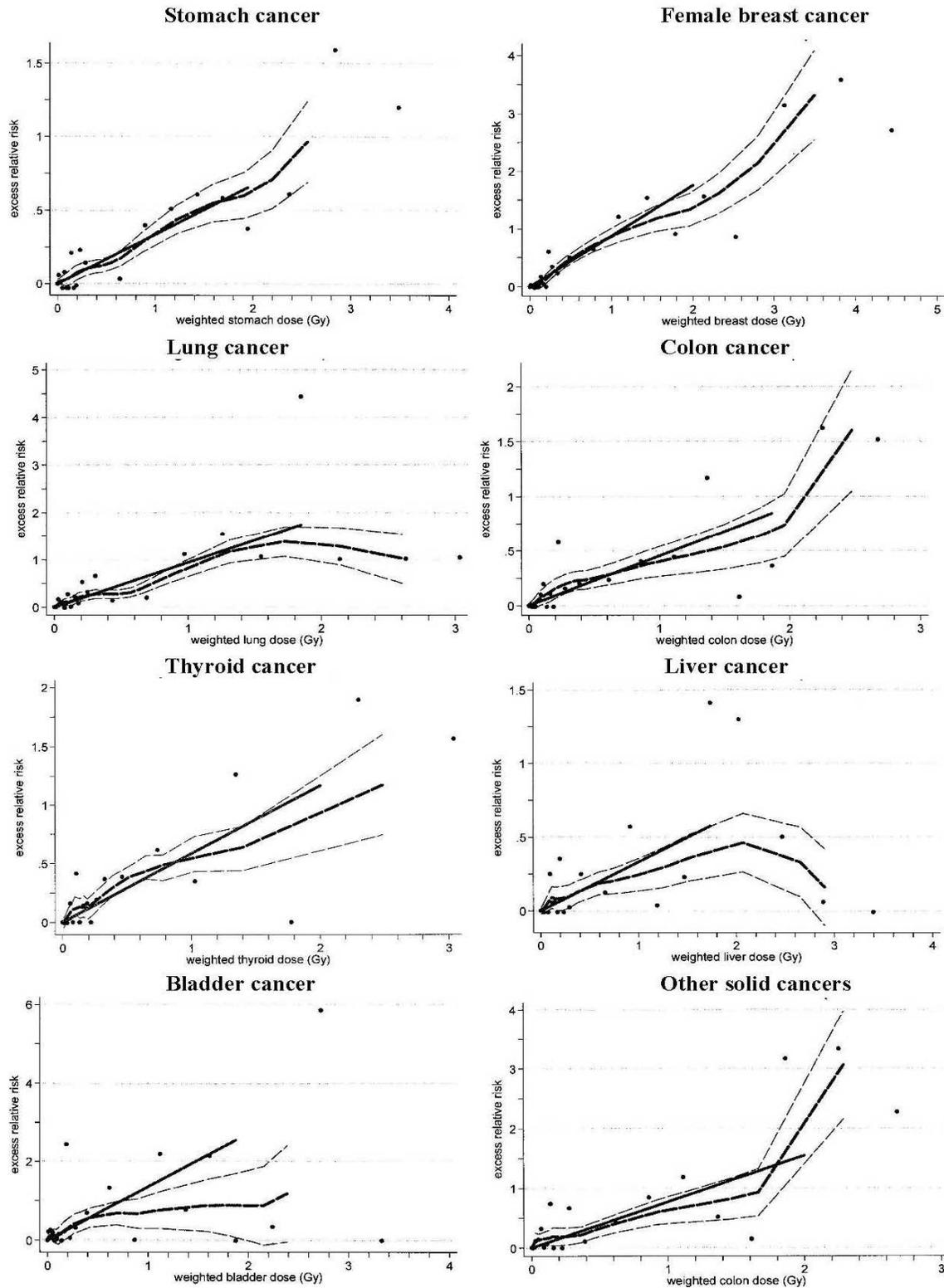


Figure 5.11. Dose-responses (ERRs) for incidence of specific solid cancers in LSS cohort at attained age 70 after exposure at age 30 based on DS02 dosimetry (Preston et al. 2007). Data points are estimates of ERR in different dose categories. Thick solid lines are fitted linear dose-responses, and dashed lines are non-parametric representations of category-specific estimates ± 1 SE.

5.2.1.7 Conclusions

Although data in the LSS cohort are critical to assessing cancer risks due to exposure to ionizing radiation, we question whether valid extrapolations of risks to low doses or low dose rates can be made without considering other information. We showed that an LDEF derived from an analysis of the curvature in acute dose-responses in the LSS cohort may not be predictive of risks at low dose rates. Based on our review of data in the LSS cohort, we also question whether extrapolations of risks based mainly on observed responses at organ doses of 0.5 Gy or greater are adequately representative of risks at low doses and, thus, can provide estimates of LDEF with an acceptably low bias.

A comparison of estimated risks at low doses in Figures 5.4 and 5.5 demonstrates the sensitivity of such estimates to the selection of a dose range of interest at low doses (ICRP 2005). Those data indicate that extrapolation of an acute dose-response in the LSS cohort to doses below 30 mGy, where a DDREF is applied in IREP, could be poorly constrained. Given that modeled dose-responses in the LSS cohort are determined mainly by data at higher doses, we think that estimated risks in lightly exposed survivors and the control groups may be substantially more uncertain than currently reported. We also showed that underestimation of the neutron RBE, the assumed formulation of a dose-response model, uncertainties in data in the LSS cohort including birth cohort effects, the choice of model parameters (e.g., modifications of modeled dose-responses to account for effects of age at exposure and attained age), and an aggregation of data for specific solid cancers all could have contributed to uncertainty in the response at low doses in ways that affected estimates of LDEF based on current data in the LSS cohort. Dose-response models for incidence of solid cancers developed by the BEIR VII committee (NRC 2006), Pierce and Preston (2000), Little and Muirhead (2000), and Preston et al. (2007) were designed to estimate risks from acute exposures of the LSS cohort based on the expectation that the dose-response was approximately linear. However, a variety of dose-response models are consistent with the LSS data, and UNSCEAR (2008) elected to use several non-linear models.

Because modeled dose-responses at low doses in the LSS cohort are statistically unstable, we think that verification of responses at low doses or low dose rates from other studies, such as epidemiological studies of occupational exposures or exposures of medical patients, is needed. This conclusion is supported by observed dose-responses in studies of cancer in animals (Section 4.3) and in epidemiological studies of breast cancer in females discussed in Section 5.3.4, which also indicate that DDREFs estimated from data for chronic or highly fractionated exposures could be larger than DDREFs estimated from data in the LSS cohort. This is particularly the case when such data are considered along with new information from studies in radiation cytogenetics (Section 2.3) and other areas of radiobiology (Sections 3, 4.2, and 4.3) that appear to limit the general application of an LQ dose-response model.

Heidenreich et al. (2002, 2004) argued that a mechanistic understanding of radiation carcinogenesis for specific cancer types is necessary in extrapolating responses to lower doses and over time and that it is not possible to differentiate among possible mechanisms of carcinogenesis using data in the LSS cohort, despite its size. Heidenreich et al. (2002) asserted that a number of biologically-based models describe cancer incidence in the LSS cohort equally well but can predict different temporal patterns of risk after irradiation and, thus, that temporal patterns of risk cannot be characterized reasonably well using current empirical approaches to dose-response modeling. Those conclusions were partially refuted by Pierce (2003), who also acknowledged that there are unresolved challenges in characterizing the effects of prolonged exposures using empirical models. This issue also is discussed by Thomas (1990).

Our concern is that the uncertainty in DDREF could be much larger than indicated by analyses of acute dose-responses in the LSS cohort using simple empirical models. As discussed in Section 5.3, we also think that similar levels of uncertainty can be introduced into risk estimates based on other epidemiological data when effects of an RBE for lower-energy photons (e.g., orthovoltage x rays) or dose fractionation or protraction are not considered. These concerns are heightened by data discussed in Section 5.2.2.4 that appear to show a pattern of higher ERRs in persons who received chronic exposures at low doses from occupational or environmental sources compared with ERRs in the LSS cohort.

Although LDEFs derived from analyses of the curvature in dose-responses for solid cancers in the LSS cohort need to be considered in developing a probability distribution of DDREF for those cancers, the foregoing considerations led us to conclude that those LDEFs should not be used exclusively or necessarily given the highest weight, as is often the case.⁵⁷ For example, we think that comparisons of estimated risks in cohorts that received chronic or protracted exposures with risks from acute exposure in the LSS cohort, which give estimates of DREF, are important and should be taken into account. This type of analysis is considered in the following section and in Sections 5.3–5.8.

5.2.2 Epidemiological Studies of Chronic or Protracted Exposures

Information bearing on a DDREF can be obtained from analyses of dose-responses for solid cancer mortality or incidence in epidemiological studies of cohorts of nuclear workers or persons exposed to

⁵⁷ UNSCEAR (2008) did not perform an independent analysis of DDREF. The LQ and LQE dose-response models for solid cancer mortality developed in that report incorporate an extrapolation to low doses implicitly, so a DDREF is not needed. However, UNSCEAR noted that a “DDREF of about 2, as recommended by others [ICRP 1991], was consistent with the dose protraction effects predicted by these models and with a large body of epidemiological and experimental data.” A DDREF also was not applied in modeling incidence of solid cancers on the basis of evidence of linearity in the dose-response for all solid cancers in the LSS cohort (e.g., Preston et al. 2007) and a conclusion that “as a first approximation, linear extrapolation of the estimates of risk following an acute dose of 1 Sv can be used for estimating solid cancer risks at lower doses” (UNSCEAR 2008).

radiation from environmental sources [other than exposure to high levels of natural background (Hendry et al. 2009)]. Estimated risks to members of those cohorts who received chronic, protracted, or highly fractionated exposures can be compared with estimated risks from acute exposure in the LSS cohort, assuming linear dose-responses in both cohorts, to estimate a DREF; a DREF is estimated as the ratio of an age- and sex-matched risk (ERR or EAR) in the LSS cohort to the risk in a cohort of workers or members of the public. Except when the form of a probability distribution of an uncertain estimate of risk was reported, we estimated DREFs by assuming that ERRs or EARs and their uncertainties are described by Weibull distributions with modes at their central values (either MLEs or 50th percentiles).

A DDREF also could be estimated if the dose-response in an occupationally or environmentally exposed cohort is non-linear. In such cases, a DDREF at a dose of 1 Gy based on an analysis of the curvature in the dose-response would be estimated.

5.2.2.1 Studies of Mayak workers

In a study of mortality from all solid cancers in Russian nuclear workers at the Mayak complex (Shilnikova et al. 2003), the dose-response showed a significant concave downward curvature at doses to the whole body <3 Gy similar to the shape of an acute dose-response in the LSS cohort at much lower colon doses when distal survivors were excluded (Section 5.2.1.1, Figure 5.2). Estimates of ERR/Gy at doses <3 Gy were about twice the estimates obtained by assuming a linear dose-response over the entire dose range of 0–>10 Gy. This result suggests a DDREF of about 0.5, because it is based on a comparison of responses at high doses with responses at lower doses, even though exposures were protracted and highly fractionated. However, uncertainties in estimates of ERR as a function of dose in Mayak workers were large, and the influence of internal exposures to plutonium could not be excluded. Additional limitations to the study by Shilnikova et al. (2003) include incomplete information on smoking histories of the workers and a lack of information on exposures to hazardous chemicals.

Shilnikova et al. (2003) noted that external doses to Mayak workers probably were overestimated during the period when doses were the highest and concluded that those errors may partially explain the observed downward curvature in the dose-response. Now that improved estimates of external dose and characterization of internal exposures are available, studies of Mayak workers could include more subjects and yield more accurate estimates of risk. Average whole-body doses from external exposure to photons during the period of greatest exposure now are estimated to be 0.30–0.44 Gy in males and 0.23–0.32 Gy in females (Vasilenko et al. 2007). These estimates are more than an order of magnitude higher than reported external doses in an international pooled study of nuclear workers in other countries (Vrijheid et al. 2007).

5.2.2.2 Studies of cohorts of western nuclear workers

There have been few attempts to estimate DREFs by comparing cancer risks in chronically exposed radiation workers with risks in the LSS cohort. This section presents estimates of ERRs obtained from epidemiological studies of workers and ERRs in the LSS cohort that could be suitable for use in making such comparisons. With the exception of a reanalysis of data in Canadian nuclear workers by Zablotska et al. (2014), which updated a previous study (Zablotska et al. 2004), estimated risks to workers in analyses conducted prior to 2006 are presented in Table 5.9. More recent results, which we judged to be more useful, are presented in Table 5.10. This section discusses estimates of ERRs for all solid cancers and provides estimates of DREFs based on the more recent data for that endpoint. Estimated risks of leukemia, excluding chronic lymphocytic leukemia (CLL), in Tables 5.9 and 5.10 are discussed in Section 5.8.3.1.

Using the data for all solid cancers in Table 5.9, comparisons of estimated risks in the LSS cohort with estimates in workers who were chronically exposed at low doses yield a range of central estimates of DREF from <1 to much greater than 2, including ∞ . However, when estimated risks in Canadian workers that are believed to be biased (Table 5.9, footnote *e*) are excluded, none of the estimated ERRs in workers are statistically significant, and estimates of DREF and their uncertainties probably are not meaningful.

Results from the 15-country study (Cardis et al. 2005b, 2007) summarized in Table 5.10 led to concerns about estimated risks to workers in Canada that were used in that study. The estimated ERR/Sv of 6.7 [90% CI: (2.6, 13)] for mortality from all cancers excluding leukemia in Canadian workers (Cardis et al. 2007) was substantially higher than a later estimate by Zablotska et al. (2014) given in Table 5.9, footnote *f*, and an estimate in workers in the other 14 countries (the third entry from the 15-country study in Table 5.10), both of which were not statistically significant (lower limits of 90% CIs were <0). The estimated risk in Canadian workers thus was responsible for the statistically significant ERR/Sv of 0.97 [90% CI: (0.27, 1.80)] for mortality from all cancers excluding leukemia reported by Cardis et al. (2007). That estimate also tends to be higher than other estimates for the same endpoint in Table 5.10.

One reason why the ERR/Sv for all cancers excluding leukemia in Canadian workers used by Cardis et al. (2005b, 2007) was higher than the later estimate by Zablotska et al. (2014) in Table 5.9, footnote *f*, was that Canadian workers with very low risks were excluded from the 15-country study on the grounds that data on socio-economic status were missing. Concerns also were raised about inadequacies of dosimetry records for workers at Atomic Energy of Canada Limited (AECL) facilities during the period 1956–1964 (Wakeford 2005, 2009, 2013; UNSCEAR 2008; Ashmore et al. 2010). These considerations prompted the reanalysis of the data on cancer mortality in Canadian workers by Zablotska et al. (2014).

Table 5.9. Estimates of ERR/Sv for cancer mortality from selected studies of radiation workers and LSS cohort^a

Study cohort	Leukemia (excluding CLL)	All solid cancers (except as noted)
2 nd NRRW ^b analysis of radiation workers in U.K. (Muirhead et al. 1999): mean dose, 30.5 mSv		
ERR/Sv (90% CI)	2.6 (−0.032, 7.2)	0.086 (−0.28, 0.52) ^c
Canadian nuclear industry workers (Zablotska et al. 2004): mean dose, 13.5 mSv		
ERR/Sv (95% CI)	53 (0.2, 290)	2.8 (−0.04, 7.1)
Canadian nuclear industry workers (Zablotska et al. 2014): mean dose, 21.6 mSv		
Workers first monitored in 1956–1994		
ERR/Sv (95% CI): entire cohort ^d	9.8 (<−1.5, 107) ^e	1.8 (−0.42, 5.3) ^{e,f}
ERR/Sv (95% CI): Atomic Energy of Canada Limited (AECL) workers	—	3.3 (0.11, 8.9) ^e
ERR/Sv (95% CI): nuclear power plant workers	—	−0.32 (<−1.9, 8.2)
AECL workers first monitored in 1956–1964		
ERR/Sv (95% CI)	−1.5 (not estimated)	7.9 (1.9, 19.5) ^{e,g}
Workers first monitored after 1964		
ERR/Sv (95% CI): AECL workers	—	−1.0 (<−1.7, 5.8)
ERR/Sv (95% CI): AECL and nuclear power plant workers	14 (<−1.5, 146)	−1.2 (<−1.5, 2.4) ^h
U.S nuclear power industry workers (Howe et al. 2004): mean dose, 25.7 mSv		
ERR/Sv	5.7	0.51
90% CI	(−1.8, 25)	(−1.7, 3.9)
95% CI	(−2.6, 30)	(−2.0, 4.6)
International combined analysis of nuclear workers (3-country study; Cardis et al. 1995): mean dose, 40.2 mSv		
ERR/Sv (90% CI)	2.2 (0.13, 5.7)	−0.07 (−0.39, 0.30) ^c
LSS cohort (ERRs based on DS86 dosimetry, except as noted)		
Little and Muirhead (1998)		
ERR/Sv (95% CI)	4.5 (3.2, 6.3) ⁱ	0.44 (0.33, 0.55) ⁱ
Cardis et al. (2005b, 2007)		
ERR/Sv	3.2 ^j	0.32 ^j
90% CI	(1.8, 5.2)	(0.07, 0.47)
95% CI	(1.6, 5.7)	(0.01, 0.50)
Preston et al. (2004)		
ERR/Sv (90% CI)	—	0.29 (0.21, 0.39) ^k
Muirhead et al. (1999)		
ERR/Sv (90% CI)	2.2 (0.43, 4.7) ^m	0.24 (0.12, 0.37) ^{c,n}

Table 5.9 (continued)

- ^a Estimated ERRs based on linear dose-response models, except as noted. Reported central values are MLEs. In workers, reported ERR/Sv is essentially ERR/Gy when exposures were due predominantly to low-LET radiations. In LSS cohort, reported ERR/Sv is ERR/Gy calculated using indicated neutron RBE.
- ^b NRRW = National Registry for Radiation Workers.
- ^c Estimate applies to all cancers excluding leukemia but including lymphomas and multiple myeloma.
- ^d Cohort includes workers monitored at multiple facilities.
- ^e Estimate believed to be biased due to inaccuracies in estimated doses to AECL workers prior to 1965 (Zablotska et al. (2014)).
- ^f Estimated ERR/Sv for all cancers excluding leukemia is 1.2 [95% CI: (-0.7, 4.3)].
- ^g Estimated ERR/Sv for all cancers excluding leukemia is 6.0 [95% CI: (1.0, 16)].
- ^h Estimated ERR/Sv for all cancers excluding leukemia is -1.4 [95% CI: (<-1.5, 2.0)].
- ⁱ Estimate based on linear dose-response model at neutron-weighted doses to bone marrow (leukemia) or colon (all solid cancers) <4 Sv assuming neutron RBE of 10 applies to males and females.
- ^j Estimates based on linear dose-response models at unspecified doses to bone marrow (leukemia) or colon (all solid cancers) and neutron RBE. ERR/Sv for leukemia is based on data in males at ages at exposure 20–60; ERR/Sv for solid cancers applies to males at age at exposure 35. ERR/Sv for leukemia based on linear term in LQ dose-response model and data in males at ages at exposure 20–60 is 1.5 [90% CI: (-0.8, 4.6); 95% CI: (-1.1, 5.3)].
- ^k Estimate based on DS02 dosimetry at shielded kerma free-in-air from photons and neutrons <4 Gy, with estimates of shielded kerma >4 Gy truncated to 4 Gy, and neutron-weighted doses to colon assuming neutron RBE of 10 applies to males at age at exposure 30 and attained age 70.
- ^m Estimate based on linear term in LQ dose-response model and data from Pierce et al. (1996a) at shielded kerma free-in-air from photons and neutrons <4 Gy, with estimates of shielded kerma >4 Gy truncated to 4 Gy, and neutron-weighted doses to colon assuming neutron RBE of 10 applies to males at ages at exposure 20–60.
- ⁿ Estimate based on data from Pierce et al. (1996a) at shielded kerma free-in-air from photons and neutrons <4 Gy, with estimates of shielded kerma >4 Gy truncated to 4 Gy, and neutron-weighted doses to colon assuming neutron RBE of 10 applies to males at ages at exposure 20–60.

In the reanalysis of data in Canadian workers by Zablotska et al. (2014) summarized in Table 5.9, the estimated ERR/Sv for all solid cancers in AECL workers first monitored in 1956–1964 tended to be higher than in the comparable group of nuclear power plant workers. That difference was thought to be due in part to an incomplete transfer of dosimetry records for AECL workers with low doses to the National Dose Registry (Zablotska et al. 2014). The estimated ERR/Sv of -0.32 [95% CI: (<-1.9, 8.2)] for all solid cancers in the nuclear power plant workers and the estimated ERR/Sv of -1.4 [95% CI: (<-1.5, 2.0)] for all cancers excluding leukemia in AECL and nuclear power plant workers first monitored after 1964 suggest an absence of risk or a threshold or hormetic dose-response.

In contrast, the estimated ERR/Sv for mortality from all cancers excluding leukemia from the 3rd NRRW analysis in the U.K. (Muirhead et al. 2009) given in Table 5.10, which included an expanded cohort, was marginally significant ($P \leq 0.08$). That study also gave the first statistically significant excess risk of incidence of solid cancers in workers, even when cancers most strongly related to smoking (lung and pleural cancers) were excluded.

Table 5.10. Estimates of ERR/Sv or ERR/Gy (and 90% CIs) for cancer mortality or incidence from selected studies of radiation workers and LSS cohort^a

Study (endpoint)	Leukemia (excluding CLL)	All cancers excluding leukemia ^b	All solid cancers	Smoking-related solid cancers ^c	Solid cancers excluding lung and pleural cancers ^b	Solid cancers unrelated to smoking
15-country study (Cardis et al. 2005b, 2007) ^d						
Mortality	1.9 (<0, 7.1) ^e	0.97 (0.27, 1.80) ^f	0.87 (0.16, 1.7) ^f	0.91 (0.04, 2.0) ^f	0.59 (-0.16, 1.5) ^f	0.62 (-0.36, 1.9) ^f
		0.89 (0.21, 1.69) ^g			0.44 (-0.30, 1.36) ^h	
		0.58 (-0.10, 1.39) ^h				
3 rd NRRW analysis of radiation workers in U.K. (Muirhead et al. 2009) ⁱ						
Mortality	1.7 (0.06, 4.3)	0.28 (0.02, 0.56)	—	—	0.32 (0.02, 0.67)	—
Incidence	1.8 (0.17, 4.4)	0.27 (0.04, 0.51)	—	—	0.31 (0.05, 0.58)	—
Studies of radiation workers in France, U.K., and U.S. (Leuraud et al. 2015; Richardson et al. 2015) ^j						
Mortality	3.0 (1.2, 5.2)	0.48 (0.20, 0.79)	0.47 (0.18, 0.79)	—	0.43 (0.08, 0.82) ^k	0.37 (-0.14, 0.95)
LSS cohort (ERRs based on DS02 dosimetry) ^m						
Mortality	1.4 (0.1, 3.4) ⁿ	0.49 (0.30, 0.67) ^p	0.29 ^r (0.16, 0.45) ^s	—	—	—
	1.1 (0.1, 2.6) ^o	0.30 (0.21, 0.39) ^q	0.26 ^r (0.19, 0.35) ^t	—	—	—
Incidence	2.9 (0.53, 5.9) ^u	0.37 (0.29, 0.46) ^q	0.43 ^r (0.30, 0.62) ^w	—	—	—
	1.5 (0.26, 3.2) ^v					

^a Central values are MLEs, except as noted.

^b Lymphomas and multiple myeloma included.

^c Cancers of the lung; oral cavity; naso-, oro-, and hypopharynx; nasal cavity and paranasal sinuses; larynx; esophagus; stomach; pancreas; liver; kidney (body and pelvis); ureter; urinary bladder; and uterine cervix.

^d Reported ERR/Sv based on linear dose-response models is essentially ERR/Gy when study subjects were restricted to workers with significant external exposure to high-energy photons or internal exposure to tritium only. Mean age at exposure 30.7, mean time since exposure 15.5 years, mean age at end of follow-up 46.2, and male fraction 0.9.

^e Upper limit of 95% CI is 8.5.

^f Estimate based on analysis with Ontario Hydro workers excluded from Canadian cohort because of lack of data on socio-economic status is result from 15-country study preferred by Cardis et al. (2005b, 2007).

^g Estimate based on analysis with entire Canadian cohort included (i.e., including Ontario Hydro workers).

^h Estimate based on analysis with entire Canadian cohort excluded.

Table 5.10 (continued)

- ⁱ NRRW = National Registry for Radiation Workers. Estimates of ERR/Sv based on linear dose-response models. Workers with potential for substantial neutron doses or internal exposure were included. Mean age at first exposure 29, mean age at end of follow-up 52, and male fraction 0.9.
- ^j Estimates of ERR/Gy. Studies are similar to 15-country study but are restricted to workers in three countries with longer durations of follow-up and more recent analyses of risks of cancer mortality. Mean age at first exposure 30.7, mean time since exposure 27 years, mean age at end of follow-up 58, and male fraction 0.9.
- ^k Estimated ERR/Gy for all solid cancers excluding lung cancer is 0.46 [90% CI: (0.11, 0.85)].
- ^m Estimates are ERR/Gy based on neutron-weighted doses to colon (all cancers excluding leukemia or all solid cancers) or bone marrow (leukemia) and calculated assuming neutron RBE of 10.
- ⁿ Estimate from Cardis et al. (2007) based on linear term in LQ dose-response model for members of LSS cohort with shielded kerma <4 Gy developed by BEIR VII committee (NRC 2006) applies to males at ages at exposure ≥ 30 and time since exposure 15 years. Muirhead et al. (2009) judged that estimate provided best comparison with estimated risks from 3rd NRRW analysis of U.K. radiation workers.
- ^o Estimate from Cardis et al. (2007) based on linear term in LQ dose-response model for members of LSS cohort with shielded kerma <4 Gy developed by BEIR VII committee (NRC 2006) applies to males at ages at exposure ≥ 30 and time since exposure 25 years.
- ^p Estimate from Jacob et al. (2009) based on linear dose-response model for members of LSS cohort with shielded kerma <4 Gy applies to age at exposure 31, attained age 46, and male fraction 0.9.
- ^q Estimate from Jacob et al. (2009) based on linear dose-response model for members of LSS cohort with shielded kerma <4 Gy applies to age at exposure 29, attained age 52, and male fraction 0.9.
- ^r Estimated 50th percentile.
- ^s Estimate we derived based on linear dose-response model for solid cancers, excluding thyroid and non-melanoma skin cancers, lymphomas, and multiple myeloma, in members of LSS cohort with shielded kerma <4 Gy developed by BEIR VII committee (NRC 2006) applies to ages at exposure ≥ 31 , attained age 46, and male fraction 0.9.
- ^t Estimate we derived based on linear dose-response model for solid cancers, excluding thyroid and non-melanoma skin cancers, lymphomas, and multiple myeloma, in members of LSS cohort with shielded kerma <4 Gy developed by BEIR VII committee (NRC 2006) applies to ages at exposure ≥ 31 , attained age 58, and male fraction 0.9.
- ^u Estimate we derived based on linear term in LQ dose-response model for all leukemias in members of LSS cohort with shielded kerma <4 Gy developed by Hsu et al. (2013) applies to males and females at age at exposure 30 and time since exposure 15 years.
- ^v Estimate we derived based on linear term in LQ dose-response model for all leukemias in members of LSS cohort with shielded kerma <4 Gy developed by Hsu et al. (2013) applies to males and females at age at exposure 30 and time since exposure 25 years.
- ^w Estimate we derived based on linear dose-response model for solid cancers, excluding thyroid and non-melanoma skin cancers, lymphomas, and multiple myeloma, in members of LSS cohort with shielded kerma <4 Gy developed by BEIR VII committee (NRC 2006) applies to males at age at exposure 30 and attained age 50.

When leukemia and lung and pleural cancers were excluded, the estimated ERR/Sv for solid cancer mortality in the 15-country study did not differ significantly from the estimate in U.K. workers. The latter estimate also was comparable to the ERR/Sv of 0.58 [90% CI: (-0.10, 1.39)] for all cancers excluding leukemia that was obtained in the 15-country study when the entire Canadian cohort was excluded. In the U.K. study, the estimated ERR/Sv for all cancers excluding leukemia and lung and pleural cancers was marginally significant when the endpoint was cancer mortality ($P \leq 0.081$) and differed significantly from

zero when the endpoint was cancer incidence ($P \leq 0.045$). These results suggest that smoking may not have been an important complication in estimating risks due to external radiation in the U.K. study.

Recent studies of leukemia and solid cancer mortality in a pooled cohort of workers in France, the U.K., and the U.S. (Leuraud et al. 2015; Richardson et al. 2015) summarized in Table 5.10 were carried out in the International Nuclear Workers Study (INWORKS). Those studies were based on more recent analyses of risks to workers in the three countries (Metz-Flamant et al. 2013; Muirhead et al. 2009; Schubauer-Berigan et al. 2015) than the analyses used in the 15-country study. Although the number of workers included in those studies was 24% less than the number of workers included in the 15-country study, the person-years of follow-up was nearly 60% higher, and the number of deaths due to cancer was much higher (17,957 vs 4,770 for solid cancers and 531 vs 196 for leukemia excluding CLL). Consequently, compared with results from the 15-country study and the study of U.K. workers alone (Muirhead et al. 2009) summarized in Table 5.10, estimated risks of cancer mortality from the recent studies of French, U.K., and U.S. workers are substantially more precise and are statistically significant at a high level of confidence for all endpoints studied except solid cancers unrelated to smoking. In the study of solid cancers in French, U.K., and U.S. workers (Richardson et al. 2015), estimated risks of all cancers excluding leukemia and all solid cancers were similar to estimated risks of solid cancers excluding lung and pleural cancers, solid cancers excluding lung cancer only, and solid cancers unrelated to smoking. As in the study of U.K. workers discussed above, this comparison suggests that smoking was not an important complicating factor in the study by Richardson et al. (2015).

5.2.2.2.1 *Limitations of analyses of risks to workers*

The large uncertainties in estimated ERRs in many studies of workers summarized in Tables 5.9 and 5.10 reflect a lack of statistical power, which is a consequence of the apparently low risks associated with the low doses to workers and incomplete follow-up of some cohorts. In the 15-country study, for example, the average cumulative dose was about 20 mSv (Vrijheid et al. 2007). Only in the recent studies of workers in France, the U.K., and the U.S., in which average cumulative doses were about 15 mGy to bone marrow (Leuraud et al. 2015) and 20 mGy to the colon (Richardson et al. 2015) and the period of follow-up was substantially longer, was the statistical power sufficient to detect increases in risks of leukemia and solid cancers with a high degree of confidence. In the 15-country study, a statistically significant increase in risk was seen only in workers in mixed-activity facilities that engaged in the production of nuclear fuel, radioisotopes, and weapons and in research and waste management (Cardis et al. 2007), where significant exposures to chemical carcinogens were more likely than at other facilities. In addition, no consistent pattern of increased risk for any single cancer type was seen across cohorts (Cardis

et al. 2007). With the exception of the 15-country study (Cardis et al. 2007; Thierry-Chef et al. 2007) and the recent studies of workers in France, the U.K., and the U.S. (Leuraud et al. 2015; Richardson et al. 2015), systematic errors (biases) in estimated doses were not considered in analyses of cancer risks.

Because of concerns about the reliability of estimated ERRs in workers in Canada that were included in the 15-country study, especially ERRs in AECL workers who were first monitored during the period 1956–1964 (Zablotska et al. 2014), we concluded that estimated ERRs from the 15-country study with the entire Canadian cohort excluded (a 14-country study) in Table 5.10 are more representative of risks to workers than estimated ERRs from the 15-country study with all or part of the Canadian cohort included. In a study discussed in Section 5.2.2.4, Jacob et al. (2009) also used an estimated ERR for all cancers excluding leukemia from the 15-country study with the entire Canadian cohort excluded in comparing estimated ERRs in cohorts of workers with estimated ERRs in the LSS cohort.

Workers included in the 3rd NRRW analysis in the U.K. (Muirhead et al. 2009) were exposed mainly to x and gamma radiation and, to a lesser extent, neutrons and internal beta emitters. Issues with the 3rd NRRW analysis raised by Wakeford (personal communication to P. Jacob, December 1, 2009) include effects of internal doses and early unrecorded neutron doses, effects of smoking and drinking habits, and significant trends with dose for rectal and laryngeal cancer that were contrary to expectations based on results from other studies.

Workers with substantial doses from neutrons and internal contamination were excluded from the 15-country study because of uncertainties in the biological effectiveness of high-LET radiations and internal dosimetry models. In contrast, in the recent study of leukemia mortality in workers in France, the U.K., and the U.S. (Leuraud et al. 2015), workers with potential exposures to neutrons and internal contamination, in which about 24% of all deaths caused by leukemia excluding CLL occurred, were included in the analysis. However, a sensitivity analysis showed that internal contamination might have little effect on the ERR for leukemia mortality from external exposure. In the recent study of solid cancer mortality in workers in the same three countries (Richardson et al. 2015), estimated ERRs were adjusted for the effect of neutron monitoring status. Additional analyses showed that adjustments for the effect of uptake or monitoring of radionuclides had little effect on estimated ERRs for mortality from all cancers excluding leukemia. For the same endpoint, estimated ERRs in workers with no evidence of exposure to neutrons or internal contamination were not significantly different from the estimated ERR in Table 5.10.

None of the analyses summarized in Tables 5.9 and 5.10 accounted for the possibility of a higher biological effectiveness of lower-energy photons or beta particles in decay of tritium. In the 15-country study, about 20% and 10% of the doses from photons to workers in mixed-activity facilities and nuclear power plants, respectively, were due to photons of energy ≤ 300 keV (Thierry-Chef et al. 2007), but no doses from intakes of tritium were reported. The latter contributed significantly to doses to some workers

in Canada who engaged in research and development or operation of nuclear power plants (Wilson 1977; Hurst 1997; Nuttall 2005). However, inclusion of doses from tritium beta particles did not affect revised estimates of ERRs in the Canadian cohort (Zablotska et al. 2014). Photons of energy as low as 100 keV contributed to external doses to workers in France, the U.K., and the U.S. (Richardson et al. 2015).

Another concern about the studies summarized in Tables 5.9 and 5.10 is the lack of information on other complicating factors, particularly smoking history. For example, lung cancers comprised 39% of all solid cancers in the initial Canadian study (Zablotska et al. 2004). Potentially important complicating factors in the 15-country study include smoking, diet, exposure to chemical carcinogens, variable periods of follow-up that typically were much shorter than the follow-up period for the LSS cohort, and the relatively young ages of members of several cohorts. Results from limited surveys of smoking history in seven cohorts, which were inconsistent, were judged to be inadequate to account for smoking in estimating ERRs associated with radiation exposure (Cardis et al. 2007). Smoking, diet, and exposure to chemical carcinogens (e.g., benzene) also were potentially important complicating factors in the recent studies of workers in France, the U.K., and the U.S. (Leuraud et al. 2015; Richardson et al. 2015).

Although an attempt was made to adjust estimated ERRs in the 15-country study to account for lifestyle factors, such as smoking history, on the basis of data on socio-economic status, the definition of a worker's socio-economic status was country-specific and was not consistent across all cohorts. Nonetheless, socio-economic status had a substantial effect on estimated ERRs (Cardis et al. 2007; Vrijheid et al. 2007). Stratification on the basis of industrial classification (a surrogate for socio-economic status) was performed in the 3rd NRRW analysis in the U.K. (Muirhead et al. 2009), but effects of lifestyle factors, such as smoking history, or exposures to chemical carcinogens were not considered. Adjustments to account for socio-economic status in the recent studies of workers in France, the U.K., and the U.S. were similar to adjustments in the 15-country study (Richardson et al. 2015).

The potential importance of smoking history is indicated by the result that lung cancer was the only cancer type with a statistically significant increase in risk in the 15-country study; the estimated ERR/Sv was 1.9 [90% CI: (0.49, 3.6)] (Cardis et al. 2007). As with the estimated ERR/Sv for all cancers excluding leukemia, the increased risk of lung cancer was driven by risks to workers at mixed-activity facilities.

When deaths from smoking-related solid cancers, which comprised 57% of all solid cancer cases analyzed, were excluded from the 15-country study, results in Table 5.10 indicate that the central estimate of ERR/Sv for all solid cancers decreased from 0.87 to 0.62 and the 90% CI of (-0.36, 1.92) overlapped zero. However, Cardis et al. (2007) concluded that it was unlikely that the entire increase in the risk of solid cancers in the 15-country study could be explained by an effect of smoking, and they recommended that an association of lung cancer with radiation be interpreted with caution, pending "further investigation in studies that can collect information about individual smoking habits and other occupational exposures."

A similar effect of excluding smoking-related solid cancers was seen in the recent analysis of risks of solid cancers in workers in France, the U.K., and the U.S. (Richardson et al. 2015). These observations illustrate the difficulty in obtaining quantitative information on effects of radiation at low doses or low dose rates on cancer risks in humans from epidemiological studies of population groups other than those exposed at intermediate and high doses and high dose rates, particularly when such other factors as smoking and socio-economic status could have important effects on risks.

UNSCEAR (2008) noted that the approach in the 15-country study to selection of data in the Canadian cohort had a large and potentially undue influence on the results; this concern also is discussed by Wakeford (2005, 2009). The ERR/Sv of 6.7 [90% CI: (2.6, 13)] for mortality from all cancers excluding leukemia in the Canadian cohort that was included in the 15-country study (Cardis et al. 2007) was considered unusual, because it was significantly greater than the preferred estimate from that study of 0.97 [90% CI: (0.27, 1.80)] given in Table 5.10 and, in addition, was the only estimate in a particular cohort that differed significantly from the estimate for all cohorts combined. As noted previously, the ERR/Sv of 6.7 [90% CI: (2.6, 13)] also was larger than the estimate of 2.8 [95% CI: (-0.04, 7.1)] by Zablotska et al. (2004) given in Table 5.9, because data in the Ontario Hydro subcohort, in which there was a significant negative trend in cancer mortality with increasing dose, were excluded on the grounds that information on socio-economic status was lacking (Cardis et al. 2007; Vrijheid et al. 2007).

We think that exclusion of data in the Ontario Hydro subcohort can be questioned when analyses showed that socio-economic status did not have a significant effect on estimated ERRs in Canadian workers (Zablotska et al. 2004, 2014). In addition, as indicated in Table 5.10, inclusion of the Ontario Hydro subcohort in the 15-country study had an insignificant effect on the estimated ERR for all cancers excluding leukemia and the ERR for all cancers excluding leukemia, lung, and pleural cancers. However, when the entire Canadian cohort was excluded, the estimated ERR/Sv for all cancers excluding leukemia in the 15-country study decreased to 0.58 [90% CI: (-0.10, 1.39)]. As noted above, we concluded that this is the most representative estimate of the risk to workers from the 15-country study.

In discussing the strengths and limitations of the recent study of solid cancer mortality in workers in France, the U.K., and the U.S., Richardson et al. (2015) noted that further work on internal doses from incorporated radionuclides is ongoing and could allow for increased attention to effects of internal exposures in future analyses. Those investigators also cautioned that the large number of workers included in their study and the statistical precision of estimated ERRs for solid cancer mortality in Table 5.10 “are no protection against bias.” Richardson et al. (2015) attempted to address some concerns about biases in designing their study. To that end, the intent was to assemble cohorts of workers that were “most informative with regard to quality and completeness of exposure and follow-up data.”

5.2.2.2.2 *Derivation of DREFs based on recent estimates of risks to workers and LSS cohort*

We used estimates of ERR/Sv or ERR/Gy for all cancers excluding leukemia or all solid cancers in radiation workers and comparable estimates of ERR/Gy in the LSS cohort in Table 5.10 to derive estimates of DREF given in Table 5.11. Three estimates of DREF for mortality from all cancers excluding leukemia based on results from the 15-country study are included to investigate the effect of different definitions of the cohort of Canadian workers, including exclusion of the entire cohort (a 14-country study). Such effects could not be studied for mortality from all solid cancers based on results reported by Cardis et al. (2005b, 2007).

Risks in the LSS cohort estimated by Jacob et al. (2009) were used to estimate several DREFs in Table 5.11, including DREFs based on estimated risks in U.K. workers, because the BEIR VII committee did not provide estimated risks for all cancers excluding leukemia. The study by Jacob et al. (2009), which compared risks in several worker cohorts with risks in the LSS cohort, is described in Section 5.2.2.4.

The three estimates of DREFs based on estimated risks from the 15-country study with all or parts of the Canadian cohort included are similar and are statistically significant at the 90% confidence level, whereas the estimated DREF with the entire Canadian cohort excluded (a 14-country study) has a substantially larger uncertainty and a lower limit of a 90% CI <0. Despite the larger uncertainty and lack of statistical significance, we think that the DREF of 0.7 [90% CI: (-3.1, 4.5)] that we estimated using an estimated ERR/Sv from a 14-country study is the most representative result based on the 15-country study, given the concern about unreliable estimates of doses to AECL workers that were first monitored during the period 1956–1964 (Zablotska et al. 2014) and the impact of estimated risks to those workers on estimated risks in the 15-country study with all or part of the Canadian cohort included.

All estimates of DREFs in Table 5.11 are based on comparisons of age-averaged ERRs in workers with age-specific ERRs in the LSS cohort. Data on the average age at first exposure and average age at the end of follow-up in the worker cohorts were used to define an age at exposure and attained age for a member of the LSS cohort at which the estimated ERR provides the best practical match to the estimated ERR in each worker cohort. Defining the age at exposure to be assumed in comparing ERRs from protracted and acute exposures is problematic (Jacob et al. 2009) and introduces additional uncertainty to estimates of DREF. Although use of an older age at exposure in the LSS cohort would be more correct when exposures of workers were protracted over many years, estimating such an age usually is not practicable, e.g., due to a lack of published data on age distributions of exposures in most worker cohorts (Jacob et al. 2009). More generally, Leenhouts and Chadwick (2011) argued that comparisons of estimated risks in the LSS and worker cohorts of the kind presented in Table 5.11 are flawed because estimates in the LSS cohort at low doses based on an assumption of a linear dose-response are too high.

Table 5.11. DREFs derived by comparing estimates of ERR/Sv or ERR/Gy for all cancers excluding leukemia or all solid cancers from selected studies of radiation workers with matched estimates of ERR/Gy in LSS cohort based on DS02 dosimetry (except as noted)^a

Worker population (reference)	Cancer outcomes	Cohort definition	ERR/Sv or ERR/Gy (90% CI) ^b		DREF (90% CI) ^c
			Workers	LSS cohort	
Workers in 15 countries (Cardis et al. 2005b, 2007)	Mortality from all cancers excluding leukemia ^d	Canadian cohort excluding Ontario Hydro workers	0.97 ^e (0.27, 1.80)	0.49 (0.30, 0.67) ^f	0.49 (0.22, 1.7)
		Entire Canadian cohort included	0.89 ^e (0.21, 1.69)		0.52 (0.23, 2.1)
		Entire Canadian cohort excluded (14-country study)	0.58 ^e (-0.10, 1.39)		0.7 (-3.1, 4.5)
	Mortality from all solid cancers	Canadian cohort excluding Ontario Hydro workers	0.87 ^e (0.16, 1.71)	0.29 ^g (0.16, 0.45)	0.32 (0.12, 1.4)
U.K. workers (Muirhead et al. 2009)	Mortality from all cancers excluding leukemia ^d	Entire cohort	0.28 ^h (0.02, 0.56)	0.30 (0.21, 0.39) ^f	1.0 (0.39, 5.0)
	Incidence of all cancers excluding leukemia ^d		0.27 ⁱ (0.04, 0.51)	0.37 (0.29, 0.46) ^f	1.4 (0.64, 5.9)
Workers in France, U.K., and U.S. (Richardson et al. 2015)	Mortality from all solid cancers	Entire cohort	0.47 ^h (0.18, 0.79)	0.32 (0.07, 0.47) ^j	0.62 (0.14, 1.8)
				0.26 ^g (0.19, 0.35)	0.55 (0.30, 1.5)

^a Estimates from Table 5.10, except as noted.

^b Except as noted, central values are MLEs and ERRs are assumed to be described by Weibull distributions with modes at MLEs.

^c 50th percentiles and 90% CIs we estimated as ratio of ERR/Gy in LSS cohort to ERR/Sv or ERR/Gy in workers using Monte Carlo uncertainty propagation techniques.

^d Lymphomas and multiple myeloma are included.

^e MLE is at 48th percentile of assumed Weibull distribution.

^f ERR was described by normal distribution (Jacob et al. 2009).

^g Estimated 50th percentile.

^h MLE is at 49th percentile of assumed Weibull distribution.

ⁱ MLE is at 50th percentile of assumed Weibull distribution.

^j Estimate for men at age at exposure 35 derived by Cardis et al. (2007) based on DS86 dosimetry (Table 5.9); MLE is at 57th percentile of assumed Weibull distribution. Estimate was used by Richardson et al. (2015) to compare with estimated ERR/Gy in workers in France, U.K., and U.S.

Estimates of DREF that we derived based on estimated ERRs in U.K. workers tend to be higher than DREFs based on estimated ERRs from the 15-country study and the study of workers in France, the U.K., and the U.S. However, differences in estimated DREFs based on estimated ERRs in the three study populations are not significant when their uncertainties are taken into account.

Results from the 15-country study summarized in Table 5.10 suggest that a consideration of smoking history (e.g., by excluding lung and pleural cancers) could have affected estimated ERRs for mortality from solid cancers and their uncertainties and, hence, estimates of DREF. However, results from the 3rd NRRW analysis and the study of workers in France, the U.K., and the U.S. do not appear to show such an effect; i.e., estimated ERRs are about the same regardless of whether lung and pleural cancers are excluded from the analysis or whether the endpoint is cancer mortality or incidence. The magnitude of any such effect on an estimate of DREF is uncertain, because we do not have a suitable estimate of an ERR in the LSS cohort that has been adjusted for smoking history (e.g., by excluding lung and pleural cancers).

Contributions to estimated cancer risks in the U.K. workers due to exposures to high-LET radiation are not known. Thus, DREFs derived based on estimated ERRs from the 3rd NRRW analysis have additional uncertainty that cannot be quantified. Exposures to high-LET radiation should be less important in the 15-country study when workers with significant external and internal exposures to high-LET radiation were excluded (Cardis et al. 2007), and exposures to neutrons or internal contamination probably were not important in the recent study of workers in three countries by Richardson et al. (2015).

Although there are significant differences between the 15-country study and the study of workers in the U.K. and each study has strengths and weaknesses, there appears to be no reason to exclude either study, nor is there any reason to exclude the recent study by Richardson et al. (2015). However, of the four estimates based on the 15-country study, we concluded that the estimated DREF obtained by excluding the entire Canadian cohort (the DREF based on a 14-country study) is the most representative result until concerns about estimated doses to AECL workers prior to 1965 are resolved.

5.2.2.3 Studies of Techa River cohort

Risks of solid cancer mortality and incidence have been assessed in the Russian population that was exposed to fission products that were released into the Techa River from the Mayak plutonium production complex during the years 1949–1956. The Techa River cohort received protracted external exposures and internal exposures to ⁹⁰Sr, ¹³⁷Cs, and other radionuclides that were released into the river.

Risks of solid cancers have been estimated in individuals who lived along the Techa River at some time during the period 1950–1960. Because cancer was not routinely recorded as a cause of death before 1956 and qualified medical care was lacking, cancer ascertainment is an issue. A register of exposed

persons was not created until the 1980s, and only half the population received a medical examination (Kossenko 2010). Potentially important sources of uncertainty and other complications in assessing risks in the Techa River cohort are discussed by Kossenko (2010) and Kellerer (2002).

An analysis of solid cancer mortality (excluding bone cancer) by Krestinina et al. (2005) used estimated doses to the stomach based on Techa River Dosimetry System (TRDS)-2000 (Degteva et al. 2000a,b). The estimated ERR/Gy using a linear dose-response model of 0.92 [95% CI: (0.2, 1.7)] was about 50% higher than a comparable risk of solid cancer mortality in the LSS cohort (Preston et al. 2003b). The data were described equally well using an EAR model in which the excess rate increased with attained age; the estimated EAR/10⁴ person-y/Gy at age 70 was 71 [95% CI: (25, 118)].

Eidemüller et al. (2008) analyzed data on solid cancer mortality in the Techa River cohort based on TRDS-2000 dosimetry using a biologically based two-stage clonal expansion model. Estimated risks were compared with risks in the LSS cohort at age at exposure 28 and attained age 63 (Preston et al. 2004), which correspond to the mean age of the Techa River mortality cohort in 1950 and the mean age at the time of death, respectively. MLEs and 95% CIs of risks of solid cancer mortality (excluding bone cancer) in the Techa River cohort obtained by Eidemüller et al. (2008) are an ERR/Gy of 0.76 (0.23, 1.29) and an EAR/10⁴ person-y/Gy of 33 (9.8, 53), and MLEs and 95% CIs of comparable risks in the LSS cohort were an ERR/Gy of 0.49 (0.39, 0.60) and an EAR/10⁴ person-y/Gy of 19.6 (15.4, 23.7). MLEs of these risks are at the 50th, 53rd, 50th, and 50th percentiles, respectively, of assumed Weibull distributions. By giving equal weight to estimates based on ratios of ERRs or EARs in the LSS and Techa River cohorts, we estimated a DREF with a 50th percentile and 90% CI of 0.63 (0.36, 1.7).

A more recent analysis of solid cancer mortality (including bone cancer) by Schonfeld et al. (2013) was based on data from an additional 8 years of follow-up and estimates of dose from TRDS-2009 (Degteva et al. 2006, 2012). The reported MLE and 95% CI of the ERR/Gy in the Techa River cohort assuming a linear dose-response is 0.61 (0.04, 1.27). An assumption of an LQ model gave no evidence of non-linearity ($P > 0.5$), but a purely quadratic model described the dose-response as well as a linear model. We assumed a comparable ERR/Gy in the LSS cohort with a 50th percentile and 95% CI of 0.41 (0.30, 0.53) based on the dose-response model for solid cancer mortality developed by the BEIR VII committee (NRC 2006) for age at exposure 28, attained age 64, and male fraction 0.42 (Eidemüller et al. 2008; Schonfeld et al. 2013). The ratio of the two ERRs, assuming Weibull distributions, gives an estimated DREF for solid cancer mortality with a 50th percentile and 90% CI of 0.64 (0.31, 2.7). The MLE of the ERR in the Techa River cohort is at the 49th percentile of the assumed distribution.

An initial analysis of solid cancer incidence (excluding bone cancers) based on TRDS-2000 dosimetry by Krestinina et al. (2007) included individuals who had neither died nor had a recorded cancer diagnosis prior to January 1, 1956, and who resided along the Techa River or in Chelyabinsk city at some

time between 1956 and the end of 2002. The dose-response for solid cancer incidence was fitted with a linear model with an ERR/Gy of 1.0 [95% CI: (0.3, 1.9)] or with a quadratic model with an ERR/Gy² of 2.9 [95% CI: (0.9, 5.3)]. Krestinina et al. (2007) noted a comparable estimate of the ERR/Gy for solid cancer incidence in the LSS cohort of about 0.6, which suggests a DREF of about 0.6.

A more recent analysis of solid cancer incidence (including bone cancer) in the Techa River cohort by Davis et al. (2015) was based on data from an additional 5 years of follow-up, TRDS-2009 dosimetry, and an adjustment for smoking. The estimated mean and maximum doses to stomach were 60 and 960 mGy, respectively. The reported MLE and 95% CI of the ERR/Gy in the Techa River cohort assuming a linear dose-response is 0.77 (0.13, 1.5). An LQ dose-response model did not fit the data better than a linear model ($P = 0.2$), and a quadratic model with an estimated ERR at 1 Gy of 0.22 [95% CI: (0.05, 0.4)] fit the data as well as the linear model. The ERR/Gy based on a linear model did not depend significantly on sex, ethnicity, age at exposure, or attained age. We assumed a comparable ERR/Gy in the LSS cohort with a 50th percentile and 95% CI of 0.49 (0.39, 0.60) based on the dose-response model for solid cancer incidence developed by the BEIR VII committee (NRC 2006) for age at exposure 27, attained age 63, and male fraction 0.43 (Krestinina et al. 2007; Davis et al. 2015). The ratio of the two ERRs, assuming Weibull distributions, gives an estimated DREF for solid cancer incidence with a 50th percentile and 90% CI of 0.63 (0.33, 2.2). The MLE of the ERR in the Techa River cohort is at the 49th percentile of the assumed distribution. This DREF is nearly the same as the estimated DREF based on the analysis of data for solid cancer mortality in the Techa River cohort by Schonfeld et al. (2013) given above.

Davis et al. (2015) also estimated risks of incidence of specific solid cancers in the Techa River cohort. Except for an estimated ERR/Gy of 4.6 [95% CI: (0.4, 12)] for incidence of cancer of the esophagus, all estimates of cancer-specific risks were not statistically significant. If we use the ERR/Gy for cancer of the esophagus in the LSS cohort of 0.52 [90% CI: (0.15, 1.0)] reported by Preston et al. (2007), which applies at attained age 70 and any age at exposure, we estimate a DREF of 0.1 [90% CI: (0.02, 0.5)]. However, given the unknown uncertainties in estimating doses to the esophagus from internal exposure in the Techa River cohort and the potential importance of risk transfer for that cancer type, which is not accounted for in the estimated DREF, we do not consider this estimate to be reliable.

As summarized above, results of recent analyses of dose-responses for solid cancer mortality or incidence in the Techa River cohort assuming a linear model, when compared with estimated risks in the LSS cohort, suggest a DREF <1. However, estimated DREFs have substantial uncertainties, and the similarities in fits to dose-responses in the Techa River cohort using linear or purely quadratic models indicate that there may be considerable uncertainty in responses at very low doses that is not reflected in estimates of DREF. In addition, there are still concerns about uncertainties in estimated doses (Schonfeld et al. 2013; Davis et al. 2015) and various other factors that could affect results of a risk assessment.

5.2.2.4 Analysis of multiple studies by Jacob et al. (2009)

5.2.2.4.1 Description of analysis and presentation of results

Jacob et al. (2009) assembled estimates of ERR/Gy obtained from the following cohort studies of cancer incidence (three studies) or cancer mortality (nine studies) from chronic or protracted exposures:

- three studies of cleanup workers at Chernobyl, one of which provided data on cancer incidence;
- studies of cancer mortality and cancer incidence in the Techa River cohort by Krestinina et al. (2005, 2007) discussed in the previous section;
- a study of cancer incidence and mortality in the 3rd NRRW analysis of radiation workers in the U.K. discussed in Section 5.2.2.2;
- the 15-country study of cancer mortality in radiation workers discussed in Section 5.2.2.2, with data for the entire Canadian cohort excluded (a 14-country study);
- studies of cancer mortality in radiation workers in France and at the Hanford, Oak Ridge National Laboratory (ORNL), and Rocketdyne facilities in the U.S.

Linear dose-responses were assumed in all cohorts. Most risk assessments were based on estimates of external dose; internal exposures, mainly to low-LET radiations, were taken into account in the studies of Rocketdyne and Hanford workers and Techa River cohort only. Mean doses ranged from 8 to 130 mGy. ERRs reported by Jacob et al. (2009) applied to a variety of cancer types and groupings.

DREFs, referred to as DDREFs by Jacob et al. (2009), can be estimated by comparing ERRs in the worker or Techa River cohorts with ERRs in the LSS cohort. Jacob et al. (2009) matched estimated ERRs in the cohorts that received chronic or protracted exposures with estimated ERRs in the LSS cohort based on DS02 dosimetry and an assumed neutron RBE of 10 that were modified to account for differences in sex ratios, types of cancers evaluated, and estimates of the corresponding average age at exposure (typically the age at first exposure) and at the end of follow-up that were assumed to represent the age at exposure and attained age for which ERRs in the LSS cohort should be estimated. Matching ERRs in the LSS cohort were based on dose-response models for solid cancer mortality (Preston et al. 2004) and solid cancer incidence (Preston et al. 2007).

To avoid calculating ratios of ERRs in the LSS cohort to ERRs in the other cohorts of infinity (∞), which would occur if DDREFs were calculated, Jacob et al. (2009) calculated the reciprocal of a DDREF, referred to as a risk ratio. To calculate probability distributions of risk ratios, uncertain ERRs in all cohorts were represented by normal probability distributions.

Estimates of ERR/Gy in the cohorts that received chronic or protracted exposures, matched estimates of ERR/Gy in the LSS cohort, and risk ratios obtained by Jacob et al. (2009) and their uncertainties are given in Tables 5.12 and 5.13. Those tables also give central estimates of DDREF calculated as the reciprocal of central estimates of risk ratios. As described below, Jacob et al. (2009) then obtained pooled estimates of risk ratios based on three combinations of studies of chronic or protracted exposures using an inverse-variance method to assign weights to the estimated ERRs from each study; i.e., the ERR/Gy from each study was weighted by the reciprocal of its variance.

Because several studies had data in common (e.g., the study of radiation workers in 14 countries included the French, Hanford, ORNL, and most of the U.K. data), two comparisons using estimated ERRs for cancer mortality in Table 5.12 were made. In the first, which Jacob et al. (2009) characterized as their main analysis, the 14-country study [the 15-country study by Cardis et al. (2007) with the Canadian cohort excluded] and the first study of Chernobyl cleanup workers by Ivanov et al. (2001) were omitted; i.e., the main analysis included seven studies. The weighted average risk ratio obtained by combining the risk ratios from those studies was 1.21 [90% CI: (0.51, 1.90)] (Jacob et al. 2009). By assuming that the average risk ratios are represented by normal probability distributions (Jacob et al. 2009), this risk ratio suggests a DDREF for cancer mortality with a 50th percentile and 90% CI of 0.83 (0.53, 2.0).

The second comparison of data on cancer mortality included four studies: the 14-country study, the first study of Chernobyl clean-up workers by Ivanov et al. (2001), and the studies of Rocketdyne workers and the Techa River cohort; the Rocketdyne and Techa River cohorts were included in both analyses of cancer mortality. The weighted average risk ratio obtained by combining the risk ratios for the four studies selected was 2.08 [90% CI: (1.16, 3.01)] (Jacob et al. 2009). This risk ratio suggests a DDREF for cancer mortality with a 50th percentile and 90% CI of 0.48 (0.33, 0.86).

The third comparison included the three studies of cancer incidence in Table 5.13. The weighted average risk ratio obtained by combining the risk ratios from the three studies was 0.98 [90% CI: (0.41, 1.54)] (Jacob et al. 2009). This risk ratio suggests a DDREF for cancer incidence with a 50th percentile and 90% CI of 1.0 (0.65, 2.4).

Jacob et al. (2009) contrasted the risk ratios they calculated with the DDREF of 2 recommended by ICRP (2007), the DDREF developed by the BEIR VII committee (NRC 2006), which has a central estimate of 1.5, and the DDREFs in IREP (Land et al. 2003a), which have central estimates of 1.6 and 1.8. They concluded that those DDREFs are not supported by their analyses of epidemiological studies, which suggest central estimates of about 0.5–1. They also noted, however, that the main value of their study is a general evaluation of the implications of the various epidemiological studies they considered, rather than a quantitative risk assessment. It also is the case that DDREFs of 1.5–2 fall within the 90% CI of the reciprocal of the risk ratio of (0.53, 2.0) obtained in the main analysis by Jacob et al. (2009).

Table 5.12. Risk ratios derived by comparing estimates of ERR/Gy for cancer mortality in nine cohorts that received chronic or protracted exposures with matched estimates in LSS cohort based on DS02 dosimetry^a

Study cohort: mean dose (reference)	Cancer outcomes	ERR/Gy (study cohort) (CI) ^b	ERR/Gy (LSS cohort) ^c (CI) ^b	Risk ratio (90% CI) [DDREF] ^d
Rocketdyne workers: 14 mGy (Boice et al. 2006)	All cancers except leukemia ^e	0.0 (-1.9, 2.4) ^f	0.26 (0.16, 0.35) ^f	0.0 (-7.3, 7.3) [∞]
Radiation workers in 14 countries: 20 mGy (Cardis et al. 2007) ^g	All cancers except leukemia ^e	0.6 (-0.1, 1.4)	0.49 (0.30, 0.67)	1.19 (-0.34, 3.12) [0.83]
Chernobyl cleanup workers: 37 mGy (Ivanov et al. 2001) ^g	All neoplasms	2.1 (1.3, 2.9) ^f	0.47 (0.29, 0.65) ^f	4.49 (2.79, 7.17) [0.22]
Chernobyl cleanup workers: 130 mGy (Ivanov et al. 2006)	Solid cancers	1.5 (0.2, 2.9) ^f	0.23 (0.11, 0.34) ^f	6.7 (1.7, 14.7) [0.15]
Techa River cohort: 30 mGy (Krestinina et al. 2005)	Solid cancers except bone cancer	0.9 (0.2, 1.7) ^f	0.54 (0.42, 0.65) ^f	1.71 (0.52, 3.04) [0.59]
U.K. radiation workers: 25 mGy (Muirhead et al. 2009)	All cancers except leukemia ^e	0.3 (0.02, 0.6)	0.30 (0.21, 0.39)	0.91 (0.01, 2.01) [1.1]
ORNL radiation workers: 15 mGy (Stayner et al. 2007)	All cancers except leukemia ^e	4.8 (0.4, 13.3) ^h	0.25 (0.16, 0.33)	20 (-6.4, 51) [0.05]
French nuclear workers: 8 mGy (Telle-Lamberton et al. 2007)	All cancers except leukemia ^e	1.5 (-0.5, 4.0) ⁱ	0.33 (0.23, 0.43)	4.6 (-2.3, 12.6) [0.22]
Hanford workers: 28 mGy (Wing and Richardson 2005)	All cancers	0.3 (-0.3, 1.0)	0.41 (0.33, 0.49)	0.73 (-0.87, 2.35) [1.4]

^a Jacob et al. (2009). Reported central values of ERRs and risk ratios are MLEs.

^b 90% CI, except as noted.

^c ERR/Gy at neutron-weighted doses to colon, stomach, or skin corresponding to shielded kerma of 0–4 Gy and assumed neutron RBE of 10 matched to ERR/Gy in study cohort by cancer outcomes included, male fraction, average age at exposure (typically age at first exposure), and average age at end of follow-up (attained age).

^d Risk ratio is ratio of ERR/Gy in worker cohort to matched ERR/Gy in LSS cohort; DDREF is central estimate calculated as reciprocal of central estimate of risk ratio.

^e Lymphomas and multiple myeloma included.

^f 95% CI.

^g Study excluded from main analysis based on results from seven studies of cancer mortality.

^h Estimate after correction for dose uncertainties; estimate without correction is 5.4 [90% CI: (0.5, 12.6)].

ⁱ Estimate provided by personal communication from M. Telle-Lamberton to P. Jacob.

Table 5.13. Risk ratios derived by comparing estimates of ERR/Gy for cancer incidence in three cohorts that received chronic or protracted exposures with matched estimates in LSS cohort based on DS02 dosimetry^a

Study cohort: mean dose (reference)	Cancer outcomes	ERR/Gy (study cohort) (CI) ^b	ERR/Gy (LSS cohort) ^c (CI) ^b	Risk ratio (90% CI) [DDREF] ^d
Chernobyl cleanup workers: 130 mGy (Ivanov et al. 2004)	Solid cancers	0.3 (-0.4, 1.2) ^e	0.33 (0.21, 0.46) ^e	0.99 (-1.10, 3.25) [1.0]
Techa River cohort: 30 mGy (Krestinina et al. 2007)	Solid cancers except bone cancer	1.0 (0.3, 1.9) ^e	0.59 (0.49, 0.69) ^e	1.70 (0.54, 2.92) [0.59]
U.K. radiation workers: 25 mGy (Muirhead et al. 2009)	All cancers except leukemia ^f	0.3 (0.04, 0.5)	0.37 (0.29, 0.46)	0.71 (0.09, 1.42) [1.4]

^a Jacob et al. (2009). Reported central values of ERRs and risk ratios are MLEs.

^b 90% CI, except as noted.

^c ERR/Gy at neutron-weighted doses to stomach or skin corresponding to shielded kerma of 0–4 Gy and assumed neutron RBE of 10 matched to ERR/Gy in study cohort by cancer outcomes included, male fraction, average age at exposure (typically age at first exposure), and average age at end of follow-up (attained age).

^d Risk ratio is ratio of ERR/Gy in worker cohort to matched ERR/Gy in LSS cohort; DDREF is central estimate calculated as reciprocal of central estimate of risk ratio.

^e 95% CI.

^f Lymphomas and multiple myeloma are included.

Jacob et al. (2009) discussed a number of issues that could compromise their results, including:

- uncertainties in estimated doses;
- effects on estimated risks due to radiation of other risk factors, mainly smoking (exposures to hazardous chemicals, which affected most of the study cohorts, were not mentioned);
- combining estimated risks for different cancer types and groupings;
- differences in baseline risks in the various study cohorts, which affect the validity of an assumption that ERRs in one population apply to other populations;
- difficulties in defining ages at exposure in chronically exposed cohorts (Section 5.2.2.2.2).

Other concerns not mentioned by Jacob et al. (2009) include the issue of comparing estimated risks from studies with significant differences in follow-up after exposure and the importance of an assumed minimum latency period for cancer induction. Similar concerns raised by other investigators about

analyses of the kind performed by Jacob et al. (2009) are discussed in Section 5.2.2.2, which presents other DDREFs that can be derived by comparing estimated risks in workers with risks in the LSS cohort.

5.2.2.4.2 Critique of analysis

For several reasons, we do not think that DDREFs based on the analysis by Jacob et al. (2009) should provide the primary basis for defining a probability distribution of DDREF for solid cancers.

A major concern we have about the study by Jacob et al. (2009) is the use of an unnormalized inverse (reciprocal) of the variance of estimated ERRs on an arithmetic scale to assign weights to risk ratios based on results from individual epidemiological studies for the purpose of deriving a risk ratio that applies to several studies combined. We think it would be more appropriate to normalize the variance of each ERR by dividing by the central estimate. Also, the statistical variance of a dose-response is often a poor indicator of the overall merit of an epidemiological study. We think that weights of merit should be based, at least in part, on a subjective evaluation of the strengths and weaknesses of each study. To do otherwise can lead to artificially low estimates of uncertainty in risk ratios. Another concern we have about the approach to weighting individual studies is that an inverse (reciprocal)-variance weighting scheme assumes complete statistical independence of estimated ERRs from each study and, thus, would underestimate the uncertainty in a combined risk ratio when individual risk ratios are correlated to some degree or include systematic uncertainties. The condition of statistical independence clearly is not met when all estimates of ERRs in the LSS cohort that are used in deriving individual risk ratios are based on the same data set. We also note that the ratio of two normally distributed ERRs, as assumed by Jacob et al. (2009), is a Cauchy distribution, which has undesirable properties described later in this section.

As described below, we also have concerns about the studies that Jacob et al. (2009) selected for use in deriving risk ratios that apply to several studies combined, including that the selection of studies can have a significant effect on the result.

- When the Techa River cohort was excluded from the main analysis, which included seven studies, the risk ratio for cancer mortality changed from 1.21 [90% CI: (0.51, 1.90)] to 0.96 [90% CI: (0.12, 1.80)] (Jacob et al. 2009). The main effect of that change was a substantial reduction in the lower limit of the 90% CI, which results in an increase in the upper limit of the 90% CI of DDREF from about 2 to about 8. Concerns about the study of cancer mortality in the Techa River cohort include an uncertainty in whether the dose-response is linear (Krestinina et al. 2005), the large uncertainties in estimated doses, possible effects on estimated risks of exposures to toxic chemicals, differences in ethnicity among members of the cohort, and possible birth cohort

effects; other concerns are discussed in Sections 5.2.2.3, 5.3.4, and 5.8.3.3 and also by Kossenko (2010). An analysis of the same data using a biologically based two-stage clonal expansion model (Eidemüller et al. 2008) gave an ERR/Gy of 0.76 [95% CI: (0.23, 1.29)], which differs somewhat from the ERR/Gy of 0.92 [95% CI: (0.2, 1.7)] from Krestinina et al. (2005) that was used by Jacob et al. (2009), but that result was excluded from the analyses without mention. The difference in estimated risks resulting from different formulations of a dose-response model suggests that the uncertainty introduced by the use of data from the Techa River studies in the main analysis by Jacob et al. (2009) has not been accounted for fully.

- The main analysis of cancer mortality included results from one study of Chernobyl cleanup workers, even though the BEIR VII committee concluded that studies of those workers did not provide reliable risk estimates because of difficulties in follow-up and the lack of validation of estimated doses (NRC 2006). Doses to those workers often were monitored inadequately or not at all (Kryuchkov et al. 2009), and ascertainment bias in health screening programs has been raised as an issue that limits interpretation of those studies (Wakeford 2009). UNSCEAR (2011) also considered the results of studies of Chernobyl cleanup workers to be inconclusive. The use of three sets of results in those workers, one in each of the three analyses, seems to place undue weight on the significance of ERRs derived from those studies.
- There appears to be an inconsistency between estimates of ERR/Gy for cancer mortality in Chernobyl cleanup workers of 2.1 [95% CI: (1.3, 2.9)] and 1.5 [95% CI: (0.2, 2.9)] that were used by Jacob et al. (2009) and the estimated ERR/Gy for cancer incidence in those workers of 0.3 [95% CI: (-0.4, 1.2)]. Jacob et al. (2009) indicated that the ERR for cancer incidence was based on follow-up beginning in 1996, in which case it is reasonable to compare that estimate with an estimated ERR for cancer incidence in the LSS cohort based on follow-up beginning 13 years after exposure. However, the ERR/Gy for cancer incidence used by Jacob et al. was based on follow-up from 1991 to 2001 (Ivanov et al. 2004), rather than 1996 to 2001. Furthermore, Ivanov et al. (2004) considered that a somewhat lower ERR/Gy for cancer incidence of 0.19 [95% CI: (-0.66, 1.27)] based on follow-up from 1996 to 2001 was more reliable. Such differences in estimates of ERR/Gy for cancer mortality and incidence in Chernobyl cleanup workers are not seen in comparisons of ERRs for cancer incidence and mortality in the LSS cohort (Preston et al. 2007; Ozasa et al. 2012) or U.K. radiation workers (Muirhead et al. 2009).
- As noted in Section 5.2.2.3, a dose-response for incidence of solid cancers in the Techa River cohort could be fit with a linear or a quadratic model. Differences between the two models lead to significant uncertainty in the response at low doses (Krestinina et al. 2007), which was not addressed by Jacob et al. (2009). The same pattern was seen in an analysis of the dose-response

for solid cancer mortality (Schonfeld et al. 2013) discussed in Section 5.2.2.3. If we omit this data set in analyzing data on cancer incidence because of concerns about an ambiguous dose-response, we are left with results from studies of Chernobyl cleanup workers and U.K. nuclear workers. We would argue that only the latter should be used in estimating a DDREF for cancer incidence, as we have done in Section 5.2.2.2. We estimate that substitution of the lower ERR/Gy for cancer incidence in Chernobyl workers (central estimate of 0.19) from Ivanov et al. (2004) and removal of the ERR/Gy in the Techa River cohort for reasons discussed above would give a risk ratio of about 0.6–0.7, which is similar to an estimate based on the U.K. data alone and suggests a DDREF of about 1.5, rather than a central estimate of 0.98 based on data on cancer incidence obtained by Jacob et al. (2009). We also note, however, that although Ivanov et al. (2004) preferred the lower estimate of ERR based on follow-up from 1996 to 2001, it is questionable whether an estimate based on such a short period of follow-up is valid.

- Studies of cancer mortality in workers in the U.S. (Howe et al. 2004; Schubauer-Berigan et al. 2005), France (Rogel et al. 2005), and Canada (Zablotska et al. 2004) were not included in the analysis by Jacob et al. (2009). The first three studies were included in the 15-country study, and all gave central estimates of ERR < 0 (Cardis et al. 2007). The concerns that led Jacob et al. (2009) to exclude the data in Canadian workers from results of the 15-country study led us to consider using some of the data from the study of those workers reported by Zablotska et al. (2004) (L.B. Zablotska, personal communication, July 21, 2009). However, as described in Section 5.2.2.2, we concluded on the basis of the reanalysis of data on Canadian workers by Zablotska et al. (2014) that this was not feasible.
- Estimated ERRs, other than ERRs in Chernobyl cleanup workers and the Techa River cohort, that were used in the main analysis of cancer mortality came from five studies of workers, only one of which (the 3rd NRRW analysis in the U.K.) appears to have sufficient statistical power to enable derivation of a DREF that does not overlap zero at the 90% confidence level (Section 5.2.2.2 and Table 5.10). The positive but not statistically significant ERR/Gy in Hanford workers of 0.3 [90% CI: (–0.3, 1)] was determined mainly by cancer risks in workers of age 55 and older and was due primarily to an association with lung cancer (Wing and Richardson 2005), which suggests the potential for an effect of smoking history on the estimated ERR. The estimated ERR from the study of French radiation workers was provided as a personal communication, and its validity and significance cannot be assessed independently.

Another concern we have about the analysis by Jacob et al. (2009) involves the approach of representing the uncertainty in the estimated ERR/Gy in each cohort by a normal probability distribution.

Central estimates and CIs of ERRs in Tables 5.12 and 5.13 indicate that at least some of those ERRs are not normally distributed. More importantly, when a risk ratio is calculated as the ratio of two normal distributions, the result is a Cauchy distribution, which has an undefined mean and variance due to the unstable extreme values in the tails of the distribution. This problem is exacerbated when the coefficient of variation associated with a normal distribution is sufficiently large that negative values in the lower tail are generated. As indicated in Tables 5.12 and 5.13, negative values were included in several probability distributions of risk ratios reported by Jacob et al. (2009). Given these problems, which affect most of the estimated risk ratios and, thus, DDREFs estimated as the reciprocal of risk ratios, we conclude that the risk ratios and their pooled estimates obtained by assuming normal distributions and using an inverse (reciprocal)-variance weighting have uncertainties that cannot be fully characterized.⁵⁸ Although central estimates of risk ratios could be reasonable, given that the median and mode of a Cauchy distribution are stable, we think that the reported CIs are too narrow to adequately represent the uncertainty in risk ratios and, consequently, the uncertainty in a DDREF.

We also recognize that it is not clear how best to estimate a DDREF (or risk ratio) and its uncertainty using estimates of ERR/Gy from the various studies reported by Jacob et al. (2009). Use of an inverse (reciprocal)-variance approach to weighting of individual estimates would be considered valid by many because it minimizes the need for subjectivity in an analysis. Although we think that 90% CIs of risk ratios reported by Jacob et al. (2009) are too narrow, those results indicate the need for further study of the main issue raised by their analysis, which is that results from radiobiological studies cited by ICRP and the BEIR VII committee and discussed in Section 4.3 suggest a lower risk at low dose rates than at higher acute doses that is not reflected in many central estimates of risk ratios that Jacob et al. (2009) derived on the basis of results from epidemiological studies. Despite the issues we have raised, the study by Jacob et al. (2009) provides support for a DREF <1, if data in the LSS cohort are an appropriate baseline for comparisons of estimated risks from protracted and acute exposures.

Our concerns about the study by Jacob et al. (2009) notwithstanding, we think that studies that suggest a DREF <1 should be considered in developing a probability distribution of DDREF, given that linear dose-responses from acute exposure have been based on responses at moderate-to-high doses in the LSS cohort. However, if the pattern of risks at low doses in the LSS cohort shown in Figure 5.4 is valid, risks in chronically exposed populations at low doses could be comparable to risks to members of the LSS

⁵⁸ Cauchy distributions have defined percentiles, as well as a defined median and mode, so the problem of an undefined variance could be overcome by defining the weight to be given to each study by the reciprocal of the square of the ratio of the 95th to the 5th percentile, for example. However, problems associated with assuming complete statistical independence of uncertainties in ERRs from each study and the presence of negative values in normal distributions of ERR/Gy and the resulting risk ratios would remain.

cohort at the same low doses; i.e., a DREF could be about 1–2 if risks at low doses in radiation workers and the LSS cohort were compared.⁵⁹

5.2.2.5 Conclusions

It has been suggested that comparisons of estimated risks from epidemiological studies of nuclear workers with estimated risks in the LSS cohort are not particularly informative, e.g., for the purpose of estimating a DDREF, due to large uncertainties in the data (Cardis et al. 2005b; UNSCEAR 2008; Shore 2009). However, exposure conditions of workers that have been studied closely resemble those of energy workers whose cancer risks are estimated using NIOSH-IREP, and we believe that use of epidemiological data clearly is preferable to use of data from radiobiological studies of laboratory animals and cells.

As summarized in Table 5.11, a comparison of an estimated ERR/Sv for mortality from all cancers excluding leukemia from the 15-country study with the entire Canadian cohort excluded (a 14-country study) with an estimated ERR/Gy in the LSS cohort gave an estimated DREF of 0.7 [90% CI: (-3.1, 4.5)]. Of the four estimates of risks to workers based on the 15-country study, we concluded that this estimate is the most representative result. When the Canadian cohort excluding Ontario Hydro workers was included in the 15-country study, as preferred by Cardis et al. (2005b, 2007), a DREF of 0.49 [90% CI: (0.22, 1.7)] was obtained, and the estimated DREF with the entire Canadian cohort included was 0.52 [90% CI: (0.23, 2.1)]. A DREF of 0.32 [90% CI: (0.12, 1.4)] for mortality from all solid cancers was estimated based on data from the 15-country study with Ontario Hydro workers in the Canadian cohort excluded. Comparisons of estimates of ERR/Sv for mortality and incidence of all cancers excluding leukemia from the 3rd NRRW analysis of U.K. workers with estimates of ERR/Gy in the LSS cohort gave estimated DREFs of 1.0 [90% CI: (0.39, 5.1)] and 1.4 [90% CI: (0.64, 5.9)], respectively. Finally, a comparison of a

⁵⁹ To illustrate this point, the non-linear response implied by the data in Figure 5.4 suggests an LDEF of about 0.5 when the ERR/Gy in the lowest dose group is compared with the ERR/Gy in the moderate-to-high dose groups. This LDEF is comparable to DREFs of about 0.5–1 suggested by studies of chronically exposed populations when linear responses at moderate-to-high doses in the LSS cohort are used in comparing risks. When combined, these two estimates yield a DREF of about 1–2 based on comparisons of risks at doses of a few tens of mGy in the chronically exposed and LSS cohorts. However, if the non-linear dose-response in the LSS cohort shown in Figure 5.5 is considered to be more reasonable, the higher risks in chronically exposed populations would yield a much lower estimate of DREF of about 0.1. The data in Figure 5.5 suggest an LDEF of about 7 when estimates of ERR/Gy in the lowest dose group and the moderate-to-high dose groups are compared. In this case, the effects of the lower DREFs estimated from studies of chronic exposure and the higher LDEF obtained from the comparison of risks at low doses and moderate-to-high doses in the LSS cohort yield a DREF for chronic exposure of about 0.1. There is no satisfactory explanation for such a low DREF, unless contributions to risk from deleterious non-targeted and delayed effects are much greater when exposures are chronic than when exposures are acute. On the basis of current information, this seems highly unlikely. Although this exercise is hypothetical and the comparisons could be invalid due to large errors in estimated cancer risks at low doses in the LSS cohort, as well as effects of such risk factors as smoking history on estimated risks in the other cohorts, it illustrates the limitations in using epidemiological data, including data in the LSS cohort, to estimate a DDREF.

recent estimate of an ERR/Gy for mortality from all solid cancers in workers in France, the U.K., and the U.S. with an estimated ERR/Gy in the LSS cohort based on DS02 dosimetry gave an estimated DREF of 0.55 [90% CI: (0.30, 1.5)]. All central values of these DREFs are 50th percentiles we estimated based on assumptions summarized in Table 5.11.

If data on the effects of smoking were taken into account, estimated risks in Table 5.10 suggest that there would be little impact on DREFs based on the data in U.K. workers and the data in workers in France, the U.K., and the U.S., but there could be a slight increase in DREFs based on the 15-country study. However, the magnitude of the effect of smoking on estimates of DREF is uncertain because we do not have suitable estimates of ERR in the LSS cohort that have been adjusted for smoking history (e.g., by excluding lung and pleural cancers).

Despite questions about the applicability of results from the three studies of workers summarized in Table 5.10, including potential effects of other risk factors, we think that use of such estimates of DREF in developing a revised probability distribution of DDREF is justifiable when serious questions also apply to data in animals and to estimates of LDEF based on data in the LSS cohort only. We also think that estimates of DREF based on the multiple-cohort study by Jacob et al. (2009), as summarized in Section 5.2.2.4 should be considered despite our concerns about the methods used to estimate uncertainties; that study appears to provide support for a DREF <1. However, we chose not to use estimates of DREF based on estimated ERRs from studies of other individual worker cohorts summarized in Sections 5.2.2.1 and 5.2.2.2 and studies of the Techa River cohort summarized in Section 5.2.2.3.

5.3 STUDIES OF FEMALE BREAST CANCER

A DDREF for breast and thyroid cancer different from a DDREF for all other solid cancers is used in IREP (Section 1.1.1). Use of a separate DDREF for those cancers was based in part on a greater tendency for linear dose-responses in epidemiological data and some animal data. However, a recent analysis of incidence of female breast cancer in the LSS cohort by Preston et al. (2007) shows evidence of a non-linearity in the dose-response at neutron-weighted doses to the breast of 0–>4 Gy (Section 5.2.1.6, Figure 5.11). In addition, an analysis of dose-responses in the LSS cohort by Little and Muirhead (2000, 2004) summarized in Table 5.14 suggests that LDEFs for breast and thyroid cancer may not differ from LDEFs for most other cancers. Central estimates and distributions of LDEF for female breast and thyroid cancer are similar to those for respiratory and stomach/esophageal cancers, and all solid cancers combined. They also are similar to LDEFs in Table 5.2 for incidence of all solid cancers in the LSS cohort based on analyses by the BEIR VII committee (NRC 2006) and Preston et al. (2007) when estimates for similar dose ranges are compared, despite differences in dosimetry systems and length of follow-up.

Table 5.14. LDEFs (and 95% CIs) derived from analyses of curvature in dose-responses (ERRs) for incidence of various solid cancers in LSS cohort based on DS86 dosimetry^a

Dose range (Gy)	Thyroid cancer	Female breast cancer	Respiratory cancers	Stomach and esophageal cancers	All solid cancers ^b
0–4 ^c	0.80 (0.37, 3.34) [1.2 (0.4, 2.9)] ^e	0.77 (0.47, 1.59) [0.9 (0.5, 1.5)] ^f	0.95 (0.47, 3.62) [1.4 (0.5, 3.2)] ^f	0.92 (0.42, >1000)	1.06 (0.78, 1.62) [1.1 (0.8, 1.5)] ⁱ
0–2 ^d	1.7 (0.6, >1000)	1.03 (0.54, 10.3) [2.7 (0.7, 8.7)] ^g	1.14 (0.56, 21.0) [4.9 (0.8, 17)] ^h	1.12 (0.48, >1000)	1.21 (0.81, 2.45) [1.4 (0.9, 2.3)] ^j

^a Little and Muirhead (2000, 2004). Reported central values are MLEs. Entries in brackets are 50th percentiles and 90% CIs we estimated by describing reported LDEFs by Weibull distributions with modes at MLEs.

^b Analyses of dose-responses were based on neutron-weighted doses to colon.

^c Shielded kerma free-in-air from photons and neutrons. Neutron-weighted organ doses were calculated assuming neutron RBE of 20. Members of LSS cohort with shielded kerma >4 Gy were omitted.

^d Neutron-weighted organ doses calculated assuming neutron RBE of 20.

^e MLE is at 36th percentile of assumed Weibull distribution.

^f MLE is at 26th percentile of assumed Weibull distribution.

^g MLE is at 14th percentile of assumed Weibull distribution.

^h MLE is at 9.7th percentile of assumed Weibull distribution.

ⁱ MLE is at 41st percentile of assumed Weibull distribution.

^j MLE is at 34th percentile of assumed Weibull distribution.

An approach of developing a single DDREF distribution for all solid cancers is supported by an analysis of incidence of female breast cancer using data from a pooled analysis of eight cohorts by Preston et al. (2002). As discussed below, when effects of dose rate, dose fractionation, and differences in the biological effectiveness of x rays and high-energy gamma rays are taken into account, there is little justification for a separate DDREF distribution for breast cancer.

We first review the study of female breast cancer by Preston et al. (2002) and observations those investigators made about the relationship between their risk estimates and estimates of DDREF. We then apply an adjustment to their risk estimates for two medically exposed cohorts to account for a potentially higher biological effectiveness (REF_L) for x rays compared with high-energy gamma rays and consider the effect of that adjustment on estimates of DDREF. Next we evaluate whether data on breast cancer mortality in Canadian tuberculosis fluoroscopy cohorts can be used to estimate a DDREF. We then review a study of breast cancer incidence in the Techa River cohort, whose members were chronically exposed to beta and gamma radiation from internal and external sources. We conclude by discussing the implications of all available information on estimation of a probability distribution of DDREF for breast cancer.

5.3.1 Effects of Dose Rate in Analysis of Data on Breast Cancer Incidence by Preston et al. (2002)

Dose-responses for incidence of female breast cancer in eight cohorts were analyzed by Preston et al. (2002). There was no evidence of a significant non-linearity in dose-responses in any of the cohorts, which included Asian women who received a single acute exposure mainly to high-energy gamma rays (LSS cohort), North American women who received fractionated acute exposures to x rays of various energies between 60 and 250 kVp (tuberculosis fluoroscopy, acute post-partum mastitis, infant thymic enlargement, and benign breast disease cohorts), and European women who received protracted exposures to high-energy gamma rays mainly from ^{226}Ra applicators (infant skin hemangioma cohorts). Ages at exposure ranged from infancy in the skin hemangioma cohorts to post-menopausal. The different studies had long follow-up times and were thought to be free from serious complications or bias due to unobserved factors. However, possible differences in the biological effectiveness of the different types of low-LET radiation to which those cohorts were exposed were not taken into account.

In the full pooled analyses by Preston et al. (2002) summarized in Table 5.15, EARs in the infant thymic irradiation, tuberculosis fluoroscopy, and LSS cohorts were sufficiently similar to be presented as a combined estimate using a single EAR model, whereas the ERR in the LSS cohort was about three times higher than ERRs in the thymic irradiation and tuberculosis fluoroscopy cohorts, in which ERRs were sufficiently similar to be presented as a combined estimate using a single ERR model. The difference in ERRs in the LSS cohort and the thymic irradiation and tuberculosis fluoroscopy cohorts is a consequence of the similarity in EARs and the lower baseline rate of female breast cancer in the LSS cohort compared with U.S. populations. Exposures of those cohorts included acute exposures at high dose rates (LSS cohort and some members of the thymic irradiation cohort) and highly fractionated exposures at low doses (≈ 10 mGy per fraction) and high dose rates (>10 mGy min^{-1}) (tuberculosis fluoroscopy cohorts).

The ERR in the acute post-partum mastitis cohort may be an anomaly when baseline rates of breast cancer were much higher than in other cohorts and the effects of age at exposure and attained age on estimated risks of breast cancer were different than in the other cohorts (Preston et al. 2002). Risks in that cohort also may have been affected by the treated medical condition (inflammation of the breast after pregnancy) (Preston et al. 2002). A similar concern applies to the Swedish benign breast disease cohort, which had the highest EAR in the full pooled analysis. That effect was most pronounced in young women and may have been a consequence of an underlying association of the benign breast disease with breast cancer (Ronckers et al. 2005). In addition, a significant fraction of the acute post-partum mastitis and Swedish benign breast disease cohorts received very high doses, with mean doses to the breast of 5.8 Gy and 3.8 Gy, respectively, compared with doses in the other cohorts. The high mean doses in those two cohorts were similar to maximum doses to members of the LSS cohort.

Table 5.15. Estimates of ERR and EAR (and 95% CIs) for incidence of female breast cancer from full pooled analysis of eight cohort studies of external exposure to low-LET radiation^a

Cohort	Mean dose (Gy)	ERR/Gy	EAR/10 ⁴ person-y/Gy at age 50 ^b
Life Span Study (LSS): single acute exposure to high-energy gamma rays with small contribution from neutrons (DS86 dosimetry; shielded kerma <4 Gy; neutron RBE of 10)	0.3	2.10 (1.6, 2.8) ^c	—
Swedish benign breast disease: small number of dose fractions at high dose rate	5.8	1.9 (1.3, 2.8) ^d	32 (21, 47) ^{e,f}
New York acute post-partum mastitis: small number of dose fractions at high dose rate	3.8	0.56 (0.3, 0.9) ^g	15 (7.7, 24) ^{e,h}
Massachusetts tuberculosis fluoroscopy (original): many low-dose fractions at high dose rate	1.0	0.74 (0.4, 1.2) ⁱ	—
Massachusetts tuberculosis fluoroscopy (extended): many low-dose fractions at high dose rate	0.7	0.74 (0.4, 1.2) ⁱ	—
Rochester thymic irradiation (infants): single acute exposure or small number of dose fractions at high dose rate	0.7	0.74 (0.4, 1.2) ⁱ	—
Combined Life Span Study (LSS), Massachusetts tuberculosis fluoroscopy (original and extended), and Rochester infant thymic irradiation	1.0; 0.7	—	9.9 (7.1, 14) ^{e,j}
Combined Swedish skin hemangioma (infants in Stockholm and Gothenburg): protracted exposures at low dose rates from ²²⁶ Ra applicators	0.52; 0.17	0.34 (0.1, 0.7) ^g	5.1 (1.3, 11) ^k

^a Preston et al. (2002). Reported central values are MLEs.

^b Exponent of power function for dependence of EAR on attained age in all cohorts was 3.5 [95% CI: (2.4, 4.9)] before age 50 and 1.1 [95% CI: (-0.4, 2.4)] after age 50.

^c Estimate for women at attained age 50. Exponent of power function dependence of ERR on attained age was -2.0 [95% CI: (-2.8, -1.1)]. No dependence of ERR on age at exposure was included.

^d Estimate for women exposed at age 25. Percent change in ERR per decade increase in age at exposure was -60 [95% CI: (-71, -44)]. No dependence of ERR on attained age was included.

^e Estimate for women exposed at age 25.

^f Percent change in EAR per decade increase in age at exposure was -58 [95% CI: (-71, -40)].

^g Estimate applies at all ages at exposure and attained ages.

^h Percent change in EAR per decade increase in age at exposure was 24 [95% CI: (-46, 174)].

ⁱ Estimate for women at attained age 50 based on data in thymic irradiation and tuberculosis fluoroscopy cohorts combined. Exponent of power function dependence of ERR on attained age was -2.0 [95% CI: (-2.8, -1.1)]. No dependence of ERR on age at exposure was included.

^j With allowance for assumed dependence on age at exposure in all four cohorts—i.e., percent change in EAR per decade increase in age at exposure of -40 [95% CI: (-51, -28)]—model gave good fits to data in thymic irradiation cohort. Predicted EAR for age at exposure of 6 months is 34 cases/10⁴ person-y/Gy.

^k Estimate for women exposed at age of 6 months. No dependence of EAR on age at exposure was included.

Estimated risks in the skin hemangioma cohorts (mean age at exposure about 6 months) that received protracted external exposures to high-energy gamma rays tend to be lower than estimated risks in the other cohorts. Dose rates in the Gothenburg cohort (mean of about 1 mGy min⁻¹) were approximately uniform over the treatment period of about 30 years (Karlsson et al. 1998). However, dose rates in the Stockholm cohort increased by more than two orders of magnitude over a similar treatment period (Lundell 1994; Karlsson et al. 1998), and the mean dose rate (about 3 mGy min⁻¹) was higher than in the Gothenburg cohort. In neither cohort would the mean dose rate be characterized as “low” on the basis of the criterion for defining chronic exposures in IREP, i.e., a dose rate ≤ 0.1 mGy min⁻¹.

Although the lower risks in the skin hemangioma cohorts appear to be an effect of dose rate, Preston et al. (2002) noted that other unknown factors may have affected rates of breast cancer in those cohorts. Genetic differences in susceptibility to breast cancer probably do not explain the lower rates, given that age-specific baseline rates in Massachusetts, Connecticut,⁶⁰ and Sweden were similar and were much higher than in Japan (Preston et al. 2002), which appears to eliminate the possibility of a substantial subpopulation in Sweden that was less sensitive to radiation-induced breast cancer. In the LSS cohort, the ERR at ages at exposure <20 was higher than at older ages, and there was no consistent variation with age at exposure at ages <20 (Land et al. 2003b).

In addition to the full pooled analysis summarized in Table 5.15, Preston et al. (2002) performed a simple pooled analysis summarized in Table 5.16, in which estimates of ERR and EAR were obtained for individual cohorts and simple combinations of the tuberculosis fluoroscopy and skin hemangioma cohorts. Only in the full pooled analysis were data in the LSS, tuberculosis fluoroscopy, and thymic irradiation cohorts combined. In the simple analysis, ERRs in the skin hemangioma cohorts (mean age at exposure about 6 months) were much lower than in the infant thymic irradiation cohort (mean age at exposure 2.4 months) that mainly received acute exposures. When ERRs in the two hemangioma cohorts in Table 5.16 are averaged, ERRs in the thymic irradiation cohort are about 4 or 7 times higher than in the hemangioma cohorts, depending on the type of ERR model. Furthermore, results in Table 5.15 (including footnote *j*) indicate that the EAR in the combined skin hemangioma cohorts obtained from the full pooled analysis is about one-seventh of the predicted EAR for exposure at age 6 months based on the analysis of pooled data in the LSS, tuberculosis fluoroscopy, and thymic irradiation cohorts.⁶¹ These observations suggest that there is a significant dependence of the risk of breast cancer on dose rate.

⁶⁰ Data in women in Connecticut were included in comparisons of baseline rates, even though they were not included in any of the exposed cohorts.

⁶¹ A more recent pooled analysis of data in the skin hemangioma cohorts using a two-stage clonal expansion model (Eidemüller et al. 2009, 2011) yielded an estimated ERR/Gy at attained age 50 of 0.25 [95% CI: (0.14, 0.37)], which is similar to the ERR obtained by averaging estimates for the two hemangioma cohorts in Table 5.16 and the ERR for the two cohorts combined in Table 5.15. The estimated EAR/10⁴ person-y/Gy of 31 [95% CI: (17, 43)] from the more recent analysis is about 50% higher than the estimate for the two cohorts combined in Table 5.16.

Table 5.16. Estimates of ERR and EAR (and 95% CIs) for incidence of female breast cancer from simple pooled analysis of eight cohort studies of external exposure to low-LET radiation^a

Cohort	Mean dose (Gy)	ERR/Gy		EAR/10 ⁴ person-y/Gy ^{b,c}
		Age-at-exposure model ^b	Attained-age model ^{b,c}	
Life Span Study (LSS): single acute exposure to high-energy gamma rays with small contribution from neutrons (DS86 dosimetry; shielded kerma <4 Gy; neutron RBE of 10)	0.3	1.8 (1.3, 2.4)	2.16 (1.6, 2.8)	11.6 (7.3, 17)
Swedish benign breast disease: small number of dose fractions at high dose rate	5.8	1.94 (1.3, 2.8)	1.79 (1.0, 2.8)	23.1 (13, 40)
New York acute post-partum mastitis: small number of dose fractions at high dose rate	3.8	0.52 (0.25, 0.9)	0.56 (0.3, 0.9)	18.8 (8.1, 37)
Massachusetts tuberculosis fluoroscopy (original): many low-dose fractions at high dose rate	1.0	0.39 (<0, 1.02)	0.74 (0.2, 1.5)	—
Massachusetts tuberculosis fluoroscopy (extended): many low-dose fractions at high dose rate	0.7	0.29 (−0.06, 0.8)	0.37 (−0.07, 1.7)	—
Combined Massachusetts tuberculosis fluoroscopy (original and extended)	1.0; 0.7	—	—	5.7 (0.7, 16)
Life Span Study (LSS): estimates for age at exposure ≈0.5 years	0.3	4.5 (2.2, 8.8) ^d	2.16 (1.6, 2.8)	34 (16, 62) ^d
Rochester thymic irradiation (infants): single acute exposure or small number of dose fractions at high dose rate	0.7	1.56 (0.5, 3.9)	1.14 (0.2, 3.6)	30 (7.7; 71)
Gothenburg skin hemangioma (infants): protracted exposures at low dose rates from ²²⁶ Ra applicators	0.17	0.06 (<0, 1.0)	0.06 (<0, 0.5)	—
Stockholm skin hemangioma (infants): protracted exposures at low dose rates from ²²⁶ Ra applicators	0.52	0.38 (0.1, 0.8)	0.52 (0.16, 1.1)	—
Combined Swedish skin hemangioma cohorts (infants)	0.17; 0.52	—	—	20 (6, 124)

^a Preston et al. (2002). Reported central values are MLEs.

^b Estimates for women exposed at age 25, except at 6 months in thymic irradiation and skin hemangioma cohorts.

^c Estimates for women at attained age 50.

^d Estimates for women exposed at age about 0.5 years are based on age-at-exposure extrapolation using models developed by Preston et al. (2002). No extrapolation was necessary for ERR model modified by attained age only.

DREFs of about 4 or 7 that are suggested by the comparisons of ERRs described above are considerably higher than the DDREF of 1.5 [95% CI: (0.8, 2.7)] for all solid cancers that was derived by the BEIR VII committee on the basis of data in the LSS cohort and animals (NRC 2006). Furthermore, the ERRs at age at exposure 0.5 years in the LSS cohort of about 4.5 and 2.2 Gy⁻¹ in Table 5.16 are about 8 or 20 times higher than the average ERRs in the two skin hemangioma cohorts. A DREF of 8 or 20 also is considerably higher than the DDREF that was derived by the BEIR VII committee.

While there was a suggestion of an effect like cell sterilization at doses of several Gy or more in most of the cohorts exposed at high dose rates, the analysis by Preston et al. (2002) provided no evidence of a significant non-linearity in the dose-response at low doses. That result could support an LDEF of about one, were it not for the lower risks observed in the skin hemangioma cohorts. An LDEF of about one would be consistent with earlier studies that showed little effect of dose fractionation or protraction on breast cancer incidence (NCRP 1997; UNSCEAR 2000; Boice 2001). However, it makes the much lower risks in the skin hemangioma cohorts compared with risks in the other cohorts all the more intriguing, given that data in cells obtained using mFISH and data in animals also showed significantly lower risks from chronic exposure compared with acute exposure when acute dose-responses appeared to be linear.

The analysis by Preston et al. (2002) indicated that no single model adequately described excess risks in all cohorts. For example, as indicated in Table 5.16, those investigators first considered ERR models that depended on age at exposure or attained age only, but they could not fit the data in all cohorts with a model that included both effects. In the final pooled analysis summarized in Table 5.15, an effect of age at exposure or attained age was taken into account for some cohorts but not for the post-partum mastitis and skin hemangioma cohorts. This result, along with the effects of cell sterilization described previously, reinforces the concern discussed in Section 5.2.1 about the effects of model specification on uncertainties in estimated risks and DDREF.

On the basis of comparisons of EARs and ERRs in the thymic irradiation, tuberculosis fluoroscopy, and LSS cohorts, Preston et al. (2002) suggested that while fractionation of acute doses may have little effect on incidence of breast cancer, dose protraction at low dose rates may result in lower risks. They then recommended that an EAR model based on a fit to the data in the LSS, tuberculosis fluoroscopy, and thymic irradiation cohorts summarized in Table 5.15 should be used in estimating risks of breast cancer in general populations that received acute or fractionated exposures; in the recommended model, EAR depends on age at exposure and attained age. When exposures are protracted, Preston et al. (2002) recommended that risks estimated using that model should be reduced by a factor of two or three, because they did not think that the limited data in the skin hemangioma cohorts that suggested a DREF as high as about 7, as estimated above, provided sufficient justification for assuming larger reductions in risks at low dose rates. Although we reached a similar conclusion about the magnitude of a DDREF suggested by data

in the skin hemangioma cohorts, as described in the following section, uncertainties in estimated risks indicate that DDREFs of 7 or more cannot be excluded from consideration in developing a probability distribution of DDREF for breast cancer.

We also think that the conclusion by Preston et al. (2002) about the absence of an effect of fractionation of acute doses on estimated risks (and, hence, on DDREF) and the general applicability of an EAR model would have been different if their analysis had taken into account the potential influence on estimated risks in several cohorts of a biological effectiveness (REF_L) for medical x rays compared with high-energy gamma rays as high as 2–3; this issue is considered in the following section. As noted in Section 4.3.5.2, Bartstra et al. (2000) concluded that data in the tuberculosis fluoroscopy and LSS cohorts indicate a significant effect of dose fractionation because risks in both cohorts are best characterized using ERR models, even without considering the effect of a higher REF_L for x rays. In addition, the idea that risks from highly fractionated exposures delivered in fractions of about 10 mGy should be much higher than risks from chronic exposure is not in accord with expectations based on microdosimetry (Section 2.1) or radiobiological data (Figure 4.2).

5.3.2 Potential Influence of Energy Dependence of REF_L for Photons on Analysis of Data on Breast Cancer Incidence by Preston et al. (2002)

Prior to the study by Preston et al. (2002), Brenner (1999b) challenged the similarity in estimated risks of breast cancer in the tuberculosis fluoroscopy and LSS cohorts on the grounds that a higher RBE_M for 60–80 kVp x rays compared with high-energy gamma rays of about 1.6–1.9, as estimated in studies of cell transformation, compensated for the expected lower risks from fractionated exposures. Brenner's assumption about the biological effectiveness of 60–80 kVp x rays is consistent with our modified probability distribution of REF_L for 30–250 keV photons discussed in Section 2.4.2.5, which has a central estimate of 2 and 95% CI of (1, 3).

Absent an effect of RBE as suggested by Brenner (1999b), Ullrich (1999) concluded that (1) the conceptual basis for a DDREF and current mechanistic models of radiation carcinogenesis are incorrect, (2) target cells for radiation-induced breast cancer are somehow unique in being deficient in the ability to repair damage that could lead to cancer, or (3) there is a substantial subpopulation of individuals who are sensitive to radiation-induced breast cancer as a result of such a repair defect. Elkind (1999) supported the idea that a deficient repair mechanism was involved, and studies in animals reviewed in Section 4.3.5 provided evidence that such deficiencies can increase the sensitivity to radiation-induced mammary cancers. However, the existence of genetic links to explain an increased sensitivity is controversial, and no radiosensitive populations have been identified with the frequency and hypersensitivity required to explain observed dose-responses in humans (Brenner et al. 2003). One prediction based on a genetic link of this

type is that the dose-response at low doses would be supralinear (Brenner et al. 2003), but dose-responses of that type were not reported by Preston et al. (2002).

Although differential expression of genes that code for key proteins in the primary DNA-repair pathways has not yet been linked to susceptibility to radiation-induced breast cancer in humans, Moll et al. (1999) reported that the expression of several proteins in the NHEJ pathway (DNA-PKcs and Ku80) is greatly influenced by hormone-dependent changes in physiological state that result, for example, in stronger expression in lactating human breast tissue. Such an effect could explain the observed links between child-bearing status and lactation history and risks of breast cancer (Land et al. 2003b), but it would not explain the observed patterns of dose-responses for breast cancer in humans.

Rossi (1999) appeared to favor Brenner's hypothesis about the effect of a higher RBE for x rays, but he also pointed out that complex dose-response relationships can occur, even for monoclonal tumors, if pre-existent malignant cells can be killed at low doses, e.g., due to hyper-radiosensitivity. Rossi (1999) also noted that epidemiological data on induction of lung cancer and leukemia at low doses were inconsistent with an LQ relationship; this matter is discussed in Sections 5.5 and 5.8. That observation also is consistent with some data in animals reviewed in Sections 4.3.1 and 4.3.2.

If we accept Brenner's argument, estimated risks of breast cancer in all cohorts exposed to x rays could have been compromised by assuming no increase in the biological effectiveness of lower-energy photons. An important consequence could be an underestimation of an effect of dose fractionation on estimated risks, particularly in the tuberculosis fluoroscopy cohorts in which patients received about 100 doses of x rays of 10 mGy each over a period of 2–3 years. The following discussion considers the effect of an increased REF_L for x rays compared with high-energy gamma rays on estimates of risks of female breast cancer reported by Preston et al. (2002) and a DDREF based on those estimates.

To consider the effect of a higher REF_L for medical x rays on estimated risks in the tuberculosis fluoroscopy cohorts and to facilitate comparisons with estimated risks in the LSS and skin hemangioma cohorts exposed to high-energy gamma rays, we used estimated risks in individual cohorts or simple pairings of cohorts given in Table 5.16. We excluded estimated risks in the acute post-partum mastitis and benign breast disease cohorts because of questions about their relevancy, as discussed in the previous section, and because of the low level of dose fractionation (few acute doses) in those cohorts. To evaluate information bearing on a DDREF for chronic exposure, we also excluded estimated risks in the Rochester thymic irradiation cohort, most of whose members received a single acute exposure.

For the following reasons, we also elected not to use updated risk estimates for incidence of female breast cancer in the LSS cohort based on dose-response models developed by Preston et al. (2007) in our comparisons with estimated risks in cohorts exposed to medical x rays:

- Although the analysis of data on incidence of female breast cancer in the LSS cohort by Preston et al. (2007) was based on five years of additional follow-up, differences in estimated ERRs compared with ERRs at the same ages at exposure and attained ages reported by Preston et al. (2002) are not significant.
- Although Preston et al. (2007) concluded that recent data in the LSS cohort do not indicate a significant effect of age at exposure on the ERR for female breast cancer, alternative analyses conducted by those investigators and other analyses by Land et al. (2003b) and Ronckers et al. (2005) indicated the contrary.
- Estimated risks of female breast cancer based on the EAR model developed by Preston et al. (2007) cannot be compared with risks estimated using models developed by Preston et al. (2002) when an effect of menopause—i.e., a significantly greater dependence of EAR on attained age prior to age 50 than at older ages—was not included in the more recent analysis. As indicated in Table 5.15, footnote *b*, EAR models for all eight cohorts developed by Preston et al. (2002) incorporate such an effect. Although Preston et al. (2007) noted that “allowing the EAR to vary with age in a manner similar to that seen for the baseline rates (described in terms of a quadratic spline in log age with a knot at age 50) led to a marked improvement in fit ($P = 0.001$),” they did not incorporate this improvement in their risk models for female breast cancer.

We then estimated DDREFs by comparing estimated risks in the LSS cohort in the first row of Table 5.16 with estimated risks in the two tuberculosis fluoroscopy cohorts divided by the central estimate of our modified REF_L of 2 for 30–250 keV photons and by comparing estimated risks in infants in the LSS cohort with estimated risks in the two skin hemangioma cohorts. In making these comparisons, we excluded estimated risks in tuberculosis fluoroscopy and skin hemangioma cohorts with unspecified lower limits of 95% CIs <0 . A ratio of a risk in the LSS cohort to the corresponding risk in one of the other cohorts gives a DREF when exposures of the tuberculosis fluoroscopy and skin hemangioma cohorts were highly fractionated (many low-dose fractions) or chronic. The resulting estimates of DREF and their uncertainties are given in Table 5.17. By accounting for a higher biological effectiveness of medical x rays relative to high-energy gamma rays, we think that a more credible estimate of the effect of dose fractionation on risks of breast cancer is obtained.

To pool the ERR-based DREFs in the two tuberculosis fluoroscopy cohorts in Table 5.17 that were estimated using attained-age models, we assigned a fractional weight to each estimate based on the reciprocal of the square of its relative error. Because those DREF distributions were asymmetrical and could not be represented by a single type of distribution (e.g., lognormal), we represented the relative error in each DREF by the ratio $(95^{\text{th}} \% \text{-tile} - 5^{\text{th}} \% \text{-tile}) / (50^{\text{th}} \% \text{-tile})$.

Table 5.17. DREFs (50th percentiles and 90% CIs) derived by comparing estimates of ERR and EAR for breast cancer incidence in four cohort studies of highly fractionated or chronic exposures with matched estimates in LSS cohort based on DS86 dosimetry and accounting for increased biological effectiveness (REF_L) of medical x rays compared with high-energy gamma rays

Cohort	DREFs based on ERRs			DREFs based on EARs ^a	Combined estimates of DREF
	Age-at-exposure model ^a	Attained-age model ^a	Pooled estimate		
Massachusetts tuberculosis fluoroscopy (original)	—	5.5 (3.0, 16) ^{b,c}	—	—	—
Massachusetts tuberculosis fluoroscopy (extended)	10 (-38, 68) ^{b,c}	7.1 (-36, 55) ^{b,d}	—	—	—
Combined tuberculosis fluoroscopy	10 (-38, 68)	5.5 (3.0, 17) ^e	5.5 (2.9, 20) ^h	3.4 (1.4, 16) ^{b,i}	4.0 (1.4, 17) ^k
Stockholm skin hemangioma	12 (5.0, 40) ^{b,f}	3.9 (2.0, 11) ^{b,g}	—	—	—
Combined skin hemangioma	12 (5.0, 40)	3.9 (2.0, 11)	5.8 (2.1, 28) ^h	0.93 (0.28, 4.7) ^{b,j}	1.5 (0.29, 14) ^k
Combined tuberculosis fluoroscopy and skin hemangioma					3.6 (0.7, 17) ^m
					3.4 (0.6, 17) ⁿ

^a 50th percentiles and 90% CIs we estimated using Monte Carlo uncertainty propagation techniques and assumption that ERRs and EARs in Table 5.16 are described by Weibull distributions with modes at reported MLEs; DREFs are not estimated based on ERRs and EARs in tuberculosis fluoroscopy and skin hemangioma cohorts with unspecified lower limits of 95% CIs <0. Except as noted, REF_L for x rays of 2, with no uncertainty, is assumed.

^b DREF is ratio of ERR or EAR in appropriate age group in LSS cohort to corresponding ERR in individual cohort or EAR in combined cohort given in Table 5.16, with DREFs in tuberculosis fluoroscopy cohorts increased by factor of 2, with no uncertainty except as noted, to account for REF_L for medical x rays.

^c MLEs of ERRs in LSS and tuberculosis fluoroscopy cohorts are at 50th and 46th percentiles, respectively, of assumed Weibull distributions.

^d MLEs of ERRs in LSS and tuberculosis fluoroscopy cohorts are at 50th and 35th percentiles, respectively, of assumed Weibull distributions.

^e DREF in combined cohort estimated as described in text by weighting estimates in individual cohorts using reciprocal of squares of their relative errors.

^f MLEs of ERRs in LSS and skin hemangioma cohorts are at 42nd and 45th percentiles, respectively, of assumed Weibull distributions.

^g MLEs of ERRs in LSS and skin hemangioma cohorts are at 50th and 44th percentiles, respectively, of assumed Weibull distributions.

^h DREF estimated as described in text by weighting estimates based on age-at-exposure and attained-age models using reciprocal of squares of their relative errors.

ⁱ MLEs of EARs in LSS and tuberculosis fluoroscopy cohorts are at 48th and 40th percentiles, respectively, of assumed Weibull distributions.

^j MLEs of EARs in LSS and skin hemangioma cohorts are at 45th and 23rd percentiles, respectively, of assumed Weibull distributions.

Table 5.17 (continued)

^k DREF estimated as described in text by assigning weight of 25% to pooled estimate based on ERR models and weight of 75% to estimate based on EAR model to take into account uncertainty in transferring risks of female breast cancer from LSS cohort to cohorts in U.S. and Sweden. Combined estimates of DREF obtained by assigning equal weights to estimates based on ERR or EAR models are 4.5 (1.5, 18) for combined tuberculosis fluoroscopy cohort and 2.6 (0.3, 20) for combined skin hemangioma cohort; assigning equal weights to ERR- or EAR-based estimates gives equal weight to assumptions of multiplicative or additive risk-transfer.

^m DREF estimated by weighting combined estimates for tuberculosis fluoroscopy and skin hemangioma cohorts using reciprocal of squares of their relative errors.

ⁿ DREF that takes into account assumed uncertainty in REF_L for medical x rays [95% CI: (1, 3)] described in Section 2.4.2.5 in exposures of tuberculosis fluoroscopy cohorts.

Using our weighting procedure, the ERR-based DREFs in the two tuberculosis fluoroscopy cohorts that were estimated using attained-age models were combined to obtain the distribution for the combined cohort in the second column of results in Table 5.17. This procedure was not needed in the other three cases of ERR-based DREFs when the estimated ERR in the original tuberculosis fluoroscopy cohort using an age-at-exposure model and estimated ERRs in the Gothenburg skin hemangioma cohort using either model had unspecified lower limits of 95% CIs <0 and were excluded from our analysis.

For each of the combined cohorts, the two estimates of DREF based on the different ERR models were pooled using the same weighting procedure to give the distributions in the third column of results in Table 5.17. Both distributions were determined primarily by the DREF distributions based on attained-age models (weights of 96% and 60% in the combined tuberculosis fluoroscopy and combined skin hemangioma cohorts, respectively).

For each combined cohort, the pooled estimate of DREF based on the two ERR models was combined with the DREF based on an EAR model by taking into account an uncertainty in transferring risks in the LSS cohort to the cohorts of medical patients with different baseline rates of breast cancer (Preston et al. 2002). An approach to addressing uncertainty in risk transfer is discussed in Section 5.1.1. If the EAR in any population is assumed to be a constant multiple of the baseline rate (B), in which case a multiplicative risk-transfer model would apply, $ERR = EAR/B$ is a constant and, thus, would transfer directly without adjustment for a difference in baseline rates, and a DREF based on ERR models would be correct. However, if the EAR in any population is assumed to be independent of the baseline rate, an additive risk-transfer model would apply, EAR would transfer directly, and a DREF based on EAR models would be correct. Uncertainty in the correct risk-transfer model can be represented by assigning nonzero weights to the DREFs based on ERR and EAR models.

In this analysis, we assigned a weight of 75% to the DREFs based on EAR models in the combined tuberculosis fluoroscopy and skin hemangioma cohorts in Table 5.17 and a weight of 25% to the pooled

DREFs based on ERR models in those cohorts. This assumption, which gives greater weight to an additive risk-transfer model as suggested by Preston et al. (2002), is consistent with the assumption in IREP about the uncertainty in risk transfer for female breast cancer (Land et al. 2003a; Kocher et al. 2008). Using these weights, the combined estimates of DREF in the tuberculosis fluoroscopy and skin hemangioma cohorts in the last column in Table 5.17 are obtained.

The central estimate (50th percentile) of DREF for the combined tuberculosis fluoroscopy cohort is a factor of 2.7 higher than the central estimate of DREF for the combined skin hemangioma cohort. These central estimates would differ by a factor of about 1.3 if an REF_L of 2 for medical x rays had not been applied to estimated risks in the tuberculosis fluoroscopy cohorts. However, since the uncertainties in the estimated DREFs for the combined tuberculosis and skin hemangioma cohorts are large, it cannot be determined on the basis of our results whether the sparing effect of highly fractionated doses is about the same as the effect of chronic exposure.

Finally, we developed an overall pooled estimate of DREF by combining the two estimates in the last column in Table 5.17, with each estimate weighted by the reciprocal of the square of its relative error. This approach gives an estimated DREF based on all the data for breast cancer with a 50th percentile and 90% CI of 3.6 (0.7, 17). By accounting for the assumed uncertainty in REF_L for 30–250 keV photons [95% CI: (1, 3)] described in Section 2.4.2.5 in exposures of the tuberculosis fluoroscopy cohorts, the combined estimate of DREF is changed slightly to 3.4 (0.6, 17). This result incorporates an assumption that a DDREF for x rays and higher-energy gamma rays should not differ significantly.

The issue of how to weight estimates of DREF based on ERR and EAR models is important because, as indicated by the results in Table 5.17, the choice of the risk model had a substantial effect on DREFs for the two combined cohorts. For the combined skin hemangioma cohort, the EAR-based central estimate of DREF (0.93) is a factor of 6.2 lower than the central value of the pooled estimate based on the ERR models (5.8). By giving 75% weight to the EAR-based estimates, those estimates had a substantially greater influence on the combined estimates of DREF in the last column of Table 5.17.

Because baseline rates of breast cancer are substantially lower in the LSS cohort than in the tuberculosis fluoroscopy and skin hemangioma cohorts (Preston et al. 2002) and baseline rates have increased nearly to U.S. levels in Japanese immigrants (IARC 2002), comparisons of estimated risks based mainly on EAR models could be appropriate, as recommended by Preston et al. (2002) and assumed in our analysis. However, that assumption is not supported by the recent analysis of the effects of birth cohort on excess rates of breast cancer in the LSS cohort (Preston et al. 2007). In addition, there is support from studies of mammary tumors in animals (Section 4.3.5.2) for the use of ERR-based estimates in

modeling risk transfer (NRC 2006).⁶² If equal weights were given to the ERR- and EAR-based estimates of risks in the third and fourth columns of results in Table 5.17, the combined estimates of DREF in the last column in Table 5.17 would be 4.5 [90% CI: (1.5, 18)] for the tuberculosis fluoroscopy cohorts and 2.6 [90% CI: (0.3, 20)] for the skin hemangioma cohorts. By combining the two estimates weighted by the reciprocal of the squares of their relative errors and accounting for the uncertainty in REF_L in exposures of the tuberculosis fluoroscopy cohorts, the overall pooled estimate of DREF would be 4.2 [90% CI: (1.0, 18)]. This estimate is somewhat higher than, but not significantly different from, the overall pooled estimate of 3.4 [90% CI: (0.6, 17)] in Table 5.17.

Our DREF for female breast cancer of 3.4 [90% CI: (0.6, 17)] in Table 5.17 is higher than an LDEF with a 50th percentile and 90% CI of 0.9 (0.5, 1.5) based on an analysis of the dose-response in the LSS cohort at a DS86 shielded kerma of 0–4 Gy (Little and Muirhead 2000, 2004) (Table 5.14). However, an LDEF with a 50th percentile and 90% CI of 2.7 (0.7, 8.7) based on the dose-response at doses to the breast of 0–2 Gy in Table 5.14 is similar to our DREF distribution, although the upper limit of the CI is lower.

As noted above, data on radiation-induced mammary tumors in animals support an assumption that a DDREF for breast cancer in humans can be estimated on the basis of ERR models alone. Using the estimated DREFs based on ERRs in the tuberculosis fluoroscopy and skin hemangioma cohorts given in Table 5.17, this assumption would increase the central estimate of DREF for the two cohorts combined to nearly 6. It also is possible that the assumed REF_L of 2 for x rays in exposures of the fluoroscopy cohorts is too low. If we had assumed a central value of REF_L of 3 for x rays, which is consistent with the upper limit of the range noted by ICRP (2003) as possibly appropriate for use in risk analysis, the central estimate of the weighted average of our DREFs would have been about 8. That result would be comparable to DREFs obtained in studies of induction of mammary tumors in mice and rats in which hormone levels were not depressed as an effect of exposure of the ovaries (Section 4.3.5.1).

5.3.3 Analysis of Breast Cancer Mortality in Canadian Tuberculosis Fluoroscopy Cohorts

Risks of mortality from breast cancer have been estimated in Canadian tuberculosis fluoroscopy cohorts. Significant differences in risks in different groups of patients, which could be related to an effect of dose fractionation or dose rate, were described by Howe and McLaughlin (1996).

In patients in Nova Scotia, the estimated ERR/Gy at age at exposure 15 was 3.56 [95% CI: (1.85, 6.82)], whereas the ERR/Gy at the same age at exposure in patients in the rest of Canada was 0.40 [95%

⁶² Kellerer et al. (2006) suggested that their analysis that indicated a high RBE of ≈ 100 for neutrons in exposures of the LSS cohort reduces the ERR for the gamma-ray component “sufficiently to render the postulate of additive risk transfer unnecessary.” Given the preliminary nature of their findings and the uncertainty in the effect of the neutron RBE on the curvature in the dose-response for gamma rays, we have not incorporated their findings in our analysis.

CI: (0.13, 0.77)] (Howe and McLaughlin 1996). Similarly, the estimated EAR/10⁴ person-y/Gy at 20 years after exposure at age 15 was 10.3 [95% CI: (6.37, 16.2)] in patients in Nova Scotia but 1.22 [95% CI: (0.42, 2.34)] in patients elsewhere (NRC 2006).⁶³ These differences have not been explained satisfactorily. They could reflect differences in irradiation practices, such as a higher frequency of anterior-posterior exposures in patients in Nova Scotia that resulted in an average dose to the breast per fluoroscopy procedure of 35 mGy vs 8 mGy in patients elsewhere (Howe and McLaughlin 1996), errors in dosimetry, cancer ascertainment, or other biological responses not accounted for, or an effect of dose fractionation or dose rate (UNSCEAR 1993, 2000; NRC 2006). Doses to patients in Nova Scotia generally were less fractionated than elsewhere, and doses per fraction and total doses were higher (NRC 2006).

Another difference was that the dose rate in exposures in Nova Scotia was more than an order of magnitude higher than elsewhere, although the higher dose rate was still much lower than in the LSS cohort (UNSCEAR 1993). Differences in estimated risks in the two groups in earlier studies led UNSCEAR (1993) to conclude that those differences were consistent with a DREF of about 3. However, DREFs based on comparisons of central estimates of ERRs and EARs in the two Canadian groups reported by Howe and McLaughlin (1996) and given above are about 8–9. Since the risk of mortality from breast cancer per unit dose in the non-Nova Scotia patients was similar to the risk in patients in Massachusetts and risks in the Nova Scotia subcohort were determined mainly by risks in women with doses to the breast >10 Gy (Howe and McLaughlin 1996), UNSCEAR (2000) concluded that risks in the non-Nova Scotia patients alone might be more representative of risks at lower doses.

Risks of breast cancer mortality in women in the LSS cohort exposed at age 15 estimated by Howe and McLaughlin (1996) based on DS86 dosimetry and an assumed neutron RBE of 20 are an ERR/Gy of 1.56 [95% CI: (0.41, 3.53)] and an EAR/10⁴ person-y/Gy at 20 years after exposure of 0.85 [95% CI: (0.24, 1.71)]. By assuming that all central values of estimated risks are MLEs and accounting for an assumed REF_L for x rays of 2 [95% CI: (1, 3)] described in Section 2.4.2.5, a comparison of ERRs and EARs in non-Nova Scotia patients and the LSS cohort yields estimated DREFs with 50th percentiles and 90% CIs of 7.8 (1.9, 28) and 1.3 (0.35, 4.4), respectively. The MLEs of ERRs and EARs in both cohorts are at the 43rd and 46th percentiles, respectively, of assumed Weibull distributions. Combining the two estimates by assigning weights of 25% and 75% to the ERR- and EAR-based estimates, respectively, to account for uncertainty in risk transfer, as in the analysis described in the previous section, gives an estimated DREF of 1.8 [90% CI: (0.4, 19)]. This estimate is less than, but not significantly different from, the DREF based on data on incidence of breast cancer in the Massachusetts tuberculosis fluoroscopy

⁶³ An ERR/Gy for incidence of breast cancer in women of ages 15–19 in the LSS cohort reported by Land et al. (2003b) was significantly higher than in women of ages 20 and older, but there was no evidence of a consistent dependence of risk on age at exposure at ages less than 20.

cohorts and is comparable to the DREF based on incidence data in the Swedish skin hemangioma cohorts summarized in Table 5.17.

5.3.4 Analysis of Breast Cancer Incidence in Techa River Cohort

An analysis of data on breast cancer incidence in the Techa River cohort based on follow-up through 2006 (Ostroumova et al. 2008) gave a significant dose-response with an ERR/Gy of 5.0 [95% CI: 0.80, 12.8]. The mean age at diagnosis was 49. When compared with ERRs at age at exposure 25 or attained age 50 in the LSS cohort given in Table 5.16, this estimate suggests a DREF of about 0.4. However, the low statistical power due to the high migration of exposed individuals from the study area, low doses (mean dose about 40 mGy), and small numbers of cases (estimated excess of 12% of 109 total breast cancers) did not permit firm conclusions about the effects on risk of age at exposure, attained age, and ethnicity. Significant effects of birth cohort, attained age, and ethnicity (Slavs vs Tartars and Bashkirs) on baseline risks of breast cancer also were observed. For unexplained reasons, risks in women who arrived in the area along the Techa River in 1953–1960 were significantly higher than risks in women who lived there during the period of highest contamination in 1950–1951, which suggests that risk factors other than radiation exposure (e.g., later chemical exposures) could have been important.

Another concern about the Techa River study is that doses to the breast were equated with estimated doses to the stomach from a dose reconstruction completed in 2000. Estimated doses have other limitations that could bias estimates of ERR, and Ostroumova et al. (2008) noted several areas where improvements in dose estimates were needed or planned. However, those investigators concluded that while improvements were likely to reduce uncertainties in estimated doses to individuals, they were not expected to substantially modify estimated risks. As with other studies of this cohort, Ostroumova et al. (2008) noted that the observed linear trend in the dose-response should be interpreted with caution. However, unlike other studies of the Techa River cohort in which uncertainties in estimated doses were judged to be the most important source of uncertainty in estimated risks, such as the studies of leukemia discussed in Section 5.8.3.3, the main concern in the study by Ostroumova et al. (2008) was the small number of excess breast cancers.

For reasons discussed in Section 5.8.3.3, we think that the conclusion by Ostroumova et al. (2008) about the effects of dosimetric uncertainties on uncertainties in estimated risks in the Techa River cohort may be optimistic. Our concerns were reinforced by a review of the 2008 draft of a report to document the latest attempt to define the timing and composition of releases to the Techa River from the Mayak facility for use in dose reconstructions. Factors that limit dose reconstructions and epidemiological studies in this

cohort are described by Kossenko (2010). Until our concerns are addressed, we remain skeptical about the validity of estimated risks of breast cancer for purposes of risk assessment or estimating a DREF.

5.3.5 Discussion of Studies of Breast Cancer

Results we obtained from studies of breast cancer after applying an REF_L for x rays to estimated risks in tuberculosis fluoroscopy cohorts indicate that DREFs from highly fractionated acute exposures at low doses per fraction may be similar to DREFs from chronic exposure in the skin hemangioma cohorts. This result does not appear to depend on assumptions about weights assigned to estimates of DREF based on additive or multiplicative risk-transfer models or uncertainties in REF_L . It also is in better accord with microdosimetric considerations and radiobiological data than the alternative hypothesis that risks from highly fractionated acute exposures are higher than risks from chronic exposure at the same total dose.

Our results demonstrate the importance of considering a higher biological effectiveness of x rays in assessing risks of breast cancer. Indeed, we do not think that epidemiological data, much of which has been obtained in studies of the effects of exposures to medical x rays, can be used to estimate a DDREF unless the potentially higher biological effectiveness of x rays, compared with higher-energy photons, is taken into account. In order to fully represent the current state of knowledge, we think it is necessary to account for an uncertain REF_L in estimating risks from exposure to x rays. While we recognize that there is not a consensus opinion on the existence of a higher biological effectiveness of x rays or the magnitude of such an effect (NRC 2006; Hunter and Muirhead 2009), we think that a substantial body of information supports an assumption that a higher biological effectiveness of lower-energy photons should be incorporated in cancer risk assessments, its uncertainty notwithstanding. A reluctance to include such an assumption is based in part on the lack of evidence of an energy dependence of REF_L for low-LET radiations in epidemiological studies (e.g., see NRC 2006). However, as noted by Hunter and Muirhead (2009), uncertainties in epidemiological data are sufficiently large that the data neither support nor disprove the hypothesis that medical x rays are biologically more effective than higher-energy photons.

On the basis of data on breast cancer incidence in cohorts of medical patients exposed to x rays or higher-energy photons summarized in Table 5.17, we obtained a probability distribution of a DREF with a 50th percentile and 90% CI of 3.4 (0.6, 17). In addition, by comparing estimated risks of breast cancer mortality in Canadian tuberculosis fluoroscopy cohorts exposed to medical x rays, excluding patients in Nova Scotia, with estimated risks in the LSS cohort, we estimated a DREF of 1.8 [90% CI: (0.4, 19)], as described in Section 5.3.3. These two distributions do not differ significantly.

The two probability distributions of DREF we developed also can be compared with an estimated LDEF with a 50th percentile and 90% CI of 2.7 (0.7, 8.7) given in Table 5.14, which was based on an

analysis by Little and Muirhead (2000, 2004) of the curvature in the dose-response for female breast cancer in the LSS cohort at doses to the breast of 0–2 Gy. The main difference is that the upper limit of the 90% CI of that LDEF is lower than upper limits of the 90% CIs of the two DREFs. We think that both data sets should be taken into account in estimating a DDREF for breast cancer.

Our analysis demonstrates that the assumption of a separate DDREF for breast cancer in IREP (Section 1.1.1) is difficult to justify. The overall weight of evidence indicates that the uncertainty in a DDREF for breast cancer is sufficiently large that a DDREF for breast cancer cannot be distinguished from a DDREF for other solid cancers.

The remaining uncertainties in estimated risks of breast cancer and in the REF_L for medical x rays cannot be resolved based on current information. An uncertainty in the RBE for neutrons in exposures of the LSS cohort could have introduced additional uncertainty in estimates of DDREF for breast cancer.

The unresolved issues described above suggest that caution should be exercised in interpreting the epidemiological data on radiation-induced breast cancer. Uncertainties in estimated risks and in LDEFs or DREFs derived from such data may be larger than suggested by the analyses presented in this report, regardless of whether or not an adjustment to account for an REF_L for medical x rays is included.

Finally, an important conclusion from the studies of breast cancer incidence in the Massachusetts tuberculosis fluoroscopy cohorts is that there was an excess risk associated with dose fractions of about 10 mGy when the mean total dose to the breast was about 1 Gy and maximum doses were 5 or 6 Gy (Preston et al. 2002), regardless of the extent to which dose fractionation reduced the excess risk per unit dose; see also ICRP (2005) and Boice (2011). This conclusion is consistent with data on induction of mammary cancer in rats, which showed significant excess risks when dose fractions of 2.5 or 10 mGy were given at 12- or 24-hour intervals and total doses were 1–2 Gy (Bartstra et al. 2000). While the data in humans and animals do not provide direct evidence of whether or not estimated risks can be extrapolated to total doses of 10–20 mGy, the contrary view that such risks do not exist cannot be refuted by existing epidemiological studies, because of their limited statistical power. For our purposes, evidence that the effects of such small dose fractions are cumulative, as in the data in animals reported by Bartstra et al. (2000) which indicate that radiation damage associated with doses of that magnitude is not fully repaired with a lapse of several weeks before the next dose is administered, provides a strong argument for a deleterious effect at total doses as low as 10 mGy. These results seem to argue against the existence of a threshold or a hormetic effect at doses of 10–100 mGy.

Unless excess risks associated with the cumulative effects of repeated low-dose exposures can be attributed to a mechanism for induction of breast cancer that would imply a threshold, we think it would be unwise to abandon a nonthreshold approach to extrapolating risks at low doses. However, we cannot

rule out the possibility that such exposures, when delivered at a dose rate much lower than the dose rate in exposures of members of the skin hemangioma cohorts, might result in significantly different outcomes.

5.4 STUDIES OF THYROID CANCER

We also evaluated epidemiological data on radiation-induced thyroid cancer for the purpose of estimating a DDREF. Estimated risks of thyroid cancer from external exposure of various cohorts of children that were included in a pooled analysis by Ron et al. (1995) are given in Table 5.18. Data from studies of three of the cohorts (LSS and two skin hemangioma cohorts) also were used in estimating a DDREF for breast cancer. However, unlike the situation with breast cancer, studies of thyroid cancer in medical patients were concerned with effects of exposure of children of ages < 15, rather than adults, and the extent of fractionation of doses from x rays in medically exposed children was much less than in the tuberculosis fluoroscopy cohorts discussed in Section 5.3.

With the exception of estimated risks in the two skin hemangioma cohorts, it is not clear at the outset that estimated risks in Table 5.18 can be used to define a DDREF for chronic exposure. However, a potential advantage of the data on thyroid cancer is that mean doses to medical patients often were lower than mean doses in the breast cancer cohorts given in Table 5.15. Thus, the studies of thyroid cancer may be useful in assessing the approach used in IREP to phase in a DDREF for acute exposure at doses less than 30–200 mGy (Land et al. 2003a; Kocher et al. 2008).

Until recently, models to estimate risks of thyroid cancer in the different study cohorts did not include a dependence on sex, age at exposure, attained age, or time since exposure, even though Ron et al. (1995) thought that the combined effect of these parameters on estimated risks was significant. However, models of risks of thyroid cancer in the LSS cohort that include a dependence on sex, age at exposure, and attained age have now been developed (Preston et al. 2007; Richardson 2009; Furukawa et al. 2013).

The risk model for thyroid cancer in IREP was based on an independent analysis of data assembled by Ron et al. (1995). In pooling those data, Land et al. (2003a) judged that no correction was needed to account for a possible difference in the biological effectiveness of high-energy gamma rays from the atomic bombs and medical x rays because most exposures to x rays were fractionated and, thus, a DDREF should apply. Land et al. (2003a) concluded that, at moderate to high doses, fractionation of exposures to x rays and an increased biological effectiveness of x rays should have had opposite and approximately equal effects on risk; i.e., it was assumed that the risks of thyroid cancer from fractionated exposures to medical x rays and acute exposure to high-energy gamma rays should be about the same. Although this may have been a reasonable assumption, no uncertainty was included to account for the possibility that the two risks were not the same.

Table 5.18. Estimates of ERR and EAR (and CIs) for thyroid cancer incidence from cohort studies of external exposure to low-LET radiation before age 15

Cohort	Mean dose (Gy)	ERR/Gy (CI) ^a	EAR/10 ⁴ person-y/Gy (CI) ^a
Pooled analysis of five cohort studies (Ron et al. 1995) ^b	—	7.7 (2.1, 29)	4.4 (1.9, 10)
Life Span Study (LSS): single acute exposure to high-energy gamma rays with small contribution from neutrons; age at exposure < 15 (Ron et al. 1995; Thompson et al. 1994) (DS86 dosimetry; shielded kerma <4 Gy; neutron RBE of 10)	0.27	4.7 (1.7, 11)	2.7 (1.2, 4.6)
Life Span Study (LSS): subset of cohort with ages at exposure 0–9 years (UNSCEAR 2000; Thompson et al. 1994)	—	9.9 (4.1, 19) ^c	4.3 ^c
Rochester thymic irradiation: single or small number of high-dose-rate exposures to 75–250 kVp x rays; age at exposure <1 year (Adams et al. 2010) ^d	1.36	3.2 (1.5, 6.6)	2.2 (1.4, 3.2)
Israeli tinea capitis: five high-dose-rate exposures to 70–100 kVp x rays on successive days; 9% of patients received multiple treatments (up to four), with at least 1 year between treatments; mean age at exposure 7 years (Ron et al. 1989; Ron et al. 1995)	0.09	35 (16, 73)	7.6 (2.7, 13)
Israeli tinea capitis: reanalysis incorporating adjustments to estimated doses (Lubin et al. 2004)	0.11	31 (14, 64)	6.7 (2.4; 12) ^e
Israeli tinea capitis: reanalysis based on 16 years of additional follow-up (Sadetzki et al. 2006)	0.093	18 (11, 28) ^f	8.7 (5.0, 13) ^f
Enlarged tonsils (Michael Reese Hospital, Chicago): three acute exposures to 200 kVp x rays, each one week apart; 12% of patients received second set of treatments; mean age at exposure 4.3 years (Schneider et al. 1993; Ron et al. 1995) ^g	0.59	2.5 (0.6, 26) ^h	3.0 (0.5, 17) ^h
Lymphoid hyperplasia (Children’s Hospital Medical Center, Boston): two treatments each day with 250 kVp x rays, repeated one week later; 11% of patients received additional treatments; mean age at exposure 6 years (Pottern et al. 1990; Shore 1992; Ron et al. 1995; UNSCEAR 2000)	0.24	5.9 [90% CI: (1.8, 12)]	9.1 [90% CI: (2.7, 18)]
Stockholm skin hemangioma: protracted exposures (about 2 hours) at low dose rates from ²²⁶ Ra applicators; some patients received multiple treatments, often on same day; mean age at exposure 0.5 years (Lundell et al. 1994)	0.26	4.9 (1.3, 10)	0.9 (0.2, 1.9)
Gothenburg skin hemangioma: conditions same as in Stockholm cohort (Lindberg et al. 1995)	0.12	7.5 (0.4, 18)	1.6 (0.09, 3.9)

Table 5.18 (continued)

^a 95% CI, except as noted. Reported central values are MLEs.

^b Cohorts included in pooled analysis were members of LSS cohort exposed at ages <15 and thymic irradiation, tinea capitis, enlarged tonsils, and lymphoid hyperplasia cohorts.

^c Average of estimated risks at ages at exposure 0–9.

^d Risks used in pooled analysis by Ron et al. (1995) were based on earlier study of cohort by Shore et al. (1993); estimated risks were ERR/Gy of 9.1 [95% CI: (3.6, 29)] and EAR/10⁴ person-y/Gy of 2.6 [95% CI: (1.7, 3.6)].

^e Lubin et al. (2004) did not estimate EAR. Estimate was obtained by reducing EAR given by Ron et al. (1995) by 12% to account for adjustments to estimated doses.

^f Estimate obtained by reducing risk reported by Sadetzki et al. (2006) by 12% to account for adjustments to estimated doses in reanalysis by Lubin et al. (2004). Estimate is used in deriving DDREF for thyroid cancer based on data in Israeli tinea capitis cohort. Estimated risks reported by Sadetzki et al. (2006) are ERR/Gy of 20 [95% CI: (12, 32)] and EAR/10⁴ person-y/Gy of 9.9 [95% CI: (5.7, 15)].

^g More than 75% of thyroid cancers occurred in children first exposed at ages ≤4 (Ron et al. 1995); 90% of those cancers occurred in children exposed at ages 1–4, and estimated ERR/Gy at those ages was 2.8 (Schneider et al. 1993).

^h Estimate used in pooled analysis by Ron et al. (1995). Estimated ERR/Gy from study by Schneider et al. (1993) reported by UNSCEAR (2000, 2006) is 3.0 [90% CI: (2.6, 3.5)], and screening-adjusted EAR/10⁴ person-y/Gy given by Schneider et al. (1993), taking misprint in published paper into account (Ron et al. 1995), is 1.7 [95% CI: (1.3, 2.3)]. Use of these estimates would not substantially affect estimates of DDREF.

5.4.1 Risks from Exposure to External Radiation

Data in Table 5.18 indicate that there is considerable variation among the different cohort studies in risks of thyroid cancer from external exposure to x rays or high-energy gamma rays, regardless of whether the excess risk is expressed as an ERR or an EAR. When expressed as an ERR, the risk was lowest in the enlarged tonsils cohort at the Michael Reese Hospital and highest in the Israeli tinea capitis cohort. However, the lowest EAR occurred in the Stockholm skin hemangioma cohort, and the highest EAR occurred in the lymphoid hyperplasia cohort. Similar variations in ERRs in these cohorts are seen in the results of a recent analysis by Veiga et al. (2016). Factors that have been proposed to explain the variations in estimated risks include errors in estimated doses; concomitant exposure of the pituitary gland resulting in a hormonal effect; differences in socio-economic status, ethnicity, or local medical care; and differences in radiation quality and the degree of dose fractionation (Ronckers et al. 2006).

As shown in Figure 5.12, results of the pooled analysis by Ron et al. (1995) of the five cohort studies that provided the basis for the risk model for thyroid cancer in IREP (Land et al. 2003a) indicated a linear dose-response at doses from about 100 mGy to more than 4 Gy. However, there was clear evidence of an increased risk of thyroid cancer [relative risk = 2.5; 95% CI: (2, 4)] at doses of 10–90 mGy (mean dose of 50 mGy) compared with risk based on a linear fit over the full dose range (Brenner et al. 2003). The average age at exposure in the five cohorts was about 2.5 years (NRC 2006).

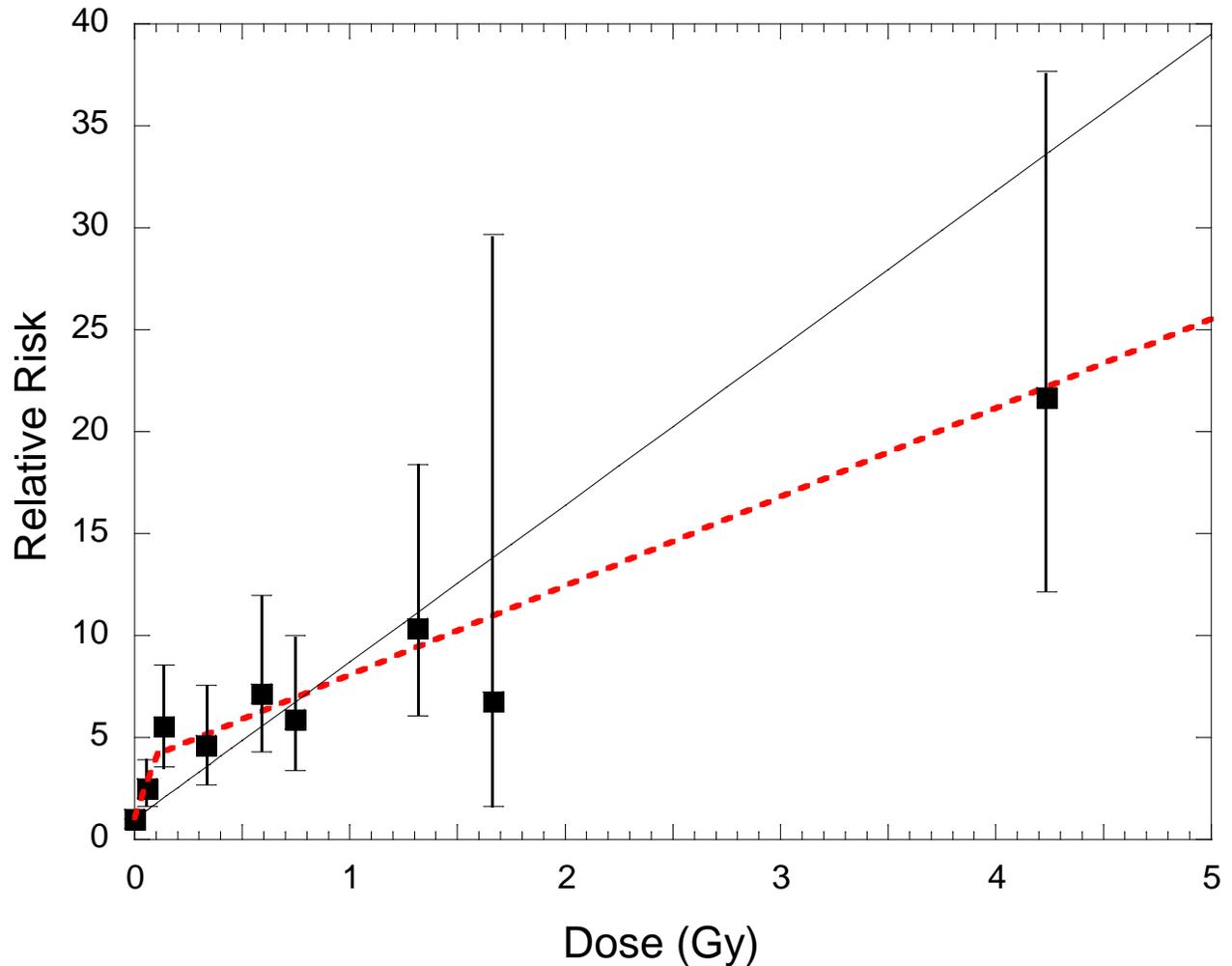


Figure 5.12. Pooled dose-responses (relative risks) for incidence of thyroid cancer and fitted curves based on five cohort studies of childhood (age <15) exposure to external x or gamma radiation. Data and linear fit given by solid line [relative risk = $1 + (7.7 \times \text{dose})$] were taken from Ron et al. (1995). Dashed curve is linear-spline fit with knot at 0.1 Gy described in Section 5.4.3, which represents observation that linear fit underestimates risk at low doses and overestimates risk at high doses.

As noted above, the highest ERRs occurred in children in the Israeli tinea capitis cohort who received fractionated x-ray exposures of the scalp for treatment of ringworm (Ron et al. 1989; Lubin et al. 2004; Sadetzki et al. 2006). The lowest dose group (mean dose to the thyroid about 75 mGy) showed a statistically significant increase in risk compared with matched unirradiated subjects [relative risk = 3; 95% CI: (2, 6)] (Lubin et al. 2004). Higher risks were seen at ages at exposure <5 years (relative risk = 5.5 at 0.1 Gy; CI not reported) (Lubin et al. 2004).

Data on radiation-induced thyroid cancer in adults are more limited. Analyses of data in the LSS cohort prior to the study by Preston et al. (2007) indicated that there was little risk at ages at exposure >20 (Thompson et al. 1994; Ron et al. 1995; NCRP 2001; Imaizumi et al. 2006; NRC 2006; UNSCEAR 2008). Dose-responses in the LSS cohort modeled by Preston et al. (2007) by including all age groups and a dependence of risks on sex, age at exposure, and attained age indicated significant excess risks in both sexes at ages at exposure ≥ 20 ; ERRs were slightly higher in females than in males, whereas EARs were substantially higher in females. In the ERR model, however, the dependence on age at exposure was not statistically significant and the dependence on attained age was only marginally significant. The stronger dependence on age at exposure in the EAR model developed by Preston et al. (2007) led UNSCEAR (2008) to include a dependence on sex and age at exposure only in its preferred EAR model.

A later analysis of the dose-response in the LSS cohort by Richardson (2009) gave an excess risk of thyroid cancer in females exposed at ages ≥ 20 [ERR/Gy = 0.70; 90% CI: (0.20, 1.46)], but there was no evidence of an excess risk in males exposed at the same ages [ERR/Gy = -0.25; 90% CI: (<0, 0.35)]. The recent analysis of risks in the LSS cohort from exposures at ages ≥ 20 by Furukawa et al. (2013) based on follow-up through 2005 found no statistically significant dose-response in males [ERR/Gy = -0.18; 95% CI: (-0.24, 1.8)] or females [ERR/Gy = 0.34; 95% CI: (-0.18, 1.3)], nor was the sex-averaged risk at those ages at exposure statistically significant [ERR/Gy = 0.27; 95% CI: (<0, 1.1)].

The recent analyses of risks of thyroid cancer in adults in the LSS cohort based on DS02 dosimetry by Preston et al. (2007), Richardson (2009), and Furukawa et al. (2013) summarized above indicate that the question of whether there are excess risks in adults cannot be answered definitively at the present time.

Table 5.19 gives estimated risks of thyroid cancer in the LSS cohort based on the recent ERR and EAR models developed by Furukawa et al. (2013) that can be compared with estimated risks in the medically exposed cohorts given in Table 5.18. Estimated risks in the LSS cohort are sex-averaged and apply to the mean age at exposure and mean attained age in the medically exposed cohorts. Estimated risks in Tables 5.18 and 5.19 are used to estimate DDREFs in Section 5.4.5.

5.4.2 Risks from Internal Exposure to Radioiodine

Risks of thyroid cancer following internal exposure to ^{131}I are less well understood than risks from external exposure. Several early studies suggested that the risk of thyroid cancer from internal exposure to ^{131}I may be lower than the risk from external exposure at high dose rates (NCRP 1980), but those studies included small numbers of children. Although a large body of information described below has been obtained since the reactor accident at Chernobyl, most epidemiological studies have not yielded quantitative data suitable for use in risk analysis (NCRP 2001; UNSCEAR 2000, 2008).

Table 5.19. Estimates of ERR and EAR (and 95% CIs) for thyroid cancer incidence in LSS cohort based on DS02 dosimetry that can be compared with estimates in cohorts of medical patients that received external exposures to low-LET radiation^a

Mean age at exposure (y)	Mean attained age (y)	ERR/Gy ^b	EAR/10 ⁴ person-y/Gy ^b	Cohorts for comparison of risks with risks in LSS cohort ^c
0.5	30	5.1 (2.4, 10.8)	2.8 (1.3, 4.7)	Skin hemangioma
4	30	4.2 (2.0, 8.9)	2.2 (1.0, 3.7)	Enlarged tonsils
6	30	3.8 (1.8, 8.0)	1.9 (0.89, 3.2)	Lymphoid hyperplasia
7	36.5	2.8 (1.3, 6.0)	2.2 (1.0, 3.7)	Israeli tinea capitis, analysis by Sadetzki et al. (2006)

^a Estimated risks based on dose-response models at thyroid doses of 0–4.2 Gy assuming a neutron RBE of 10 developed by Furukawa et al. (2013) are sex-averaged and depend on age at exposure and attained age.

^b Central values are MLEs.

^c Estimated risks in comparison cohorts are given in Table 5.18.

A strong association of thyroid cancer with dose to the thyroid of children, due mainly to exposure to ¹³¹I released in the Chernobyl accident, was found in a case-control study of children of ages <15 in Belarus and the Russian Federation (Cardis et al. 2005a) and in three cohort studies of individuals of ages <18 in Ukraine (Tronko et al. 2006; Brenner et al. 2011) or Belarus (Zablotska et al. 2011). Estimates of ERR/Gy based on linear dose-response models were 4.5 [95% CI: (1.2, 7.8)] (Cardis et al. 2005a), 5.3 [95% CI: (1.7, 28)] (Tronko et al. 2006), 1.9 [95% CI: (0.4, 6.3)] (Brenner et al. 2011), and 2.2 [95% CI: (0.8, 5.5)] (Zablotska et al. 2011).⁶⁴ In the study by Brenner et al. (2011), the risk varied significantly by region, but not by time since exposure, iodine prophylaxis or status, sex, age, or tumor size. Risks estimated by Cardis et al. (2005a) and Tronko et al. (2006) are similar, whereas estimates by Brenner et al. (2011) and Zablotska et al. (2011) tend to be lower. In addition, all four estimates tend to be lower than estimated ERRs from childhood exposure to external radiation in the subset of the LSS cohort of ages 0–9 and in the pooled analysis of five cohort studies of medical exposures by Ron et al. (1995), as given in Table 5.18. However, uncertainties in all ERRs are substantial and the various CIs overlap.

The effect of uncertainties in estimated doses on analyses of dose-responses was not evaluated in the studies of risks of thyroid cancer in children exposed to releases in the Chernobyl accident described

⁶⁴ The risk estimated by Cardis et al. (2005a) was based on linear dose-responses at doses to the thyroid up to 2 Gy only, because dose-responses at higher doses appeared to be non-linear. However, the risk estimated by Tronko et al. (2006) was based on a linear fit to the dose-response at all doses (up to 48 Gy).

above.⁶⁵ In addition, all risk estimates may have been influenced by effects of iodine deficiencies in the exposed populations, even though no such effect was seen in the study by Brenner et al. (2011).⁶⁶ Tronko et al. (2006) identified other limitations to their analysis, such as the effect of non-participation in thyroid screenings, but potential biases in their estimated risk due to those limitations are unknown.

In another study of thyroid cancer in Ukraine and Belarus, Jacob et al. (2006a) estimated risks from exposure to radioiodine that were much higher than risks from other studies summarized above; the ERR/Gy was 19 [95% CI: (11, 27)], and the EAR/10⁴ person-y/Gy was 2.66 [95% CI: (2.19, 3.13)]. Jacob et al. (2006a) noted that uncertainties in their estimated risks were too small, although this was attributed mainly to factors other than uncertainties in estimated doses.

Estimated risks of thyroid cancer from exposure to radioiodine, when compared with risks from external exposure at high dose rates, could be interpreted as suggesting a DREF of about 1. However, given the major unanswered questions about all the studies of internal exposure to radioiodine, we have not included those studies in our evaluation of a DDREF for thyroid cancer.

5.4.3 Effects of Dose Fractionation or Protraction on Estimates of DDREF

In the pooled analysis by Ron et al. (1995) summarized in Table 5.18, four of the five study cohorts (all but the LSS cohort) received fractionated exposures to x rays. The number of dose fractions and the dose per fraction varied among the four cohorts. However, Ron et al. (1995) evaluated the effects of fractionation only in the three cohorts in which the standard treatment courses were repeated at intervals of six months to one year in some of the cohort members (i.e., excluding the thymic irradiation cohort). When fractionation was defined as a repetition of standard treatment courses at such intervals, ERRs in members of the three cohorts who received two or more courses of treatment were consistently lower than ERRs in members who received a single course of treatment. When data for the three cohorts were pooled, the ratio of ERRs from fractionated and single exposures was 0.7 [95% CI: (0.5, 1.1)]. The reciprocal of this ratio suggests a DDREF (a DREF) of 1.4 [95% CI: (0.9, 2.0)]. However, we do not consider that this estimate is relevant to our study, because it does not represent a comparison of risks from fractionated exposures with risks from a single acute exposure in the LSS cohort.

Ron et al. (1995) also noted that the linear fit to the pooled dose-responses shown in Figure 5.12 appeared to underestimate the risk at low doses and overestimate the risk at high doses. To evaluate the

⁶⁵ In an analysis of risks of thyroid cancer in children in southern Russia, Kopecky et al. (2006) showed that taking uncertainties in estimated doses into account could increase the central estimate of ERR/Gy by about a factor of three and widen the CI by more than an order of magnitude if uncertainties in doses are assumed to be entirely classical.

⁶⁶ Cardis et al. (2005a) found that relative risks were three times higher in iodine-deficient areas than elsewhere, and Tronko et al. (2006) noted that northern Ukraine has historically been an area of moderate iodine insufficiency.

significance of this observation, we fit the pooled data with a linear spline with a knot at 0.1 Gy shown in Figure 5.12. This alternative was suggested by dose-responses in several cohorts studied by Ron et al. (1995), as well as the dose-response for thyroid carcinomas in rats reported by Lee et al. (1982). The alternative fit to the pooled data does not exclude a supralinear response at low doses with an ERR/Gy at doses <200 mGy about twice the ERR/Gy based on the linear model, which suggests an LDEF of about 0.5. This suggestion contrasts with the DREF of about 1.4 noted above. As indicated by the dose-response for thyroid cancer in adults in the LSS cohort shown in Figure 5.11 (Preston et al. 2007), there also is evidence of a concave downward curvature at the lowest doses, which suggests an LDEF of about 0.6–0.7.

We think that comparisons of risks in the various cohorts summarized in Table 5.18 should be interpreted with caution since four of the cohorts were exposed to x rays but the others (the LSS and the two skin hemangioma cohorts) were exposed primarily to high-energy gamma rays. Thus, the possible effect of a difference in biological effectiveness of medical x rays and high-energy gamma rays that we considered in deriving a probability distribution of DDREF from the data for breast cancer also applies to comparisons of EARs and ERRs for incidence of thyroid cancer in Table 5.18. The effect of a higher biological effectiveness of medical x rays is considered in Section 5.4.5.

5.4.4 Updated Analysis of Risks of Thyroid Cancer from Childhood Exposures

A recent analysis by Veiga et al. (2016) presents an update of the pooled analysis of risks of thyroid cancer from childhood exposures by Ron et al. (1995). In addition to more recent data in the LSS cohort and most cohorts of medical patients, the updated analysis included a skin hemangioma cohort in France and four cohorts of children in the Childhood Cancer Survivors Study who received doses to the thyroid from prior treatment for other cancers as high as 55–76 Gy.

Veiga et al. (2016) found that the best fit to the pooled data on ERRs from childhood exposures in the 12 study cohorts was a linear-exponential dose-response model of the form $ERR(D) = \alpha D \exp[\gamma_1 D + \gamma_2 D^2 + \gamma_3 \ln(D)]$. This dose-response is concave downward at thyroid doses <20 Gy; i.e., ERR/Gy decreases with increasing dose (LDEF <1). Since the coefficient γ_3 was found to be negative, the slope of the modeled dose-response approaches infinity (∞) as $D \rightarrow 0$. However, since the dose-response at doses ≤ 0.1 Gy showed no evidence of a departure from linearity, an LDEF at 1 Gy can be estimated as the ratio of the ERRs at 0.1 Gy and 1 Gy. By assuming an average age at exposure of 5 and average attained age of 41 in the 12 study cohorts (Veiga et al. 2016) and taking into account correlations of the model parameters (Lena Veiga, personal communication), our estimate of this ratio is 0.62 [90% CI: (0.46, 0.83)].

The approach to estimating an LDEF based on the pooled analysis by Veiga et al. (2016) and a similar analysis by Ron et al. (1995) described in the previous section is questionable when pooling of

data from several studies did not take into account a possible REF_L in exposures to x rays in many cohorts and the possibility that a DDREF may apply to exposures of some cohorts but not others. That is, any effects of an REF_L and a DDREF on a pooled analysis of dose-responses may not be equal and opposite.

More relevant to estimation of a DDREF is an analysis by Veiga et al. (2016) of the dose-response in the LSS cohort at ages at exposure ≤ 19 using data from Preston et al. (2007) and Furukawa et al. (2013) at neutron-weighted thyroid doses of 0–4.2 Gy. The best fit to the dose-response was a linear-exponential model of the form $ERR(D) = \alpha D \exp(\gamma_1 D)$. Since the coefficient γ_1 was found to be negative, the modeled dose-response is concave downward. However, in contrast to the four-parameter linear-exponential model used in the pooled analysis by Veiga et al. (2016), the modeled dose-response in the LSS cohort has a finite slope (α) at zero dose. Using the coefficient α and ERR at 1 Gy with reported MLEs and 95% CIs of 5.2 (2.7, 9.9) and 3.5 (3.2, 6.7), respectively, and an assumption that those parameters are uncorrelated, we estimated an LDEF at 1 Gy with a 50th percentile and 90% CI of 0.66 (0.34, 1.35). MLEs of α and the ERR at 1 Gy are at the 41st and 43rd percentiles, respectively, of assumed Weibull distributions. The assumption of uncorrelated parameters probably results in an overestimate of the uncertainty. Assuming a full positive correlation, which should result in an underestimate of the uncertainty, gave an estimated LDEF at 1 Gy with a 50th percentile and 90% CI of 0.66 (0.59, 0.79).

5.4.5 Potential Influence of Energy Dependence of REF_L on Estimates of DDREF

To address the concern about a possible increase in biological effectiveness of medical x rays compared with high-energy gamma rays and to facilitate comparisons of estimated risks of thyroid cancer in medical patients with risks in the LSS and skin hemangioma cohorts, we estimated DREFs using estimated risks in cohorts exposed to x rays in Table 5.18 by dividing them by our modified REF_L of 2 for 30–250 keV photons, as in the analysis for breast cancer in Section 5.3.2.⁶⁷ Because our objective was to estimate a DDREF for chronic exposure, we excluded estimated risks in the Rochester thymus cohort, most of whose members received a single acute exposure at a high dose. The other cohorts exposed to x rays might also be excluded, given the small number of dose fractions in exposures of most members of those cohorts. However, we retained them because two of the three cohorts received relatively low doses.

Estimated ERRs and EARs from individual studies in Table 5.18 and age-matched estimates of risks in children in the LSS cohort in Table 5.19 were used to estimate DDREFs. The resulting 50th percentiles and 90% CIs of DDREFs are given in Table 5.20. In addition to DDREFs that we estimated by comparing

⁶⁷ The possibility that a high RBE for neutrons in exposures of members of the LSS cohort could have affected estimated cancer risks from exposure to high-energy gamma-rays in lightly shielded organs, such as the thyroid, is discussed in Section 2.4.3.

risks in each of the five cohorts with age-matched risks in the LSS cohort, we developed pooled estimates of DDREF based on ERRs and EARs from each study and overall pooled estimates that were obtained using two different approaches. Except as noted, DDREFs in Table 5.20 were estimated without accounting for uncertainty in the REF_L of 2 for medical x rays.

The choice of risk model (ERR or EAR) appears to have a smaller effect on estimates of DDREF based on data for thyroid cancer than it did in the analysis for breast cancer, and NCRP (2009) concluded that there was no compelling reason to prefer either model. Thus, the combined estimate of DDREF from each study in Table 5.20 was obtained by assigning equal weights to the estimates based on ERRs or EARs. This assumption is equivalent to assigning equal weights to multiplicative and additive models to describe transfer of risks of thyroid cancer from the LSS cohort to the other cohorts.

In the first approach to pooling estimates of DDREF from the five studies given in Table 5.20 (Approach A), the combined estimates of DDREF from each study that were obtained by weighting DDREFs based on ERRs and EARs equally were assigned equal weights, without regard for their uncertainties. The resulting pooled estimate of DDREF given in the table has a 50th percentile and 90% CI of 0.82 (0.22, 6.0).

In the second approach to pooling estimates of DDREF from the five studies (Approach B), we first pooled the ERR- and EAR-based estimates from each study separately by assigning a 20% weight to DDREFs based on the tinea capitis study and an 80% total weight to DDREFs based on the other four studies, with the fractional weight assigned to the DDREF from each of those four studies assumed to be proportional to the reciprocal of the square of its relative error, where the relative error is defined in Section 5.3.2 as the ratio $(95^{\text{th}} \% \text{-tile} - 5^{\text{th}} \% \text{-tile}) / (50^{\text{th}} \% \text{-tile})$. The pooled ERR- and EAR-based estimates of DDREF obtained using this approach then were combined by assigning equal weights to the two DDREFs. The resulting pooled estimate of DDREF given in Table 5.20 has a 50th percentile and 90% CI of 0.94 (0.21, 5.4), which differs little from the pooled estimate obtained using Approach A.

We prefer the approach to weighting of DDREFs from individual studies in Approach B because it accounts for uncertainties in estimated risks without giving undue weight to DDREFs based on questionable estimates of risks in the tinea capitis cohort. Estimates of DDREF based on the tinea capitis study are considerably lower than DDREFs based on the other studies, due to the higher estimates of risk in that cohort; possible explanations for the higher risks are discussed in the following section. In Approach B, DDREFs based on estimated risks in the other four cohorts were assigned the following weights: Stockholm skin hemangioma cohort, 33%; lymphoid hyperplasia cohort, 27%, Gothenburg skin hemangioma cohort, 14%; and enlarged tonsils cohort, 6%.

Table 5.20. DDREFs (50th percentiles and 90% CIs) derived by comparing estimates of ERR and EAR for thyroid cancer incidence in five cohort studies of fractionated or chronic exposures with matched estimates in LSS cohort based on DS02 dosimetry and accounting for increased biological effectiveness (REF_L) of medical x rays compared with high-energy gamma rays

Cohort	ERR-based estimate ^a	EAR-based estimate ^a	Combined estimate
Israeli tinea capitis: reanalysis by Lubin et al. (2004) and Sadetzki et al. (2006)	0.33 (0.15, 0.68) ^{b,c}	0.52 (0.25, 0.97) ^{b,d}	0.42 (0.17, 0.88) ⁿ
Enlarged tonsils: Michael Reese Hospital	1.4 (0.35, 10) ^{b,e}	0.83 (0.25, 5.3) ^{b,f}	1.1 (0.27, 7.8) ⁿ
Lymphoid hyperplasia	1.4 (0.51, 5.1) ^{b,g}	0.41 (0.17, 1.5) ^{b,h}	0.76 (0.19, 3.8) ⁿ
Skin hemangioma: Stockholm	1.1 (0.44, 3.7) ^{b,i}	2.9 (1.2, 9.5) ^{b,j}	1.8 (0.49, 7.5) ⁿ
Skin hemangioma: Gothenburg	0.69 (0.22, 3.4) ^{b,k}	1.7 (0.58, 8.3) ^{b,m}	1.1 (0.25, 6.3) ⁿ
Pooled estimate (all five cohorts combined)	Approach A – Equal weights assigned to each of five combined estimates		0.82 (0.22, 6.0)
	Approach B – Alternate approach to weighting and pooling of estimates from each study		0.82 (0.19, 6.0) ^o
	0.87 (0.22, 4.2) ^p	0.98 (0.21, 6.9) ^p	0.94 (0.21, 5.4) ⁿ
			0.98 (0.19, 6.0) ^o

^a 50th percentiles and 90% CIs we estimated using Monte Carlo uncertainty propagation techniques and assumption that ERRs and EARs in Tables 5.18 and 5.19 are described by Weibull distributions with modes at MLEs. Except as noted, REF_L for x rays of 2, with no uncertainty, is assumed.

^b DDREF is ratio of ERR or EAR in appropriate age group in LSS cohort given in Table 5.19 to corresponding estimate given in Table 5.18, with DDREFs in tinea capitis, enlarged tonsils, and lymphoid hyperplasia cohorts increased by factor of 2, with no uncertainty, to account for REF_L for medical x rays.

^c MLEs of ERRs in LSS and tinea capitis cohorts are at 40th and 45th percentiles, respectively, of assumed Weibull distributions.

^d MLEs of EARs in LSS and tinea capitis cohorts are at 47th and 49th percentiles, respectively, of assumed Weibull distributions.

^e MLEs of ERRs in LSS and enlarged tonsils cohorts are at 40th and 17.5th percentiles, respectively, of assumed Weibull distributions.

^f MLEs of EARs in LSS and enlarged tonsils cohorts are at 47th and 26th percentiles, respectively, of assumed Weibull distributions.

^g MLEs of ERRs in LSS and lymphoid hyperplasia cohorts are at 40th and 45th percentiles, respectively, of assumed Weibull distributions.

^h MLEs of EARs in LSS and lymphoid hyperplasia cohorts are at 47th and 46th percentiles, respectively, of assumed Weibull distributions.

ⁱ MLEs of ERRs in LSS and skin hemangioma cohorts are at 40th and 46th percentiles, respectively, of assumed Weibull distributions.

^j MLEs of EARs in LSS and skin hemangioma cohorts are at 47th and 46th percentiles, respectively, of assumed Weibull distributions.

Table 5.20 (continued)

^k MLEs of ERRs in LSS and skin hemangioma cohorts are at 40th and 45th percentiles, respectively, of assumed Weibull distributions.

^m MLEs of EARs in LSS and skin hemangioma cohorts are at 47th and 45th percentiles, respectively, of assumed Weibull distributions.

ⁿ Estimate obtained by assigning equal weights to ERR- and EAR-based estimates.

^o DDREF that takes into account assumed uncertainty in REF_L for medical x rays [95% CI: (1, 3)] described in Section 2.4.2.5 in exposures of tinea capitis, enlarged tonsils, and lymphoid hyperplasia cohorts.

^p Estimate obtained by assigning 20% weight to DDREF based on tinea capitis study and 80% total weight to DDREFs based on other four studies, with the fractional weight assigned to each of those DDREFs assumed to be proportional to the reciprocal of the square of its relative error, as described in text.

We also considered DDREFs that would be obtained if estimated ERRs and EARs in the three cohorts exposed to x rays were not adjusted by our modified REF_L for x rays of 2. Central estimates of DREF based on EARs in those cohorts, obtained by dividing the central estimates (50th percentiles) in Table 5.20 by 2, range from 0.21 to 0.42, with a mean of 0.29. Central estimates of DREF based on EARs in the two skin hemangioma cohorts exposed to high-energy gamma rays are higher (2.9 and 1.7, mean of 2.3). Comparisons based on unadjusted ERRs result in smaller differences in DREFs. Central estimates of unadjusted DREFs in the cohorts exposed to x rays range from 0.17 to 0.7 (mean of 0.52), and central estimates of DREFs in the skin hemangioma cohorts are 1.1 and 0.69 (mean of 0.9).

Our evaluation of DDREFs based on unadjusted estimates of risks of thyroid cancer incidence in cohorts exposed to x rays compared with DDREFs based on estimated risks in the skin hemangioma cohorts leads to conclusions that differ from conclusions based on DDREFs for breast cancer. Estimates of DREF for thyroid cancer based on estimated ERRs in the skin hemangioma cohorts do not show a significant effect of dose protraction, whereas EAR-based estimates of DREF in those cohorts are about eight times higher than in the cohorts exposed to x rays, as noted above. We also note that differences between ERR- and EAR-based estimates of DREF for thyroid cancer as a whole are not large.

As indicated by the second combined estimates using Approaches A and B in Table 5.20, taking the uncertainty in the modified REF_L for 30–250 keV x rays [95% CI: (1, 3)] into account expands the CIs of estimated DDREFs for thyroid cancer only slightly. The uncertainty in REF_L is represented by a discrete probability distribution with 25% weight to the value 1.0, 50% weight to the value 2.0, and 25% weight to the value 3.0. An overall combined estimate of a DDREF for thyroid cancer based on Approach B that accounts for this uncertainty has a 50th percentile and 90% CI of 0.98 (0.19, 6.0).

5.4.6 Influence on DDREF of Uncertainty in Risks in Israeli Tinea Capitis Cohort

A puzzling aspect of the analysis of data for thyroid cancer summarized in Table 5.20 is that DDREFs based on estimated risks in the Israeli tinea capitis cohort, especially the ERR-based estimate, are so low as to suggest a supralinear dose-response (DDREF <1). The ERR associated with fractionated exposures in that cohort given in Table 5.18—an ERR/Gy of 18 [90% CI: (11, 28)]—is substantially higher than the ERR in any other cohort. The higher ERR might have been due in part to a higher REF_L for 70–100 kVp x rays to which that cohort was exposed, compared with the REF_L for higher-energy x rays, combined with a possibly lower DDREF for the lower-energy x rays (Section 2.4.2). However, such an effect was not seen in ERRs for breast cancer in tuberculosis fluoroscopy cohorts exposed to lower-energy (60–80 kVp) x rays (Section 5.3). Deleterious bystander effects associated with the low average dose per fraction of about 20 mGy are another possible cause of elevated risks in the tinea capitis cohort. However, such an effect also contrasts with the sparing effect of similar low-dose fractions suggested by estimated risks of breast cancer in the tuberculosis fluoroscopy cohorts.

More recently, the high ERR in the tinea capitis cohort has been attributed to the high frequency (1.2%) of a founder mutation in the ATM DNA-damage response gene in North African Jews, who exhibited the highest risk of thyroid cancer in that cohort, and the high EAR has been attributed to the high baseline risk of thyroid cancer in Israel compared with most Western countries (Sadetzki et al. 2006).

An adjustment by Ron et al. (1995) to the ERR in the Israeli tinea capitis cohort for the effects of a nonzero intercept in the modeled dose-response, which accounted for possible intrinsic differences between exposed and unexposed members of that cohort, indicated that an ERR/Gy of 6.6, with a large uncertainty [95% CI: (<0, 300)], could be compatible with the data;⁶⁸ the estimated ERR/Gy is a factor of about five lower than the central estimate of 35 obtained by Ron et al. (1995) and given in Table 5.18. Using the lower central estimate of ERR/Gy, the matching ERR/Gy in the LSS cohort given in Table 5.17, and an adjustment to account for an REF_L of 2 for x rays, an estimated DDREF of about 0.8 would be obtained. That estimate is consistent with central estimates (50th percentiles) of the ERR-based DDREFs in the skin hemangioma cohorts (1.1 and 0.69) and lymphoid hyperplasia cohort (1.4) given in Table 5.20.

Aurengo et al. (2005) criticized the high estimate of ERR in the Israeli tinea capitis cohort on the grounds that the study on which it is based “suffers from a dosimetric methodological bias.” However, a revised estimate of ERR that incorporated adjustments to estimated doses by Lubin et al. (2004) was used

⁶⁸ The lower estimate is comparable to the ERR/Gy of 7.7 [90% CI: (<0, 60)] for incidence of thyroid cancer in the New York tinea capitis cohort estimated by UNSCEAR (2000, 2008) on the basis of information reported by Shore (1992) and Shore et al. (2003). However, we have not used that estimate in our analysis because of its large uncertainty, which is a consequence of the small number of cancers in the exposed group (2) and the relatively small size of the New York cohort (2,224 children; mean age 7.8 years).

in our analysis. As indicated in Table 5.18, the adjusted dosimetry resulted in a reduction in the ERR by little more than 10%, contrary to the implication of a large effect by Aurengo et al. (2005).

We used the results in Table 5.20 that were obtained using Approach B to define our probability distribution of DDREF for thyroid cancer. We did not consider the ERR in the tinea capitis cohort obtained by Ron et al. (1995) and described above, because Ron et al. (1995), Lubin et al. (2004), and Sadetzki et al. (2006) did not use the alternative dose-response model as the primary basis for estimating risks in that cohort. Furthermore, the uncertainty in the alternative estimate is very large. However, we recognize that the magnitude of uncertainties in estimated risks in this cohort may be an open question.

5.4.7 Discussion of Studies of Thyroid Cancer

The probability distribution of DDREF for thyroid cancer currently used in IREP (mean of 1.6 and range of 0.5–4; Section 1.1.1) is narrower than the distribution with a 50th percentile and 90% CI of 0.98 (0.19, 6.0) that we derived using a modified REF_L of 2 [95% CI: (1, 3)] for 30–250 keV photons to adjust estimated risks in cohorts exposed to medical x rays. However, the two distributions do not differ significantly. An estimated LDEF based on an analysis by Little and Muirhead (2000, 2004) of the curvature in the dose-response for thyroid cancer in the LSS cohort at a shielded kerma of 0–4 Gy (Table 5.14) is similar to the distribution in IREP and the distribution we derived.

In contrast, the LDEF with a 50th percentile and 90% CI of 0.66 (0.34, 1.35) we estimated on the basis of the concave downward curvature in a modeled dose-response for thyroid cancer in the LSS cohort (Veiga et al. 2016; Section 5.4.4) is more strongly suggestive of a DDREF <1 than our estimate in Table 5.20, especially when our estimate of the uncertainty in this LDEF probably is too large. This LDEF suggests that values <1 may warrant a greater weight than currently assumed in IREP.

Although our results suggest that a DDREF for thyroid cancer could be developed separately from a DDREF for other cancers, there are a number of reasons why this approach might not be advisable:

- Estimated risks of thyroid cancer we used to estimate a DDREF apply to children (average age at exposure about 2.5 years), who clearly are more susceptible to radiation-induced thyroid cancer than adults. The question of whether a DDREF based on risks in children applies to adults cannot be investigated when studies of thyroid cancer in adults exposed to medical x rays are lacking.
- The 50th percentile in our distribution of DDREF for thyroid cancer of about 1.0 is similar to the 50th percentiles of 1.4 and 1.5 that we estimated based on recent analyses of dose-responses for incidence of all solid cancers combined in the LSS cohort (Table 5.2).

- Our distribution of DDREF does not account for all uncertainties in the underlying estimates of risk, especially uncertainties in estimated risks in the Israeli tinea capitis cohort.
- The high ERRs and EARs in the Israeli tinea capitis cohort could have biased our distribution of DDREF, even though we attempted to minimize the impacts of those estimates.
- Effects of sex, age at exposure, attained age, and genetic background on estimated risks of thyroid cancer were not accounted for in exposed populations other than the LSS cohort. We compared age-averaged estimates of risk in medically exposed children with age-specific estimates in the LSS cohort, which potentially adds to the uncertainty in estimates of DDREF.

However, there are a number of reasons why a separate distribution of DDREF for thyroid cancer might be justified:

- Unlike the situation with breast cancer, results of studies of different exposed cohorts show little evidence of a consistent effect of dose fractionation or protraction on estimated risks of thyroid cancer, although a modest effect of chronic exposure is seen in estimates of DDREF based on EARs in the skin hemangioma cohorts.
- Use of a lower estimate of ERR in the Israeli tinea capitis cohort, as suggested in an analysis by Ron et al. (1995), would not change our DDREF distribution, due to the very large uncertainty in that estimate.
- If our results were incorporated in the National Institutes of Health (NIH) version of IREP (Land et al. 2003a), which provides estimates of risk in all age groups including children, it could be argued that a separate DDREF for thyroid cancer should be used in assessing risks from childhood exposures (ages ≤ 15).

The issue is not whether a separate distribution of DDREF for thyroid cancer could be proposed. Rather, the issue is whether available information indicates that differences in DDREFs for thyroid and other cancers are significant and would warrant use of a DDREF for thyroid cancer derived mainly from studies of exposures of children to estimate risks of thyroid cancer in adults. Another issue is whether data from studies of the Israeli tinea capitis cohort indicate that differences in genetic susceptibility in different ethnic groups can mask the effects of dose fractionation or protraction and, if so, how such observations should be taken into account in characterizing the uncertainty in DDREF for any cancer, not just thyroid cancer. These issues are not easily resolved on the basis of available data.

Despite reservations about use of our distribution of DDREF for thyroid cancer to estimate risks to adults and the large uncertainties in most of the estimated risks of thyroid cancer, we think that our

estimate in Table 5.20, an estimated LDEF based on an analysis by Little and Muirhead (2000, 2004) of a dose-response in the LSS cohort at a shielded kerma of 0–4 Gy (Table 5.14), and an estimated LDEF we derived in Section 5.4.4 all suggest that a DDREF <1 should be given greater weight than in the distribution for thyroid cancer currently used in IREP. However, uncertainties in a DDREF for thyroid cancer are sufficiently high that the distinction in IREP between a DDREF for thyroid cancer and a DDREF for other solid cancers is difficult to justify. The available information appears to reinforce our earlier conclusion that the uncertainty in deviations from predictions of the LNT model at low doses or low dose rates could serve to increase or decrease estimated cancer risks.

5.5 STUDIES OF LUNG CANCER

Several epidemiological studies of radiation-induced lung cancer discussed in the following sections could be used to estimate a DDREF. However, as with the cohorts of western nuclear workers described in Section 5.2.2.2, uncertainty about the influence of smoking on radiation dose-responses appears to limit the validity of much of the data.

5.5.1 Incidence of Lung Cancer in LSS Cohort: Complication by Effects of Smoking

Pierce et al. (2003) analyzed the joint effect of smoking and radiation on the data on lung cancer incidence in the LSS cohort that were analyzed by Thompson et al. (1994) based on DS86 dosimetry and concluded that risks from smoking and radiation combined were sub-multiplicative and consistent with an additive model when a single model was used to describe the dependence of ERR/Gy on smoking level. In an additive model, the increase in EAR is the sum of increases due to smoking and radiation, and smoking reduces the ERR due to radiation, whereas in a multiplicative model, the increase in EAR is the product of increases due to smoking and radiation, and the ERR due to radiation is independent of smoking. However, there was a weak suggestion in the analysis by Pierce et al. (2003) of a multiplicative interaction in light smokers and an additive interaction in heavy smokers. The adjustment for smoking by Pierce et al. (2003) based on DS86 dosimetry substantially reduced the ratio of the ERR/Gy in females to the ERR/Gy in males, even though 84% of men but only 16% of women were smokers. With that adjustment, risks of lung cancers in nonsmokers were similar to risks of other cancers; the sex-averaged ERR/Gy was about 0.9, and the female-to-male ratio was about 1.6 (Pierce et al. 2003). When adjusted for smoking, there also was evidence of a decrease in the ERR/Gy with increasing attained age that was comparable to the decrease for other cancer types, but there was no evidence of a modification by age at exposure.

A recent analysis of the joint effect of smoking and radiation exposure on lung cancer incidence in the LSS cohort based on DS02 dosimetry (Furukawa et al. 2010) indicated that neither an additive nor a multiplicative model could explain the interaction at all smoking levels. After adjusting for smoking with a model that allowed a more complicated interaction that depended on smoking intensity, the sex-averaged ERR/Gy for lung cancer incidence was 0.59 [95% CI: (0.31, 1.00)] in nonsmokers of attained age 70 after exposure at age 30. In light and moderate smokers, the joint effect of radiation and smoking was found to be super-multiplicative, with the excess risk due to radiation increasing rapidly with smoking intensity up to about 10 cigarettes per day. In heavy smokers (about one pack or more per day), however, the joint effect of radiation and smoking was found to be additive or sub-additive, and there was little indication of an excess risk due to radiation. Furukawa et al. (2010) noted that the previous analysis by Pierce et al. (2003) discussed above found a qualitatively similar pattern of the joint effect of radiation and smoking.

In contrast to results in the LSS cohort described above, data in underground miners who were exposed to radon (NRC 1999) or patients with Hodgkin's disease who were treated with high doses of radiation (Gilbert et al. 2003) indicated that an additive interaction could be rejected and a multiplicative interaction was compatible with the data. However, the BEIR VII committee (NRC 2006) concluded that those studies may be less relevant to estimating risks at low doses of low-LET radiation than studies of the LSS cohort. Underground miners were exposed to alpha-emitting radon progeny (high-LET radiation), and evidence for a multiplicative interaction between radiation and smoking comes primarily from analyses of miners in Colorado and China with estimated doses to the lung (in Sv) much higher than doses in the LSS cohort (NRC 1999). Patients with Hodgkin's disease were given very high doses to the lung (mean of 25 Gy), and they were subject to an immunodeficiency inherent in lymphoma, which also is associated with subsequent chemotherapy many of the patients received.

The overall weight of evidence, especially the study of the LSS cohort by Furukawa et al. (2010), indicates that the interaction between low-LET radiation and smoking in inducing lung cancer is complex (not simply additive or multiplicative) and strongly influenced by smoking intensity. However, Furukawa et al. (2010) noted several limitations of their study. The most important limitation was that historical smoking data in the LSS cohort based on mail surveys were incomplete. Smoking status was unknown for about 60% of the total follow-up time and smoking status at the time of diagnosis was unknown in about 40% of all cases, which greatly reduced the power to describe the interaction of smoking and radiation.

As summarized in Table 5.14, estimates of LDEF for cancers of the respiratory system derived by Little and Muirhead (2000, 2004) from data in the LSS cohort based on DS86 dosimetry are comparable to LDEFs for breast and thyroid cancers. The results for respiratory cancers presumably were strongly influenced by data on incidence of lung cancers, which comprised 75% of the cancers in this grouping

(Thompson et al. 1994; Little and Muirhead 2000). However, the potential effects of smoking behavior on risks of lung cancer limits the use of this information for reasons noted above.

As shown in Figure 5.1, the analysis of lung cancer mortality in the LSS cohort based on follow-up through 2003 and DS02 dosimetry by Ozasa et al. (2012) gave a sex-averaged ERR/Gy of 0.63 [95% CI: (0.42, 0.88)]. The analysis of lung cancer incidence based on follow-up through 1998 and DS02 dosimetry by Preston et al. (2007) gave a sex-averaged ERR/Gy of 0.81 [90% CI: (0.56, 1.1)] at attained age 70 after exposure at age 30. However, no adjustment for smoking behavior was included in either analysis.

Given the available information, we concluded that the study by Furukawa et al. (2010), in which a complex model of the interaction between low-LET radiation and smoking described above was developed, is the most suitable for use in comparing risks of lung cancer in the LSS cohort with risks in other cohorts, despite the fact that it was based on data on cancer incidence rather than cancer mortality as in the studies of other cohorts. Comparisons of risks of lung cancer mortality and incidence are judged to be appropriate given the high lethality fraction (95%) of lung cancer in humans (NCRP 1993a).

5.5.2 Mortality from Lung Cancer in Mayak Workers

A study of lung cancer in Mayak workers (Tokarskaya et al. 2002) suggested that the interaction between smoking and low-LET radiation might depend on the level of smoking. At external doses >2 Gy, the interaction appeared to be more multiplicative at higher smoking levels but more additive at lower levels. That pattern is the opposite of the pattern in the LSS cohort reported by Furukawa et al. (2010), which was sub-additive at high smoking levels and super-multiplicative at lower smoking levels. However, the conclusion from the study in Mayak workers is uncertain, due to the large uncertainties in estimated risks based on additive and multiplicative interaction models.

A follow-up study of Mayak workers by Gilbert et al. (2004) showed that lung cancer mortality was associated with external dose and that risks were adequately described by a linear dose-response model. Risks estimated using either an ERR or an EAR model were judged to be comparable to risks in the LSS cohort. Limitations of this and earlier analyses of risks of lung cancer in Mayak workers are similar to the limitations of analyses of risks of all solid cancers in those workers discussed in Section 5.2.2.1, and an inability to fully adjust for smoking coupled with potential biases in estimated risks due to risks from internal exposure to plutonium are of even greater concern with respect to lung cancer. Thus, we judged that results from the study by Gilbert et al. (2004) are unsuitable for our purposes, as are results from the study of mortality from all solid cancers by Shilnikova et al. (2003) discussed in Section 5.2.2.1.⁶⁹

⁶⁹ Other attempts to model lung cancer mortality in Mayak workers (Jacob et al. 2005, 2006b, 2007) did not address concerns about estimated doses and limitations in the data on smoking history.

A recent study of Mayak workers based on improved estimates of annual external and internal organ doses gave a sex-averaged ERR/Gy for lung cancer mortality due to external exposure to gamma radiation with an MLE and 95% CI of 0.19 (0.05, 0.39), with no evidence of a statistically significant dependence on attained age or age at first external exposure (Sokolnikov et al. 2008). An adjustment for smoking, which was based on self-reported responses (yes/unknown/no), did not change estimated risks significantly, which suggests that smoking may not be an important risk factor in that study.

To estimate a DREF, we compared the ERR/Gy for lung cancer mortality in Mayak workers given above with an estimated ERR/Gy for lung cancer incidence in the LSS cohort based on the analysis by Furukawa et al. (2010) at a shielded kerma of 0–4 Gy described above that accounted for the joint effects of radiation and smoking. We assumed that an age at exposure of 35 and attained age of 65 in the LSS cohort provided a reasonable match to the distributions of ages at diagnosis of lung cancer and ages at first exposure in the Mayak workers (Sokolnikov et al. 2008). Based on the fractions of males and females in the Mayak workers, the fractions of male and female workers that reported as smokers, never-smokers, or unknown, and baseline rates of lung cancer in males and females relative to the baseline rates in nonsmokers reported by Sokolnikov et al. (2008), we used data on baseline rates of lung cancer in smokers as a function of smoking history (Bach et al. 2003) and baseline rates in never-smokers (Thun et al. 2008) to develop three scenarios of smoking history (number of cigarettes per day times years of smoking) that matched the ratios of baseline rates in smokers and nonsmokers in the Mayak worker population.⁷⁰ In each scenario, the model for lung cancer incidence in the LSS cohort developed by Furukawa et al. (2010) was used to estimate an ERR/Gy in that cohort with uncertainty; 50th percentiles and 90% CIs of assumed Weibull distributions of the three estimates of ERR/Gy are 0.91 (0.60, 1.35), 0.59 (0.37, 0.91), and 0.47 (0.27, 0.77). By calculating an unweighted average of the three estimates of ERR/Gy for the different smoking histories in the LSS cohort and by accounting for risk transfer and its uncertainty for lung cancer, we obtained an estimated DREF based on data on lung cancer mortality in Mayak workers with a 50th percentile and 90% CI of 3.4 (1.2, 12). The MLE of the ERR for lung cancer mortality in Mayak workers given above is at the 46th percentile of an assumed Weibull distribution.

5.5.3 Mortality from Lung Cancer in Western Nuclear Workers

No consistent pattern of increased risk due to radiation has been seen for any single cancer type across all cohorts of nuclear workers (Cardis et al. 2007; Muirhead et al. 2009). Lung cancer was the only cancer type for which a statistically significant increase in risk was observed in the 15-country study; the

⁷⁰ For example, in one scenario, the smoking history that matched the ratio of baseline rates in male smokers and nonsmokers was 10 cigarettes per day for 50 years. In all scenarios, smoking was assumed to begin at age 20.

ERR/Sv was 1.9 [90% CI: (0.5, 3.6)] (Cardis et al. 2007). However, the increase was significant only in workers at mixed-activity facilities, where significant exposures to chemical carcinogens were more likely and the estimated ERR/Sv for lung cancer mortality was 2.7 [90% CI: (1.0, 5.0)].

A drawback of all studies of occupational exposure, including the 15-country study, is the lack of information on potentially important risk factors other than radiation, especially smoking. Potential risk factors in the 15-country study include smoking, diet, and exposure to chemical carcinogens. Results from limited smoking surveys conducted in seven cohorts were inconsistent (Cardis et al. 2007). Although an attempt was made to adjust estimated risks in the 15-country study to account for the effects of lifestyle factors, such as smoking, based on socio-economic status, the specification of socio-economic status was country-specific and not consistent across all cohorts.

When deaths from solid cancers that might be associated with smoking, which comprised 57% of all cases of solid cancer analyzed in the 15-country study, were removed, the central estimate of ERR/Sv for solid cancers from that study decreased from 0.87 to 0.62 and the 90% CI of (-0.36, 1.9) overlapped zero (Cardis et al. 2007; see Table 5.10). Nearly the same result was obtained when lung and pleural cancers were removed from the grouping of all cancers excluding leukemia; the central estimate of ERR/Sv decreased from 0.97 to 0.59 and the 90% CI of (-0.16, 1.5) overlapped zero (Table 5.10). Similarly, when results for the Canadian cohort, in which smoking was identified as a potential risk factor, were removed but data for cancers that might be associated with smoking in the other 14 cohorts were retained, the estimated ERR/Sv decreased to 0.58 [90% CI: (-0.10, 1.39)], which is not statistically significant (Wakeford 2005; Cardis et al. 2007; UNSCEAR 2008). While Cardis et al. (2007) concluded that it was unlikely that the entire increase in the risk of solid cancers from the 15-country study could be explained by the effect of smoking, they also recommended that an association of lung cancer with radiation should be interpreted with caution, pending further studies to collect information about individual smoking habits and other occupational exposures. Until such information is included in a risk assessment, we are reluctant to use the estimated risk of lung cancer from the 15-country study noted above, which is about three times higher than the estimate in the LSS cohort by Furukawa et al. (2010), to derive a DREF.

5.5.4 Mortality from Lung Cancer in Tuberculosis Fluoroscopy Cohorts

Although the carcinogenicity of fractionated acute doses to the breast was clearly seen in studies of tuberculosis fluoroscopy cohorts (Section 5.3.3), fractionated exposures of the lung in members of those cohorts appeared to be much less carcinogenic than exposures considered to be acute (Ron 2003). Studies of tuberculosis patients who received multiple fluoroscopies have shown that while doses to the lung were considerable (about one-third of the doses to the breast) and the risk of breast cancer was substantial

(Boice et al. 1991; Howe and McLaughlin 1996), there was no indication of an increased risk of mortality from lung cancer (Davis et al. 1989; Boice et al. 1991; Howe 1995; NCRP 2001).

Risks of lung cancer mortality due to radiation in the Canadian tuberculosis fluoroscopy cohorts reported by UNSCEAR (2008) based on an analysis by Howe (1995) were consistent with zero: an ERR at 1 Gy of 0.00 [95% CI: (-0.06, 0.07)] and an EAR/10⁴ person-y/Gy of 0.0 [95% CI: (-0.4, 0.4)]. Estimated risks in the Massachusetts tuberculosis fluoroscopy cohorts—an ERR at 1 Gy of -0.19 [90% CI: (<-0.2, 0.04)] and an EAR/10⁴ person-y/Gy of -0.90 [90% CI: (<-1.8, 0.2)] (Davis et al. 1989; UNSCEAR 2008)—tended to be <0. The central estimates of risks imply a DREF of ∞. Reported risks of lung cancer mortality in the LSS cohort at comparable ages at exposure of 20–39 based on DS86 dosimetry and an assumed neutron RBE of 10 are an ERR/Gy of 0.78 [90% CI: (0.43, 1.19)] and an EAR/10⁴ person-y/Gy of 0.51 [90% CI: (<0, 1.83)] (Preston et al. 2003b; UNSCEAR 2008).

Because lower limits of 90% CIs of the ERR and EAR in the Massachusetts fluoroscopy cohorts and the EAR in the LSS cohort given above are not specified, it is doubtful that meaningful estimates of a DREF can be developed based on those data, and any such estimates would have large uncertainties. Similarly, a DREF estimated as the ratio of the ERR in the LSS cohort to the ERR in the Canadian fluoroscopy cohort, adjusted to account for an assumed REF_L of 2 for x rays as in our analysis of data on breast and thyroid cancer in Sections 5.3 and 5.4, would have a very large uncertainty, due to the narrow CI of the ERR in the Canadian cohort centered at 0.0, and would be largely uninformative. On the basis of these considerations, we did not develop a probability distribution of DREF using these data.

Grogan et al. (2000) concluded that ERRs in the Canadian fluoroscopy cohorts reported by Howe (1995) and given above suggested a DDREF of 8 when compared with an estimated ERR in the LSS cohort of 0.6 [95% CI: (0.26, 0.99)] (Howe 1995). EPA (1999) interpreted those data differently, concluding that because the use of an EAR model would reduce the projected risk in a North American population by about a factor of four, the data would be consistent with a DDREF of 2. In effect, EPA (1999) incorporated a larger uncertainty in risk transfer in their estimate risks, in lieu of using a separate DDREF for lung cancer, on the grounds that the case for a large reduction in risks at low dose rates based on data in the fluoroscopy cohorts was not compelling, as discussed below. However, neither Grogan et al. (2000) nor EPA (1999) took into account a potentially higher REF_L for fluoroscopic x rays compared with high-energy gamma rays when comparing risks in the different cohorts. In its revised cancer risk models, EPA (2011) used the DDREF recommended in the BEIR VII report (NRC 2006) to estimate risks of all solid cancers, including lung cancer, and did not consider a separate DDREF for lung cancer.

Howe (1995) attributed the discrepancy between the very low risks of lung cancer in tuberculosis fluoroscopy patients and risks in the LSS cohort to the fractionated nature of exposures of the patients. Other investigators noted the potential influence of other risk factors in studies of those patients, including

smoking history, which has not been fully documented, and the effect of severe pulmonary tuberculosis (NCRP 2001; UNSCEAR 2000; NRC 2006). ICRP (2005) noted that the below-average exposure of tuberculosis patients to tobacco smoke could have masked a radiation-related increase in the risk of lung cancer, even though there were attempts to control for smoking in the analyses. Richardson (2002) suggested that necrosis and surgical removal of lung tissues associated with tuberculosis would preclude a clear interpretation of dose or dose-rate effects on lung cancer, e.g., by reducing the volume of lung tissue remaining at risk of developing a later malignancy (Davis et al. 1989). In addition, misdiagnosis of lung cancer as tuberculosis could have affected dose-response analyses for lung cancer. Although most concerns were refuted by Howe (1995) with respect to the Canadian fluoroscopy cohorts, NCRP (2001) cautioned that data on lung cancer mortality in the tuberculosis fluoroscopy cohorts do not definitively demonstrate that fractionated exposures of the lung to low-LET radiation impose little or no risk.⁷¹

UNSCEAR (2000) appeared to be less dismissive of a real difference in risks of lung cancer in the LSS and tuberculosis fluoroscopy cohorts, as implied by the available data, due specifically to the virtually complete repair of radiation damage to lung tissue when acute doses of x rays of about 10 mGy (Howe 1995) are fractionated at intervals >7 days (Elkind 1999); see also Boice (2011). Similarly, the BEIR VII committee concluded that “[t]he study of tuberculosis patients, based on a very large number of lung cancer deaths, appears to indicate that substantial fractionation of exposure leads to a reduction in risk” (NRC 2006).⁷² If the effect of an RBE for x rays suggested by Brenner (1999b) and used in our analysis of data on breast and thyroid cancer were operative, the difference in risks of lung cancer in the tuberculosis patients and the LSS cohort should have been partially offset by a factor of about two, which would make the lack of a dose-response in the patients all the more significant.

5.5.5 Conclusions from Studies of Lung Cancer

On the basis of available data, the absence of excess lung cancers in tuberculosis patients who received fractionated acute doses of x rays could be an aberration, and data from other epidemiological

⁷¹ Tuberculosis patients also have tended to be of lower socio-economic status, more susceptible to other infections, generally less healthy overall than the average person, and at greater risk of dying from another condition before they acquire lung cancer (J. Neton, personal communication, 2004).

⁷² A similar discrepancy is found when data on mortality from lung and stomach cancer in ankylosing spondylitis patients are compared with data in the LSS cohort (Weiss et al. 1994; NRC 2006). There is no evidence of an excess risk of lung cancer in the patients more than 25 years after exposure. There also is little evidence of an excess risk of stomach cancer in the spondylitis patients, which is all the more striking when the baseline risk is much lower than in the LSS cohort. The number of dose fractions and the time interval between fractions were much less than in the tuberculosis cohorts, while the mean total doses to the lung and stomach were higher. Such results indicate that all aspects of the observed patterns of dose-responses in epidemiological studies cannot be explained satisfactorily.

studies are consistent with an LDEF or a DREF ranging from <1 to about 10 or more. We concluded that the following estimates of LDEF or DREF could be used to estimate a DDREF for lung cancer:

- LDEFs with 50th percentiles and 90% CIs of 4.9 (0.8, 17) and 1.4 (0.5, 3.2) based on analyses by Little and Muirhead (2000, 2004) of the curvature in the dose-response in the LSS cohort at lung doses of 0–2 Gy and a shielded kerma of 0–4 Gy, respectively (Table 5.14);
- A DREF with a 50th percentile and 90% CI of 3.4 (1.2, 12) we derived by comparing estimated ERRs for lung cancer mortality in Mayak workers and lung cancer incidence in the LSS cohort (Section 5.5.2).

Despite our concerns about the effects of smoking on risks of lung cancer, there is a general consistency in the estimates of LDEF or DREF when the large uncertainties are taken into account.

5.6 STUDIES OF NON-MELANOMA SKIN CANCERS

Evidence of a possible threshold for induction of skin cancer by radiation was seen in early data on incidence of non-melanoma skin cancers in the LSS cohort (Thompson et al. 1994) and in studies in mice and rats (UNSCEAR 1993, 2000; NCRP 2001; NRC 2006). Data in the LSS cohort based on DS86 dosimetry were consistent with a threshold dose of about 1 Gy. This result may not mean that there is a true threshold in the dose-response. An analysis of data on individual types of non-melanoma skin cancer in the LSS cohort (Ron et al. 1998) showed an excess risk of basal cell carcinoma, with a suggestion of a non-linear dose-response, but no dose-response for squamous cell carcinoma was seen.

5.6.1 Recent Epidemiological Studies

The BEIR VII committee (NRC 2006) concluded that the dose-response for non-melanoma skin cancers in the LSS cohort based on DS02 dosimetry is highly curvilinear, with a statistically significant excess risk seen only at neutron-weighted doses above about 0.5 Gy.

An analysis of the dose response for incidence of all non-melanoma skin cancers in the LSS cohort based on DS02 dosimetry by Preston et al. (2007) is shown in Figure 5.13. A linear-spline model with a change in slope (knot) at a dose to skin of 1 Gy fit the data better than a simple linear model. Reported sex-averaged MLEs and 90% CIs of ERR/Gy at age 70 after exposure at age 30 are 0.17 (0.003, 0.55) at doses <1 Gy and 1.2 (0.57, 2.3) at doses >1 Gy. The ratio of the two ERRs gives an estimated LDEF with

a 50th percentile and 90% CI of 5.4 (0.9, 40). MLEs of the ERRs at doses <1 Gy and >1 Gy are at the 38th and 42nd percentiles, respectively, of assumed Weibull distributions.

Dose-responses for incidence of the two main types of non-melanoma skin cancer in the LSS cohort reported by Preston et al. (2007) were quite different. Incidence of basal cell carcinoma was strongly associated with exposure to radiation, but there was no evidence of an association for incidence of squamous cell carcinoma. Using a linear-spline model, Preston et al. (2007) obtained sex-averaged MLEs and 90% CIs of ERR/Gy for incidence of basal cell carcinoma at age 70 after exposure at age 30 of 0.48 (0.12, 1.3) at skin doses <1 Gy and 2.6 (2.2, 3) at doses >1 Gy. The ratio of the two ERRs gives an estimated LDEF with a 50th percentile and 90% CI of 4.4 (2.0, 22). MLEs of the ERRs at doses <1 Gy and >1 Gy are at the 38th and 48th percentiles, respectively, of assumed Weibull distributions.

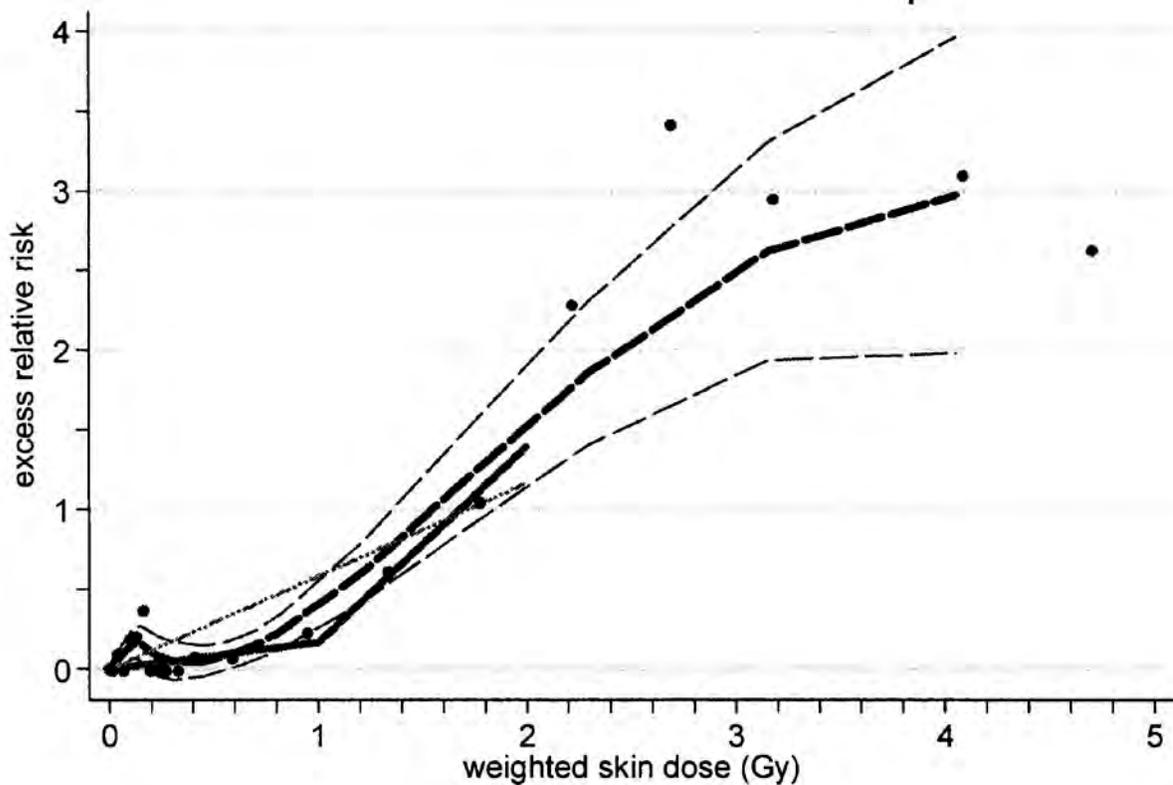


Figure 5.13. Dose-response (ERRs) for incidence of all non-melanoma skin cancers in LSS cohort based on DS02 dosimetry (Preston et al. 2007). Solid line is linear-spline fit with knot at 1 Gy to sex-averaged ERR at age 70 after exposure at age 30 at doses of 0–2 Gy, and dot-dashed line is linear fit over that dose range. Points are non-parametric estimates of ERR in dose categories. Thick dashed line is non-parametric smooth fit to those ERRs, and outer dashed lines are one standard error above and below that fit.

UNSCEAR (2008) analyzed the dose-response for all non-melanoma skin cancers in the LSS cohort based on DS02 dosimetry and concluded that a quadratic-exponential dose-response model gave the best fit, which implies that LDEF approaches ∞ at very low doses. The use of different models to fit the same data suggests that the uncertainty in an LDEF derived from data in the LSS cohort may be substantially greater than the uncertainties based on our comparisons of estimates of ERR/Gy at low and high doses using a linear-spline model. Since individual types of non-melanoma skin cancer were not separated in the analysis by UNSCEAR (2008), we have not used their results in deriving a DDREF.

An interaction between ultraviolet (UV) and ionizing radiation in inducing skin cancer, which could be a complicating factor in estimating risks of radiation-induced skin cancer, was not supported by an analysis of data in the LSS cohort by Ron et al. (1998), because the ERR for radiation-induced basal cell carcinoma was high in a population with low rates of UV-induced skin cancer and the ERR was higher in parts of the body that usually are shielded from UV radiation than in exposed parts. However, a study of the New York tinea capitis cohort, in which children received high doses to the scalp, indicated that a light complexion, severe sunburning, and North European ancestry, but not chronic exposure to the sun, were predictive of an increase in basal cell carcinoma (Shore et al. 2002). Ron et al. (1998) also noted that the suggestion of an interaction between UV and ionizing radiation in other studies may have been an effect of age at exposure. In the analysis of data in the LSS cohort (Preston et al. 2007), the risk clearly decreases with increasing age at exposure. The evidence for an effect of age at exposure in the study of children of ages 1–15 in the New York tinea capitis cohort was weaker (Preston et al. 2007; Shore et al. 2002).

Statistically significant ERRs and EARs for incidence of basal cell carcinoma were seen in studies of the Israeli and New York tinea capitis cohorts that received x-ray treatments of the scalp at ages 1–15 (Ron et al. 1991; Shore et al. 2002; UNSCEAR 2008); estimates of ERR/Gy in the Israeli and New York cohorts based on linear fits to dose-responses at all doses were 0.70 [90% CI: (0.35, 1.32)] and 0.6 [95% CI: (0.3, 1.1)], respectively, and estimates of EAR/10⁴ person-y/Gy were 1.31 [90% CI: (0.94, 1.77)] and 1.9 [95% CI: (0.5, 3.3)]. Estimated risks in the tinea capitis cohorts, adjusted to account for an REF_L for x rays, could be compared with age-matched risks in the LSS cohort. However, such comparisons would not yield estimates of DDREF when exposures of the tinea capitis cohorts occurred over a short period (10–20 minutes) at high dose rates and mean doses to skin of 6.8 and 4.3 Gy were much higher than the mean dose of 0.32 Gy in the LSS cohort.

Estimated ERRs and EARs for incidence of all skin cancers in adults in the cervical cancer, Massachusetts tuberculosis fluoroscopy, and New York post-partum mastitis cohorts were reported (UNSCEAR 2008). However, estimated risks in those cohorts are not statistically significant. In addition, members of the cervical cancer and mastitis cohorts received a small number of high-dose fractions at a high dose rate, and mean doses to skin of 2.6–10 Gy in the three cohorts were much higher than the mean

dose in the LSS cohort. Therefore, even if risks in those cohorts were statistically significant, comparisons with risks to adults in the LSS cohort would not yield estimates of DDREF.

Baseline rates of non-melanoma skin cancers, especially basal cell carcinoma, differ greatly in Japanese and Caucasian populations. As a result, transfer of risks due to radiation between those populations and its uncertainty is an important consideration, and basing estimates of DDREF on ratios of ERRs or EARs only may give highly erroneous results. In addition, baseline rates of basal cell carcinoma often are underreported. Consequently, DDREFs for non-melanoma skin cancers or basal cell carcinoma that are estimated by comparing risks in Japanese and Caucasian populations should be based on ERRs and EARs in the two populations, with equal weights assigned to ERR- and EAR-based DDREFs.

5.6.2 Conclusions from Studies of Skin Cancer

We concluded that the only relevant estimates of a DDREF for skin cancer based on analyses of epidemiological data are LDEFs with 50th percentiles and 90% CIs of 5.4 (0.9, 40) and 4.4 (1.9, 20) that we estimated from linear-spline fits to dose-responses for incidence of all non-melanoma skin cancers and basal cell carcinoma, respectively, in the LSS cohort based on DS02 dosimetry (Preston et al. 2007). Those LDEFs are ratios of the slopes of linear dose-responses at skin doses >1 Gy and <1 Gy. It is important to note that if risk coefficients for basal cell and squamous cell carcinomas in IREP were revised to represent dose-responses at doses <1 Gy only, the LDEFs we estimated would not apply.

Limited data in animals summarized in Table 4.2 indicate that there could be significant effects of dose and dose rate on induction of skin cancers, including a threshold in the dose-response. A threshold also could be consistent with the highly curvilinear dose-responses for all non-melanoma skin cancers based on DS02 dosimetry reported by the BEIR VII committee (NRC 2006) and UNSCEAR (2008). Given the importance of the difference in patterns of dose-responses for individual types of skin cancer on dose-responses for all non-melanoma skin cancers reported by Ron et al. (1998) and Preston et al. (2007), it is difficult to draw firm conclusions about the significance of the quadratic-exponential dose-response model developed by UNSCEAR (2008) or the existence of a threshold dose in humans.

5.7 STUDIES OF BONE CANCER

Few epidemiological studies are informative about risks of radiation-induced bone cancers in adults, due in part to the rarity of malignant bone cancers (UNSCEAR 2008). The lack of a statistically significant dose-response in the LSS cohort could be interpreted as evidence of a possible threshold (LDEF = ∞). The BEIR VII committee (NRC 2006) did not develop a risk model for bone cancer.

UNSCEAR (2008) concluded that a quadratic dose-response model provided the best fit to data from Preston et al. (2007) on incidence of bone cancer in the LSS cohort based on DS02 dosimetry. However, the significance of the UNSCEAR model is questionable when it was based on only 19 cases.

The ERR/Gy for mortality from bone cancer in Mayak workers due to chronic external exposure to gamma radiation estimated by Sokolnikov et al. (2008) was positive (0.35) but not significantly different from zero [95% CI: (<0, 4.4)]. This estimate was obtained in a study that used recently improved estimates of annual external and internal organ doses to individual workers.

On the whole, data in humans and data in animals summarized in Table 4.2 suggest that a DDREF for bone cancer and its uncertainty could be very high, given the evidence of a “practical” threshold in dose-responses in animals at cumulative doses <5 Gy (Raabe 2010). On the basis of the limited data, we do not believe that a credible probability distribution of a DDREF for bone cancer can be developed. If future studies support the existence of a quadratic (or threshold) dose-response for bone cancer in the LSS cohort, use of a DDREF in estimating risks at low doses or low dose rates would not be appropriate.

5.8 STUDIES OF LEUKEMIA

5.8.1 Introduction

A review of studies of radiation-induced leukemia serves several purposes. The first is to investigate whether the LDEF of 2 at a neutron-weighted dose to bone marrow of 1 Gy that is implicit in the LQ dose-response model for acute exposure in IREP (Land et al. 2003a) is consistent with recent analyses of the curvature in the acute dose-response for all leukemias (excluding CLL) in the LSS cohort.

Second, estimated risks of all leukemias at 1 Gy in the LSS cohort based on an LQ dose-response model can be compared with estimated risks per Gy from chronic exposure of workers or members of the public based on linear dose-response models to estimate a DREF at 1 Gy. Those DREFs can be compared with LDEFs based on data in the LSS cohort, as in analyses of data for solid cancers discussed previously.

Third, acute dose-responses for all leukemias in the LSS cohort at doses sufficiently low that the quadratic term in a modeled LQ dose-response is unimportant can be compared with dose-responses from chronic exposure of workers based on linear models to evaluate the validity of an assumption in IREP that risks of leukemias from chronic exposure can be estimated using the coefficients (α) of the linear terms in the LQ dose-response models for acute exposure (Land et al. 2003a). The desired quantity is the ratio of the coefficient of the linear term in the dose-response in the LSS cohort to the coefficient of the linear dose-response in workers, denoted by $\alpha_{\text{acute}}/\alpha_{\text{chronic}}$. This ratio is similar to a DREF, but it is not a DREF when the numerator does not represent a response at high acute doses.

Fourth, as noted in Section 5.2.1.3, estimates of LDEF for all leukemias in the LSS cohort might be used to represent an LDEF for solid cancers when the curvature in the dose-response for leukemias should be less affected by contributions from neutrons, which have a linear dose-response, due to the much lower biological effectiveness of neutrons in inducing leukemias compared with solid cancers.

Finally, we considered whether recent data in the LSS cohort and populations that received chronic or protracted exposures indicate that CLL is radiogenic. Although CLL usually is not considered to be radiogenic, CLL is assumed to be radiogenic in NIOSH-IREP. The risk model for CLL is based on data on dose-responses for lymphoma and multiple myeloma in the LSS cohort.

5.8.2 Analysis of Data on Leukemia in LSS Cohort

Analyses of data for all leukemias combined (excluding chronic lymphocytic leukemia, CLL) in the LSS cohort have shown a pronounced upward curvature in dose-responses for incidence (Preston et al. 1994; Little and Muirhead 2000, 2004; Hsu et al. 2013) and mortality (Preston et al. 2004; UNSCEAR 2000, 2008; Little et al. 2008; Richardson et al. 2009). However, as illustrated in Figures 5.14 and 5.15, for example, there is considerable uncertainty in the form of the dose-response at the lowest doses. Those data have been interpreted by some as evidence of a possible threshold or hormetic response for leukemia (Mossman 2001; UNSCEAR 2000).

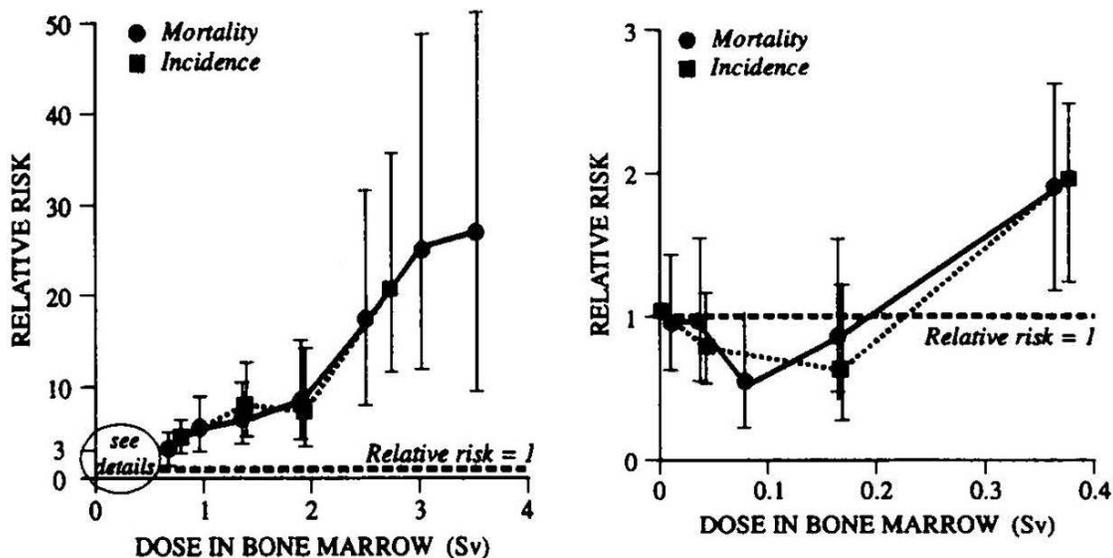


Figure 5.14. Relative risks of leukemia mortality and incidence in LSS cohort estimated by Little and Muirhead (1998) based on DS86 dosimetry. Dose to bone marrow is neutron-weighted dose calculated assuming neutron RBE of 20.

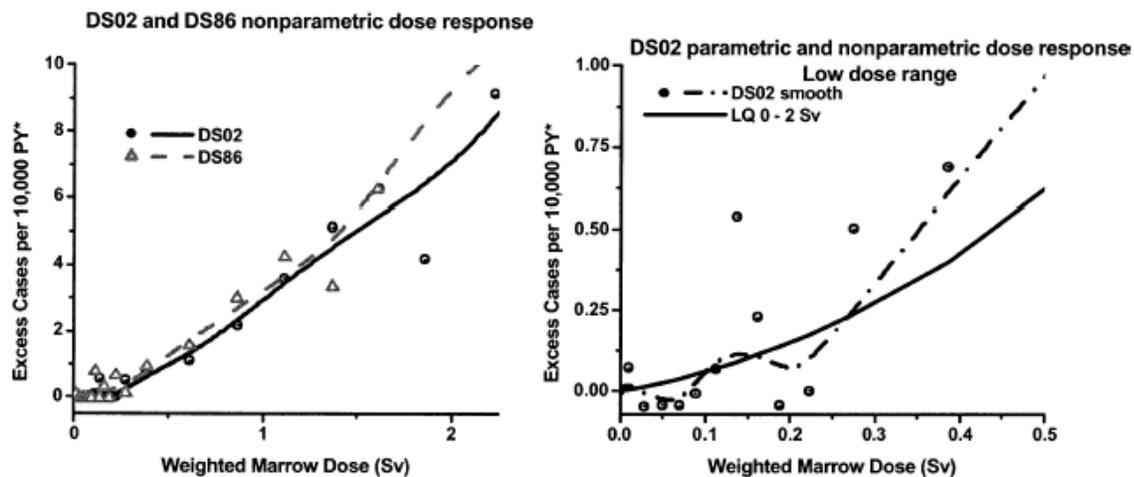


Figure 5.15. Excess cases (EARs) of leukemia mortality in LSS cohort based on DS86 or DS02 dosimetry estimated by Preston et al. (2004). Latter estimates are based on data from 10 years of additional follow-up. Dose to bone marrow is neutron-weighted dose calculated assuming neutron RBE of 10.

Estimates of LDEF based on analyses of the curvature in dose-responses for incidence or mortality from all leukemias as a group (excluding CLL) in the LSS cohort are given in Tables 5.21 and 5.22. As in our analyses of data for solid cancers and except as noted, we estimated 50th percentiles and 90% CIs of LDEFs by assuming that reported coefficients with specified CIs are described by Weibull distributions with modes at the reported MLEs. When an upper limit of a CI was not specified, a 50th percentile of LDEF is not estimated. As described in Section 5.2.1, a correlation between the parameters β and α with an assumed correlation coefficient of -1 was taken into account in the analyses of data from Little et al. (2008) in which an LQ dose-response model was assumed and in the analysis of data from Richardson et al. (2009). Estimated LDEFs in those cases did not depend greatly on the assumed correlation coefficient. In the analysis of data from Ozasa et al. (2012), there should be no correlation between the parameters α_L and α_{LQ} that were used to estimate an LDEF.

The upper limit of ∞ in two LDEFs estimated by Preston et al. (2004) in Table 5.21 is consistent with a quadratic dose-response. Similarly, the linear coefficients (α) in the LQE dose-responses based on ERR and EAR models for leukemia mortality developed by Little et al. (2008) are consistent with zero, and a quadratic dose-response with an exponential cell-sterilization term, which implies an LDEF of ∞ , was consistent with the data. Although Little et al. (2008) considered that an LQE model for leukemia mortality was optimal statistically, results obtained using an LQ model were preferred.

Table 5.21. LDEFs derived from analyses of curvature in modeled dose-responses (EARs or ERRs) for incidence of all leukemias (excluding CLL) in LSS cohort based on DS86 or DS02 dosimetry^a

Dose range (Gy)	Follow-up period	Method of calculation ^b	Age-related modifiers	LDEF (95% CI)	Source
0–4 ^c	1950–1987	α_L/α_{LQ} [1 + (β/α) D] at 1 Gy (ERR model) [$\beta/\alpha = 1.81 \text{ Gy}^{-1}$; 95% CI: (0.21, >1000)]	Age at exposure; time since exposure	2.5 ^d (1.2, >1000) 2.8 ^e (1.2, >1000)	Little and Muirhead (2000, 2004)
0–2 ^f		α_L/α_{LQ} [1 + (β/α) D] at 1 Gy (ERR model) [$\beta/\alpha = 1.09 \text{ Gy}^{-1}$; 95% CI: (–0.25, 117)]		1.73 ^d (0.79, 148) [30 (2.1, 120)] ^g 2.1 ^e (0.75, 118) [24 (1.8, 97)] ^h	
0–4 ⁱ	1950–2001	[1 + (β/α) D] at 1 Gy (ERR model) [$\beta/\alpha = 1.20 \text{ Gy}^{-1}$; 95% CI: (0.23, 49.4)] [1 + (β/α) D] at 1 Gy (EAR model) [$\beta/\alpha = 1.03 \text{ Gy}^{-1}$; 95% CI: (0.20, 8.52)]	Attained age; time since exposure Age at exposure; attained age	2.2 ^e (1.2, 50) [11 (1.7, 42)] ^j 2.0 ^e (1.2, 9.5) [3.4 (1.3, 8.3)] ^k	Hsu et al. (2013)

^a ERRs and EARs are sex-averaged. Analyses were based on linear-quadratic (LQ) dose-response models and neutron-weighted doses to bone marrow.

^b See Sections 2.2 and 2.4.1 for details of dose-response models and methods of calculating LDEF; α_L is linear risk coefficient (ERR/Gy) based on linear fit to data over indicated dose range; α_{LQ} is linear risk coefficient based on linear-quadratic (LQ) fit to data; β/α is curvature parameter; D is neutron-weighted dose in Gy.

^c Shielded kerma free-in-air from photons and neutrons based on DS86 dosimetry. Neutron-weighted doses to bone marrow were calculated assuming neutron RBE of 20. Members of LSS cohort with shielded kerma >4 Gy were omitted.

^d Reported central value is MLE.

^e MLE based on reported central value of β/α .

^f Neutron-weighted doses to bone marrow based on DS86 dosimetry and calculated assuming neutron RBE of 20.

^g 50th percentile and 90% CI we estimated from reported MLE and 95% CI of α_L/α_{LQ} . MLE of α_L/α_{LQ} is at 4.3rd percentile of assumed Weibull distribution.

^h 50th percentile and 90% CI we estimated from reported MLE and 95% CI of β/α . MLE of β/α is at 5.8th percentile of assumed Weibull distribution.

ⁱ Shielded kerma free-in-air from photons and neutrons based on DS02 dosimetry, with estimates of shielded kerma >4 Gy truncated to 4 Gy. Neutron-weighted doses to bone marrow were calculated assuming neutron RBE of 10.

^j 50th percentile and 90% CI we estimated from reported MLE and 95% CI of β/α . MLE of β/α is at 7.7th percentile of assumed Weibull distribution.

^k 50th percentile and 90% CI we estimated from reported MLE and 95% CI of β/α . MLE of β/α is at 21st percentile of assumed Weibull distribution.

Table 5.22. LDEFs derived from analyses of curvature in modeled dose-responses (EARs or ERRs) for mortality from all leukemias (excluding CLL) in LSS cohort based on DS86 or DS02 dosimetry^a

Dose range (Gy)	Follow-up period	Method of calculation ^b	Age-related modifiers	LDEF	Source
0–4 ^c	1950–1990	[1 + (β/α)D] at 1 Gy (EAR model) (β/α = 1.53 ± 1.35 Gy ⁻¹)	Age at exposure; time since exposure	2.5 ^d ± 1.4 2.5 (0.3, 4.8) ^e	Pierce et al. (1996a)
0–4 ^f	1950–2000	[1 + (β/α)D] at 1 Gy (EAR model) [β/α = 0.89 Gy ⁻¹ ; 90% CI: (0.2, 6.0)]	Age at exposure; time since exposure	1.9 ^g (2.9) ^h (1.2, 7.0) (90% CI)	Preston et al. (2004)
0–4 ⁱ		[1 + (β/α)D] at 1 Gy (EAR model) [β/α = 1.6 Gy ⁻¹ ; 90% CI: (0.4, ∞)]		2.6 ^g (1.4, ∞) (90% CI)	
0–2 ^j		[1 + (β/α)D] at 1 Gy (EAR model) [β/α = 2.0 Gy ⁻¹ ; 90% CI: (0.2, ∞)]		3.0 ^g (1.2, ∞) (90% CI)	
0–4 ^k	1950–2000	[1 + (β/α)D] at 1 Gy (ERR model) [β/α = 0.87 Gy ⁻¹ ; 95% CI: (0.16, 15)]	Age at exposure; time since exposure	1.9 ^g (1.2, 16) (95% CI) 4.6 (1.3, 14) ^k	NRC (2006)
		[1 + (β/α)D] at 1 Gy (EAR model) [β/α = 0.88 Gy ⁻¹ ; 95% CI: (0.16, 15)]		1.9 ^g (1.2, 16) (95% CI) 4.6 (1.3, 14) ^k	
0–4 ^l	1950–2000	[1 + (β/α)D] at 1 Gy (ERR model)	Age at exposure; attained age	2.2 (1.2, 10) ^m	Little et al. (2008)
		[1 + (β/α)D] at 1 Gy (EAR model)		2.1 (1.2, 9.2) ⁿ	
		[1 + (β/α)D] exp(-γD) at 1 Gy (LQE ERR model)	Age at exposure; attained age	-0.4 (-25, 27) ^o	Little et al. (2008)
		[1 + (β/α)D] exp(-γD) at 1 Gy (LQE EAR model)		1.0 (-27, 27) ^p	
0–4 ^q	1950–2000	[1 + (β/α)D] at 1 Gy (ERR model)	Age at exposure; time since exposure	1.5 (1.1, 3.4) ^q	Richardson et al. (2009)

Table 5.22 (continued)

Dose range (Gy)	Follow-up period	Method of calculation ^b	Age-related modifiers	LDEF	Source
0–4 ^f	1950–2003	α_L/α_{LQ} at 1 Gy (ERR model)	Age at exposure; attained age	1.9 (0.8, 9.2) ^f	Ozasa et al. (2012)

^a Risks are sex-averaged. Analyses were based on linear-quadratic (LQ) dose-response models, except as noted, and neutron-weighted doses to bone marrow.

^b See Sections 2.2 and 2.4.1 for details of dose-response models and methods of calculating LDEF; α_L is linear risk coefficient (ERR/Gy) based on linear fit to data over indicated dose range; α_{LQ} is linear risk coefficient based on LQ fit to data; β/α is curvature parameter; LQE denotes linear-quadratic-exponential dose-response; γ is linear coefficient in exponential term to represent cell sterilization in LQE model; D is neutron-weighted dose in Gy.

^c Shielded kerma free-in-air from photons and neutrons based on DS86 dosimetry. Neutron-weighted doses to bone marrow were calculated assuming neutron RBE of 10. Members of LSS cohort with shielded kerma >4 Gy were omitted.

^d Reported central value is MLE.

^e 50th percentile and 90% CI we estimated by assuming that reported β/α is described by normal distribution.

^f Shielded kerma free-in-air from photons and neutrons based on DS02 dosimetry, with estimates of shielded kerma >4 Gy truncated to 4 Gy. Neutron-weighted doses to bone marrow were calculated assuming neutron RBE of 10.

^g MLE based on reported central value of β/α .

^h 50th percentile we estimated from reported MLE and 90% CI of β/α . MLE of β/α is at 23rd percentile of assumed Weibull distribution. LDEF based on DS86 dosimetry has MLE of 1.8 and estimated 50th percentile and 90% CI of 2.6 (1.2, 5.4).

ⁱ Shielded kerma free-in-air from photons and neutrons based on DS02 dosimetry. Neutron-weighted doses to bone marrow were calculated assuming neutron RBE of 10. Members of LSS cohort with shielded kerma >4 Gy were omitted.

^j Neutron-weighted doses to bone marrow calculated assuming neutron RBE of 10.

^k 50th percentile and 90% CI we estimated from reported MLE and 95% CI of β/α . MLE of β/α is at 13th percentile of assumed Weibull distribution.

^m 50th percentile and 90% CI we estimated from reported MLEs and 90% CIs of α [1.60 (0.13, 3.31)] and β [2.13 (0.93, 3.38)] and assumption that α and β are negatively correlated (correlation coefficient of -1). MLEs of α and β are at 48th and 50th percentiles, respectively, of assumed Weibull distributions. Assumed parameter correlation should result in slight overestimate of uncertainty in LDEF.

ⁿ 50th percentile and 90% CI we estimated from reported MLEs and 90% CIs of α [1.19 (0.16, 2.35)] and β [1.38 (0.54, 2.33)] and assumption that α and β are negatively correlated (correlation coefficient of -1). MLEs of α and β are at 49th percentiles of assumed Weibull distributions. Assumed parameter correlation should result in slight overestimate of uncertainty in LDEF.

^o 50th percentile and 90% CI we estimated from reported MLEs and 90% CIs of α [-0.14 (-2.16 , 2.35)], β [7.37 (0.17, 13.2)], and γ [-0.47 (-0.84 , 0.014)] and assumption that α , β , and γ are uncorrelated. MLEs of α , β , and γ are at 47th, 53rd, and 47th percentiles, respectively, of assumed Weibull distributions. Assumption that parameters are uncorrelated should result large overestimate of uncertainty in LDEF.

^p 50th percentile and 90% CI we estimated from reported MLEs and 90% CIs of α [0.027 (-1.72 , 1.80)], β [5.25 (0.94, 10.3)], and γ (-0.46 (-0.85 , 0.041)] and assumption that α , β , and γ are uncorrelated. MLEs of α , β , and γ are at 50th, 48th, and 47th percentiles, respectively, of assumed Weibull distributions. Assumption that parameters are uncorrelated should result large overestimate of uncertainty in LDEF.

^q 50th percentile and 90% CI we estimated from reported MLEs and 90% CIs of α [1.55 (0.63, 2.94)] and β [0.83 (0.29, 1.53)] and assumption that α and β are negatively correlated (correlation coefficient of -1). MLEs of α and β are at 44th and 47th percentiles, respectively, of assumed Weibull distributions. Assumed parameter correlation should result in slight overestimate of uncertainty in LDEF.

Table 5.22 (continued)

^r 50th percentile and 90% CI we estimated from reported MLEs and 95% CIs of α_L [3.1 (1.8, 4.30)] and α_{LQ} [1.5 (-0.1, 3.1)] and assumption that α_L and α_{LQ} are uncorrelated. MLEs of α_L and α_{LQ} are at 52nd and 50th percentiles, respectively, of assumed Weibull distributions.

Differences in the various LDEFs summarized in Tables 5.21 and 5.22 are insignificant, due to their large uncertainties. Therefore, we could not assess whether LDEFs depend on the response analyzed (leukemia incidence or mortality), type of dose-response model (ERR or EAR), length of follow-up of survivors, dosimetry system, or extent of cell sterilization at higher doses (>2 Gy). Any effect of the difference in approaches to estimating an LDEF based on an assumed LQ dose-response [α_L/α_{LQ} or $1 + (\beta/\alpha)D$ at 1 Gy] also cannot be assessed. The uncertainty in LDEF based on the analysis of leukemia mortality by Richardson et al. (2009) is much smaller than uncertainties based on other analyses. The reason for this difference is not apparent when other analyses of leukemia mortality by Preston et al. (2004), the BEIR VII committee (NRC 2006), and Little et al. (2008) were based on the same data and similar formulations of an LQ dose-response model, and the only difference in the data used by Ozasa et al. (2012) was an increase of three years in the period of follow-up.

In contrast to the non-zero responses at low doses implied by the LQ models summarized in Tables 5.21 and 5.22, NCRP (2001) concluded that data in the LSS cohort based on DS86 dosimetry indicated that there was no increase in risk at doses to bone marrow <0.2 Sv. That conclusion is consistent with the data in Figure 5.14. However, given the uncertainties in the data in Figure 5.14, a threshold or perhaps a quadratic dose-response is consistent with the data at doses <0.2 Sv. Data at doses <0.2 Sv based on DS02 dosimetry in Figure 5.15 also are consistent with a negative slope in the dose-response, which would imply a hormetic or threshold response.

UNSCEAR (2008) judged that inclusion of a linear term in the modeled dose-response for leukemia mortality in the LSS cohort based on DS02 dosimetry did not improve the fit to the data at doses to bone marrow <2 Sv compared with the fit using a purely quadratic model. On this basis, it was suggested that a purely quadratic model may best describe the dose-response at low doses. However, UNSCEAR (2008) also cautioned that a similar dose-response had not been seen in the data on leukemia incidence.

Dose-responses for leukemia in the LSS cohort described above represent data for all leukemias as a group (excluding CLL). As described below, dose-responses for specific types of leukemia indicate that data for all leukemias probably cannot be used to estimate LDEFs for those types.

An early analysis by Preston et al. (1994) based on DS86 dosimetry indicated that the non-linearity in the dose-response for incidence of all leukemias in the LSS cohort could be attributed primarily to the

dose-response for acute myeloid leukemia (AML), which contributed about 45% of all cases. The curvature parameter (β/α) in the fitted LQ dose-response for AML was about three times higher than in the dose-response for all leukemias as a group, whereas the dose-responses for acute lymphocytic leukemia (ALL) and chronic myeloid leukemia (CML) were approximately linear, with no evidence of curvature.

In an analysis of data on leukemia incidence in the LSS cohort, women treated for cervical cancer, and patients treated for ankylosing spondylitis using an ERR model that depended on age at exposure and time since exposure, Little et al. (1999) concluded that the optimal dose-response for the three main types of radiogenic leukemias (AML, ALL, and CML) was purely quadratic with an exponential term to represent cell sterilization. The addition of a linear term did not improve the fit of the model.

In a later analysis of leukemia mortality in the LSS cohort based on DS02 dosimetry by Richardson et al. (2009), the fitted dose-response for AML, which contributed 40% of all cases included in the analysis, was purely quadratic, with no evidence of linearity, whereas the dose-responses for ALL and CML were approximately linear, with no evidence of curvature. As in the previous analysis of leukemia incidence by Preston et al. (2004), these results indicated that the curvature in the dose-response for all leukemias as a group is attributable primarily to the non-linear dose-response for AML.

As shown in Figure 5.16, a recent analysis of dose-responses for leukemia incidence in the LSS cohort based on follow-up through 2001 and DS02 dosimetry by Hsu et al. (2013) indicated the same pattern seen by Richardson et al. (2009) for leukemia mortality: a quadratic dose-response for AML, which contributed nearly 50% of all cases included in the analysis, and dose-responses for CML and ALL that were approximately linear, with no evidence of curvature.

Hsu et al. (2013) also reported a statistically significant linear dose-response for incidence of CLL in the LSS cohort, which suggested that the risk of CLL might be increased at higher doses ($P < 0.05$); CLL usually is considered to be non-radiogenic. However, the dose-response analysis for CLL was based on only 12 cases in the LSS cohort, and Hsu et al. (2013) cautioned that generalization of their finding to other populations may be unwarranted when CLL comprises a much lower percentage of leukemia cases in Japan (about 3%) than in western populations (about 20% or more, with an even higher percentage of leukemia cases late in life). Hsu et al. (2013) also noted that clinical data suggest that CLLs in Japan are genetically and biologically different from CLLs in western populations. Studies of populations that received chronic or protracted exposures that were cited by Hsu et al. (2013) were inconclusive on the question of whether CLL is radiogenic; some studies showed evidence of an increased risk of CLL associated with radiation exposure (Rericha et al. 2006; Romanenko et al. 2008; Kesminiene et al. 2008), but other studies did not indicate an increase in risk (Shilnikova et al. 2003; Vrijheid et al. 2008; Muirhead et al. 2009; Krestinina et al. 2010). A study of U.S. nuclear workers that included an assessment of the risk of CLL (Daniels et al. 2013) is discussed in Section 5.8.3.5.

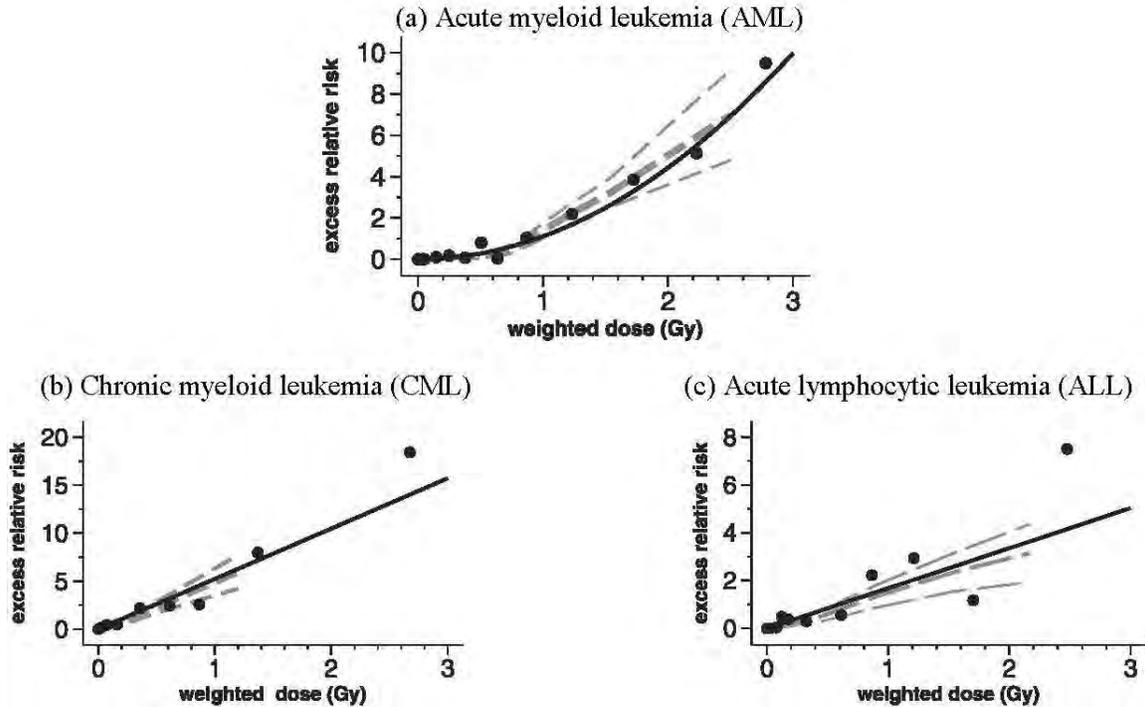


Figure 5.16. Dose-responses (ERRs) for incidence of specific types of leukemia in LSS cohort based on DS02 dosimetry (Hsu et al. 2013). ERRs are sex-averaged risks at attained age 70 after exposure at age 30. Data for AML were fitted with a quadratic model, and data for other two types were fitted with linear models. Data points are based on nonparametric dose-response model. Solid lines are fitted quadratic or linear dose-responses, middle dashed lines are smoothed representations of data points based on nonparametric model, and upper and lower dashed lines are ± 1 SE from smoothed fit.

A concern that applies to all studies of the LSS cohort is that only those cases of leukemia diagnosed on or after October 1, 1950, were included in the analyses (Preston et al. 2004). Given the short minimum latency period for leukemia (Land et al. 2003a), particularly in young children, the omission of leukemias that occurred during the first five years after the bombings presumably has introduced an unquantifiable bias (i.e., an underestimation of risks).

In summary, most results from recent analyses of data on incidence or mortality from all leukemias (excluding CLL) in the LSS cohort based on an LQ dose-response model and DS02 dosimetry indicated a central value (50th percentile) of an LDEF at a neutron-weighted dose to bone marrow of 1 Gy in the range of 1.5–5; most lower limits of 90% CIs are >1.0 , and most upper limits of 90% CIs are <15 . The LDEF at 1 Gy of 2 for all leukemias from acute exposure incorporated in IREP is roughly consistent with results of the recent analyses, although it is questionable whether the model in IREP adequately accounts for uncertainty in LDEF.

More importantly, recent analyses by Richardson et al. (2009) and Hsu et al. (2013) showed that fits to dose-responses for all leukemias as a group using an LQ model give estimates of LDEF that do not apply to specific types of leukemia, including AML, which exhibits a quadratic dose-response, and CML and ALL, both of which exhibit approximately linear dose-responses. A quadratic dose-response implies that LDEF approaches ∞ at the lowest doses, whereas a linear dose-response implies an LDEF of 1. Thus, an LQ dose-response for all leukemias as a group is an artifact of combining several dose-responses, none of which appears to be LQ in form. Although these results do not invalidate the use of an LQ model for all leukemias for purposes of risk assessment (e.g., estimating future risks of unspecified leukemias), an LQ model does not appear to be appropriate for purposes of estimating PC/AS of a diagnosed leukemia of a specific type in an exposed individual. These results also indicate that an LDEF derived from analyses of dose-responses for all leukemias combined should not be used to represent an LDEF for solid cancers.

5.8.3 Data on Leukemia in Chronically Exposed Cohorts

The following sections discuss data on dose-responses for leukemia in chronically exposed cohorts that can be compared with dose-responses in the LSS cohort to estimate a DREF or the ratio $\alpha_{\text{acute}}/\alpha_{\text{chronic}}$ described in Section 5.8.1. All such comparisons are based on estimates of ERRs.

Given that most Western workers were male and the assumption in IREP that baseline rates of leukemia in males in Western countries and Japan differ by less than 10% (Land et al. 2003a), accounting for uncertainty in risk transfer between the LSS and western cohorts is not an important concern for leukemia. Therefore, comparisons of ERRs alone can provide valid estimates of DREF or $\alpha_{\text{acute}}/\alpha_{\text{chronic}}$. If we accounted for uncertainty in risk transfer, central estimates of DREF or $\alpha_{\text{acute}}/\alpha_{\text{chronic}}$ would decrease by only about 5%, and uncertainties in central estimates would increase by an insignificant amount.

5.8.3.1 Western nuclear workers

Most studies of fractionated or protracted exposures at low cumulative doses reviewed by NCRP (2001) did not show an excess of leukemias. The 3-country study of nuclear workers (Cardis et al. 1995) summarized in Table 5.9 (Section 5.2.2.2) was an exception. Since that time, evidence of significant excess risks of leukemia was seen in some of the other studies of radiation workers summarized in Tables 5.9 and 5.10. Uncertainties in some estimates of excess risks are large, which precludes meaningful comparisons with data from acute exposure in the LSS cohort. For example, although the central estimate of the ERR/Sv of 53 from the study of Canadian workers by Zablotska et al. (2004) given in Table 5.9 is

more than an order of magnitude higher than central estimates based on data in the LSS cohort given in the same table, the 95% CI encompasses the estimates in the LSS cohort.⁷³

The analysis of data in U.K. radiation workers by Muirhead et al. (2009) summarized in Table 5.10 gave estimates of ERR/Sv for leukemia mortality and incidence significantly different from zero at the 90% confidence level. We estimated DREFs by comparing those ERRs with age- and sex-matched ERRs in the LSS cohort. Using an ERR at 1 Gy for leukemia mortality in the LSS cohort for age at exposure 29, attained age 52, and male fraction 0.9 (Table 5.10, footnote *i*) with a 50th percentile and 95% CI of 2.3 (1.2, 4.1) that we derived based on the LQ dose-response model developed by the BEIR VII committee (NRC 2006), we estimated a DREF at 1 Gy with a 50th percentile and 90% CI of 1.1 (0.3, 7.1). Using an ERR at 1 Gy for leukemia incidence in the LSS cohort for the same ages and any male fraction with an MLE and 95% CI of 3.8 (2.3, 5.6) that we derived from the LQ dose-response model developed by Hsu et al. (2013) we estimated a DREF at 1 Gy with a 50th percentile and 90% CI of 1.8 (0.6, 10). MLEs of the ERRs for leukemia mortality and incidence in U.K. workers are at the 44th percentiles of assumed Weibull distributions, and the MLE of the ERR for leukemia incidence in the LSS cohort is at the 48th percentile. These DREFs, which have large uncertainties, are generally consistent with LDEFs based on data in the LSS cohort given in Tables 5.21 and 5.22.

Comparisons of modeled ERRs at low doses in the LSS and U.K. worker cohorts were based on estimated risks assuming linear dose-responses in Table 5.10. For leukemia mortality, the estimated ratio of the linear risk coefficient in the LSS cohort of 1.4 [90% CI: (0.1, 3.4)] for ages at exposure ≥ 30 and time since exposure 15 years to the linear risk coefficient in the workers, $\alpha_{\text{acute}}/\alpha_{\text{chronic}}$, has a 50th percentile and 90% CI of 0.8 (-0.2, 5.9). For leukemia incidence, the estimated ratio of the linear risk coefficient in the LSS cohort of 2.9 [90% CI: (0.53, 5.9)] to the linear risk coefficient in the workers has a 50th percentile and 90% CI of 1.4 (0.03, 8.8). MLEs of the ERRs for leukemia mortality and incidence in U.K. workers are at the 44th percentiles of assumed Weibull distributions, and MLEs of the corresponding ERRs in the LSS cohort are at the 44th and 47th percentiles, respectively.

The estimated ERR/Sv for leukemia mortality from the 3-country study (Cardis et al. 1995) given in Table 5.9 initially appeared to be useful in estimating a DREF or ratio of linear risk coefficients, $\alpha_{\text{acute}}/\alpha_{\text{chronic}}$. However, the statistically significant dose-response obtained in that study was attributable mainly to a few cases in workers with doses >0.4 Sv, and all but one of those cases were excluded from

⁷³ A nested case-control study of civilian workers at the Portsmouth Naval Shipyard, in which leukemia deaths (including deaths from CLL) were age-matched with controls, gave an ERR at 10 mSv for leukemia mortality of 0.23 [95% CI: (0.03, 0.88)] when adjusted for exposure to solvents (Kubale et al. 2005). As with the study of Canadian workers by Zablotska et al. (2004), the central estimate is much larger than central estimates in the LSS cohort but the confidence intervals overlap. Because of the type of study, the inclusion of CLL cases (which are not included in the definition of leukemia in the LSS cohort), and the potential importance of other risk factors, we have not used results from the study in Portsmouth Shipyard workers in our analysis.

the 15-country study (Cardis et al. 2007). Analyses that were restricted to lower doses did not show a statistically significant dose-response (Cardis et al. 1995; Cardis et al. 1996; UNSCEAR 2000).

Results from the 15-country study of leukemia mortality in workers summarized in Table 5.10 are similar to results from the earlier 3-country study summarized in Table 5.9. The estimated risk of leukemia mortality in the 15-country study was not affected by concerns about the influence of data in the Canadian cohorts discussed in Section 5.2.2.2, because the numbers of deaths from leukemia in those cohorts were much smaller than in all 15 countries combined. However, because the estimated ERR from the 15-country study is not statistically significant and the lower limit of the CI is not specified, we do not think that meaningful estimates of DREF or $\alpha_{\text{acute}}/\alpha_{\text{chronic}}$ can be developed on the basis of that ERR.

In a study of more than 300,000 radiation workers in France, the U.K., and the U.S. (INWORKS), Leuraud et al. (2015) reported an ERR/Gy for leukemia mortality with an MLE and 90% CI of 3.0 (1.2, 5.2) using a linear dose-response model. This estimate was compared with an ERR at 1 Gy in males of ages 20 to 60 in the LSS cohort with an MLE and 90% CI of 2.6 (1.5, 4.3), which was estimated using data on leukemia mortality from Ozasa et al. (2012) and a linear dose-response model (Metz-Flamant et al. 2013). The ratio of the two ERRs gives an estimated DREF at 1 Gy with a 50th percentile and 90% CI of 0.89 (0.40, 2.5). MLEs of the ERRs in the LSS and worker cohorts are at the 44th and 47th percentiles, respectively, of assumed Weibull distributions. As an alternative, we used the LQ dose-response model for leukemia mortality developed by the BEIR VII committee (NRC 2006) to estimate an ERR at 1 Gy in males in the LSS cohort for age at exposure 31 and attained age 58 with a 50th percentile and 90% CI of 2.2 (1.1, 5.5). The ratio of this ERR to the ERR/Gy in the French, U.K., and U.S. workers gives an estimated DREF at 1 Gy with a 50th percentile and 90% CI of 0.76 (0.29, 2.7). The two estimates of a DREF for leukemia mortality are similar. Using the LQ dose-response model developed by the BEIR VII committee, we estimated a linear risk coefficient in males in the LSS cohort for age at exposure 31 and attained age 58, α_{acute} , with a 50th percentile and 90% CI of 1.08 (0.25, 2.3). The estimated ratio of the linear risk coefficient in the LSS cohort to the ERR/Gy in the French, U.K., and U.S. workers, $\alpha_{\text{acute}}/\alpha_{\text{chronic}}$, has a 50th percentile and 90% CI of 0.36 (0.07, 1.15). The estimated $\alpha_{\text{acute}}/\alpha_{\text{chronic}}$ suggests that the linear term in the LQ dose-response model in the LSS cohort underestimates the ERR/Gy in the pooled worker cohort, but this finding is not statistically significant.

In summary, comparisons of estimated ERRs for leukemia mortality and incidence in radiation workers with age- and sex-matched ERRs in the LSS cohort described above give estimates of a DREF at 1 Gy that are generally consistent with estimates of LDEF based on data in the LSS cohort summarized in Tables 5.21 and 5.22. However, uncertainties in estimated ERRs in workers are sufficiently large that the data also are consistent with threshold or quadratic dose-responses that are suggested by data in the LSS cohort discussed in Section 5.8.2 or, alternatively, a DREF at 1 Gy as high as about 10. At doses

sufficiently low that ERRs for leukemia mortality and incidence in the LSS cohort can be represented by the linear term in an LQ dose-response, probability distributions of ratios of linear risk coefficients in the LSS and worker cohorts, $\alpha_{\text{acute}}/\alpha_{\text{chronic}}$, encompass the value 1.0, which suggests that the linear term in an LQ dose-response model in the LSS cohort could be used to estimate ERRs from chronic or protracted exposure. However, estimates of $\alpha_{\text{acute}}/\alpha_{\text{chronic}}$ are sufficiently uncertain that values <0.1 , including negative values, and as high as about 9 also are consistent with the data in radiation workers.

5.8.3.2 Mayak workers

An analysis of data in workers at the Mayak complex in Russia gave an estimated ERR/Gy for leukemia mortality at doses <1 Gy with an MLE and 90% CI of 0.99 (0.45, 2.12) (Shilnikova et al. (2003). Risks were best described by a linear dose-response model; the fit was not improved by use of LQ or purely quadratic models. When compared with an estimated ERR at 1 Gy for leukemia mortality in the LSS cohort based on an LQ model (NRC 2006) given in the previous section, the estimated ERR/Gy in Mayak workers suggests a DREF at 1 Gy with a 50th percentile and 90% CI of 2.2 (0.9, 5.8). The MLE of the ERR in Mayak workers is at the 39th percentile of an assumed Weibull distribution. When compared with the estimated ERR/Gy in the LSS cohort at doses sufficiently low that only the linear term in an LQ dose-response is significant, as also given in the previous section, the ratio $\alpha_{\text{acute}}/\alpha_{\text{chronic}}$ has an estimated 50th percentile and 90% CI of 1.3 (0.08, 4.6). However, results of the study of Mayak workers are potentially compromised by biases discussed in Section 5.2.2.1. Therefore, we have not included results from this study in our analysis.

5.8.3.3 Techa River cohort

In an analysis of leukemia mortality (excluding CLL) in the Techa River cohort, Krestinina et al. (2005) estimated an ERR/Gy of 6.5 [95% CI: (1.8, 24)] based on TRDS-2000 dosimetry and assuming a linear dose-response model with no dependence on age at first exposure, attained age, or time since exposure. There was no evidence of a significant non-linearity in the dose-response. The estimated ERR/Gy was somewhat higher than a comparable estimate in the LSS cohort of 4 (Pierce et al. 1996a), but the two estimates did not differ significantly when uncertainties were taken into account. The EAR model that gave the best fit to the data was a linear model with a dependence on age at initial exposure; the EAR/10⁴ person-y/Gy at age 25 was 1.7 [95% CI: (0.90, 2.4)]. Using an alternative model with a dependence on attained age gave an EAR/10⁴ person-y/Gy at age 70 of 2.9 [95% CI: (0.8, 4.4)]. The data for CLL did not indicate a significant dose-response; the estimated ERR/Gy was 0.5 [95% CI: (<-0.8 , 9)].

In an analysis of leukemia incidence (excluding CLL) in the Techa River cohort, Krestinina et al. (2010) estimated an ERR/Gy of 4.9 [95% CI: (1.6, 14)] based on TRDS-2000 dosimetry and assuming a linear dose-response model with no dependence on age at exposure, attained age, or time since exposure. The estimated relative risk ($RR = ERR + 1$) was similar to a previous estimate by Ostroumova et al. (2006) of the odds ratio (OD)/Gy for leukemia incidence (excluding CLL) of 5.4 [95% CI: (1.1, 27)];⁷⁴ this estimate, which was obtained in a nested case-control study, was based on TRDS-1996 dosimetry. There was no indication of a significant non-linearity in the dose-response; the estimated curvature was -0.12 [95% CI: (<0.5 , 17)]. Krestinina et al. (2010) noted that the estimated ERR at 1 Gy was similar to an estimate in the LSS cohort (Preston et al. 1994, 2004). The data for CLL did not indicate a significant dose-response; the estimated ERR/Gy was -0.2 with an upper 95% confidence limit of 1.4.

In a recent analysis of leukemia incidence (excluding CLL) in the Techa River cohort, Krestinina et al. (2013) estimated an ERR/Gy of 2.2 [95% CI: (0.8, 5.4)] based on TRDS-2009 dosimetry and assuming a linear dose-response model. The mean and maximum doses to bone marrow of 0.42 and 9 Gy, respectively, were substantially higher than the previous estimates based on TRDS-2000 dosimetry of 0.29 and 2 Gy, respectively. The higher estimates of dose based on TRDS-2009 dosimetry were the primary cause of the reduction in the estimated risk of leukemia incidence by more than a factor of two compared with the previous estimate by Krestinina et al. (2010) described above. There was no statistically significant dependence of the ERR on sex, ethnicity, age at exposure, attained age, or time since exposure. The addition of a quadratic term did not improve the fit with a linear model, and a purely quadratic dose-response model did not describe the data quite as well as a linear model. Krestinina et al. (2013) noted that at a dose of 0.1 Gy, the ERR in the Techa River cohort of 0.22 [95% CI: (0.08, 0.54)] is somewhat higher than the ERR in the LSS cohort of 0.079 [95% CI: (0.003, 0.193)] at attained age 70 following exposure at age 30 based on the linear term in the LQ dose-response model developed by Hsu et al. (2013). However, this difference is not statistically significant when the large uncertainties in the estimated risks in the two cohorts are taken into account. There was no evidence of a dose-response for CLL in the Techa River cohort; the estimated ERR/Gy is 0.1 [95% CI: (<0 , 1.2)].

Krestinina et al. (2013) also analyzed data on incidence of specific types of non-CLL leukemias in the Techa River cohort. That analysis found statistically significant linear dose-responses for CML, with an estimated ERR/Gy of 3.1 [95% CI: (0.5, 18)], and for acute/subacute leukemias as a group (including AML, ALL), with an estimated ERR/Gy of 1.8 [95% CI: (0.4, 5.9)]. Estimated risks of non-Hodgkin's

⁷⁴ In an exposed population, let S_E denote the number of individuals with a disease, F_E denote the number of individuals without that disease, and N_E denote the sum of the two, and let S_C , F_C , and N_C denote the corresponding quantities in a control group. The odds ratio (OR) is estimated as $(S_E/F_E)/(S_C/F_C)$, whereas the relative risk (RR) is estimated as $(S_E/N_E)/(S_C/N_C)$. The two quantities are essentially the same when $S_E \ll F_E$ and $S_C \ll F_C$.

lymphoma, Hodgkin's lymphoma, and multiple myeloma were not statistically significant; upper limits of 95% CIs of estimates of ERR/Gy were 0.7, 1.7, and 3.5, respectively.

As in the analyses of data in Mayak workers, uncertainties in estimated risks in the Techa River cohort summarized above are due in large part to uncertainties in estimate doses, which are discussed by Napier et al. (2001), Seltzer et al. (2001), Romanyukha et al. (2001), Kellerer (2002), Mokrov (2002), Balonov et al. (2006), and Degteva et al. (2006, 2012). Other limitations in studies of the Techa River cohort include uncertain follow-up and cancer ascertainment and the lack of an evaluation of potential contributions to risks from exposures to chemical carcinogens (UNSCEAR 2000; Krestinina et al. 2013). Anspaugh et al. (2006) also noted out that, in contrast to the LSS cohort, the Techa River cohort includes two ethnic groups of different character (Russians and Bashkir-Tartars) with substantially different baseline rates of cancer mortality. However, analyses of data on leukemias described above and data on solid cancers in the Techa River cohort described in Section 5.2.2.3 did not find a statistically significant dependence of ERRs on ethnicity. Factors that have hampered dose reconstructions and epidemiological studies are described by Kossenko (2010). In particular, the apparent occurrence of chronic radiation sickness in significant numbers of Techa River residents during the 1950s, which implies that accumulated doses were >1 Gy, and its influence on an interpretation of estimated risks has not yet been explained. Given the uncertainties in estimating doses to bone marrow in the Techa River cohort, we did not estimate a DREF and the ratio $\alpha_{\text{acute}}/\alpha_{\text{chronic}}$ based on results from studies of leukemias in that cohort.

5.8.3.4 Meta-Analysis by Daniels and Schubauer-Berigan (2011)

Daniels and Schubauer-Berigan (2011) assembled estimates of ERR at a dose to bone marrow or the whole body of 0.1 Gy for leukemia incidence or mortality, excluding CLL, from 23 case-control or cohort studies of chronic or protracted radiation exposures; all but three of the studies selected provided estimates of ERR for mortality. Both stand-alone studies of single cohorts and pooled studies of multiple cohorts were available for analysis. The studies that were selected by Daniels and Schubauer-Berigan (2011) for inclusion in their meta-analysis and the estimated ERRs at 0.1 Gy are summarized in Table 5.23.

Daniels and Schubauer-Berigan (2011) combined results from the studies summarized in Table 5.23 in two ways: (1) a Model I analysis in which stand-alone studies of a single population of workers were preferred (but not used exclusively), and (2) a Model II analysis in which pooled studies of multiple populations were preferred (but not used exclusively). The different studies were pooled in either analysis using inverse (reciprocal)-variance weighting in which the variance between studies and the variance within each study were taken into account. Estimated risks in both analyses included an adjustment to account for potentially unpublished studies that gave a null result (referred to as "publication bias").

Table 5.23. Estimates of ERRs (and CIs) from studies of leukemia mortality or incidence from chronic or protracted exposures included in analysis by Daniels and Schubauer-Berigan (2011)^a

ID	Study population (reference)	Leukemia outcome	Mean dose (mGy) ^b	Cases	ERR at 0.1 Gy (CI) ^c
1	Taiwanese building residents exposed to ⁶⁰ Co sources (Hwang et al. 2008)	Incidence	48	6	0.19 [90% CI: (0.01, 0.31)]
2	Mayak workers (Shilnikova et al. 2003)	Mortality	810	66	0.10 [90% CI: (0.05, 0.21)]
3	Techa River residents (Krestinina et al. 2005)	Mortality	500	49	0.65 [95% CI: (0.18, 2.4)]
4	Chernobyl cleanup workers (Romanenko et al. 2008)	Incidence	76	32	0.27 [95% CI: (<0, 1.35)]
5a	Workers at four U.S. DOE sites and Portsmouth Naval Shipyard (Schubauer-Berigan et al. 2007)	Mortality	30	184	0.26 [95% CI: (-0.10, 1.03)]
5b	5a excluding Savannah River Site	Mortality	—	— ^d	0.10 [95% CI: (<0, 0.65)]
6	Rocketdyne workers (Boice et al. 2006)	Mortality	14	18	0.34 [95% CI: (-0.27, 1.45)]
7b	Workers in 15 countries with U.S. cohorts excluded (Cardis et al. 2007)	Mortality	19	104	0.27 [90% CI: (<0, 1.4)]
8	Chernobyl cleanup workers (Kesminiene et al. 2008)	Incidence	15	19	0.50 [90% CI: (-0.38, 5.7)]
9	U.K. workers (NRRW ^e)	Mortality	25	198	0.17 [90% CI: (0.01, 0.43)]
10	Karunagappally, India, residents (Nair et al. 2009)	Incidence	161	20	0.37 [95% CI: (<0, 34)]
11	U.S. workers at Savannah River Site (Richardson and Wing 2007)	Mortality	44	62	0.77 [90% CI: (0.14, 2.0)]
12	French Cogema and Atomic Energy Commission workers (Telle-Lamberton et al. 2007)	Mortality	17	20	3.1 [90% CI: (0.40, 11.4)]
13	U.S. workers at Idaho National Laboratory (Schubauer-Berigan et al. 2005)	Mortality	13	52	0.54 [95% CI: (-0.11, 2.4)]
15	U.S. commercial nuclear power workers (Howe et al. 2004)	Mortality	26	26	0.57 [95% CI: (-0.26, 3.0)]
16	Canadian workers (Ashmore et al. 1998)	Mortality	6.3	23	0.04 [90% CI: (-0.49, 0.57)]

Table 5.23 (continued)

ID	Study population (reference)	Leukemia outcome	Mean dose (mGy) ^b	Cases	ERR at 0.1 Gy (CI) ^c
17	Korean workers (Ahn et al. 2008)	Mortality	6.1	7	1.7 [90% CI: (-3.4, 15)]
18	U.S. workers at Rocky Flats facility (Gilbert et al. 1993)	Mortality	41	6	-0.72 [95% CI: (<0, 4.2)]
19	Japanese workers (Iwasaki et al. 2003)	Mortality	12	60	0.0 [90% CI: (-1.0, 1.0)]
20	French National Electric Company workers (Rogel et al. 2005)	Mortality	5.6 ^f	5	0.68 [90% CI: (-0.84, 6.2)]

^a Other studies considered by Daniels and Schubauer-Berigan but not included in their meta-analysis are omitted.

^b Dose to bone marrow or whole body.

^c Reported central values are MLEs.

^d Number of cases not given.

^e NRRW = National Registry for Radiation Workers.

^f Median value.

Results from the Model I and Model II analyses by Daniels and Schubauer-Berigan (2011) are presented in Table 5.24. The full analyses included the studies identified in the table, and the models labeled b through f included selected subsets of those studies. In general, estimated risks from Model I analyses were less sensitive to the studies selected than estimated risks from Model II analyses.

The study of Mayak workers (ID 2) had the greatest influence on results from the full analyses, due to the relatively high precision of the estimated ERR. In Models Ib and Iib, that study was excluded from the full analyses on the grounds that (1) the average dose to those workers was much higher than the average dose in most of the other studies selected, and (2) a later study by Vasilenko et al. (2007) indicated that external doses to many Mayak workers had been overestimated substantially, which resulted in an estimated ERR that was too low (i.e., a bias toward the null).

The study of Taiwanese residents (ID 1) had the next-greatest influence on results from the full analyses. In Models Ic and Iic, that study was excluded from the Model Ib and Iib analyses on the grounds that (1) the high precision of the estimated ERR in the Taiwanese residents was questionable given the much lower precision of estimated ERRs in other studies of similar size (e.g., number of leukemia cases) and exposure characteristics, and (2) individual doses to the residents were estimated without the availability of personal dosimetry measurements. We also note that the estimated ERR was based on a log-linear dose-response model.

Table 5.24. Estimates of ERRs (and 95% CIs) from meta-analysis of studies of leukemia mortality or incidence from chronic or protracted exposures by Daniels and Schubauer-Berigan (2011)

Model	Description	Study IDs	ERR at 0.1 Gy (95% CI) ^a	
I	Full	Prefers stand-alone to pooled studies	1–5b, 6, 8–13, 15–20	0.15 (0.07, 0.23)
	b	Full excluding study ID 2	—	0.18 (0.08, 0.29)
	c	Model Ib excluding study ID 1	—	0.18 (0.02, 0.36)
	d	Model Ic limited to studies of mortality	3, 5b, 6, 9, 11–13, 15–20	0.18 (0.01, 0.37)
	e	Model Ic limited to studies of occupational exposure	4, 5b, 6, 8, 9, 11–13, 15–20	0.16 (0.00, 0.35)
	f	Model Ic limited to results from linear dose-response modeling	3–5b, 8–13, 15–19	0.15 (–0.01, 0.33)
II	Full	Prefers pooled studies to stand-alone	1–5a, 6, 7b, 8, 10, 13, 18	0.15 (0.06, 0.24)
	b	Full excluding study ID 2	—	0.19 (0.07, 0.32) ^b
	c	Model IIb excluding study ID 1	—	0.34 (0.04, 0.72) ^c
	d	Model IIc limited to studies of mortality	3, 5a, 6, 7b, 13, 18	0.37 (0.03, 0.81)
	e	Model IIc limited to studies of occupational exposure	4, 5a, 6, 7b, 8, 13, 18	0.30 (–0.01, 0.70) ^c
	f	Model IIc limited to results from linear dose-response modeling	3–5a, 7b, 8, 13, 18	0.34 (0.01, 0.77) ^c

^a Estimates include adjustment for publication bias, unless otherwise noted. Reported central values are MLEs.

^b Result preferred by Daniels and Schubauer-Berigan (2011).

^c Adjustment for publication bias not applicable.

Of all the results in Table 5.24, Daniels and Schubauer-Berigan (2011) preferred the result from Model IIb—i.e., an ERR at 0.1 Gy, adjusted to account for publication bias, of 0.19 [95% CI: (0.07, 0.32)]. This result was obtained by excluding the study of Mayak workers (ID 2) from the full Model II analysis. We would note the following about the Model I and II analyses and the preferred result.

- Inclusion of the estimated ERR in the Taiwanese residents (ID 1) in the preferred Model IIb result is questionable when, as noted by Daniels and Schubauer-Berigan (2011), the reported precision in that ERR is suspect, given the small number of leukemia cases and lack of personal dosimetry measurements. Excluding that study from the Model IIb analysis (Model IIc) gave a higher and substantially less precise estimate of an ERR at 0.1 Gy of 0.34 [95% CI: (0.04, 0.72)].

- Daniels and Schubauer-Berigan (2011) did not attempt to account for differences in the average age at first exposure or at the end of follow-up among the selected studies. Since the Taiwanese (ID 1), Techa River (ID 3), and Indian (ID 10) populations included children, differences in the ages in study populations could be important when those studies were included in an analysis.
- NRC (2006) and UNSCEAR (2011) questioned the validity of estimated doses to Chernobyl cleanup workers and the reliability of estimated risks. However, comparisons of estimated ERRs based on mortality studies (Model Id or IId) with the corresponding ERRs based on studies of occupational exposure (Model Ie or IJe) suggest that inclusion of the two studies of Chernobyl cleanup workers (ID 4 and 8) did not have a significant effect on estimated risks.

For purposes of developing risk models for use in NIOSH-IREP, an estimated ERR for leukemia incidence based on studies of occupational exposure is preferable. However, since only two studies of leukemia incidence from occupational exposure (the studies of Chernobyl cleanup workers) were included in the meta-analysis by Daniels and Schubauer-Berigan (2011), we would use studies of leukemia mortality and assume that risks of leukemia incidence and mortality do not differ significantly, due to the high lethality of leukemias (NRC 2006). We also would prefer an estimate that gives greater weight to stand-alone studies than pooled studies. Thus, of the results in Table 5.24, we prefer the estimated ERR for leukemia mortality at 0.1 Gy of 0.16 [95% CI: (0.00, 0.35)] obtained using Model Ie. Although we also would exclude the two studies of Chernobyl workers (ID 4 and 8), their inclusion probably does not have a significant effect on that estimate, as noted above.

When linearly extrapolated to a dose of 1 Gy, the ERR/Gy for leukemia mortality preferred by Daniels and Schubauer-Berigan (2011) is 1.9 [95% CI: (0.7, 3.2)], and our preferred estimate is 1.6 [95% CI: (0.0, 3.5)]; the two estimates do not differ significantly. By comparing these estimates with an ERR at a neutron-weighted dose to bone marrow of 1 Gy for leukemia mortality in the LSS cohort for age at exposure 30, time since exposure 20 years, and male fraction 0.9 with a 50th percentile and 95% CI of 2.3 (1.3, 4.0) that we derived based on an LQ dose-response model developed by the BEIR VII committee (NRC 2006), we estimated DREFs at 1 Gy with 50th percentiles and 90% CIs of 1.2 (0.62, 3.0) and 1.4 (0.53, 6.6), respectively. MLEs of the ERRs in workers are at the 50th and 48th percentiles, respectively, of assumed Weibull distributions. These estimates do not differ significantly from the LDEFs for leukemia incidence or mortality in the LSS cohort given in Tables 5.21 and 5.22.

Our preferred estimate of an ERR for leukemia mortality from the meta-analysis by Daniels and Schubauer-Berigan (2011)—an ERR at 0.1 Gy of 0.16 [95% CI: (0.0, 0.35)]—can be compared with estimates of ERR at a dose to bone marrow of 0.1 Gy in the LSS cohort based on the linear term in an LQ

dose-response model to estimate the ratio $\alpha_{\text{acute}}/\alpha_{\text{chronic}}$. The following MLEs and CIs of ERR for leukemia mortality (excluding CLL) at 0.1 Gy in the LSS cohort are relevant:

- 0.15 [90% CI: (−0.08, 0.46)] for males at ages at exposure 20–60 (Cardis et al. 2005b, 2007; Table 5.9, footnote *j*);
- 0.14 [90% CI: (0.01, 0.34)] for males at ages at exposure ≥ 30 and time since exposure 15 years (NRC 2006, Cardis et al. 2007; Table 5.10),
- 0.11 [90% CI: (0.01, 0.26)] for males at ages at exposure ≥ 30 and time since exposure 25 years (NRC 2006, Cardis et al. 2007; Table 5.10);
- 0.16 [90% CI: (0.013, 0.33)] for males or females at age at exposure 25 and attained age 50 (Little et al. 2008);
- 0.16 [90% CI: (0.063, 0.29)] for males or females at ages at exposure ≥ 30 and time since exposure 30 years (Richardson et al. 2009);
- 0.15 [95% CI: (−0.01, 0.31)] for males or females at all ages at exposure (Ozasa et al. 2012).

The similarities in our preferred estimate of ERR in workers and the estimated ERRs at low doses in the LSS cohort provide support for the assumption in IREP that the linear term in an LQ dose-response for leukemia from acute exposure can be used to estimate risks from chronic or protracted exposures. However, uncertainties in the estimated ratios $\alpha_{\text{acute}}/\alpha_{\text{chronic}}$ are substantial. For example, using the ERR at 0.1 Gy in the LSS cohort based on the analysis by Richardson et al. (2009), which has the smallest uncertainty, we estimate a ratio $\alpha_{\text{acute}}/\alpha_{\text{chronic}}$ with a 50th percentile and 90% CI of 0.98 (0.24, 4.7). Using the ERR at 0.1 Gy reported by Cardis et al. (2005b, 2007), which has the largest uncertainty, we estimate a ratio $\alpha_{\text{acute}}/\alpha_{\text{chronic}}$ of 0.95 [90% CI: (−0.8, 6.0)], while using the smallest ERR in the LSS cohort gives an estimated $\alpha_{\text{acute}}/\alpha_{\text{chronic}}$ of 0.74 [90% CI: (−0.03, 3.8)]. MLEs of the ERRs in the LSS cohort are at the 46th, 46th, and 50th percentiles, respectively, of assumed Weibull distributions. Using the ERR at 0.1 Gy in workers preferred by Daniels and Schubauer-Berigan (2011) gives similar results.

5.8.3.5 Study of U.S. nuclear workers by Daniels et al. (2013)

Daniels et al. (2013) conducted a study of leukemia mortality in U.S. nuclear workers at six sites based on data through 2005. The number of deaths from leukemia in the 105,245 nuclear workers (369) was similar to the incidence of all leukemias in the study of 113,011 members of the LSS cohort (371) by Hsu et al. (2013). However, the number of cases of the three main types of leukemia (AML, CML, and ALL) combined was different (220 deaths in the workers vs 294 cases in the LSS cohort), as was their

distribution (150 deaths from AML in the workers vs 176 cases in the LSS cohort; 52 deaths from CML in the workers vs 75 cases in the LSS cohort; 18 deaths from ALL in the workers vs 43 cases in the LSS cohort). In addition, there were 74 deaths from CLL in the workers but only 12 cases in the LSS cohort.

Daniels et al. (2013) fitted the data for various types of leukemia using linear dose-response models with a preferred time lag and or exposure time window and estimated doses to bone marrow. Risks of ALL were not modeled separately, due to the small number of cases. The resulting estimates of ERR per 0.1 Gy with a time lag model, which are more compatible with risk modeling in IREP that includes an assumption about a minimum latency period for induction of leukemias (Land et al. 2003a; Kocher et al. 2008), are given in Table 5.25. All ERRs did not differ significantly from zero. When exposure time window models were used, central estimates of ERR per 0.1 Gy for the three main types of leukemia were more than an order of magnitude higher than estimates using time lag models, but the 95% CIs for CML and non-CLL leukemias still overlapped zero.

Although ERRs in Table 5.25 were estimated based on linear dose-response models, a non-linear dose-response with risks attenuated at low doses (<10 mGy) and at doses >100 mGy was observed in the preferred time lag models for all leukemias combined and AML. Daniels et al. (2013) noted that the attenuated risks at low doses could be interpreted as evidence of a threshold or protective effect, but they also noted that attenuated risks were not observed in exposure time window models. The attenuation at doses >100 mGy in the lag models has no biological explanation, because cell sterilization typically requires doses >2 Gy.

Table 5.25. Estimates of ERR (and 95% CIs) based on linear dose-responses for leukemia mortality in U.S. nuclear workers using time lag models (Daniels et al. 2013)

Leukemia type ^a	Adjusted for	Lag (y)	ERR per 0.1 Gy (95% CI) ^b
Non-CLL ^c	Sex, race, hire year	2	0.09 (−0.17, 0.65)
AML	Birth cohort	1.1	0.22 (−0.19, 1.2)
CML	Sex, race, hire year	6.3	0.29 (<0, 2.6)
CLL	Sex, race, birth cohort	24	−0.032 (−0.16, 0.74)

^a AML = acute myeloid leukemia; CML = chronic myeloid leukemia; CLL = chronic lymphocytic leukemia. Estimated doses are doses to bone marrow.

^b Reported central values are MLEs.

^c Excluding leukemias of indeterminate type.

We estimated a DREF for leukemia mortality at 1 Gy as the ratio of the ERR at a neutron-weighted dose to bone marrow of 1 Gy in the LSS cohort with a 50th percentile and 95% CI of 2.3 (1.3, 4.0) given in Section 5.8.3.4, which is based on an LQ dose-response model developed by the BEIR VII committee (NRC 2006) and applies at age at exposure 30, attained age 50, and male fraction 0.9, to ten times the ERR per 0.1 Gy for non-CLL leukemias in workers in Table 5.25. The estimated DREF at 1 Gy has a 50th percentile and 90% CI of 0.7 (−7.6, 7.6)]. The MLE of the ERR in workers is at the 40th percentile of an assumed Weibull distribution. This estimate does not differ significantly from the LDEFs for leukemia incidence or mortality in Tables 5.21 and 5.22.

The ERR for non-CLL leukemias in Table 5.25 can be compared with ERRs at 0.1 Gy for leukemia mortality in the LSS cohort given in Section 5.8.3.4 to estimate the ratio $\alpha_{\text{acute}}/\alpha_{\text{chronic}}$. For example, using the ERR in the LSS cohort from an analysis by Richardson et al. (2009), which has the smallest uncertainty, gives an estimated $\alpha_{\text{acute}}/\alpha_{\text{chronic}}$ with a 50th percentile and 90% CI of 0.5 (−5.7, 5.8). This estimate, which has a large uncertainty, does not differ significantly from 1.0. Similar results but with greater uncertainties are obtained using other ERRs at 0.1 Gy in the LSS cohort given in Section 5.8.3.4.

The estimated ERR for AML in Table 5.25 can be compared with an ERR for mortality from AML in the LSS cohort estimated by Richardson et al. (2009). We used an estimated ERR in the LSS cohort at age at exposure 30 and time since exposure 30 years. Richardson et al. (2009) described AML in the LSS cohort using a purely quadratic dose-response model, which gives an ERR at a neutron-weighted dose to bone marrow of 1 Gy with an MLE and 90% CI of 2.8 (1.6, 4.6). By comparing this estimate with an ERR/Gy in workers of ten times the estimate in Table 5.25, we estimate a DREF at 1 Gy with a 50th percentile and 90% CI of 0.6 (−4.9, 5.7). MLEs of the ERRs in the LSS cohort and in workers are at the 45th and 38th percentiles, respectively, of assumed Weibull distributions. We did not estimate a DREF for CML, for which the lower limit of the 95% CI in Table 5.25 is not specified.

5.8.3.6 Studies of childhood leukemia from exposure to natural background radiation

In a record-based case-control study of children of ages 1 to 14 in the U.K., Kendall et al. (2013) found a statistically significant association between incidence of childhood leukemia and exposure to gamma rays in natural background. The reported ERR per mGy to bone marrow for incidence of all leukemias, assuming a lag time of 2 years, has an MLE and 95% CI of 0.12 (0.03, 0.22) ($P = 0.01$). This association was attributable mainly to an increase in incidence of lymphoid leukemia, with an estimated ERR per mGy of 0.13 [95% CI: (0.02, 0.24)] ($P = 0.01$); estimated ERRs for other types of leukemia were not statistically significant. No associations between childhood leukemia and exposure to radon or associations between other childhood cancers and exposure to gamma rays or radon were found.

The ERR/Gy for leukemia incidence from chronic exposure based on the analysis by Kendall et al. (2013) has an MLE and 95% CI of 120 (30, 220). Using the LQ dose-response model for leukemia incidence in males and females in the LSS cohort developed by Hsu et al. (2013), we obtained an ERR from acute exposure at a neutron-weighted dose to bone marrow of 1 Gy with an MLE and 90% CI of 195 (47, 920). This estimate applies at an attained age of 5, which is the mean age at diagnosis of leukemias in children in the study by Kendall et al. (2013), and an age at exposure of half the attained age, or 2.5. The model developed by Hsu et al. (2013) was extrapolated to young ages using an adjustment to account for the nominal minimum latency period for leukemias in IREP of 2.25 years (Land et al. 2003a; Kocher et al. 2008). The ratio of the two ERRs gives an estimated DREF at 1 Gy for leukemia incidence with a 50th percentile and 90% CI of 2.8 (0.4, 12). MLEs of the ERRs in the LSS cohort and in children in the U.K. are at the 28th and 49th percentiles, respectively, of assumed Weibull distributions. Using the linear coefficient based on the Hsu et al. (2013) model at the same age at exposure and attained age, which gives an ERR/Gy at low acute doses with an MLE and 90% CI of 77 (10, 480), we estimated a ratio $\alpha_{\text{acute}}/\alpha_{\text{chronic}}$ with a 50th percentile and 90% CI of 1.4 (0.08, 5.9). The MLE of the ERR in the LSS cohort is at the 25th percentile of an assumed Weibull distribution. Both estimates are consistent with estimates of DREF at 1 Gy and $\alpha_{\text{acute}}/\alpha_{\text{chronic}}$ based on studies of leukemia incidence or mortality in adult workers.⁷⁵

In a census-based ecological study of cancer incidence in children of ages <16 from exposure to natural background radiation in Switzerland, Spycher et al. (2015) also found an association between incidence of childhood leukemia and exposure to gamma rays in natural background. The reported ERR per mGy for incidence of all leukemias has an MLE and 95% CI of 0.05 (0.00, 0.10). Associations with exposure to gamma rays also were found for all childhood cancers and tumors of the central nervous system, with estimated ERRs per mGy of 0.03 [95% CI: (0.01, 0.06)] and 0.05 [95% CI: (0.00, 0.11)], respectively, but lower limits of 95% CIs were <0 for ALL and lymphoma.

The ERR/Gy for leukemia incidence based on the analysis by Spycher et al. (2015) has an MLE and 95% CI of 50 (0.0, 100). Using the LQ dose-response model for leukemia incidence in the LSS cohort developed by Hsu et al. (2013), we obtained an ERR from acute exposure at 1 Gy with an MLE and 95% CI of 34 (13, 98). This estimate was based on an assumed average age at exposure of 7 and average attained age of 15 and an adjustment to account for a nominal minimum latency period for leukemias of

⁷⁵ Kendall et al. (2013) compared point estimates of risks of incidence of leukemia at each age at a dose rate to bone marrow of 1 mGy y⁻¹ obtained in their analysis with point estimates of risks from acute exposure that were calculated using dose-response models developed by the BEIR VII committee (NRC 2006) and UNSCEAR (2008). At all ages, risks estimated by Kendall et al. were greater than risks based on the BEIR VII model; the ratio of estimated risks was 1.2 at age 1 and increased with increasing age to 2.6 at age 14. When compared with risks based on the UNSCEAR model, risks estimated by Kendall et al. were lower at ages 1 to 4 but greater at ages 5 to 15, with a maximum ratio of 1.9. These comparisons suggest that a DREF at low doses and the ratio $\alpha_{\text{acute}}/\alpha_{\text{chronic}}$ both are <1. However, uncertainties in the various risk estimates were not taken into account.

2.25 years. The ratio of the two ERRs gives an estimated DREF at 1 Gy with a 50th percentile and 90% CI of 0.9 (0.2, 4.1). MLEs of the ERRs in the LSS cohort and in children in Switzerland are at the 35th and 51st percentiles, respectively, of assumed Weibull distributions. This estimate is not significantly different from the estimated DREF at 1 Gy based on the analysis by Kendall et al. (2013) given above.

We think that the DREF at 1 Gy based on the analysis by Spycher et al. (2015) probably is less reliable than the estimate based on the analysis by Kendall et al. (2013) when the appropriate age at exposure and attained age that should be used to obtain a comparable estimate of ERR at 1 Gy in the LSS cohort is uncertain and the ERR in the LSS cohort is strongly dependent on those ages (Hsu et al. 2013).

5.8.4 Summary of Analyses of Data on Leukemia

For all leukemias as a group (excluding CLL), analyses of data on acute exposures in the LSS cohort have consistently shown a positive dose-response with a significant upward curvature. Most, but not all, analyses of data on chronic or protracted exposures obtained mainly in studies of workers also have shown a positive dose-response that generally has been represented by a linear model. Some studies of the LSS cohort and cohorts of worker and children have analyzed dose-responses for specific types of leukemia, including AML, CML, and ALL. A few studies also analyzed dose-responses for CLL.

Analyses of dose-responses for all leukemias as a group and specific types of leukemia presented in Sections 5.8.2 and 5.8.3 can be summarized as follows:

- Most estimates of LDEF at a neutron-weighted dose to bone marrow of 1 Gy that were derived based on analyses of the curvature in modeled LQ dose-responses for incidence or mortality from all leukemias (excluding CLL) in the LSS cohort based on DS02 dosimetry, as given in Tables 5.21 and 5.22, have central values (50th percentiles) of 1.5–5. With one exception, lower limits of 90% CIs of those LDEFs are >1.0, which indicates that non-linearities in the modeled dose-responses are significant. Most upper limits of 90% CIs of those LDEFs are about 7–14. The much smaller uncertainty in the LDEF at 1 Gy from an analysis by Richardson et al. (2009) [90% CI: (1.1, 3.4)] compared with uncertainties from other analyses based on DS02 dosimetry has no apparent explanation. Estimates of LDEF at 1 Gy from analyses based on DS86 dosimetry are not significantly different from analyses based on DS02 dosimetry.
- Estimates of DREF at 1 Gy that were derived by comparing estimated ERRs for incidence or mortality from all leukemias (excluding CLL) in the LSS cohort at a neutron-weighted dose to bone marrow of 1 Gy based on DS02 dosimetry and an LQ dose-response model with estimates of ERR/Gy in workers and in children in the U.K. and Switzerland based on linear dose-response

models have central values (50th percentiles) of 0.7–3. All lower limits of 90% CIs of those DREFs are <1.0, and upper limits are 2.5–12. Given the uncertainties in all estimates, DREFs at 1 Gy do not differ significantly from LDEFs at 1 Gy in the LSS cohort.

- Estimates of ERR/Gy for incidence or mortality from all leukemias (excluding CLL) in the LSS cohort at DS02 doses sufficiently low that only the linear term, with coefficient α , in a modeled LQ dose-response is significant were compared with linear risk coefficients in workers and in children in the U.K. to estimate the ratio $\alpha_{\text{acute}}/\alpha_{\text{chronic}}$; a ratio consistent with 1.0 indicates that the linear term in an LQ dose-response from acute exposure can be used to estimate risks from chronic or protracted exposure. Central estimates (50th percentiles) of $\alpha_{\text{acute}}/\alpha_{\text{chronic}}$ we derived are about 0.4–1.4, all lower limits of 90% CIs are <1.0, and upper limits of 90% CIs are about 1–9.
- Recent analyses of mortality and incidence from specific types of leukemia in the LSS cohort (Richardson et al. 2009, Hsu et al. 2013) based on DS02 dosimetry confirmed that the observed non-linearities in dose-responses for mortality and incidence from all leukemias as a group were due primarily to dose-responses for AML, which could be described by quadratic dose-response models with little evidence of a significant linear term. Dose-responses for CML and ALL, which contributed significantly to dose-responses for all leukemias, could be described by linear models with little evidence of upward curvature. These findings indicate that the commonly used LQ dose-response model for all leukemias (excluding CLL) is an artifact of combining dose-responses for specific types of leukemia, none of which appears to be LQ in form.
- A comparison of an ERR for mortality from AML in the LSS cohort at a neutron-weighted dose to bone marrow of 1 Gy (Richardson et al. 2009) with an estimated ERR/Gy for that leukemia type in workers (Daniels et al. 2013) gave a central estimate (50th percentile) of DREF at 1 Gy of 0.6 with a wide CI. This result did not differ significantly from results for all leukemias as a group.
- Hsu et al. (2013) reported a statistically significant linear dose-response for incidence of CLL in the LSS cohort, which suggested an increase in risk at higher doses; CLL usually is considered to be non-radiogenic. However, no other studies of CLL in the LSS cohort have shown a significant dose-response, and reported dose-responses in cohorts that received chronic or protracted exposures are inclusive.

We also emphasize that it is difficult to draw definitive conclusions about DDREFs for leukemias and related issues, given the large uncertainties in estimated risks in the various study cohorts.

The analyses summarized above have the following implications for modeling of dose-responses for leukemias in IREP.

- The LDEF of 2 at a neutron-weighted dose to bone marrow of 1 Gy, assuming a neutron RBE of 10, that is implicit in the dose-response for all leukemias in IREP (Land et al. 2003a) is consistent with estimates of LDEF and DREF at 1 Gy based on more recent analyses of dose-responses in the LSS cohort and analyses of dose-responses in workers and in children in the U.K. and Switzerland. However, there is substantial uncertainty in estimates of LDEF and DREF at 1 Gy that may not be properly accounted for in IREP when all uncertainties in estimated risks of leukemias are incorporated in the coefficient of the linear and quadratic terms in modeled LQ dose-responses (Land et al. 2003a).
- The assumption in IREP that risks of leukemias from chronic exposure can be estimated using the linear term in an LQ dose-response for acute exposure (Land et al. 2003a; Kocher et al. 2008) is consistent with estimates of the ratio $\alpha_{\text{acute}}/\alpha_{\text{chronic}}$ based on dose-responses at low doses in the LSS cohort and linear dose-responses in workers and in children in the U.K. However, uncertainties in estimates of $\alpha_{\text{acute}}/\alpha_{\text{chronic}}$ are large, which precludes any conclusion about the validity of the assumption in IREP.
- The recent analyses of dose-responses for specific types of leukemia in the LSS cohort indicate that the assumption in IREP of LQ dose-response models for AML, CML, and ALL (Land et al. 2003a) probably is inappropriate. Consequently, an assumption by NIOSH (2002) that an LQ dose-response model for all leukemias as a group can be used to estimate ERRs and the probability of causation/assigned share (PS/AS) of a specific type of diagnosed leukemia may be unwarranted. The recent analyses for specific types of leukemia also indicate that estimates of LDEF based on analyses of dose-responses in the LSS cohort using an LQ model should not be used to represent an LDEF for solid cancers.

5.9 SUMMARY OF EPIDEMIOLOGICAL DATA AND CONCLUSIONS

Estimates of DDREF based on estimated risks of radiation-induced cancer mortality or incidence from epidemiological studies that we developed or reviewed are summarized in Tables 5.26 and 5.27. Results from analyses of dose-responses for solid cancers and leukemias are reported separately based on the consideration that estimates of a DDREF for all leukemias as a group cannot be used to estimate a DDREF for solid cancers. Table 5.27 also includes estimates of the ratio $\alpha_{\text{acute}}/\alpha_{\text{chronic}}$ for all leukemias described in Section 5.8.1; this ratio is not a DDREF. In all cases except the DDREF for thyroid cancer that was based on comparisons of risks in the LSS cohort with risks in children that received medical exposures in Table 5.26, an estimated DDREF is identified as an LDEF or a DREF.

Table 5.26. Summary of estimates of DDREF based on epidemiological studies of solid cancers

Cancer grouping or site	Factor	LSS dosimetry system	Health effect	
			Mortality ^b	Incidence ^b
All solid cancers	LDEF ^a	DS86	≤3.2; ≤6.4 ^c	≤1.9; ≤2.4 ^g
			1.55 (4.4); 1.52 (7.2); 1.54 (11) ^d	≤1.5 ^h ≤1.7 ⁱ
			1.82 (8.1) ^e	1.1 (0.8, 1.9) ^j
			1.8 (1.0, 5.1) 2.1 (1.1, 4.0) ^f	1.4 (0.9, 2.3); 1.1 (0.8, 1.5) ^k
				1.4 (0.7, 2.4); 1.0 (0.7, 1.5) ^m
	DS02	2.1 (1.0, 9.4); 3.6 (1.2, 9.4) ⁿ	1.5 (0.9, 2.4) 1.5 (1.0, 2.3)^t	
		2.3 ^o	1.4 (1.0, 1.9)^u	
		1.34 (1.01, 2.53); 2.1 (-13, 19) ^p		
		1.51 (1.07, 3.26); 2.3 (-15, 25) ^q		
		3.2 (1.2, 8.3); 2.0 (1.0, 6.8)^r		
		1.11 (0.94, 1.48); 1.16 (0.77, 1.90)^s		
DREF ^v	DS86	0.62 (0.14, 1.8) ^w	—	
	DS02	1.0 (0.39, 5.0)^x 0.7 (-3.1, 4.5); 0.49 (0.22, 1.7); 0.52 (0.23, 2.1); 0.32 (0.12, 1.4) ^y 0.63 (0.36, 1.7) ^z 0.64 (0.31, 2.7)^{aa} 0.55 (0.30, 1.5)^{bb} 0.83 (0.53, 2.0); 0.48 (0.33, 0.86) ^{cc}	1.4 (0.64, 5.9)^x 0.63 (0.33, 2.2)^{dd} 1.0 (0.65, 2.4) ^{cc}	
Female breast	LDEF ^a	DS86	—	2.7 (0.7, 8.7); 0.9 (0.5, 1.5) ^{ff}
	DREF ^v	DS86	1.8 (0.4, 19) ^{ee}	3.4 (0.6, 17) ^{gg}

Table 5.26 (continued)

Cancer grouping or site	Factor	LSS dosimetry system	Health effect	
			Mortality ^b	Incidence ^b
Thyroid	LDEF ^a	DS86	—	1.2 (0.4, 2.9) ^{hh}
		DS02	—	0.66 (0.34, 1.35) ⁱⁱ
	DDREF	DS02	—	0.98 (0.19, 6.0) ^{jj}
Lung	LDEF ^a	DS86	—	4.9 (0.8, 17); 1.4 (0.5, 3.2) ^{mm}
	DREF ^v	DS02	3.4 (1.2, 12) ^{kk}	—
Skin	LDEF ^a	DS02	—	5.4 (0.9, 40); 4.4 (2.0, 20) ⁿⁿ

^a LDEFs are estimated based on analyses of the curvature in dose-responses in LSS cohort assuming LQ model, except as noted, and neutron-weighted doses to colon (all solid cancers) or indicated organ.

^b Estimates in **bold face** were used in developing probability distribution of DDREF for all solid cancers in Section 6.3.1.

^c Upper limits of 95% CIs derived by Kellerer et al. (2002) based on ERR models at colon doses of 0–2 Gy with modeled ERRs modified by age at exposure or attained age (Table 5.3).

^d MLEs and upper limits of 95% CIs derived by Walsh et al. (2004a) based on ERR models at colon doses of 0–2 Gy with neutron RBE of 10, 20, or 35 and modeled ERRs modified by age at exposure (Tables 5.3 and 5.6).

^e MLE and upper limit of 95% CI derived by Walsh et al. (2004a) based on ERR model at colon doses of 0–2 Gy with neutron RBE of 10 and modeled ERRs modified by attained age (Table 5.3).

^f 50th percentiles and 90% CIs based on ERR model at colon doses of 0–2 Gy developed by Preston et al. (2004) and derived using different methods of estimating LDEF; MLE of LDEF with 50th percentile at 2.1 is 1.6 (Table 5.3).

^g Upper limits of 95% CIs derived by Pierce and Preston (2000) based on ERR models at colon doses of 0–2 Gy to proximal survivors or all survivors in LSS cohort (Table 5.1).

^h Upper limit of 95% CI derived by Pierce and Preston (2000) based on ERR model at colon doses of 0–3 Gy to proximal survivors in LSS cohort (Table 5.1).

ⁱ Upper limit of 95% CI derived by Kellerer et al. (2002) based on ERR model at colon doses of 0–2 Gy with modeled ERRs modified by age at exposure (Table 5.1).

^j 50th percentile and 90% CI based on analysis by ICRP (2005) using ERR model at colon doses of 0–2 Gy (Table 5.1).

^k 50th percentiles and 90% CIs based on analysis by Little and Muirhead (2000, 2004) using ERR models at colon doses of 0–2 Gy or shielded kerma of 0–4 Gy with neutron RBE of 20; MLEs are 1.21 and 1.06, respectively (Table 5.1).

^m 50th percentiles and 90% CIs based on analysis by Little and Muirhead (2000, 2004) using ERR models at colon doses of 0–2 Gy or shielded kerma of 0–4 Gy with neutron RBE of 50; MLEs are 1.16 and 0.96, respectively (Table 5.5).

ⁿ 50th percentiles and 90% CIs based on ERR model at colon doses of 0–2 Gy developed by Preston et al. (2004) and derived using different methods of estimating LDEF; MLE of LDEF with 50th percentile at 3.6 is 1.9 (Table 5.4).

^o MLE derived by Pierce et al. (2008) based on ERR model at colon doses of 0–1.5 Gy assuming increased error (uncertainty) in estimated doses; MLE assuming usual error in estimated doses is 2.1 (Table 5.4).

^p 50th percentiles and 90% CIs based on ERR models and LQ or LQE dose-response at shielded kerma of 0–4 Gy developed by Little et al. (2008) (Table 5.4).

^q 50th percentiles and 90% CIs based on EAR models and LQ or LQE dose-response at shielded kerma of 0–4 Gy developed by Little et al. (2008) (Table 5.4).

Table 5.26 (continued)

- ^r 50th percentiles and 90% CIs based on ERR model at colon doses of 0–2 Gy developed by Ozasa et al. (2012) and derived using different methods of estimating LDEF; MLEs are 1.8 and 2.0, respectively (Table 5.4).
- ^s 50th percentiles and 90% CIs based on ERR model at shielded kerma of 0–4 Gy developed by Ozasa et al. (2012) and derived using different methods of estimating LDEF; MLEs are 1.11 and 1.16, respectively (Table 5.4).
- ^t 50th percentiles and 90% CIs based on analysis by BEIR VII committee (NRC 2006) using ERR model for all solid cancers excluding thyroid and non-melanoma skin cancers at colon doses of 0–1.5 Gy and derived using different methods of estimating LDEF; MLEs are 1.3 (Table 5.2).
- ^u 50th percentile and 90% CI based on analysis by Preston et al. (2007) using ERR model at colon doses of 0–2 Gy; MLE is 1.3 (Table 5.2).
- ^v DREFs are estimated as ratios of risks from acute exposure in LSS cohort to risks from chronic, protracted, or highly fractionated occupational, medical, or environmental exposures.
- ^w 50th percentile and 90% CI estimated as ratio of ERR/Gy for all solid cancers in LSS cohort at shielded kerma of 0–4 Gy (Cardis et al. 2005b, 2007) to ERR/Gy for same endpoint in radiation workers in France, U.K., and U.S. (Richardson et al. 2015) (Tables 5.9, 5.10, and 5.11).
- ^x 50th percentile and 90% CI estimated as ratio of ERR/Gy for all cancers excluding leukemia in LSS cohort at shielded kerma of 0–4 Gy (Jacob et al. 2009) to ERR/Sv for same endpoint in U.K. radiation workers (Muirhead et al. 2009) (Tables 5.10 and 5.11).
- ^y 50th percentiles and 90% CIs estimated as ratios of ERR/Gy for all cancers excluding leukemia or all solid cancers in LSS cohort at shielded kerma of 0–4 Gy from Jacob et al. (2009) or based on dose-response model developed by BEIR VII committee (NRC (2006) for age at exposure ≥ 31 , attained age 58, and male fraction 0.9 to ERR/Sv for same endpoints in radiation workers in 15 countries (Cardis et al. 2005b, 2007) with different definitions of Canadian cohorts included or excluded from analysis (Tables 5.10 and 5.11 and Section 5.2.2.2). We consider that DREF of 0.7 [90% CI: (–3.1, 4.5)] obtained by excluding entire Canadian cohort from 15-country study is the most representative result from that study.
- ^z 50th percentile and 90% CI estimated from ratios of ERR/Gy and EAR/10⁴ person y/Gy for mortality from all solid cancers in LSS cohort to corresponding risks at age at exposure 28 and attained age 63 for same endpoint in Techa River cohort based on TRDS-2000 dosimetry (Eidemüller et al. 2008) (Section 5.2.2.3).
- ^{aa} 50th percentile and 90% CI estimated as ratio of ERR/Gy for all solid cancers in LSS cohort at shielded kerma of 0–4 Gy based on dose-response model developed by BEIR VII committee (NRC 2006) for age at exposure 28, attained age 64, and male fraction 0.42 to ERR/Gy for same endpoint in Techa River cohort based on TRDS-2009 dosimetry (Schonfeld et al. 2013) (Section 5.2.2.3).
- ^{bb} 50th percentile and 90% CI estimated as ratio of ERR/Gy for all solid cancers in LSS cohort at shielded kerma of 0–4 Gy based on dose-response model developed by BEIR VII committee (NRC 2006) for age at exposure 31, attained age 58, and male fraction 0.9 to ERR/Gy for same endpoint in radiation workers in France, U.K., and U.S. (Richardson et al. 2015) (Tables 5.10 and 5.11).
- ^{cc} 50th percentiles and 90% CIs of reciprocals of risk ratios derived by Jacob et al. (2009) by comparing estimates of ERR/Gy in occupationally or environmentally exposed cohorts with estimates of ERR/Gy in LSS cohort at shielded kerma of 0–4 Gy (Section 5.2.2.4). DREF for solid cancer mortality of 0.83 [90% CI: (0.53, 2.0)] is based on risk ratio considered by Jacob et al. (2009) to be their main result.
- ^{dd} 50th percentile and 90% CI estimated as ratio of ERR/Gy for all solid cancers in LSS cohort at shielded kerma of 0–4 Gy based on dose-response model developed by BEIR VII committee (NRC 2006) for age at exposure 27, attained age 63, and male fraction 0.43 to ERR/Gy for same endpoint in Techa River cohort based on TRDS-2009 dosimetry (Davis et al. 2015) (Section 5.2.2.3).
- ^{ee} 50th percentile and 90% CI estimated from ratios of ERR/Gy and EAR/10⁴ person-y/Gy in LSS cohort to corresponding risks in non-Nova Scotia Canadian tuberculosis fluoroscopy cohorts (Howe and McLaughlin 1996), including adjustment to account for assumption of higher biological effectiveness of medical x rays (Section 5.3.3).
- ^{ff} 50th percentiles and 90% CIs based on analysis by Little and Muirhead (2000, 2004) at doses to breast of 0–2 Gy or shielded kerma of 0–4 Gy; MLEs are 1.03 and 0.77, respectively (Table 5.14).

Table 5.26 (continued)

^{gg} 50th percentile and 90% CI obtained by pooling estimated DREFs based on comparisons of estimates of ERR/Gy and EAR/10⁴ person-y/Gy in LSS cohort at shielded kerma of 0–4 Gy with corresponding risks in Massachusetts tuberculosis fluoroscopy and Swedish skin hemangioma cohorts, including adjustment to account for assumption of higher biological effectiveness of medical x rays (Section 5.3.2 and Table 5.17).

^{hh} 50th percentile and 90% CI based on analysis by Little and Muirhead (2000, 2004) at shielded kerma of 0–4 Gy; MLE is 0.80 (Table 5.14).

ⁱⁱ 50th percentile and 90% CI estimated from analysis of concave downward curvature in dose-response for thyroid cancer in LSS cohort at thyroid doses of 0–4.2 Gy for ages at exposure ≤ 19 using linear-exponential model (Veiga et al. 2016) (Section 5.4.4). Estimated uncertainty assumes no correlation of model parameters; estimated LDEF assuming full correlation of model parameters (correlation coefficient of +1) is 0.66 [90% CI: (0.59, 0.79)].

^{jj} 50th percentile and 90% CI obtained by pooling estimates of DDREFs based on comparisons of estimates of ERR/Gy and EAR/10⁴ person-y/Gy in LSS cohort at thyroid doses of 0–4.2 Gy with corresponding risks in five cohorts of children exposed to external x or gamma radiation, including adjustment to account for assumption of higher biological effectiveness of medical x rays (Section 5.4.5 and Table 5.20). Since exposures of children involved acute and fractionated exposures, estimate is not a DREF.

^{kk} 50th percentile and 90% CI estimated from comparison of estimates of ERR/Gy in LSS cohort at shielded kerma of 0–4 Gy based on analysis that accounted for joint effects of radiation and smoking (Furukawa et al. 2010) and ERR/Gy in Mayak workers (Sokolnikov et al. 2008) (Section 5.5.2).

^{mm} 50th percentiles and 90% CIs based on analysis by Little and Muirhead (2000, 2004) at lung doses of 0–2 Gy or shielded kerma of 0–4 Gy; MLEs are 1.14 and 0.95, respectively (Table 5.14).

ⁿⁿ 50th percentiles and 90% CIs estimated from linear-spline fits to estimates of ERR/Gy for non-melanoma skin cancers or basal cell carcinoma in LSS cohort at skin doses < 1 Gy and > 1 Gy by Preston et al. (2007) (Section 5.6.1). LDEFs would not apply if linear risk coefficients used in estimating risks of those skin cancers were based on modeled dose-responses at doses of 0–1 Gy only.

We think that a DDREF for solid cancers should not be estimated based solely on analyses of the curvature in modeled dose-responses in the LSS cohort, which give LDEFs. We think that comparisons of estimated risks in cohorts of workers, medical patients, or members of the public that received chronic or highly fractionated exposures with estimated risks from acute exposure in the LSS cohort, which give DREFs, also should be considered, given the importance of chronic exposures in many cancer risk assessments. Even though studies of chronic or highly fractionated exposures often are limited by low statistical power, other risk factors of importance (e.g., exposure to chemicals), dosimetric uncertainties, and less complete follow-up of some cohorts, we think that implications of those studies need to be considered. This is especially the case when some recent studies of solid cancers in workers and the Techa River cohort suggest a DREF < 1 , contrary to expectations based on estimated LDEFs for solid cancers in humans and much of the data in laboratory animals, as well as predictions of an LQ dose-response model.

Table 5.27. Summary of estimates of DDREF based on epidemiological studies of leukemias

Cancer grouping or site	Factor	LSS dosimetry system	Health effect	
			Mortality	Incidence
All leukemias (excluding CLL)	LDEF ^a at 1 Gy	DS86	2.5 (0.3, 4.8) ^b	30 (2.1, 120);
			2.9 (1.2, 7.0) ^c	24 (1.8, 97) ^d
		DS02	4.6 (1.3, 14)	11 (1.7, 42);
			4.6 (1.3, 14) ^e	3.4 (1.3, 8.3) ^j
			2.2 (1.2, 10); −0.4 (−25, 27) ^f	
	DREF ^k at 1 Gy	DS02	2.1 (1.2, 9.2); 1.0 (−27, 27) ^g	
			1.5 (1.1, 3.4) ^h	
			1.9 (0.8, 9.2) ⁱ	
			1.1 (0.3, 7.1) ^m	1.8 (0.6, 10) ⁿ
			0.89 (0.40, 2.5); 0.76 (0.29, 2.7) ^o	2.8 (0.4, 12) ^r 0.9 (0.2, 4.1) ^s
$\alpha_{\text{acute}}/\alpha_{\text{chronic}}^t$	DS02	1.4 (0.53, 6.6); 1.2 (0.62, 3.1) ^p		
		0.7 (−7.6, 7.6) ^q		
		0.8 (−0.2, 5.9) ^u	1.4 (0.03, 8.8) ^v	
		0.36 (0.07, 1.15) ^w 0.98 (0.24, 4.7) ^x 0.5 (−5.7, 5.8) ^y	1.4 (0.08, 5.9) ^z	
Acute myeloid leukemia (AML)	DREF ^k at 1 Gy	DS02	0.6 (−4.9, 5.7) ^{aa}	—

^a LDEFs are estimated based on analyses of the curvature in dose-responses in LSS cohort assuming LQ model, except as noted, and neutron-weighted doses to bone marrow.

^b 50th percentile and 90% CI based on analysis by Pierce et al. (1996a) using EAR model at shielded kerma of 0–4 Gy; MLE is 2.5 (Table 5.22).

^c 50th percentile and 90% CI based on analysis by Preston et al. (2004) using EAR model at shielded kerma of 0–4 Gy; MLE is 1.9 (Table 5.22).

^d 50th percentiles and 90% CIs based on analysis by Little and Muirhead (2000, 2004) using ERR model at doses to bone marrow of 0–2 Gy and derived using different methods of calculating LDEF; MLEs are 1.73 and 2.1, respectively (Table 5.21).

^e 50th percentiles and 90% CIs based on analysis by BEIR VII committee (NRC 2006) using ERR or EAR model at shielded kerma of 0–4 Gy; MLEs are 1.9 (Table 5.22).

^f 50th percentiles and 90% CIs based on ERR models and LQ or LQE dose-response at shielded kerma of 0–4 Gy developed by Little et al. (2008) (Table 5.22).

^g 50th percentiles and 90% CIs based on EAR models and LQ or LQE dose-response at shielded kerma of 0–4 Gy developed by Little et al. (2008) (Table 5.22).

Table 5.27. (continued)

^h 50th percentile and 90% CI based on ERR model at shielded kerma of 0–4 Gy developed by Richardson et al. (2009) (Table 5.22).

ⁱ 50th percentile and 90% CI based on ERR model at shielded kerma of 0–4 Gy developed by Ozasa et al. (2012) (Table 5.22).

^j 50th percentiles and 90% CIs based on analysis by Hsu et al. (2013) using ERR or EAR model at shielded kerma of 0–4 Gy; MLEs are 2.2 and 2.0, respectively (Table 5.21).

^k DREFs are estimated as ratios of risks from acute exposure in LSS cohort to risks from chronic, protracted, or highly fractionated occupational, medical, or environmental exposures.

^m 50th percentile and 90% CI estimated as ratio of ERR at 1 Gy for leukemia mortality in LSS cohort based on dose-response model at shielded kerma of 0–4 Gy developed by BEIR VII committee (NRC 2006) for age at exposure 29, attained age 52, and male fraction 0.9 to ERR/Sv for same endpoint in U.K. radiation workers (Muirhead et al. 2009) (Table 5.10 and Section 5.8.3.1).

ⁿ 50th percentile and 90% CI estimated as ratio of ERR at 1 Gy for leukemia incidence in LSS cohort based on dose-response model at shielded kerma of 0–4 Gy developed by Hsu et al. (2013) for age at exposure 29, attained age 52, and male fraction 0.9 to ERR/Gy for same endpoint in U.K. radiation workers (Muirhead et al. 2009) (Table 5.10 and Section 5.8.3.1).

^o First entry is 50th percentile and 90% CI estimated as ratio of ERR at 1 Gy for leukemia mortality in males of ages 20 to 60 in LSS cohort based on dose-response model at shielded kerma of 0–4 Gy developed by Ozasa et al. (2012) (Metz-Flamant et al. 2013; Leuraud et al. 2015) to ERR/Gy for same endpoint in radiation workers in France, U.K., and U.S. (Leuraud et al. 2015); second entry is 50th percentile and 90% CI estimated as ratio of ERR at 1 Gy in males in LSS cohort based on dose-response model at shielded kerma of 0–4 Gy developed by BEIR VII committee (NRC 2006) for age at exposure 31 and attained age 58 to same ERR/Gy in workers (Table 5.10 and Section 5.8.3.1).

^p First entry is 50th percentile and 90% CI estimated as ratio of ERR at 1 Gy for leukemia mortality in LSS cohort based on dose-response model at shielded kerma of 0–4 Gy developed by BEIR VII committee (NRC 2006) for age at exposure 30, time since exposure 20 years, and male fraction 0.9 to our preferred ERR/Gy for same endpoint based on meta-analysis of studies of radiation workers by Daniels and Schubauer-Berigan (2011); second entry is 50th percentile and 90% CI estimated using same ERR at 1 Gy in LSS cohort and ERR/Gy in workers preferred by Daniels and Schubauer-Berigan (2011) (Section 5.8.3.4).

^q 50th percentile and 90% CI estimated as ratio of ERR at 1 Gy for leukemia mortality in LSS cohort based on dose-response model at shielded kerma of 0–4 Gy developed by BEIR VII committee (NRC 2006) for age at exposure 30, time since exposure 20 years, and male fraction 0.9 to ERR/Gy for same endpoint in U.S. radiation workers (Daniels et al. 2013) (Section 5.8.3.5).

^r 50th percentile and 90% CI estimated as ratio of ERR at 1 Gy for leukemia incidence in LSS cohort based on dose-response model at shielded kerma of 0–4 Gy developed by Hsu et al. (2013) for age at exposure 2.5 and attained age 5 to ERR/Gy for same endpoint in children in U.K. exposed to gamma rays in natural background radiation (Kendall et al. 2013) (Section 5.8.3.6).

^s 50th percentile and 90% CI estimated as ratio of ERR at 1 Gy for leukemia incidence in LSS cohort based on dose-response model at shielded kerma of 0–4 Gy developed by Hsu et al. (2013) for age at exposure 7 and attained age 15 to ERR/Gy for same endpoint in children in Switzerland exposed to gamma rays in natural background radiation (Spycher et al. 2015) (Section 5.8.3.6).

^t Ratio of linear (α) coefficient in modeled LQ dose-response from acute exposure in LSS cohort to coefficient in modeled linear dose-response from chronic occupational or environmental exposures. Ratio is similar to DREF but is not a DREF when numerator does not represent responses at high acute doses.

^u 50th percentile and 90% CI estimated as ratio of linear risk coefficient in LQ dose-response model for leukemia mortality in males in LSS cohort at shielded kerma of 0–4 Gy developed by BEIR VII committee (NRC 2006) for ages at exposure ≥ 30 and time since exposure 15 years (Cardis et al. 2007) to linear risk coefficient for same endpoint in U.K. radiation workers (Muirhead et al. 2009) (Table 5.10 and Section 5.8.3.1).

Table 5.27. (continued)

^v 50th percentile and 90% CI estimated as ratio of linear risk coefficient in LQ dose-response model for leukemia incidence in males in LSS cohort at shielded kerma of 0–4 Gy developed by Hsu et al. (2013) for age at exposure 30 and time since exposure 15 years (Cardis et al. 2007) to linear risk coefficient for same endpoint in U.K. radiation workers (Muirhead et al. 2009) (Table 5.10 and Section 5.8.3.1).

^w 50th percentile and 90% CI estimated as ratio of linear risk coefficient in LQ dose-response model for leukemia mortality in males in LSS cohort at shielded kerma of 0–4 Gy developed by BEIR VII committee (NRC 2006) for age at exposure 31 and attained age 58 to linear risk coefficient for same endpoint in radiation workers in France, U.K., and U.S. (Leuraud et al. 2015) (Table 5.10 and Section 5.8.3.1).

^x 50th percentile and 90% CI estimated as ratio of ERR at 0.1 Gy for leukemia mortality in LSS cohort based on dose-response model at shielded kerma of 0–4 Gy developed by Richardson et al. (2009) for ages at exposure ≥ 30 and time since exposure 30 years to our preferred ERR at 0.1 Gy for same endpoint based on meta-analysis of studies of radiation workers by Daniels and Schubauer-Berigan (2011); DREFs estimated based on other ERRs at 0.1 Gy in LSS cohort have larger uncertainties and, in some cases, lower 50th percentiles (Section 5.8.3.4).

^y 50th percentile and 90% CI estimated as ratio of ERR at 0.1 Gy for leukemia mortality in LSS cohort based on dose-response model at shielded kerma of 0–4 Gy developed by Richardson et al. (2009) for age at exposure 30 and time since exposure 30 years to ERR per 0.1 Gy for same endpoint in U.S. radiation workers (Daniels et al. 2013) (Section 5.8.3.5).

^z 50th percentile and 90% CI estimated as ratio of linear risk coefficient in LQ dose-response model for leukemia incidence in males and females in LSS cohort at shielded kerma of 0–4 Gy developed by Hsu et al. (2013) for age at exposure 2.5 and attained age 5 to linear risk coefficient for same endpoint in children in U.K. exposed to gamma rays in natural background radiation (Kendall et al. 2013) (Section 5.8.3.6).

^{aa} 50th percentile and 90% CI estimated as ratio of ERR at 1 Gy for mortality from AML in LSS cohort based on quadratic dose-response model at shielded kerma of 0–4 Gy developed by Richardson et al. (2009) for age at exposure 30 and time since exposure 30 years to ERR/Gy for same endpoint in U.S. radiation workers (Daniels et al. 2013) (Section 5.8.3.5).

Although use of epidemiological data to estimate DDREFs clearly is preferable to the use of data in animals, due to concerns about the validity of extrapolating data in animals to humans, dose-responses for cancer in humans can be complex and difficult to interpret, as indicated by the following examples.

- Effects of cell sterilization at high doses and hormonal influences on dose-responses can be important for some cancer types.
- The dose-response for incidence of non-melanoma skin cancers in the LSS cohort, which clearly is non-linear, is not well represented by an LQ model.
- The dose-response model for bone cancer in the LSS cohort developed by UNSCEAR (2008) is quadratic, which implies an LDEF of ∞ as the dose decreases to zero. An upper limit of a DDREF of ∞ also cannot be excluded by dose-responses for leukemia mortality in the LSS cohort (UNSCEAR 2008; Section 5.8.2) and lung cancer mortality in the tuberculosis fluoroscopy cohorts (Section 5.5.4).

- Several estimates of LDEFs for incidence of thyroid and stomach/esophageal cancers in Table 5.14 and incidence or mortality from leukemias in Tables 5.21 and 5.22 have very large but undefined upper limits. These LDEFs are not included in Tables 5.26 and 5.27.
- The BEIR VII committee (NRC 2006) did not include data for non-melanoma skin cancers and thyroid cancer in deriving a DDREF for all solid cancers combined, mainly because of apparent differences in the age-dependence of these cancers compared with most other solid cancers.

Given the similarity in MLEs of an LDEF for incidence of all solid cancers in the LSS cohort of 1.21 (Table 5.14) and an LDEF for incidence of all leukemias in the LSS cohort of 1.7 (Table 5.21), Little and Muirhead (2000, 2004) suggested that a single DDREF of about 1.5 for all cancers might be appropriate. However, leukemia and other hematopoietic cancers are normally considered separately from solid cancers, owing to such factors as differences in etiology and the minimum latency period (UNSCEAR 2000). In addition, the recent analyses of leukemia incidence (Hsu et al. 2013) and mortality (Richardson et al. 2009) in the LSS cohort indicated that the apparently LQ dose-responses for all leukemias (excluding CLL), and the associated LDEFs, are largely artifacts of combining dose-responses for specific types of leukemia, none of which appear to be LQ in form. Therefore, combining LDEFs or DREFs for solid cancers and leukemias is unlikely to be appropriate. Little and Muirhead (2000, 2004) also concluded that although a DDREF based on data in the LSS cohort could vary by cancer site, the statistical power of the data was insufficient to detect any such differences.

Another issue that complicates the use of an LQ dose-response model for solid cancers in the LSS cohort to estimate LDEFs is the uncertainty in the RBE for neutrons, for which dose-responses should be linear. If the RBE for induction of solid cancers by neutrons in the LSS cohort was higher than the usual assumption of 10 or 20, as some have proposed (Section 5.2.1.3), the curvature in modeled dose-responses could underestimate the true curvature in dose-responses for gamma rays from the atomic bombs, resulting in an underestimation of LDEFs. However, analyses of dose-responses in the LSS cohort using DS86 dosimetry summarized in Tables 5.5–5.7 suggested that (1) the LDEF for solid cancer incidence decreases by only about 25% or less as the assumed neutron RBE increases from 10 to 100 and (2) the LDEF for solid cancer mortality decreases by less than 10% as the assumed neutron RBE increases from 10 to 50. The weak dependence of estimated LDEFs on the neutron RBE is a consequence of the low absorbed doses from neutrons at Hiroshima and Nagasaki compared with doses from gamma rays (Preston et al. 2004). Estimates of LDEF for solid cancer incidence from analyses by Little and Muirhead (2000, 2004) based on DS86 dosimetry and an assumed neutron RBE of 50 are included in Table 5.26 for comparison with estimates using the RBE of 20 preferred by those investigators. The dependence of LDEFs on the assumed neutron RBE should be even less when dose-responses are analyzed based on DS02 dosimetry,

since estimated doses from neutrons at Hiroshima and Nagasaki decreased compared with estimates based on DS86 dosimetry (Preston et al. 2004).

On the basis of evidence from radiobiological and epidemiological studies that an RBE for induction of leukemias by neutrons should be substantially less than an RBE for induction of solid cancers, the concern about possibly underestimating LDEFs should not arise in analyses of dose-responses for leukemia in the LSS cohort.

Despite differences in the definition of the LSS cohort, dose-response models, dose ranges over which dose-responses were analyzed, dosimetry system, and period of follow-up, central estimates (50th percentiles) of LDEFs for incidence of all solid cancers in Table 5.26 are in the narrow range of about 1.1–1.5 and uncertainties are modest, with lower limits of 90% CIs of about 0.7–1.0 and upper limits of 90% CIs less than twice the central estimates. Central estimates of LDEFs for mortality from all solid cancers tend to be somewhat higher (about 2.0 on average when LDEFs are estimated based on DS02 dosimetry and LQ dose-response models), but uncertainties in some LDEFs for solid cancer mortality are substantially greater than uncertainties in LDEFs for solid cancer incidence, due mainly to the much higher upper confidence limits of LDEFs for solid cancer mortality. This difference is exemplified by recent results based on similar analyses at the Radiation Effects Research Foundation (RERF) of the curvature parameter (β/α) in modeled LQ dose-responses at doses of 0–2 Gy using DS02 dosimetry (Ozasa et al. 2012; Preston et al. 2007)—LDEFs for solid cancer mortality and incidence with 90% CIs of (1.2, 8.3) and (1.0, 1.9), respectively. Although lower confidence limits of the two LDEFs are similar, the lower limit of the 95% CI of α in the LQ model for solid cancer mortality of 0.036 is much closer to zero than the lower confidence limit of 0.19 in the model for solid cancer incidence (D. Preston, personal communication, October 27, 2016), and it is this difference in the lower confidence limits of α that leads to the pronounced difference in upper confidence limits of the LDEFs for solid cancer mortality and incidence. The LDEF for solid cancer mortality based on estimates of α_L and α_{LQ} at doses of 0–2 Gy by Ozasa et al. (2012) also has a much wider 90% CI of (1.0, 6.8) than the 90% CI of the LDEF for solid cancer incidence over the same dose range from Preston et al. (2007).

Central estimates (50th percentiles) of DREFs for incidence of all solid cancers of about 0.6–1.4 are similar to central estimates of LDEFs for that endpoint, but uncertainties are greater. Central estimates of DREFs for mortality from all solid cancers of about 0.3–1 tend to be less than central estimates of LDEFs for that endpoint. With two exceptions, upper limits of 90% CIs of DREFs for solid cancer mortality are about 3 or less. Although not definitive, due to their uncertainties, estimates of DREFs for mortality from all solid cancers suggest that risks at low doses or low dose rates might be higher than risks at high acute doses. As discussed in Section 5.2.2.4, we think that estimated 90% CIs of DREFs for solid cancer

incidence and mortality based on analyses by Jacob et al. (2009) (the last entries for all solid cancers in Table 5.26) are too narrow.

Estimates of DDREFs for female breast, thyroid, and lung cancers in Table 5.26 are consistent with estimates for all solid cancers when uncertainties are taken into account. The estimates for female breast and thyroid cancer do not provide support for the use of a separate probability distribution of DDREF for those cancer types in IREP (Land et al. 2003a). We also think that there is little justification for developing separate probability distributions of DDREF for other specific types of solid cancers.

There also may be concerns about using estimated risks of thyroid cancer from childhood exposures to medical x rays to estimate a DDREF that would apply to chronic exposures of adult workers. The uncertain influence of the genetic background of the Israeli tinea capitis cohort may affect the validity of approaches to pooling of data in the different cohorts of children. In addition, recent analyses of data for thyroid cancer in the LSS cohort (Preston et al. 2007; Richardson 2009; Furukawa et al. 2013) do not provide consistent and definitive conclusions in regard to whether there are excess risks from exposure at ages ≥ 20 and whether risks in males and females exposed at those ages differ significantly. Finally, any conclusions about DDREFs based on comparisons of estimated risks of thyroid cancer from exposures of medical patients and members of the LSS cohort are somewhat tentative due to the low degree of dose fractionation in medical patients exposed to x rays.

Estimated LDEFs for incidence of non-melanoma skin cancers or basal cell carcinoma only, which tend to be higher than estimates for other solid cancers, are based on linear-spline fits to dose-responses in the LSS cohort, rather than an LQ model. Consequently, if estimates of ERR/Sv for basal cell carcinoma and other non-melanoma skin cancers in IREP are revised on the basis of dose-responses in the LSS cohort at doses below 1 Gy—i.e., in the low-dose region of the linear-spline models developed by Preston et al. (2007)—estimates of LDEF in Table 5.26 would not apply.

No estimates of an LDEF or a DREF for bone cancer in humans are given in Table 5.26 because (1) the only reported dose-response model for the LSS cohort is quadratic and is of questionable validity, due to the small numbers of bone cancers in that cohort, and (2) the ERR for mortality from bone cancer in Mayak workers due chronic exposure to external gamma radiation is not significantly different from zero (Section 5.7). Data in animals suggest a high DDREF or a threshold in the dose-response (Table 4.2).

The impact of exposures to high-LET radiation (alpha particles and neutrons) on estimated risks of solid cancers in the recent studies of U.K. workers (Muirhead et al. 2009) and workers in France, the U.K., and the U.S. (Leuraud et al. 2015; Richardson et al. 2015) is uncertain; such exposures presumably were not important in the 15-country study (Cardis et al. 2005b, 2007). Estimated risks from all those studies also may have been influenced by smoking and exposure to chemical carcinogens in the workplace. However, as indicated by results in Table 5.10 (Section 5.2.2.2), estimated risks of solid

cancers in the U.K. workers (Muirhead et al. 2009) and workers in France, the U.K., and the U.S. (Richardson et al. 2015) were not greatly affected when cancers associated with smoking were excluded.

Although it would be preferable, in principle, to apply the concepts of LDEF and DREF separately in estimating risks of solid cancers, limitations in the available data in humans and animals make it difficult to adopt that approach in a meaningful way. Rather, consolidation of the available data into a single probability distribution of DDREF for all solid cancers appears to be the more reasonable option.

Central estimates (50th percentiles) of LDEFs at 1 Gy for mortality from all leukemias as a group based on LQ dose-response models in Table 5.27 are about 1.5–5. Lower confidence limits of those LDEFs are about 0.3–1.3, and upper confidence limits exceed central estimates by a factor of about 2–5. Excluding the LDEF with no uncertainty, central estimates of LDEFs at 1 Gy for incidence of all leukemias of about 3–30 tend to be higher than central estimates for leukemia mortality and to have larger uncertainties. Estimated 50th percentiles of LDEFs for incidence of all leukemias are much higher than reported MLEs as a consequence of the highly skewed probability distributions of α_L/α_{LQ} or β/α reported by Little and Muirhead (2000, 2004) and Hsu et al. (2013) (Table 5.21); i.e., the ratio of an upper confidence limit to an MLE is much greater than the ratio of the MLE to the lower confidence limit. The very high upper confidence limits of LDEFs based on analyses by Little and Muirhead (2000, 2004), including values >1000 from two analyses included in Table 5.21 but not shown in Table 5.27, are roughly consistent with a conclusion by UNSCEAR (2008) that a purely quadratic model may best describe the dose-response for all leukemias at low doses.

Central estimates (50th percentiles) of DREFs at 1 Gy for mortality or incidence from all leukemias tend to be less than central estimates of LDEFs at 1 Gy, and, similar to the data for all solid cancers in Table 5.26, central estimates of DREFs at 1 Gy for leukemia mortality tend to be less than central estimates for leukemia incidence. However, these differences are not significant when uncertainties are taken into account. Estimated LDEFs and DREFs for all leukemias and their uncertainties generally do not contradict the implicit assumption of a DDREF at 1 Gy of 2 for all leukemias in the LQ dose-response model in IREP (Land et al. 2003a). However, it is questionable whether the model in IREP adequately accounts for uncertainty in LDEF.

Central estimates (50th percentiles) of the ratio $\alpha_{acute}/\alpha_{chronic}$ for all leukemias are about 0.4–1.4. Central estimates for leukemia mortality of about 0.4–1 suggest that risks from chronic or protracted exposures might be higher than risks from acute exposure in the LSS cohort at low doses where only the linear term in an LQ dose-response is significant. However, all upper confidence limits of $\alpha_{acute}/\alpha_{chronic}$ are >1 and, with one exception, are about 5 or greater. Therefore, estimates of $\alpha_{acute}/\alpha_{chronic}$ for all leukemias and their uncertainties do not contradict the assumption in IREP that risks from chronic exposure can be estimated on the basis of the linear term in the LQ dose-response model for acute exposure. However,

recent analyses of dose-responses for AML, ALL, and CML in the LSS cohort by Richardson et al. (2009) and Hsu et al. (2013) indicate that the assumption of LQ dose-responses from acute exposure for those leukemia types in IREP (Land et al. 2003a) probably is inappropriate. An estimated DREF at 1 Gy for AML has a large uncertainty and probably is not informative.

In the following section, we develop a probability distribution of DDREF for all solid cancers from estimates of LDEFs and DREFs summarized in Table 5.26. As described in Section 6.3.1, the LDEFs and DREFs in **bold face** in Table 5.26 are used to derive our preferred DDREF distribution for all solid cancers. On the basis of an assumption that an LQ dose-response model for all leukemias will continue to be used in risk assessments, we do not develop a probability distribution of DDREF for that endpoint. Due to the paucity of data, we also do not consider DDREFs for specific types of leukemia.

6. DEVELOPMENT OF PROBABILITY DISTRIBUTION OF DDREF FOR ALL SOLID CANCERS

6.1 INTRODUCTION

The main purpose of this section is to develop a probability distribution of DDREF for all solid cancers on the basis of information presented in Sections 4 and 5. A DDREF is applied to risk coefficients (risks per unit dose) for solid cancers that are estimated on the basis of estimated risks from acute exposure in the LSS cohort and an assumption of a linear no-threshold (LNT) dose-response. Application of a DDREF results in estimated risks of solid cancers at low doses or low dose rates. We did not develop separate probability distributions of DDREFs for specific solid cancers (e.g., breast and thyroid) on the grounds that DDREFs based on data for specific solid cancers tend to be more uncertain than, and not significantly different from, DDREFs based on data for all solid cancers combined.

We also reviewed data on risks of leukemias associated with exposure to ionizing radiation and estimated DDREFs from results of various studies. However, we did not develop a probability distribution of DDREF for all leukemias based on the consideration that a linear-quadratic (LQ) dose-response model, which incorporates a dose-dependent DDREF implicitly, would continue to be used in cancer risk assessments. We also noted that dose-responses for specific types of leukemia in the LSS cohort are not consistent with an LQ model and, therefore, that the apparently LQ dose-response for all leukemias as a group in the LSS cohort is largely an artifact of combining dose-responses for specific leukemias (AML, CML, and CLL), none of which is LQ in form. This conclusion does not invalidate the use of an LQ model in estimating risks of all leukemias. However, it means that dose-responses for all leukemias in the LSS cohort should not be used in developing a DDREF for solid cancers. Although dose-responses for some types of leukemia appear to be linear, the available data are insufficient to estimate DDREFs.

Section 6.2 summarizes data in humans, laboratory animals, and cells that can be used to define low doses or low dose rates of low-LET radiation, i.e., doses or dose rates below which a DDREF should be applied to risk coefficients for solid cancers that are estimated by assuming linear dose-responses from acute exposure in the LSS cohort. We also recommend a change in the probability distribution of doses from acute exposure below which a DDREF for solid cancers should be applied in IREP.

Our approach to developing a probability distribution of DDREF for all solid cancers is presented in Section 6.3. Substantial judgment is required in developing a probability distribution of DDREF on the basis of data in cells, laboratory animals, and humans presented in Sections 4 and 5 and summarized in Tables 4.1, 4.2, and 5.26. The probability distribution of DDREF developed in Section 6.3 represents our

judgments about the relevance and relative importance of radiobiological and epidemiological data and uncertainties in those data to induction of solid cancers in humans. Section 6.3 includes an analysis of the sensitivity of our DDREF distribution to judgments about the applicability of specific epidemiological data and various ways of combining different estimates of DDREF. Section 6.3 also discusses how estimates of the probability of causation/assigned share (PC/AS) of diagnosed solid cancers in exposed individuals that would be generated with the DDREF distribution developed in this report compare with estimates based on the DDREF distributions for solid cancers currently used in IREP.

Finally, Section 6.4 discusses the advantages of using a risk ratio, defined as the reciprocal of a DDREF, in cancer risk assessments, rather than a DDREF, and summarizes the probability distribution of the risk ratio that corresponds to the DDREF distribution for all solid cancers developed in Section 6.3.

An initial judgment we made is that radiobiological data in cells summarized in Table 4.1 should not be used in developing a DDREF for solid cancers in humans. The main basis for this judgment is that the relevance of data in cells to induction of cancer in humans is not well established.

It is apparent from the review of animal and epidemiological data in Sections 4 and 5 that all such data that could be used in estimating a DDREF for solid cancers are limited in some way. A variety of complicating factors had to be considered in assessing the relevance and validity of those data. The principal complicating factors in evaluating data in animals included:

- Influences of genetic and epigenetic factors on tumorigenic responses, such as effects of species, strain, sex, and age at exposure;
- Effects of cell sterilization at higher doses, which may influence the shape of the dose-response at higher doses significantly by removing cells in which tumors would otherwise be initiated;
- Effects of dose or dose rate on tumor type or latency—i.e., the types, numbers, and times of appearance of tumors may be different at high acute doses or high dose rates than at low dose rates, and some non-cycling cells may require a high dose for tumor initiation because cycling is only induced by a substantial amount of cell sterilization;
- Some tumor types in animals have no human counterpart or are induced differently in animals.

Important complicating factors in evaluating epidemiological data, in addition to the frequent problem of low statistical power, especially in data for specific cancer types, included:

- Selection of ranges of doses and dose rates over which modeled dose-responses are the most relevant to estimating a DDREF (e.g., for compatibility with ranges of doses and dose rates used to derive risk coefficients and to define chronic exposures in IREP);

- Effects of differences in the biological effectiveness of different energies of low-LET radiations in comparing estimated risks in the LSS cohort from exposure mainly to high-energy photons with estimated risks in populations exposed to medical x rays of lower energies;
- Uncertainties in risk transfer in comparing estimated risks of specific cancer types in the LSS cohort with estimated risks of those cancer types in populations of other nationalities when baseline rates in the two populations differ substantially (e.g., for breast cancer);
- Difficulties in comparing modeled ERRs or EARs that include different assumptions about their dependence on sex, age at exposure, attained age, or time since exposure;
- Difficulties in defining an appropriate age at exposure and attained age in a population exposed over several years (at several ages) when comparing estimated risks with risks in the LSS cohort;
- Possible differences in risks of specific cancer types from relatively uniform exposures of the whole body in the LSS cohort compared with risks from partial-body irradiations, e.g., from exposure to medical x rays. Little is known about the effect of non-uniform distributions of dose on risks of cancer in humans.

Many other factors can introduce uncertainty into dose-response models for cancer in humans and, hence, into DDREFs, including uncertainties in dosimetry, cancer ascertainment, nature of exposed populations and the reference unexposed population used in estimating ERRs or EARs, effects of time since exposure and age on risks, duration of follow-up, and selection of models for use in risk projection. Complications introduced by such factors are well recognized, and their implications have been reviewed extensively (e.g., ICRP 1991; NCRP 1997, 2001; UNSCEAR 2000, 2008; NRC 2006). A comprehensive summary of the strengths and limitations of existing epidemiological studies in relation to such factors was compiled in Annex I of UNSCEAR (2000) and Annex A of UNSCEAR (2008).

Since the combined influence of all the complicating factors in estimating a DDREF for solid cancers in humans based on epidemiological data is uncertain, it is not always clear how to weight the results from individual studies or to combine those results. This concern is addressed in part by our sensitivity analysis to investigate how differences in some assumptions affect a DDREF distribution.

By considering all the complicating factors in studies in laboratory animals and humans, we judged that a probability distribution of DDREF for all solid cancers should be developed on the basis of epidemiological data only, and that data in animals should not be used. This judgment was based mainly on a consideration of the complicating factors in animal studies summarized above, which cast doubt on the relevance of much of the data in animals for the purpose of estimating a DDREF in humans. We also believe that epidemiological data now are sufficiently abundant and varied to allow estimation of a DDREF without having to rely on data in animals. However, Section 6.3.1 summarizes estimates of

DDREF based on data in laboratory animals and discusses whether some of the data in animals might inform judgments about a DDREF for certain solid cancers in humans.

In focusing on data in humans, we also judged that it should not be assumed at the outset that a DDREF for solid cancers should be >1 , as suggested by estimates of LDEF based on data from acute exposure in the LSS cohort and as generally assumed for purposes of radiation protection (e.g., ICRP 2007). Rather, we judged that estimates of a DDREF for solid cancers <1 , as suggested by estimates of DREF based on comparisons of risks in the LSS cohort with risks in cohorts of radiation workers or members of the public who received protracted exposures, should be included in our analysis. Indeed, we believe that inclusion of estimates of DREF is necessary in developing a probability distribution of DDREF that represents the current state of knowledge. Our objective was to develop an unbiased probability distribution of DDREF for solid cancers on the basis of epidemiological data.

6.2 DOSES AND DOSE RATES WHERE DDREF SHOULD BE APPLIED

A DDREF is used in cancer risk assessments as a modifying factor to adjust risks per unit dose at high acute doses (H) of low-LET radiation, as estimated from data in the LSS cohort, to obtain estimates of risks per unit dose at low doses or low dose rates (L); i.e., $R_L = R_H/DDREF$. An important issue is the need to define doses and dose rates below which a DDREF should be applied, i.e., a “low” dose from acute exposure and a “low” dose rate from chronic or protracted exposure. An upper limit of a low acute dose is a dose above which the dose-response is essentially linear (i.e., the curvature is insignificant).

In IREP, one of the probability distributions of DDREF for solid cancers shown in Figure 1.2 is applied in all cases of chronic exposure. An exposure is assumed to be chronic (the dose rate is “low”) whenever (1) the dose rate averaged over a period of a few hours is $\leq 6 \text{ mGy h}^{-1}$ (0.1 mGy min^{-1}) or (2) an exposure is protracted over a period of more than one day, regardless of the dose rate (Land et al. 2003a).

Under conditions of acute exposure, including acute dose fractions separated in time by at least 5 h, a DDREF for solid cancers is applied in IREP whenever the dose from a low-LET radiation is less than an uncertain reference dose, D_L (Land et al. 2003a; Kocher et al. 2008). At doses $>D_L$, DDREF is assumed to be 1 with no uncertainty on the basis of the observed linearity in acute dose-responses for all solid cancers in the LSS cohort. The uncertain dose D_L below which a DDREF is applied is assumed to be described by a log-uniform probability distribution between 30 and 200 mGy. Thus, a DDREF for solid cancers is never applied at acute doses $>200 \text{ mGy}$, is always applied at acute doses $<30 \text{ mGy}$, and is applied at acute doses between 30 and 200 mGy only if the dose is less than a randomly selected value of D_L . The upper and lower limits of the probability distribution of D_L were based on a review by UNSCEAR (1993) of radiobiological and epidemiological data that could be used to define a “low” acute dose.

By considering that the DDREFs for chronic exposure shown in Figure 1.2 should not be applied abruptly to acute exposures at doses slightly below the uncertain reference dose D_L , a DDREF distribution for acute exposure is phased in gradually in IREP (Land et al. 2003a; Kocher et al. 2008). As an acute dose decreases below D_L , DDREF is assumed to change smoothly from the value 1 at doses $\geq D_L$ to the full DDREF distribution for chronic exposure at zero dose in accordance with a logistic function of dose:

$$\text{DDREF}_{\text{acute}} = \frac{1}{1 - \left\{ \frac{1 - \frac{1}{\text{DDREF}_{\text{chronic}}}}{1 + e^{\frac{(D-D_L)}{S}}} \right\}} \quad \text{if } D < D_L,$$

where D_I is the inflection point on the curve of $\text{DDREF}_{\text{acute}}$ vs dose, D , given by $0.5 \times D_L$, and the “shape” parameter S is given by $D_I/\ln(500)$. The value of S was chosen to obtain the least steep increase of the logistic function that still reproduces the appropriate $\text{DDREF}_{\text{chronic}}$ at zero dose. The chosen value of S also ensures that $\text{DDREF}_{\text{acute}}$ is >0.99 at dose D_L .

The phasing in of $\text{DDREF}_{\text{acute}}$ as an acute dose decreases below the uncertain reference dose, D_L , is illustrated in Figure 6.1. This illustration applies to the discrete probability distribution of DDREF for solid cancers other than breast and thyroid shown in Figure 1.2. At a fixed D_L , the probability distribution of $\text{DDREF}_{\text{acute}}$ has the same form as the probability distribution of $\text{DDREF}_{\text{chronic}}$ (i.e., the full DDREF in Figure 1.2), except the distribution is compressed toward the value 1.0 in accordance with the logistic function given above, with the degree of compression increasing as the ratio D/D_L increases. For example, Figure 6.1 shows that $\text{DDREF}_{\text{acute}}$ at an acute dose of $0.5D_L$ is only about 16% of the full DDREF and that $\text{DDREF}_{\text{acute}}$ increases to about 85% of the full value at an acute dose of $0.25D_L$.

As part of this study, we considered whether the range of values of D_L to define the upper limit of a low acute dose (30–200 mGy) and the upper limit of a low dose rate (6 mGy h^{-1}) used in IREP should be revised. We also considered whether a probability distribution to represent uncertainty in the upper limit of a low dose rate, similar to the uncertain reference dose, D_L , for acute exposure, would be appropriate. As described in Appendix A, we reviewed recommendations, data, and approaches that were developed or used by expert committees, as well as a variety of more recent information including (1) microdosimetric arguments, which are based on an assumption that the cell nucleus is the appropriate target for initiation of a carcinogenic response, (2) studies of chromosome aberrations and cell transformation *in vitro*, (3) studies of animal carcinogenesis *in vivo*, and (4) epidemiological studies of cancer risks in the LSS cohort and other exposed populations.

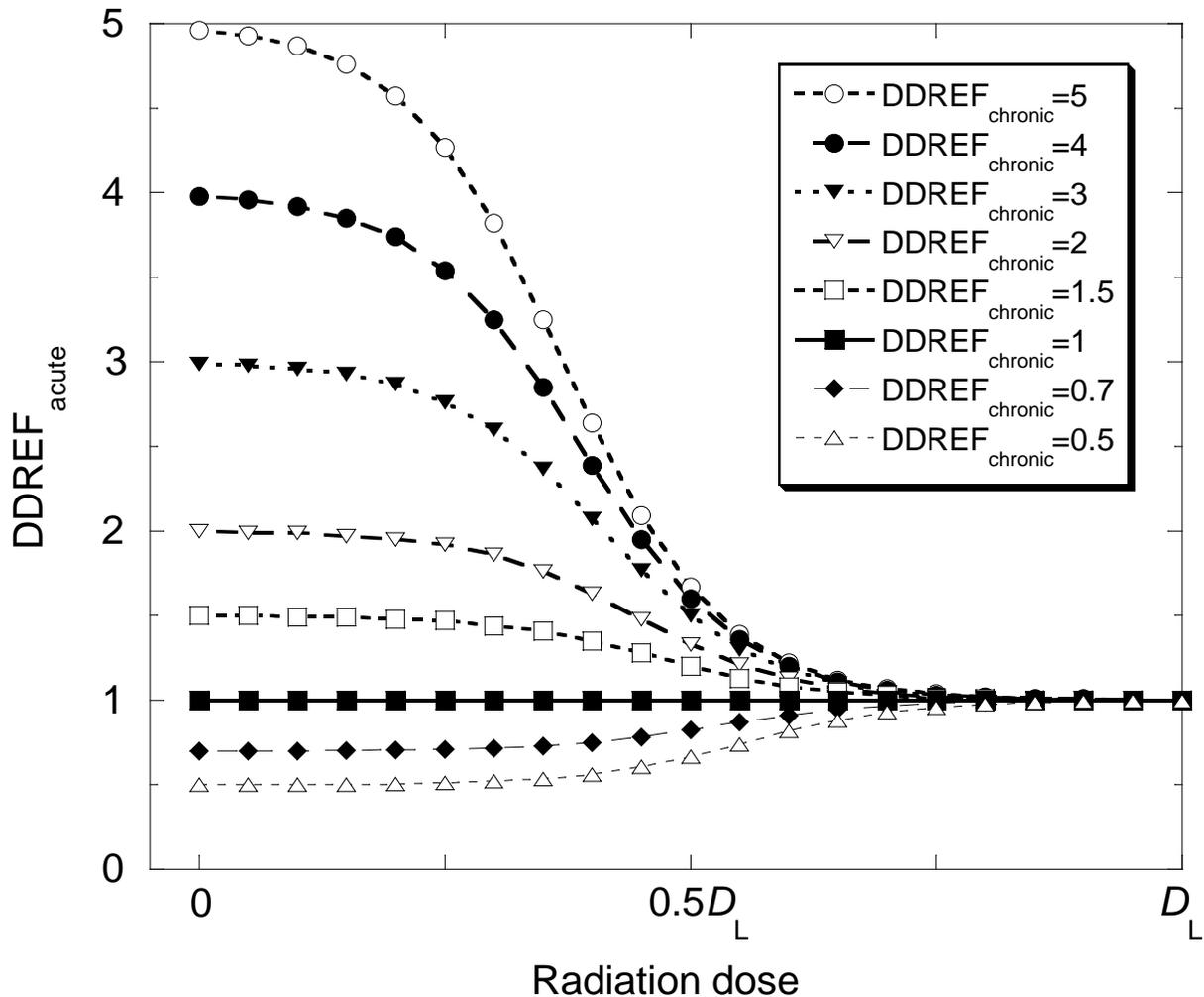


Figure 6.1. Dependence of DDREF for all solid cancers except breast and thyroid under conditions of acute exposure to low-LET radiations, $DDREF_{acute}$, on dose for assumed DDREF under conditions of chronic exposure, $DDREF_{chronic}$, and reference dose, D_L , above which acute dose-response is assumed to be linear. Uncertain D_L is represented by loguniform probability distribution between 30 and 200 mGy. Depiction represents assumptions currently used in IREP (Land et al. 2003a; Kocher et al. 2008).

6.2.1 Defining Probability Distribution of Upper Limit of Low Acute Dose

Ideally, an upper limit of a low acute dose and its uncertainty should be estimated on the basis of data in the LSS cohort, since it is those data that provide the basis for estimated risks of solid cancers. However, as described in Appendix A, Section A.2, microdosimetric considerations, data on radiation effects in cells, data on tumor induction in laboratory animals, and data on cancer risks in populations other than the LSS cohort were used to supplement evidence obtained from studies of the LSS cohort.

In our analysis, we assumed that the reference acute dose D_L should be defined as the dose at which the quadratic term in an assumed LQ or linear-quadratic-exponential (LQE) dose-response contributes no more than 5% of a modeled response for solid cancers. With this assumption, the upper limit of the probability distribution of D_L of 200 mGy used in IREP appears to be consistent with current understanding of the uncertainty in the dose-response for incidence of solid cancers in the LSS cohort (Section 5.2.1 and Appendix A, Section A.2.5.1 and Table A.1). However, we concluded that epidemiological data are inadequate to establish the lower limit of a distribution of D_L with a reasonable degree of confidence.

Basing estimates of a lower limit of a probability distribution of D_L on microdosimetric considerations is problematic when estimates are strongly dependent on the assumed size of the relevant target (Appendix A, Section A.2.2). However, recent evidence for production of genomic instability as a direct effect of DNA damage indicates that microdosimetric considerations may still be relevant to estimation of D_L . In addition, because some form of primary DNA damage in a single cell nucleus within a group of cells initiates the signaling cascade that leads to the production of non-targeted and delayed effects, a dose of about 9 mGy, as suggested by microdosimetric considerations, could provide a reasonable estimate of a lower limit of an uncertain “low” acute dose.

As indicated in Table A.1, upper limits of a low acute dose derived from *in vitro* studies of cell transformation and induction of chromosome aberrations are in the range of 10–160 mGy, and upper limits based on data in tumor induction in laboratory animals are in the range of 10–100 mGy. Leaving estimates based on microdosimetry aside, it seems reasonable to retain the upper limit of the probability distribution of D_L of 200 mGy used in IREP but reduce the lower limit from 30 to 10 mGy. Thus, a revised probability distribution for D_L would be a log-uniform distribution between 10 and 200 mGy.

Although the proposed lower limit of the D_L distribution is based in large part on data from *in vitro* studies of uncertain applicability to *in vivo* situations, there are plausible reasons for accepting such data (Appendix A, Section A.2.3). Estimates based on those data also are consistent with estimates based on data in animals. In addition, as discussed in Section 5.3.1, fractionated doses of x rays at about 10 mGy per fraction resulted in linear dose-responses for breast cancer when accumulated to total doses of 1–2 Gy. While the effects may not have been fully additive, those dose fractions nonetheless were associated with a significant excess risk, and a dose of 10 mGy thus appears to represent a valid estimate of a low acute dose for use in defining the lower limit of a D_L distribution.

The choice of 10 mGy as the lower limit of a probability distribution of D_L also is consistent with a microdosimetric estimate of a low dose of about 9 mGy when the relevant target is assumed to be the volume of nuclear chromatin and ^{60}Co gamma rays are the reference radiation. Indeed, a probability

distribution of D_L between 10 and 200 mGy appears to be consistent with all the information we reviewed, including epidemiological data on *in utero* and childhood exposures (Appendix A, Section A.2.5.2).

6.2.2 Defining Upper Limit of Low Dose Rate

A dose rate of 0.06–0.07 mGy min⁻¹ was used in a series of studies of cancer induction in animals that were widely used by expert groups to estimate DREFs. Those dose rates were rounded up to 0.1 mGy min⁻¹ by UNSCEAR (1993) to derive an upper limit of a low dose rate, i.e., a dose rate below which all dose-responses are expected to be linear (Appendix A, Section A.3.1). The rounded dose rate was assumed to define the boundary between acute and chronic exposures in IREP (Land et al. 2003a).

Although upper limits of a low dose rate of about 1–2 mGy min⁻¹ are consistent with cytogenetic data and theory summarized in Table A.2 and a recommendation by ICRP (1991), the upper limit of 0.1 mGy min⁻¹ in IREP appears to have the most appropriate and comprehensive experimental basis. Data from studies in animals and humans reviewed in Sections A.3.2 and A.3.5 do not appear to provide an adequate basis for lowering this value. We also think that current information does not support the development of a probability distribution of an upper limit of a low dose rate similar to D_L .

6.3 DEVELOPMENT OF DDREF DISTRIBUTION BASED ON EPIDEMIOLOGICAL DATA

We concluded that the probability distributions of DDREF for solid cancers currently used in IREP (Figure 1.2) do not adequately represent the current state of knowledge of DDREFs or their constituents (LDEFs or DREFs). In developing a DDREF distribution for solid cancers, we relied on epidemiological data, much of which was obtained after the distributions in IREP were developed. Estimates of DDREF based on studies of cancer induction in laboratory animals were used for comparison purposes only, and estimates based on studies of various endpoints in cells were not considered further.

We also concluded that epidemiological data do not support the distinction in IREP between a DDREF for breast and thyroid cancer and a DDREF for all other solid cancers. Therefore, we developed a single probability distribution of DDREF that is intended to apply to all solid cancers.

6.3.1 Selection and Prioritization of Epidemiological Data

Estimates of LDEF and DREF for all solid cancers combined and their uncertainties based on epidemiological data in humans that we evaluated in this study are summarized in Table 5.26. Estimates of LDEF for all solid cancers were based on analyses of the curvature in dose-responses in the LSS

cohort. With the exception of DREFs based on an analysis by Jacob et al. (2009), DREFs for all solid cancers are estimates we derived by comparing estimates of ERRs in various cohorts that received protracted or chronic exposures with age- and sex-matched estimates of ERRs in the LSS cohort; i.e., DREFs were calculated as ratios of an ERR in the LSS cohort to an ERR in a cohort that received protracted or chronic exposures.

In Table 5.26, estimates of LDEF or DREF that we selected for inclusion in our analysis to develop a probability distribution of DDREF for all solid cancers are indicated in **bold face**. All estimates of LDEF or DREF we selected were derived using estimated risks in the LSS cohort based on DS02 dosimetry. Those estimates, which included data from 11 years or more of additional follow-up than estimated risks based on DS86 dosimetry, provide a better representation of the current state of knowledge of cancer risks in the LSS cohort. Estimates of 50th percentiles and 90% CIs of the selected LDEFs and DREFs are summarized in Table 6.1 and shown in the top portion of Figure 6.2.

For reasons described below, some estimates of LDEF and DREF in Table 5.26 that were derived based on DS02 dosimetry in the LSS cohort were not included in our analysis to estimate a DDREF.

- An LDEF of 2.3 derived by Pierce et al. (2008) was excluded because its uncertainty was not reported.
- We considered that LDEFs of 2.1 (1.0, 9.4) and 3.6 (1.2, 9.4) based on an analysis at RERF of solid cancer mortality in the LSS cohort at colon doses of 0–2 Gy by Preston et al. (2004) are superseded by LDEFs based on a more recent analysis, also at RERF, of solid cancer mortality at colon doses of 0–2 or a shielded kerma of 0–4 Gy by Ozasa et al. (2012). In excluding LDEFs based on an analysis by Preston et al. (2004), we also considered that the dependence of an estimated LDEF on the method used to derive it— α_L/α_{LQ} vs $[1 + (\beta/\alpha)D \text{ at } 1 \text{ Gy}]$ —is addressed adequately in the analysis of solid cancer mortality by Ozasa et al. (2012) and an analysis of solid cancer incidence in the LSS cohort by the BEIR VII committee (NRC 2006).
- In evaluating analyses by Little et al. (2008), which represent approaches to modeling by UNSCEAR (2008) and used LQ and LQE models to fit dose-responses for solid cancer mortality in the LSS cohort, we selected only the LDEFs of 1.34 (1.01, 2.53) and 1.51 (1.07, 3.26) based on LQ models, because (1) Little et al. (2008) preferred the simpler LQ models, even though LQE models provided the best statistical fits to the data, and (2) the coefficients of the linear and quadratic terms in the three-parameter LQE models are poorly constrained, with the result that the LDEFs given in Table 5.26 have much larger uncertainties than the LDEFs based on LQ models. The large uncertainties in the estimated LDEFs based on LQE models presumably are artifacts of the poorly constrained model parameters and our lack of knowledge of parameter correlations.

Table 6.1. Estimates of 50th percentiles and 90% CIs of LDEFs and DREFs for all solid cancers included in analysis to develop probability distribution of DDREF^a

Factor	Estimate	Description
LDEF, incidence ^b	1.5 (0.9, 2.4) ^c 1.5 (1.0, 2.3)	Calculated as α_L/α_{LQ} or $[1 + (\beta/\alpha)D]$ at 1 Gy based on analysis by BEIR VII committee (NRC 2006) of ERRs in LSS cohort at colon doses of 0–1.5 Gy (Table 5.2)
	1.4 (1.0, 1.9)	Calculated as $[1 + (\beta/\alpha)D]$ at 1 Gy based on analysis by Preston et al. (2007) of ERRs in LSS cohort at colon doses of 0–2 Gy (Table 5.2)
LDEF, mortality ^b	1.34 (1.01, 2.53) 1.51 (1.07, 3.26)	Calculated as $[1 + (\beta/\alpha)D]$ at 1 Gy based on analyses by Little et al. (2008) of ERRs or EARs in LSS cohort at colon doses corresponding to shielded kerma of 0–4 Gy (Table 5.4)
	3.2 (1.2, 8.3) ^d 2.0 (1.0, 6.8)	Calculated as $[1 + (\beta/\alpha)D]$ at 1 Gy or α_L/α_{LQ} based on analysis by Ozasa et al. (2012) of ERRs in LSS cohort at colon doses of 0–2 Gy (Table 5.4)
	1.11 (0.94, 1.48) 1.16 (0.77, 1.90)	Calculated as $[1 + (\beta/\alpha)D]$ at 1 Gy or α_L/α_{LQ} based on analysis by Ozasa et al. (2012) of ERRs in LSS cohort at colon doses corresponding to shielded kerma of 0–4 Gy (Table 5.4)
DREF, incidence ^e	1.4 (0.64, 5.9)	Based on analyses of ERRs in U.K. radiation workers by Muirhead et al. (2009) and ERRs in LSS cohort by Jacob et al. (2009) (Tables 5.10 and 5.11)
	0.63 (0.33, 2.2)	Based on analyses of ERRs in Techa River cohort by Davis et al. (2015) and ERRs in LSS cohort by BEIR VII committee (NRC 2006) (Section 5.2.2.3)
DREF, mortality ^e	1.0 (0.39, 5.0)	Based on analyses of ERRs in U.K. radiation workers by Muirhead et al. (2009) and ERRs in LSS cohort by Jacob et al. (2009) (Tables 5.10 and 5.11)
	0.55 (0.30, 1.5)	Based on analyses of ERRs in radiation workers in France, U.K., and U.S. (INWORKS) by Richardson et al. (2015) and ERRs in LSS cohort by BEIR VII committee (NRC 2006) (Tables 5.10 and 5.11)
	0.64 (0.31, 2.7)	Based on analyses of ERRs in Techa River cohort by Schonfeld et al. (2013) and ERRs in LSS cohort by BEIR VII committee (NRC 2006) (Section 5.2.2.3)

^a LDEFs and DREFs are entries in **bold face** in Table 5.26.

^b LDEFs are estimated based on analyses of the curvature in modeled linear-quadratic (LQ) dose-responses in LSS cohort. Estimates of LDEF included in our analysis represent approaches to modeling by BEIR VII committee (NRC 2006), RERF (Preston et al. 2007; Ozasa et al. 2012), and UNSCEAR (Little et al. 2008).

^c Estimate based on method of calculation preferred by BEIR VII committee (NRC 2006).

^d Estimate based on curvature parameter (β/α) preferred by Ozasa et al. (2012).

^e DREFs are estimated as ratios of age- and sex-matched estimates of ERR/Gy from acute exposure in LSS cohort assuming linear dose-responses to estimates of ERR/Gy from protracted or chronic exposure of workers or Techa River cohort.

- All DREFs that we derived using estimated risks from the 15-country study of radiation workers by Cardis et al. (2005b, 2007) were excluded based on the following considerations: (1) the DREF of 0.7 (−3.1, 4.5), which we concluded was derived using the most representative estimate of risk from the 15-country study with the entire Canadian cohort excluded (a 14-country study), is largely uninformative when its 90% CI overlaps zero; (2) the other DREFs that we derived using estimated risks from the 15-country study with all or part of the Canadian cohort included probably are unreliable due to errors in estimated doses to some workers prior to 1964; and (3) a 14-country study is superseded by a more recent analysis of risks to workers in France, the U.K., and the U.S. (INWORKS) (Richardson et al. 2015; Hamra et al. 2015; Thierry-Chef et al. 2015).
- We considered that a DREF of 0.63 (0.36, 1.7) that we derived using a risk of solid cancer mortality in the Techa River cohort estimated by Eidemüller et al. (2008) was superseded by a DREF of 0.64 (0.31, 2.7) that we derived using a more recent estimate of the risk of solid cancer mortality in that cohort by Schonfeld et al. (2013).
- DREFs of 0.83 (0.53, 2.0) and 0.48 (0.33, 0.86) for solid cancer mortality and 1.0 (0.65, 2.4) for solid cancer incidence that were based on analyses by Jacob et al. (2009) are included in Table 5.26 for comparison purposes only. We consider that those DREFs represent an independent analysis of multiple sets of estimated risks to radiation workers or members of the public compared with estimated risks in the LSS cohort similar to our analysis.

We also did not include results from analyses by Little and Muirhead (2000, 2004) and Walsh et al. (2004a) that investigated the dependence of an LDEF for solid cancers on the assumed RBE for neutrons in exposures of the LSS cohort. Those analyses were based on DS86 dosimetry, which gave estimated doses from neutrons higher than estimates using DS02 dosimetry, and they suggested that estimates of LDEF do not depend significantly on the assumed neutron RBE (Tables 5.5–5.7).

DREFs that we derived using estimated risks of solid cancer mortality or incidence in the Techa River cohort (Schonfeld et al. 2013; Davis et al. 2015) were included in our analysis to estimate a DDREF for all solid cancers despite concerns about the accuracy of estimated doses, which were based on modeling. Inclusion of those DREFs was based mainly on the consideration that the Techa River cohort is the only cohort consisting of members of the public of all ages in which estimated risks of all solid cancers have been reported.

Differences in estimated LDEFs for all solid cancers that were based on analyses by the various investigators using DS02 dosimetry in the LSS cohort and an LQ model are due to differences in several factors that affected the various analyses of a dose-response. These include, for example, differences in:

- the number of survivors included in the LSS cohort;
- approaches to modeling by different expert groups, including the BEIR VII committee (NRC 2006), RERF (Preston et al. 2007; Ozasa et al. 2012), and UNSCEAR (Little et al. 2008);
- the cancer types included in “all solid cancers” [e.g., in analyses of solid cancer incidence, thyroid and non-melanoma skin cancers were excluded by the BEIR VII committee (NRC 2006) but were included by Preston et al. (2007)];
- the response under study (solid cancer mortality vs incidence);
- the measure of risk analyzed (ERR vs EAR);
- assumed uncertainties in estimated doses to survivors [e.g., a classical measurement error of 30% in analyses by Little et al. (2008) vs 35% in the analysis by Preston et al. (2007)⁸¹];
- whether survivors with an estimated shielded kerma >4 Gy were included in a dose-response analysis [e.g., those survivors were excluded by Little et al. (2008) but were included by Preston et al. (2007) and Ozasa et al. (2012) by truncating estimates of shielded kerma >4 Gy to 4 Gy and calculating doses to those survivors using a method developed by Pierce et al. (2008)];
- the period of follow-up of survivors (1958–1998 for solid cancer incidence vs 1950–2000 or 2003 for solid cancer mortality);
- the range of doses over which the curvature in a dose-response in the LSS cohort was analyzed [e.g., analyses at colon doses of 0–1.5 Gy (NRC 2006) vs 0–2 Gy (Preston et al. 2007; Ozasa et al. 2012) or colon doses at shielded kerma of 0–4 Gy (Little et al. 2008; Ozasa et al. 2012)];
- the method used to estimate an LDEF—i.e., $[1 + (\beta/\alpha)D]$ at 1 Gy vs α_L/α_{LQ} —as in analyses by the BEIR VII committee (NRC 2006) and Ozasa et al. (2012);
- assumptions about the dependence of risks on age at exposure and attained age or time since exposure.

These differences also can affect estimates of DREF.

The bottom portion of Figure 6.2 shows our estimates of 50th percentiles and 90% CIs of LDEF, DREF, or DDREF for specific solid cancers. These estimates, which also are summarized in Table 5.26, are presented for comparison purposes only and were not used in developing a probability distribution of DDREF for all solid cancers. There are relatively few estimates of LDEF, DREF, or DDREF for specific solid cancers; many of those estimates are based on DS86 dosimetry in the LSS cohort; and uncertainties in those estimates generally are larger than uncertainties in estimated LDEFs or DREFs for all solid

⁸¹ The greater the assumed classical measurement error (uncertainty), the greater the correction to increase the slope of a modeled dose-response.

cancers. The large uncertainties in estimates for specific solid cancers were the basis for our conclusion that the use of separate DDREFs for specific cancers, especially breast and thyroid cancer, is not justified.

Once estimates of LDEF and DREF for all solid cancers are selected for inclusion in an analysis to estimate a DDREF, an important consideration is how the different estimates should be combined. One important issue is the relative weights that should be given to estimates of LDEF based on analyses of the curvature in modeled dose-responses in the LSS cohort vs estimates of DREF based on comparisons of estimated risks in radiation workers or members of the public with estimated risks in the LSS cohort. Our judgment is that estimates of LDEF and DREF should be given equal weight in developing a probability distribution of DDREF for all solid cancers. Although there could be unknown biases and complicating factors in estimating DREFs by comparing estimated risks of solid cancers in different populations with different age distributions and conditions of exposure, there also are concerns that extrapolations of observed risks at higher acute doses in the LSS cohort to lower doses where risks are not observable may not be reliable (e.g., Leenhouts and Chadwick 2011).

Our judgment about the relevance of estimates of DREF differs, for example, from the approach used by the BEIR VII committee (NRC 2006) to develop a probability distribution of DDREF, which was based on an analysis of acute dose-responses in the LSS cohort (i.e., an estimate of an LDEF) augmented by data in laboratory animals (Appendix B). A critique of the BEIR VII committee's DDREF by Hoel (2015), who concluded that a reduction in the DDREF of 2 recommended for purposes of radiation protection (control of exposures) by ICRP (2007) and NCRP (1993b) to the committee's best estimate of 1.5 is not justified, also did not take into account estimates of DREF based on comparisons of estimated risks in radiation workers or members of the public and the LSS cohort. However, we think that estimates of DREF must be taken into account if a probability distribution of DDREF that represents the current state of knowledge is to be obtained.

The second important issue in prioritizing estimates of LDEF and DREF for all solid cancers based on data from epidemiological studies is the relative weights that should be given to estimates based on data on cancer incidence vs cancer mortality. As indicated in Table 5.26, most estimates of LDEF or DREF for all solid cancers have been based on data on cancer mortality.

We think that estimates of LDEF and DREF based on data on solid cancer incidence should be given substantially greater weight than estimates based on data on solid cancer mortality. Although there are potential problems in estimating risks of cancer mortality or incidence in any cohort, our judgment was based on several considerations. First, accuracy of disease ascertainment is a greater concern in estimating risks of cancer mortality, because a study subject can have one or more cancers but the cause of death may be a non-cancer effect, such as pneumonia or a fatal accident; i.e., the reported cause of death may not be cancer even when cancer is, or would be, the primary cause. Second, cancer mortality,

but not incidence, can depend on the level and intensity of medical treatment. Third, estimates of cancer mortality generally are less reliable for cancers that usually are non-fatal (e.g., thyroid cancer). We also note that IREP estimates risks of cancer incidence, so use of estimates of LDEF and DREF based on data on cancer incidence is compatible with risk modeling in IREP.

In spite of concerns about estimates of LDEF and DREF based on data on solid cancer mortality noted above, we also think that those estimates should be given substantial weight in developing a probability distribution of DDREF for all solid cancers. Not only are estimates based on data on solid cancer mortality more prevalent, but those estimates also are based on a greater variety of assumptions, including modeling of EARs in addition to ERRs and assumptions about the dependence of risks on age at exposure, attained age, and time since exposure.

Estimates of DREF, LDEF, or DDREF based on data in laboratory animals, as summarized in Table 4.2, are shown in Figure 6.3. These estimates are not used in developing a probability distribution of DDREF for all solid cancers, mainly because of concerns about genetic and epigenetic differences between laboratory animals and humans and their potential effects on estimates of DDREFs. These estimates are presented for purposes of providing information only. However, it also is possible that data on some radiation-induced cancers in animals could inform judgments about a DDREF in humans when data in humans are lacking or highly uncertain. For example, data on bone cancer, which is rare in the LSS cohort (Preston et al. 2007), suggest a threshold in the dose-response.

In the following section, we develop a probability distribution of DDREF for all solid cancers based on estimates of LDEF or DREF for all solid cancers given in Table 6.1 and shown in Figure 6.2 and assumptions about the relative weights that should be given to estimates of LDEF vs DREF and estimates based on data on solid cancer incidence vs mortality. Estimates of LDEF, DREF, or DDREF for specific cancers in humans and estimates based on data in laboratory animals are not used in this analysis.

6.3.2 Development of Preferred Probability Distribution of DDREF

6.3.2.1 Description of procedure; assumptions and results

This section describes the procedure we used to develop a probability distribution of DDREF for all solid cancers on the basis of LDEFs and DREFs for all solid cancers given in Table 6.1 and shown in the top portion of Figure 6.2. Assumptions we used to derive our preferred probability distribution of DDREF and results of applying those assumptions are presented. The following sections investigate the sensitivity of a DDREF distribution to differences in assumptions about the weights given to various estimates of LDEF or DREF and discuss our preferred probability distribution and how it was derived.

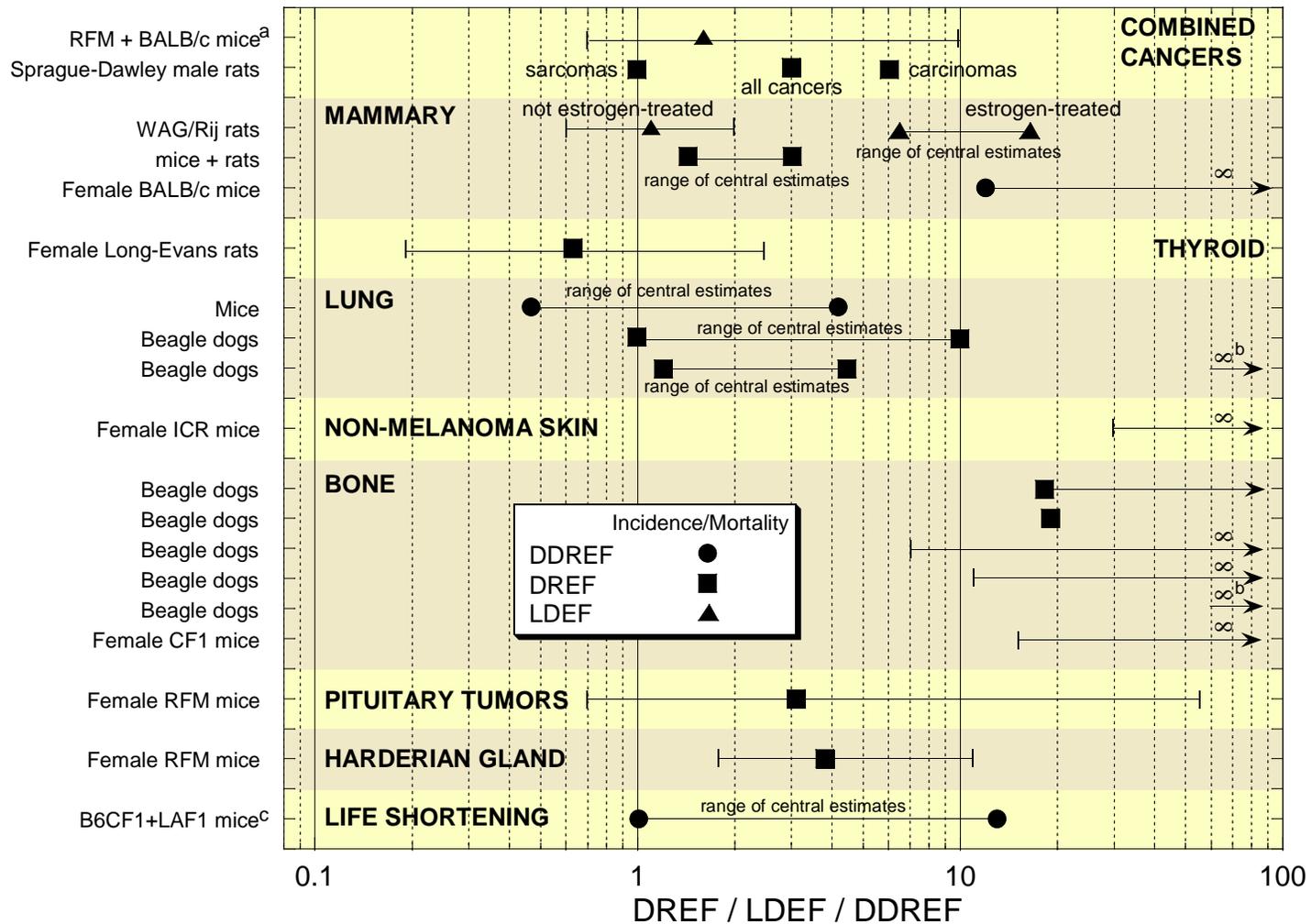


Figure 6.3. Estimates of DREF, LDEF, or DDREF and ranges or CIs based on dose-responses for various cancers and life shortening in laboratory animals (Table 4.2, except as noted). ^aCentral estimate and range based on curvature parameter ($\beta/\alpha \approx 0.4 \text{ Gy}^{-1}$; range $\approx -0.2-6 \text{ Gy}^{-1}$) estimated by BEIR VII committee (NRC 2006) from analysis of dose-responses for myeloid leukemia and Harderian gland, lung, mammary, pituitary, and uterine tumors in mice from acute exposure at doses of 0–1.5 Gy (Section 4.3.4). ^bData from chronic internal exposures indicate existence of practical threshold at total doses of about 5 Gy or higher. ^cEstimates are described in Section 4.3.6.

In developing a probability distribution of DDREF for all solid cancers, we assumed that the LNT dose-response model is correct. An analysis that accounted for the possibility that other models, such as threshold or hormetic dose-responses, are credible would increase the uncertainty in a DDREF to be applied to risks at higher acute doses that are estimated assuming an LNT model. The assumption of an LNT model is based on discussions in Section 3 that indicated that any conclusions about the direction and magnitude of deviations from an LNT model at low doses or low dose rates where a DDREF would be applied are premature. Research on non-targeted and delayed effects of radiation, although not definitive, appears to support our assumption. We also note that IREP and most other approaches to cancer risk assessment assume that the LNT model is correct.

A multi-step procedure and assumptions described below were used to combine the LDEFs and DREFs for all solid cancers given in Table 6.1 and shown in Figure 6.2 to obtain our preferred probability distribution of DDREF for all solid cancers. In all steps in the procedure, probability distributions of LDEF or risk coefficients from which an LDEF or a DREF were calculated were combined using Monte Carlo uncertainty propagation techniques with 10,000 iterations of stratified random sampling.

- **Step 1:** Combined probability distributions of LDEF for solid cancer incidence, LDEF for solid cancer mortality, DREF for solid cancer incidence, and DREF for solid cancer mortality were generated by assigning relative weights described below to the individual distributions given in Table 6.1 and shown in Figure 6.2 (three distributions of LDEF for cancer incidence, six distributions of LDEF for cancer mortality, two distributions of DREF for cancer incidence, and three distributions of DREF for cancer mortality). The result of Step 1 is two distributions of LDEF and two distributions of DREF.

The individual distributions of LDEFs or DREFs were combined based on the following assumptions:

- The combined distribution of LDEF for solid cancer incidence was obtained by giving 25% weight to each of the two distributions based on an analysis by the BEIR VII committee (NRC 2006) and 50% weight to the distribution based on an analysis by Preston et al. (2007); i.e., we give equal weight to LDEFs from the BEIR VII report (NRC 2006) and Preston et al. (2007).
- The combined distribution of LDEF for solid cancer mortality was obtained by giving 25% weight to each of the two distributions based on analyses by Little et al. (2008), 15% weight to each of the two distributions based on an analysis by Ozasa et al. (2012) at doses of 0–2 Gy, and 10% weight to each of the two distributions based on an analysis by Ozasa et al. (2012) at doses of 0–3 Gy; i.e., we give equal weight to LDEFs from Little et al. (2008) and Ozasa et al. (2012).

- The combined distribution of DREF for solid cancer incidence was obtained by giving 80% weight to the distribution based on an analysis of risks to U.K. radiation workers by Muirhead et al. (2009) and 20% weight to the distribution based on an analysis of risks in the Techa River cohort by Davis et al. (2015).
- The combined distribution of DREF for solid cancer mortality was obtained by giving 40% weight to the distribution based on an analysis of risks to U.K. radiation workers by Muirhead et al. (2009), 40% weight to the distribution based on an analysis of risks to radiation workers in France, the U.K., and the U.S. (INWORKS) by Richardson et al. (2105), and 20% weight to the distribution based on an analysis of risks in the Techa River cohort by Schonfeld et al. (2013).

In obtaining the combined distribution of LDEF for solid cancer mortality, we give substantial weight to the two estimates based on an analysis by Ozasa et al. (2012) at doses of 0–3 Gy, even though those investigators preferred an estimate based on an analysis at doses of 0–2 Gy, in order to account for the effect on LDEF of the dose range selected for analysis. In obtaining the combined distributions of DREF for solid cancer incidence or mortality, the low weights of 20% given to DREFs that were based on analyses of risks in the Techa River cohort reflect our concerns about uncertainties in estimated doses and other issues discussed in Section 5.2.2.3. We also note that the analyses of risks of solid cancer mortality in workers by Muirhead et al. (2009) and Richardson et al. (2015) are not completely independent when data in U.K. workers from Muirhead et al. (2009) were used in the analysis by Richardson et al. (2009).

The approaches to representing the LDEFs and DREFs in Table 6.1 that were used as inputs to the calculations in Step 1 of our procedure are described as follows.

Distributions of the LDEF from Preston et al. (2007), the LDEF of 1.5 (1.0, 2.3) from the BEIR VII report (NRC 2006), and the LDEF of 3.2 (1.2, 8.3) from Ozasa et al. (2012) were based on a reported curvature parameter, β/α , in a modeled LQ dose-response in the LSS cohort and its uncertainty and calculated as $[1 + (\beta/\alpha)]$. In those cases, we represented a reported β/α by a Weibull distribution with mode at the reported MLE. The same assumption was used to represent the distribution of the LDEF of 1.5 (0.9, 2.4) from the BEIR VII report (NRC 2006) that was estimated as the ratio α_L/α_{LQ} based on linear and linear-quadratic fits to a dose-response in the LSS cohort.

In contrast, distributions of the two LDEFs from Little et al. (2008) and the LDEF of 1.11 (0.94, 1.48) from Ozasa et al. (2012), which were based on our estimates of the curvature parameter, β/α , and calculated as $[1 + (\beta/\alpha)]$, were not obtained by representing β/α by particular distributions (e.g., Weibull). Rather, reported or estimated probability distributions of α and β , with an assumed correlation coefficient of -1 (Table 5.4, footnotes *j* and *k*), were entered separately into the calculations in Step 1 as Weibull distributions with modes at the reported MLEs. Similarly, the LDEFs of 2.0 (1.0, 6.8) and 1.16 (0.77,

1.90) from Ozasa et al. (2012), which were based on our estimates of the ratio α_L/α_{LQ} , were not represented by particular distributions, but estimated probability distributions of α_L and α_{LQ} were entered separately into the calculations as Weibull distributions with modes at the reported MLEs.

Similarly, all DREFs were not represented by particular distributions, but probability distributions of ERRs in the LSS cohort and ERRs in cohorts of radiation workers or the Techa River cohort given in Table 5.11 or Section 5.2.2.3 that were used to estimate DREFs were entered separately into the calculations in Step 1 as Weibull or normal distributions with modes at the reported MLEs.

Because the ratio of two Weibull distributions is not well represented by a Weibull distribution or any other commonly used distributions, the approaches described above give a better representation of all probability distributions that were obtained in later steps in our procedure that involve combinations of LDEFs or DREFs. Once the distributions of LDEFs or distributions of parameters that we used to estimate LDEFs and the distributions of ERRs that we used to estimate DREFs were entered into the calculations in Step 1, the resulting distributions from each step were carried through to the end of the procedure without making any assumptions about their form. This approach gives the best representation of the probability distribution of DDREF for all solid cancers based on the assumed input distributions.

- **Step 2:** The probability distributions of LDEF for solid cancer mortality and incidence obtained in Step 1 were combined by assigning weights of 66.7% to the incidence-based distribution and 33.3% to the mortality-based distribution; i.e., relative weights of 2:1 for the incidence- and mortality-based distributions of LDEF were assumed. The same weights were used to combine the probability distributions of DREF for solid cancer mortality and incidence obtained in Step 1. The result of Step 2 is a single distribution of LDEF and a single distribution of DREF.

The rationale for our judgment that the weight given to LDEFs or DREFs for solid cancer incidence should be twice the weight given to LDEFs or DREFs for solid cancer mortality is discussed in the previous section. In essence, estimates for solid cancer incidence are preferable, but estimates for solid cancer mortality are more prevalent and are based on a greater variety of assumptions in modeling excess risks in the LSS cohort. The sensitivity of the probability distribution of DDREF to the relative weights assigned to incidence- and mortality-based LDEFs or DREFs is investigated in the following section.

- **Step 3:** The probability distributions of LDEF and DREF obtained in Step 2 were combined by assigning equal weight to each distribution. The result of Step 3 is a single distribution of DDREF for all solid cancers.

The procedure in Step 3 reflects our judgment that estimates of LDEF based on analyses of the curvature in dose-responses in the LSS cohort and estimates of DREF based on comparisons of estimated risks in radiation workers or members of the public with estimated risks and the LSS cohort are of equal relevance in estimating a DDREF for all solid cancers.

- **Step 4:** In the final step, the probability distribution of DDREF obtained in Step 3 was truncated by removing all values less than 0.2 and greater than 20.

Truncation of the distribution obtained in Step 3 was based on our judgment that the weight of evidence from all the data in humans and animals, assuming an LNT model, is that a DDREF for all solid cancers outside the range of 0.2–20 is not credible. In making this judgment, we did not consider data on bone cancer in animals shown in Figure 6.3, which suggest a threshold in the dose-response. The truncation procedure in Step 4 removed only about 1.3% of the values in the probability distribution obtained in Step 3. Most of the values removed were <0.2 , including DDREFs <0 that resulted from negative values in the lower tails of assumed Weibull distributions used as input in Step 1.

Results obtained by applying Steps 1–4 using assumptions about probability distributions of LDEFs or probability distributions of the constituent parameters of LDEFs and DREFs described in Step 1 are presented in Table 6.2. In Step 4, truncation of the probability distribution of DDREF obtained in Step 3 had some effect in reducing uncertainty (narrowing the CIs) of our preferred distribution. This is an expected result when removing the tails narrows a probability distribution. However, the effect was not large when only a small fraction of the distribution obtained in Step 3 was removed by truncation.

6.3.2.2 Sensitivity analysis

The stepwise procedure we used to derive our preferred probability distribution of DDREF for all solid cancers described in the previous section involves assumptions about the weights given to individual LDEFs and DREFs in Step 1 of the procedure and the weights given to the combined incidence- and mortality-based distributions of LDEF and DREF in Step 2. This section describes an analysis to investigate the sensitivity of the probability distribution of DDREF we obtained to different assumptions about the weights given to different distributions of LDEFs and DREFs in Steps 1 and 2. In these alternatives, no changes were made in the assumptions in Steps 3 and 4.

As described below three alternative scenarios were included in our sensitivity analysis.

Table 6.2. Percentiles of probability distributions of LDEF, DREF, and DDREF for all solid cancers calculated using stepwise procedure for combining probability distributions of LDEF or DREF from epidemiological studies to obtain preferred DDREF distribution^a

Step in procedure	Type of combined estimate	Percentile of probability distribution				
		2.5th	5th	50th	95th	97.5th
Step 1 ^b	LDEF for cancer incidence (<i>n</i> = 3)	0.89	0.96	1.4	2.2	2.4
	LDEF for cancer mortality (<i>n</i> = 6)	0.92	0.97	1.5	5.2	7.0
	DREF for cancer incidence (<i>n</i> = 2)	0.31	0.41	1.2	5.2	8.8
	DREF for cancer mortality (<i>n</i> = 3)	0.26	0.31	0.72	3.1	5.4
Step 2	LDEF for cancer incidence and mortality obtained by combining LDEF distributions from Step 1, with weights of 0.667 and 0.333 (relative weights of 2:1) assigned to incidence- and mortality-based distributions	0.90	0.96	1.4	3.0	4.5
	DREF for cancer incidence and mortality obtained by combining DREF distributions from Step 1, with weights of 0.667 and 0.333 (relative weights of 2:1) assigned to incidence- and mortality-based distributions	0.28	0.36	1.0	4.7	7.7
Step 3	DDREF obtained by combining LDEF and DREF distributions from Step 2, with equal weight assigned to each distribution	0.36	0.44	1.3	3.8	6.1
Step 4	Preferred DDREF distribution obtained by truncating distribution from Step 3 by removing values <0.2 and >20	0.39	0.47	1.3	3.6	5.6

^a Stepwise procedure and assumptions used in obtaining preferred probability distribution of DDREF are described in Section 6.3.2.1; probability distributions of LDEF or DREF for all solid cancers obtained from epidemiological studies are summarized in Table 6.1 and shown in Figure 6.2.

^b Entries in parentheses in Step 1 are number of distributions of LDEF or DREF that were combined in each calculation.

- Alternative 1: In Step 2, weights of 80% and 20% (relative weights of 4:1) were assigned to the incidence- and mortality-based distributions of LDEF and DREF obtained in Step 1, rather than the assigned weights of 66.7% and 33.3% (relative weights of 2:1) in our preferred analysis.
- Alternative 2: In Step 2, equal weights were assigned to the incidence- and mortality-based distributions of LDEF and DREF obtained in Step 1.

Alternatives 1 and 2 investigate the sensitivity of DDREF to different assumptions about the relevance of LDEFs and DREFs for cancer incidence compared with LDEFs and DREFs for cancer mortality.

- Alternative 3: In Step 1, individual probability distributions of LDEF or DREF for cancer incidence or mortality were combined by weighting each LDEF or DREF by the reciprocal of the square of its relative error, which was calculated as the ratio $(95^{\text{th}} \text{ %-tile} - 5^{\text{th}} \text{ %-tile}) / (50^{\text{th}} \text{ %-tile})$ using the percentiles of each distribution summarized in Table 6.1.

In Alternative 3, greater weight is given to individual estimates of LDEF or DREF with smaller uncertainties and lesser weight to estimates with larger uncertainties; i.e., it is assumed that LDEFs and DREFs with the smallest uncertainties are the most informative in estimating a DDREF. For example, in combining individual estimates of LDEF for cancer mortality in Alternative 3, weights of 61% and 16% are given to the LDEFs based on an analysis by Ozasa et al. (2012) at a shielded kerma of 0–4 Gy and calculated as $[1 + (\beta/\alpha)]$ and α_L/α_{LQ} , respectively, weights of only 3% and 2% are given to the corresponding LDEFs based on an analysis by Ozasa et al. (2012) at colon doses of 0–2 Gy preferred by those investigators, and weights of 11% and 7% are given to the LDEFs based on analyses by Little et al. (2008). The other significant change in weights in Alternative 3 compared with our preferred assumptions involved the DREFs for cancer incidence, where the weight given to the DREF based on an estimated risk in the Techa River cohort increased from 20% to 64% and the weight given to the DREF based on an estimated risk in U.K. workers decreased to 36%.

Based on our judgment that estimates of LDEF and DREF are of equal relevance, we did not investigate the sensitivity of the probability distribution of DDREF to the assumption in Step 3 about the relative weights assigned to LDEFs and DREFs.

Probability distributions of DDREF obtained in Step 4 of the three alternative scenarios described above are compared with our preferred distribution in Table 6.3. One observation is that the estimated 50th percentile of DDREF did not change in Alternatives 1 and 2 and decreased by only about 15% in Alternative 3. Other aspects of these comparisons are summarized as follows.

Table 6.3. Percentiles of probability distributions of DDREF for all solid cancers based on alternative scenarios for combining probability distributions of LDEF or DREF from epidemiological studies compared with preferred DDREF distribution^a

Scenario description	Percentile of probability distribution ^b				
	2.5th	5th	50th	95th	97.5th
Preferred DDREF distribution ^c	0.39	0.47	1.3	3.6	5.6
Alternative 1 – Weights of 80% and 20% (relative weights of 4:1) assigned to incidence- and mortality-based distributions of combined LDEF and combined DREF in Step 2 of procedure	0.41	0.51	1.3	3.5	5.3
Alternative 2 – Equal weight assigned to incidence- and mortality-based distributions of combined LDEF and combined DREF in Step 2 of procedure	0.37	0.44	1.3	3.7	5.6
Alternative 3 – Individual LDEFs or DREFs for cancer incidence or mortality combined in Step 1 of procedure by weighting each estimate by reciprocal of square of its relative error ^d	0.34	0.39	1.1	2.5	3.4

^a Alternative scenarios are described in Section 6.3.2.2.

^b Percentiles of probability distributions obtained in Step 4 of procedure for each scenario.

^c Assumptions used to obtain preferred probability distribution of DDREF are summarized in Table 6.2.

^d Relative error in each LDEF or DREF was calculated as the ratio (95th %-tile – 5th %-tile)/50th %-tile using percentiles in Table 6.1.

In Alternative 1, in which the weight assigned in Step 2 to the incidence-based LDEF and DREF obtained in Step 1 was increased, the resulting DDREF has a slightly smaller uncertainty (narrower CIs) than in the preferred analysis. In Alternative 2, in which the weight assigned to the incidence-based LDEF and DREF was decreased, the resulting DDREF has a slightly larger uncertainty (broader CIs) than in the preferred analysis. However, in neither alternative did the changes in weights result in a substantial change in the DDREF distribution.

In Alternative 3, in which individual probability distributions of LDEF or DREF for cancer incidence or mortality were combined in Step 1 by weighting each LDEF or DREF by the reciprocal of the square of its relative error, the resulting DDREF distribution is shifted toward lower values, with the largest effect occurring at the upper limits of 90% and 95% CIs, and the uncertainty in DDREF is smaller (narrower CIs) than in the preferred analysis. These results are mainly a consequence of the weights assigned to the LDEFs for cancer mortality and DREFs for cancer incidence in Alternative 3 compared with the preferred analysis, as described above.

In our sensitivity analysis, we did not investigate the effect of different assumptions about the weights assigned to probability distributions of the combined LDEF and DREF in Step 3 of our procedure. The assumption that equal weight should be given to those two distributions is based on our belief that a probability distribution of DDREF for solid cancers that represents the current state of knowledge cannot be obtained without giving full consideration to estimates of DREF based on comparisons of risks in cohorts that received chronic or protracted exposure with risks from acute exposure in the LSS cohort. We think it is insufficient to rely exclusively on estimates of LDEF based on analyses of the curvature in dose-responses in the LSS cohort. Estimates of LDEF and DREF for all solid cancers summarized in Table 6.1 and Figure 6.2 and other estimates in Table 5.26 that were not used in our analysis suggest that DREF tends to be less than LDEF, although the difference is not significant when uncertainties are taken into account. Consequently, giving greater weight to LDEFs than we assumed in our analysis would tend to result in an increase in DDREF. However, any increase would not be significant.

We also did not vary our assumption about truncating the probability distribution of DDREF by eliminating values <0.2 and >20 in Step 4 of our procedure. The data in Figures 6.2 and 6.3 indicate to us that narrowing the range of credible values substantially (e.g., by excluding values >10) would not be justified. We also think that there is little justification for broadening the range of credible values, e.g., by including values as low as 0.1 and as high as 30. Furthermore, results in Table 6.2 suggest that any changes in the truncation procedure that might be justified should not have a significant effect on the resulting DDREF distribution.

6.3.2.3 Discussion of approach to obtaining preferred DDREF distribution

We recognize that assumptions about the weights to be given to various estimates of LDEF or DREF for cancer incidence or mortality in developing a probability distribution of DDREF for all solid cancers are largely a matter of judgment. Our assumptions were based on the following considerations.

We think that the assumption that LDEFs and DREFs based on data on solid cancer incidence should be given twice the weight as LDEFs and DREFs based on data on solid cancer mortality strikes a reasonable balance between a preference for developing a probability distribution of DDREF based on data on cancer incidence and the reality that there are fewer incidence-based estimates and, furthermore, that mortality-based estimates represent a greater variety of assumptions in modeling excess risks in the LSS cohort. We think that weighting incidence-based LDEFs and DREFs as much as four times higher than mortality-based estimates gives too little weight to the greater number and variety of mortality-based estimates, and that assigning equal weight to incidence- and mortality-based LDEFs and DREFs is not

justified when incidence-based estimates are preferable, especially in developing a DDREF for use in IREP, which estimates PC/AS on the basis of an estimated ERR for cancer incidence.

Although the approach in Alternative 3, which gives the greatest weight to LDEFs and DREFs with the smallest uncertainties, would be preferred by some experts [e.g., in the analyses by Jacob et al. (2009) discussed in Section 5.2.2.4], we think that the weighting scheme in Alternative 3 is difficult to justify. Such a scheme is most appropriate when individual estimates of LDEF or DREF are statistically independent. However, this condition is not met when all estimates of LDEF or DREF included in our analysis are based on much the same data in the LSS cohort, including estimates of dose based on DS02 dosimetry and follow-up of rates of cancer incidence or mortality for similar periods. For example, as discussed in Section 6.3.1, differences in 50th percentiles and 90% CIs of the six LDEFs for solid cancer mortality shown in Figure 6.2 are largely a consequence of differences in several assumptions or other factors that affected modeling of nearly the same data on dose-responses in the LSS cohort, rather than a statistical independence of those LDEFs. As suggested by a comparison with results from our preferred analysis summarized in Table 6.3, we think that the weighting scheme in Alternative 3 would tend to result in an artificial reduction in the uncertainty in DDREF based on our state of knowledge.

6.3.2.4 Discussion of alternative approach to combining distributions of LDEF or DREF

In Step 1 of the procedure described in Section 6.3.2.1, multiple distributions of LDEF or DREF for solid cancer incidence or mortality were combined by calculating a weighted average of the individual distributions in each case. For example, in calculating a combined probability distribution of LDEF for solid cancer mortality from the six distributions included in our analysis, a weight of 25% was assigned to each of the two LDEF distributions based on analyses by Little et al. (2008), and weights of 15% or 10% were assigned to each of the four distributions based on analyses by Ozasa et al. (2012). The six distributions of LDEF for solid cancer mortality then were combined in the following way. Of the 10,000 iterations of Monte Carlo sampling from the individual distributions, 2,500 iterations gave random samples from the distribution based on the analysis by Little et al. using an ERR model, 2,500 iterations gave random samples from the distribution based on the analysis by Little et al. using an EAR model, 1,500 iterations gave random samples from the distribution calculated as $[1 + (\beta/\alpha)D]$ at 1 Gy based on the analysis by Ozasa et al. at colon doses of 0–2 Gy, 1,500 iterations gave random samples from the distribution calculated as α_L/α_{LQ} based on the analysis by Ozasa et al. at colon doses of 0–2 Gy, 1,000 iterations gave random samples from the distribution calculated as $[1 + (\beta/\alpha)D]$ at 1 Gy based on the analysis by Ozasa et al. at a shielded kerma of 0–4 Gy, and 1,000 iterations gave random samples from the distribution calculated as α_L/α_{LQ} based on the analysis by Ozasa et al. at a shielded kerma of 0–4 Gy.

In this approach, only a single probability distribution of LDEF or DREF for solid cancer incidence or mortality was sampled at random in each iteration of Monte Carlo sampling.

An alternative approach to combining (averaging) multiple probability distributions of LDEF for solid cancer incidence or mortality could be considered. This approach is based on an assumption that the individual distributions of LDEF for either endpoint, all of which were based on analyses of the curvature in dose-responses in the LSS cohort, represent results of analyses of the same data, in which case the individual distributions would not be independent of one another. On the basis of this assumption, each individual distribution would be sampled at random in each iteration of Monte Carlo sampling and a weighted average of the sampled values would be calculated. In the example of an LDEF for solid cancer mortality discussed above, each iteration of random sampling would give an LDEF from each of the six individual distributions, and a weighted average of those samples would be calculated by weighting two of the samples by 25% each, two samples by 15% each, and two samples by 10% each. The combined probability distribution of LDEF for solid cancer mortality then would be formed from 10,000 weighted averages of random samples. This approach also could be used to generate a probability distribution of LDEF for solid cancer incidence from the three individual distributions summarized in Table 6.1. Since a weighted average of samples from individual distributions in a single iteration often would include lower values from some distributions and higher values from others, this approach would result in smaller uncertainties in combined distributions of LDEFs (narrower CIs) than the approach we used in our analysis. This approach would not be appropriate in combining (averaging) individual distributions of DREF for solid cancer incidence or mortality that were included in our analysis, essentially because those distributions do not represent results of analyses of the same data in cohorts that received chronic or protracted exposures at low dose rates and, therefore, are independent to a significant degree.

In our analysis to develop a probability distribution of DDREF for all solid cancers, we did not think it was appropriate to use the alternative approach to combining individual probability distributions of LDEF for solid cancer incidence or mortality described above, essentially because the individual distributions for either endpoint were not based on analyses of the same data in the LSS cohort. For example, the LDEF for solid cancer incidence based on the analysis by the BEIR VII committee (NRC 2006) excluded thyroid and nonmelanoma skin cancers and used data at colon doses of 0–1.5 Gy in modeling a dose-response, whereas the LDEF based on the analysis by Preston et al. (2007) included thyroid and nonmelanoma skin cancers and used data at colon doses of 0–2 Gy. In the case of an LDEF for solid cancer mortality, there were differences in the dose range over which a dose-response was modeled, the period of follow-up of the LSS cohort, and the dependence of modeled risks on age at exposure and attained age or time since exposure (Table 5.4).

6.3.3 Depiction of Preferred Probability Distribution of DDREF and Lognormal Equivalent

The probability distribution of DDREF for all solid cancers developed in our analysis is shown in more detail in Figure 6.4. The top portion of the figure shows the probability distribution in the form of a histogram in which each rectangle represents the fraction of the distribution in intervals of DDREF of 0.1. This depiction does not include the upper tail of the distribution at values >7. The bottom portion of Figure 6.4, which includes the entire distribution, shows the distribution of the natural logarithm of DDREF in the form of a probability plot (Chambers et al. 1983), with each circle giving a DDREF that resulted from a single random sampling of the input distributions of LDEFs, DREFs, and ERRs in Step 1 of our procedure and propagation of the combined distributions through Steps 2–4. If the probability distribution of DDREF were lognormal, the circles in this plot would lie on a straight line.

Also shown by a solid line in Figure 6.4 is a lognormal distribution that gives the best fit to our preferred probability distribution of DDREF. A lognormal distribution gives a significantly better fit than any other distribution we tested (e.g., Weibull, extreme value, gamma, logistic, or exponential). While the probability distribution of DDREF obtained in our analysis could be entered directly into IREP, the equivalent lognormal distribution would be easier to implement in most cancer risk assessments that account for uncertainty. Deviations of the best-fit lognormal distribution from our preferred distribution are most pronounced at percentiles above the 95th and at the very lowest percentiles (below about 0.2), where the lognormal distribution underestimates our preferred distribution; underestimation of a DDREF results in overestimation of risks and PC/AS of diagnosed cancers. A lognormal distribution gives a good fit to the DDREF distribution between the 0.2nd and 95th percentiles.

6.3.4 Summary of Preferred Probability Distribution of DDREF; Importance of Harmonic Mean

Our preferred probability distribution of DDREF for all solid cancers and its representation by a lognormal distribution are summarized in Table 6.4. In addition to the selected percentiles, the harmonic mean of the two distributions is given. The importance of the harmonic mean is described as follows.

The harmonic mean (HM) of a set of n numbers $\{a_1, a_2, a_3, \dots, a_n\}$, where a_i denotes the i th value in a probability distribution of DDREF, is given by

$$\text{HM} = \frac{n}{\frac{1}{a_1} + \frac{1}{a_2} + \frac{1}{a_3} + \dots + \frac{1}{a_n}} = \frac{1}{\frac{1}{n} \left[\frac{1}{a_1} + \frac{1}{a_2} + \frac{1}{a_3} + \dots + \frac{1}{a_n} \right]} .$$

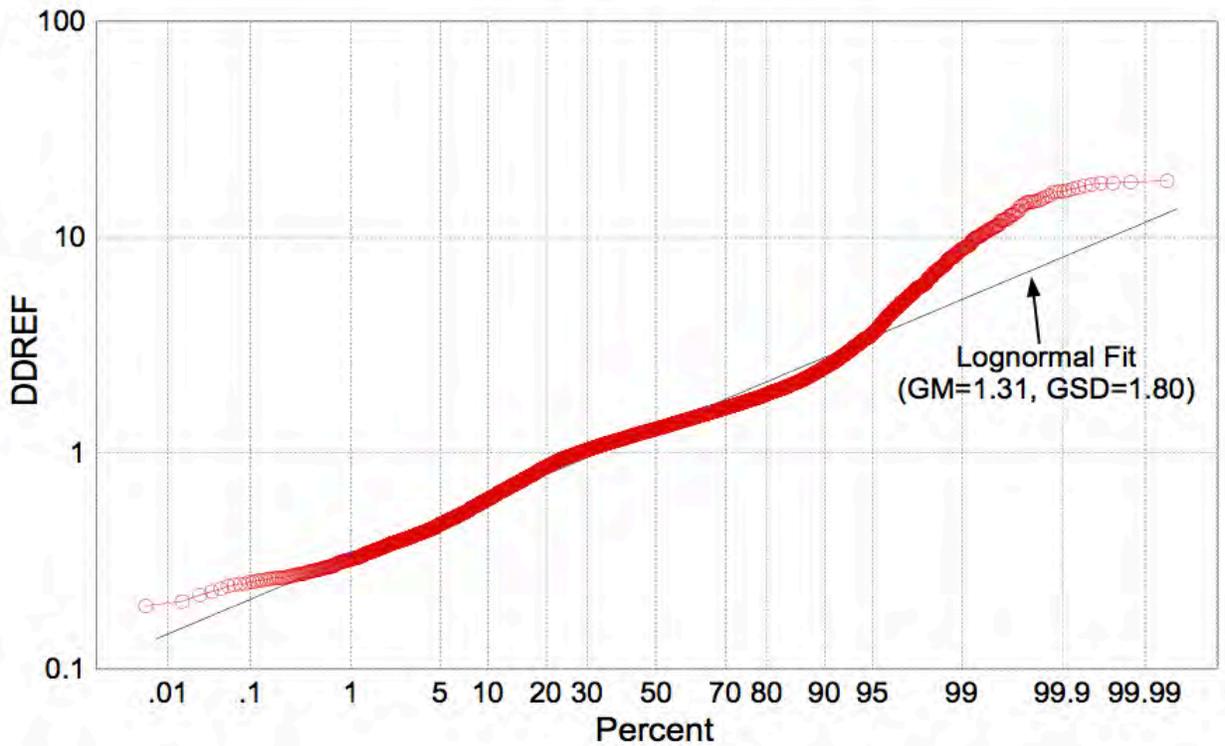
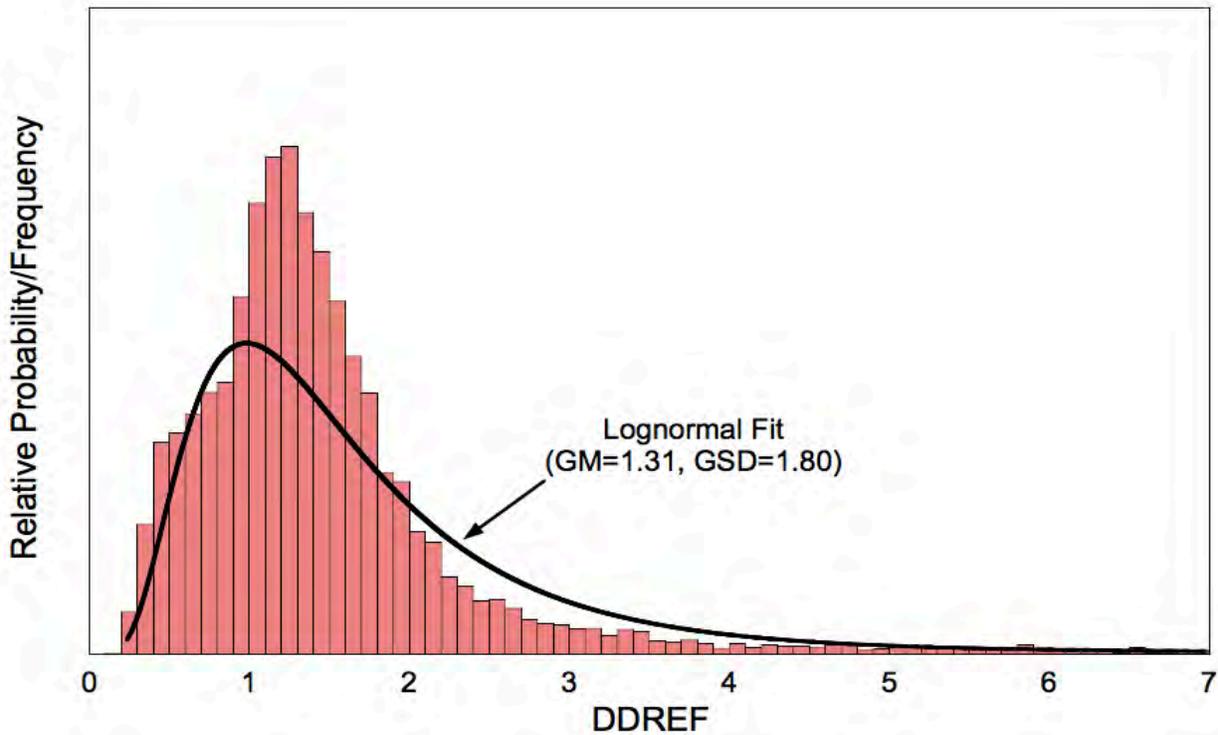


Figure 6.4. Representations of preferred DDREF distribution for all solid cancers as probability (frequency) distribution (top) and log-probability plot (bottom). Solid lines are best-fit lognormal distribution with indicated geometric mean (GM) and geometric standard deviation (GSD).

Table 6.4. Summary of preferred probability distribution of DDREF for all solid cancers and lognormal distribution that gives best fit to DDREF distribution

Distribution	Percentile of probability distribution					Harmonic mean ^a
	2.5th	5th	50th	95th	97.5th	
Preferred DDREF distribution ^b	0.39	0.47	1.3	3.6	5.6	1.1
Best-fit lognormal distribution (GM = 1.31, GSD = 1.80)	0.41	0.50	1.3	3.4	4.2	1.1

^a When probability distribution of DDREF is used in cancer risk assessments, arithmetic mean of uncertain estimate of risk at low doses or low dose rates is proportional to reciprocal of harmonic mean of DDREF (Section 6.3.4).

^b Preferred probability distribution is distribution summarized in Table 6.2.

That is, the harmonic mean is the reciprocal of the arithmetic mean of the reciprocals of the DDREFs in a distribution. The harmonic mean is less than the arithmetic mean and depends more strongly on the lowest values in a distribution, whereas the arithmetic mean depends more strongly on the highest values.

The importance of the harmonic mean of a probability distribution of DDREF is a consequence of DDREF appearing as a divisor in an equation to estimate cancer risks per unit dose at low doses or low dose rates (R_L) on the basis of estimated risks per unit dose at high acute doses (H); i.e., $R_L = R_H/DDREF$. Because DDREF is a divisor, the arithmetic mean of R_L , which is an important and commonly used measure of central tendency, is not proportional to the reciprocal of the arithmetic mean of DDREF. Rather, the arithmetic mean of R_L is proportional to the reciprocal of the harmonic mean of DDREF. Inappropriate use of the reciprocal of the arithmetic mean of the probability distribution of DDREF would result in an underestimate of the arithmetic mean of R_L .

For example, if the harmonic mean of a probability distribution of DDREF is 1.1, as in our preferred distribution and the best-fit lognormal distribution, the arithmetic mean of R_L is $1/1.1 = 0.91$ times the arithmetic mean of R_H . Thus, on average, the reduction in risks per unit dose at low doses or low dose rates indicated by our DDREF distribution is rather modest (about 10%). If the arithmetic mean of DDREF, which is 1.6 in the best-fit lognormal distribution, were used instead, the imputed reduction in the average risk per unit dose would be a factor of $1/1.6 = 0.63$. We again emphasize, however, that use of the arithmetic mean of DDREF to estimate the mean (expected value) of a cancer risk is inappropriate.

6.3.5 Comparison of Preferred Probability Distribution of DDREF with Distributions in IREP

The main purpose of this study was to provide NIOSH with a scientific basis for revising the probability distributions of DDREF for solid cancers currently used in IREP (Section 1.1.1, Figure 1.2).

An important concern for NIOSH is whether the probability distribution of DDREF for all solid cancers developed in this report would result in larger or smaller estimates of the 99th percentile of an uncertain ERR and PC/AS of diagnosed cancers associated with given doses to exposed individuals than the distributions currently used in IREP; PC/AS is calculated in IREP as $ERR/(ERR + 1)$. Eligible claims for compensation for cancer in nuclear energy workers in the U.S. that are adjudicated on the basis of estimated doses generally are granted when the 99th percentile of an uncertain PC/AS is at least 50%.

It is apparent that the 99th percentile of PC/AS that would be calculated using our preferred probability distribution of DDREF for solid cancers would be greater than the 99th percentile calculated using the probability distributions shown in Figure 1.2. The main reasons for this conclusion are that, as indicated in Table 6.4, nearly 5% of the values in our preferred DDREF distribution are less than the minimum DDREF of 0.5 in the distributions shown in Figure 1.2 and, as indicated in Figure 6.4, a much higher fraction of the values in our distribution (nearly 30%) are <1. In addition, the harmonic mean of our DDREF distribution (1.1) is less than the harmonic means of the distributions shown in Figure 1.2 (1.49 for solid cancers other than breast and thyroid and 1.36 for breast and thyroid cancer), so that the arithmetic mean of PC/AS obtained using our distribution would be greater than the arithmetic mean obtained using the distributions in Figure 1.2.

6.4 CONSIDERATIONS ON USE OF RISK RATIO IN CANCER RISK ASSESSMENTS

In an analysis discussed in Section 5.2.2.4 and summarized in Tables 5.12 and 5.13, Jacob et al. (2009) compared estimates of ERR/Gy for cancer incidence or mortality in several cohorts of workers or members of the public that received chronic or protracted exposures with matched estimates of ERR/Gy in the LSS cohort. However, instead of estimating DDREFs (i.e., DREFs) as ratios of an ERR/Gy in the LSS cohort to an ERR/Gy in a cohort of workers or members of the public, Jacob et al. calculated reciprocals of DDREFs, i.e., ratios of an ERR/Gy in a cohort of workers or members of the public to an ERR/Gy in the LSS cohort, which were referred to as “risk ratios.” Using a risk ratio (RR), a cancer risk per unit dose at low doses or low dose rates would be estimated as the product of a risk per unit dose at high acute doses and a risk ratio [$R_L = R_H \times RR$], rather than a risk per unit dose at high acute doses divided by a DDREF [$R_L = R_H/DDREF$].

Jacob et al. (2009) chose to calculate risk ratios, rather than DDREFs, because several probability distributions of ERR/Gy in cohorts of workers had negative lower limits of 90% or 95% CIs and, therefore, included the value zero, which would result in a DDREF that is undefined; i.e., the probability distribution of DDREF would be unstable. Since lower limits of CIs of the probability distributions of ERR/Gy in the LSS cohort were well above zero, risk ratios of infinity would not be calculated.

There is an additional concern about calculating a DDREF of infinity when a probability distribution of an ERR/Gy in a population that received chronic or protracted exposures includes the value zero. As the uncertain ERR in the denominator of the ratio used to calculate a DDREF approaches zero from positive values, DDREF approaches $+\infty$. However, as that ERR approaches zero from negative values, DDREF approaches $-\infty$ and, thus, there is a discontinuity in the mapping of ERR to DDREF. While this discontinuity does not lead to difficulties in calculating ratios of ERRs (i.e., the resulting probability distribution of DDREF is continuous), it is a concern at a conceptual level.

We agree with Jacob et al. (2009) that use of a risk ratio in cancer risk assessments is advantageous, compared with using a DDREF, when a risk assessment accounts for uncertainty in a risk ratio or DDREF and the probability distribution of either modifying factor includes the value zero. In addition to the advantages noted above, the mean risk per unit dose at low doses or low dose rates would be proportional to the arithmetic mean of a risk ratio, rather than the reciprocal of the harmonic mean of DDREF.

The probability distribution of the risk ratio corresponding to our preferred probability distribution of DDREF for all solid cancers and its representation by a best-fit lognormal distribution are shown in Figure 6.5 and summarized in Table 6.5.⁸² As expected on the basis of the probability plot in Figure 6.4, deviations of the best-fit lognormal distribution from the distribution of the risk ratio are most pronounced at the 5th percentile and below and at the very highest percentiles (above about the 99.8th), where the lognormal distribution gives higher estimates of cancer risks and PC/AS. In contrast to the frequency distribution in Figure 6.4, the entire distribution of DDREF is included in the top portion of Figure 6.5.

6.5 SUMMARY AND CONCLUSIONS

On the basis of analyses of dose-responses for solid cancer incidence or mortality in the LSS cohort and cohorts of radiation workers or members of the public, we developed a probability distribution of DDREF for all solid cancers that is intended to represent the current state of knowledge of this uncertain quantity. Although the DDREF distribution developed in this report is intended for use in any future revision of IREP, which calculates probability distributions of ERR associated with given doses of ionizing radiation and PC/AS of diagnosed cancers in exposed individuals (Land et al. 2003a; Kocher et al. 2008), our DDREF distribution also is intended to be suitable for use in any cancer risk assessments that account for uncertainty. To this end, our intention was to develop an unbiased representation of an uncertain DDREF for all solid cancers, i.e., a probability distribution that would not intentionally lead to over- or underestimates of cancer risks and PC/AS.

⁸² The reciprocal of a lognormal distribution also is a lognormal distribution with the same GSD.

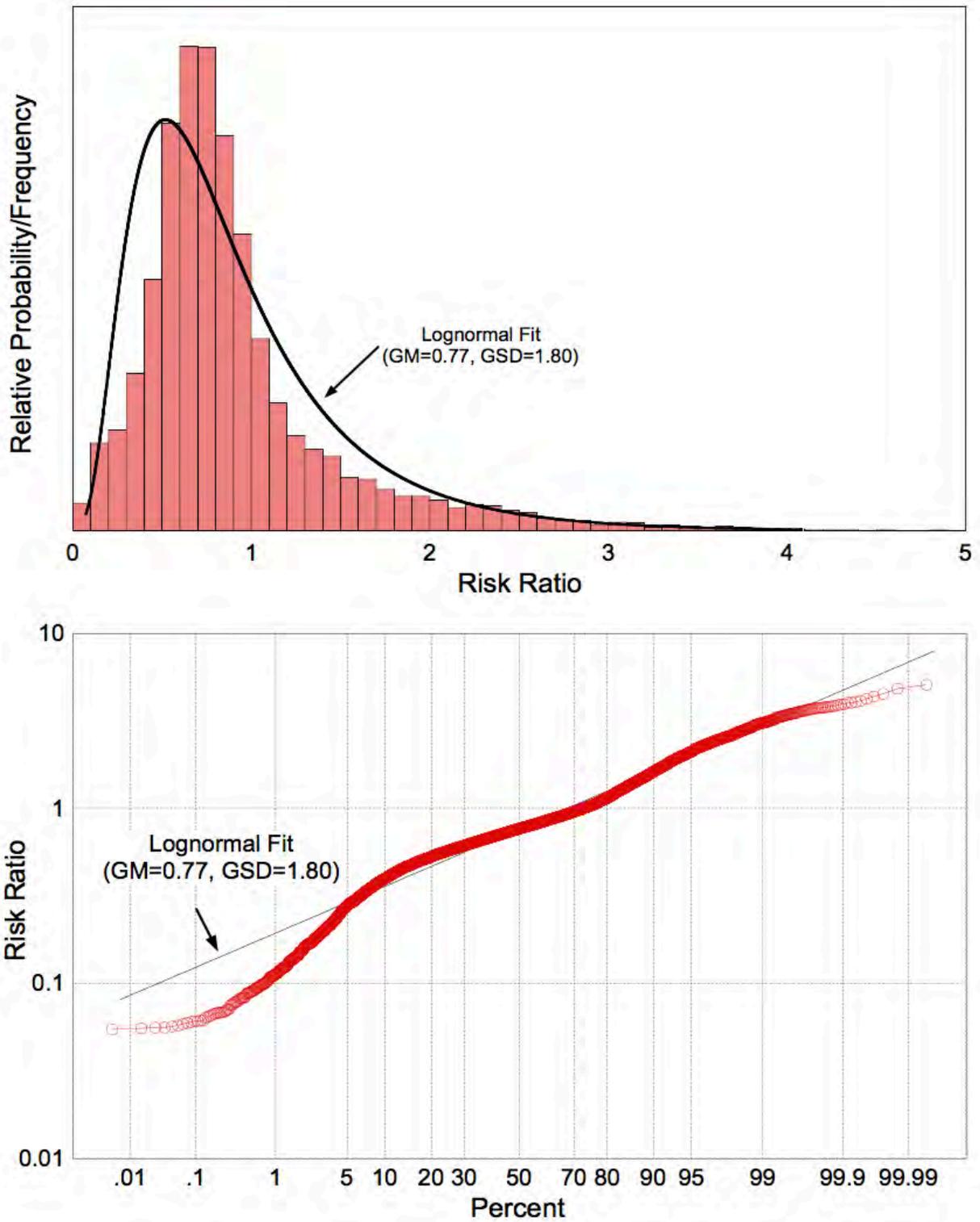


Figure 6.5. Representations of risk ratio corresponding to preferred DDREF distribution for all solid cancers as probability (frequency) distribution (top) and log-probability plot (bottom); risk ratio is reciprocal of DDREF. Solid lines are best-fit lognormal distribution with indicated geometric mean (GM) and geometric standard deviation (GSD).

Table 6.5. Summary of probability distribution of risk ratio for all solid cancers corresponding to preferred probability distribution of DDREF and lognormal distribution that gives best fit to distribution of risk ratio^a

Distribution	Percentile of probability distribution					Arithmetic mean ^b
	2.5th	5th	50th	95th	97.5th	
Distribution of risk ratio	0.18	0.28	0.77	2.1	2.6	0.91
Best-fit lognormal distribution (GM = 0.73, GSD = 1.81)	0.24	0.29	0.77	2.0	2.4	0.91

^a Risk ratio is reciprocal of DDREF. Preferred probability distribution of DDREF is summarized in Table 6.3.

^b If probability distribution of risk ratio were used in cancer risk assessments, arithmetic mean of uncertain estimate of risk would be proportional to arithmetic mean of risk ratio (Section 6.3.4).

The probability distribution of DDREF developed in this report can be used in any assessment in which the risk of solid cancers is assumed to be a linear function of dose. The risk per unit dose at low doses or low dose rates, R_L , then is estimated as $R_L = R_H/DDREF$, where R_H is the risk per unit dose at high acute doses as estimated on the basis of a dose-response for all solid cancers in the LSS cohort.

An extensive review of data in cells and laboratory animals that could be used to estimate a DDREF also was carried out as part of this study. However, we judged that DDREFs based on those data should not be used to develop a DDREF for induction of solid cancers in humans. Rather, we concluded that a DDREF for all solid cancers should be based on epidemiological data in humans alone.

A variety of data on radiation-induced solid cancers in humans was used to develop a probability distribution of DDREF, including results from published analyses of dose-responses for all solid cancers in the LSS cohort, which were used to estimate LDEFs for solid cancer incidence or mortality, and results from published analyses of risks of all solid cancers in cohorts of radiation workers or members of the public, which were compared with estimated risks in the LSS cohort matched by age and sex to estimate DREFs for solid cancer incidence or mortality. Risks in the LSS cohort that we used to estimate LDEFs and DREFs were based on a variety of approaches to modeling dose-responses in that cohort by different expert groups, including the BEIR VII committee (NRC 2006), RERF (Preston et al. 2007; Ozasa et al. (2012), UNSCEAR (Little et al. 2008), and Jacob et al. (2009). The various estimates of LDEF or DREF then were combined based on assumptions about their relevance to obtain a probability distribution of DDREF for all solid cancers. Thus, the DDREF distribution we developed was based on a judgment that, in order to represent the current state of knowledge, it had to account for dose-responses in radiation workers or members of the public that received protracted exposures at low doses, in addition to analyses of the curvature in dose-responses from acute exposure at higher doses in the LSS cohort.

We also reviewed data on dose-responses for specific solid cancers in the LSS cohort and cohorts of radiation workers and medical patients, including data on breast, thyroid, lung, and skin cancers. Although estimates of LDEF, DREF, or DDREF for those cancers are roughly consistent with estimates based on dose-responses for all solid cancers combined, we did not use the cancer-specific data in developing a probability distribution of DDREF for all solid cancers. We also concluded that there is little justification for developing separate probability distributions of DDREF for specific cancer types, such as the DDREF distribution for breast and thyroid cancers currently used in IREP (Figure 1.2).

The probability distribution of DDREF for all solid cancers developed in this report and a lognormal distribution that gave the best fit to the DDREF distribution are shown in Figure 6.4 and summarized in Table 6.4. The best-fit lognormal distribution should be suitable for general use in cancer risk assessments that account for uncertainty.

A summary of results from our analysis and a comparison of our probability distribution of DDREF for all solid cancers with probability distributions developed by other investigators is shown in Figure 6.6. The top portion of the figure shows the probability distributions of LDEF or DREF for solid cancer incidence or mortality that were used to develop our DDREF distribution. The bottom portion shows our probability distribution of DDREF for all solid cancers compared with DDREF distributions based on an analysis by Jacob et al. (2009), the distribution developed by the BEIR VII committee (NRC 2006), and the distribution for all solid cancers except breast and thyroid currently used in IREP (Figure 1.2).

We would note the following about the probability distributions shown in Figure 6.6.

- As indicated in the bottom portion of Figure 6.4, nearly 30% of the values in the probability distribution developed in this report are <1 ; i.e., a weight of nearly 30% is given to an assumption that the risk of solid cancers at low doses or low dose rates is greater than the risk at high acute doses in the LSS cohort. This result is a consequence of including DREFs for solid cancer incidence or mortality that were based on comparisons of risks in cohorts of workers or members of the public with risks in the LSS cohort, since most of the values in the distributions of LDEFs based on analyses of the curvature in dose-responses in the LSS cohort are >1 .
- The 90% CI of the probability distribution developed in this report includes higher values than 90% CIs of the distributions based on the analysis by Jacob et al. (2009), and the latter distributions give greater weight to values <1 . The main reason for these differences is that Jacob et al. considered comparisons of risks in cohorts that received chronic or protracted exposures at low dose rates with risks in the LSS cohort only; estimates of LDEF based on analyses of the curvature in dose-responses in the LSS cohort were not considered.

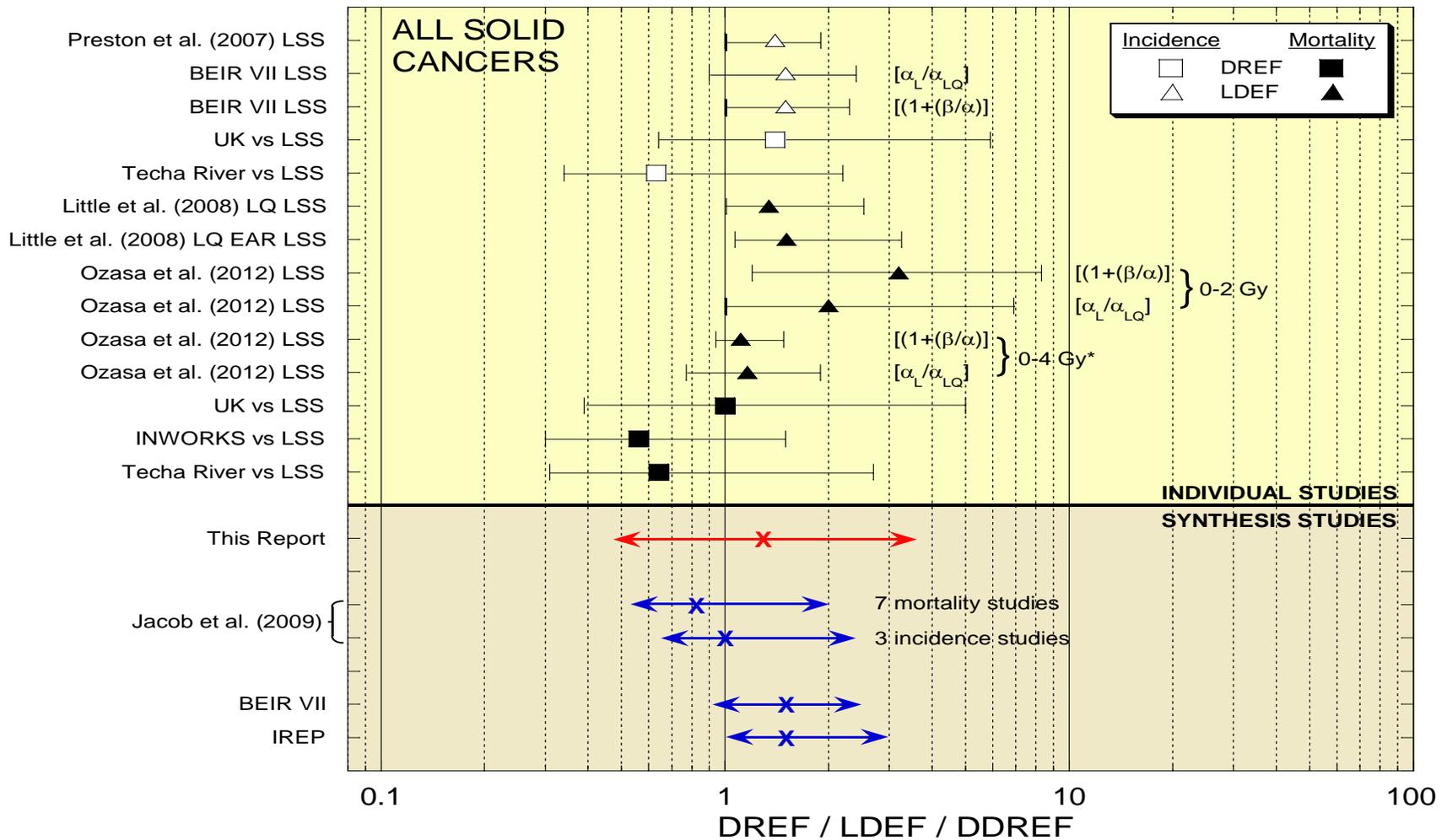


Figure 6.6. Estimates of 50th percentiles and 90% CIs of DREF or LDEF for solid cancer incidence or mortality used to develop probability distribution of DDREF for all solid cancers in this report (top) and comparison of our preferred distribution with DDREF distributions developed by Jacob et al. (2009) and BEIR VII committee (NRC 2006) and DDREF distribution for most solid cancers currently used in IREP (bottom). Distributions at top of figure are shown in Figure 6.2. * Range of shielded kerma from photons and neutrons (neutron-weighted doses to colon otherwise).

- The probability distribution developed in this report and the distribution for all solid cancers excluding breast and thyroid currently used in IREP have similar 50th percentiles (1.3 vs 1.5), but our distribution is substantially broader. We note that the technical basis for the distribution in IREP is not well documented.
- The probability distribution developed in this report and the distribution developed by the BEIR VII committee (NRC 2006) have similar 50th percentiles (1.3 vs 1.5), but our distribution is substantially broader. The committee's distribution was based on the LDEF for solid cancer incidence in the LSS cohort calculated as α_L/α_{LQ} and shown in the top portion of Figure 6.6 and a slight modification of that distribution based on data in animals (Appendix B). The committee did not take into account estimates of LDEF for solid cancer mortality based on data in the LSS cohort or estimates of DREF based on comparisons of estimated risks in cohorts of workers or members of the public with risks in the LSS cohort.

On the basis of the LDEFs for solid cancer incidence shown in Figure 6.6, it might be argued that our distribution of DDREF is overly broad, especially if it is used to estimate risks of solid cancer incidence. However, if a DDREF based on data for all solid cancers combined is used to estimate risks of specific cancers, as in IREP, it is important to account for the possibility that such a DDREF might not represent DDREFs for specific solid cancers. Data shown in Figure 6.2 suggest that DDREFs for some cancer types (e.g., thyroid and skin) could differ substantially from a DDREF for all solid cancers.

As part of this study, we also discussed the concept of a risk ratio, defined as the reciprocal of a DDREF, and its use in cancer risk assessments that account for uncertainty. We think that use of a risk ratio has important advantages, including that (1) the arithmetic mean of a probability distribution of an estimated cancer risk at low doses or low dose rates is proportional to the arithmetic mean of a risk ratio, rather than the reciprocal of the arithmetic mean of DDREF, and (2) probability distributions of DREF based on ratios of risks in the LSS cohort to risks in cohorts that received chronic or protracted exposures often include a value of infinity, because of CIs of risks to workers or members of the public that overlap zero, and, thus, are unstable. The latter concern led Jacob et al. (2009) to calculate risk ratios, rather than DDREFs, in their analysis, since probability distributions of risk ratios generally do not exhibit this instability. If a risk ratio (RR) were used in cancer risk assessments, risks of solid cancers per unit dose at low doses or low dose rates, R_L , would be estimated as $R_L = R_H \times RR$, where R_H is the risk per unit dose at high acute doses as estimated on the basis of data in the LSS cohort.

APPENDIX A

DOSES AND DOSE RATES FOR APPLICATION OF DDREFs

A.1 BACKGROUND

In NIOSH-IREP, a DDREF is applied to risk coefficients (risks per unit dose) for induction of solid cancers by low-LET radiation under conditions of acute exposure, including fractionated acute exposures separated by five hours or more, at doses less than an uncertain reference dose, D_L (Land et al. 2003a; Kocher et al. 2008). The uncertain D_L is described by a log-uniform probability distribution between 30 and 200 mGy. At acute doses above D_L , a DDREF is not applied. A DDREF also is applied to risk coefficients for solid cancers under conditions of chronic exposure. A protracted exposure is considered to be chronic if the dose rate is less than 6 mGy h^{-1} (0.1 mGy min^{-1}). The upper limits of a low acute dose and low dose rate used in NIOSH-IREP were based on recommendations by UNSCEAR (1993).

This appendix reviews information to assess the appropriateness of the current assumptions in NIOSH-IREP about the range of values of an uncertain upper limit of a low acute dose, D_L , and the value of an upper limit of a low dose rate when exposures are protracted. A key assumption is that an LNT model appropriately modified by a DDREF properly characterizes the risks of radiation-induced solid cancers, and that dose-responses are inherently linear at low doses or low dose rates.

Information reviewed in this appendix includes recommendations on upper limits of a low acute dose and a low dose rate by expert groups, including the BEIR VII committee, ICRP, NCRP, and UNSCEAR, and values suggested by (1) microdosimetric arguments, which assume that the cell nucleus is the appropriate target for initiation of a carcinogenic response, (2) studies of chromosome aberrations and cell transformation, (3) studies of carcinogenesis in laboratory animals, and (4) epidemiological studies of Japanese atomic-bomb survivors (the LSS cohort), which provide the primary data used in assessing cancer risks to due radiation, and epidemiological studies of other population groups.

A.2 SPECIFICATION OF LOW DOSE FROM ACUTE EXPOSURE

This section addresses the question of how to define an upper limit of a low acute dose, i.e., a range of doses, D_L , below which a DDREF should be phased in. This question is addressed by considering previous recommendations and other relevant information summarized in Table A.1.

Table A.1. Estimates of upper limit of low dose from acute exposure to low-LET radiation^a

Source or basis	Low dose (mGy)
NCRP (1980)	200
UNSCEAR (1986)	200
UNSCEAR (1993)	200 ^b
ICRP (1991)	200
NCRP (2001)	10
IREP (Land et al. 2003a; Kocher et al. 2008)	30–200
ICRP (2005)	100–200
BEIR VII report (NRC 2006)	100 ^c
ICRP (2007)	100
UNSCEAR (2008)	100
Dose-responses for all cancers, excluding leukemia, in LSS cohort: dose at which contribution to total risk from quadratic term in fitted LQ dose-response is 5% of contribution from linear term ^d	
Cancer mortality	
Preston et al. (2004)	53 90% CI: (6, 310)
Pierce et al. (2008)	38
Little et al. (2008); UNSCEAR (2008)	
Linear-quadratic (LQ) model	140
Linear-quadratic-exponential (LQE) model	12
Cancer incidence	
BEIR VII report (NRC 2006)	170 95% CI: (33, NA ^e)
Preston et al. (2007)	170 90% CI: (55, 5000)
Other epidemiological studies	
Childhood cancer following <i>in utero</i> exposure (Doll and Wakeford 1997; UNSCEAR 2000; Ron 2003)	10–20
Thyroid cancer incidence in children from external exposure (Ron et al. 1995)	75
Breast cancer incidence in patients who received x-ray fluoroscopy treatments (Preston et al. 2002)	10 or higher
Brain tumor incidence from CT scans in children and young adults (Pearce et al. 2012)	50
Tumor induction in laboratory animals	10–100 ^f

Table A.1 (continued)

Chromosome aberrations	
Human lymphocytes	20 ^g
Human fibroblasts	160 ^h
Oncogenic cell transformation	10 ⁱ
Microdosimetric considerations	0.2 ^j ; 10 ^k

^a Dose from acute exposure below which DDREF should be applied in estimating risks of cancer except leukemias on the basis of risk coefficients (risks per unit dose) at higher acute doses in LSS cohort. DDREF is not applied in estimating risks of leukemias at low acute doses of low-LET radiation when linear-quadratic dose-response in LSS cohort, which incorporates dose-dependent DDREF implicitly, is assumed.

^b Dose at which quadratic term in assumed linear-quadratic dose-response for all fatal cancers, excluding leukemias, in LSS cohort contributed about 20% of total risk, as estimated from reciprocal of curvature parameter, β/α (Gy^{-1}), in linear-quadratic fit. Estimate applies at any dose rate.

^c Value specified without explanation.

^d Calculated as $0.05(\beta/\alpha)^{-1}$, where β/α is curvature parameter (Gy^{-1}) that represents relative importance of quadratic and linear terms in modeled dose-responses. Linear-quadratic dose-response was assumed, except as noted.

^e Upper limit of 95% CI cannot be estimated when lower limit of 95% CI of $(\beta/\alpha)^{-1}$ is negative.

^f Estimate based on studies of induction of mammary tumors in mice or rats reported by Bartstra et al. (2000) and Ullrich et al. (1987).

^g Lowest dose at which dose-response was linear in cell culture studies reviewed by BEIR VII committee (NRC 2006) and UNSCEAR (2000). At doses below 20 mGy, data could not distinguish between linear and threshold dose-response models (NRC 2006).

^h Lowest dose at which dose-response was linear in cell culture studies reported by Cornforth et al. (2002).

ⁱ Lowest dose reported by NCRP (2001) at which statistically significant increase in cell transformations was observed.

^j Estimate based on assumed diameter of cell nucleus of 8 μm and requirement that <2% of cell nuclei are traversed by more than one track (i.e., average of 0.2 tracks per cell nucleus) due to irradiation by ^{60}Co gamma rays (UNSCEAR 1993).

^k Estimate derived from low acute dose of 0.2 mGy estimated by UNSCEAR (1993) by assuming that appropriate target is volume of nuclear chromatin and that biological damage is due primarily to secondary electrons of energy less than about 5 keV at ends of radiation tracks. Estimate applies in cases of exposure to higher-energy photons (e.g., ^{60}Co gamma rays). In cases of exposure to lower-energy photons, estimated upper limit would be reduced, due to greater importance of low-energy secondary electrons, and would approach 3 mGy when dose is due primarily to such electrons.

A.2.1 Recommendations by Expert Groups

The concept underlying the definition of an upper limit of a low acute dose was first stated by NCRP (1980) as:

“The straight or essentially straight, very low dose portion of the low-LET dose-response curve. For many endpoints, the dose range is roughly 0 to 20 rads [200 mGy]. In *Tradescantia* and for life shortening in mice, [200 mGy] is the dose at which significant deviations from the linear term can be detected.”

Although more recent information suggests that the upper limit of a low acute dose of 200 mGy recommended by NCRP (1980) and subsequently adopted by nearly all other expert groups should be lowered to about 100 mGy, NCRP’s characterization of what a “low dose” represents seems as valid today as it was in 1980 if an LNT model is assumed to apply.

Recommendations on an upper limit of a low acute dose from exposure to low-LET radiation have been developed by several expert groups, including ICRP, NCRP, UNSCEAR, and the BEIR VII committee. Excluding the later recommendation by NCRP (2001), the recommendations of expert groups have not changed greatly over time; the trend is a decrease from about 200 to about 100 mGy. The earliest estimates were based mainly on analyses of dose-response relationships in laboratory animals, whereas the more recent estimates were based on analyses of dose-responses for all cancers, excluding leukemias, in the LSS cohort. In the more recent analyses, an upper limit of a low acute dose was estimated either as the lowest dose at which a statistically significant increase in risk was observed or as the lowest dose at which the quadratic term in an assumed linear-quadratic dose-response contributed significantly to the modeled risk.

The upper limit of a low acute dose of 10 mGy estimated by NCRP (2001) is an order of magnitude lower than the other recommendations by expert groups. That estimate was based on a variety of information, including an estimate of the lowest dose at which a statistically significant increase in cell transformations had been observed, as given in Table A.1 and discussed in Section A.2.3, and microdosimetric considerations discussed in Section A.2.2.

The upper limit of a low acute dose incorporated in IREP (Land et al. 2003a; Kocher et al. 2008) was developed by a working group of the National Cancer Institute (NCI) and the Centers for Disease Control and Prevention (CDC). That upper limit differs from the recommendations by other expert groups in that it is considered to be uncertain and is described by a probability distribution. As noted above, the upper limit of a low acute dose, D_L , is described by a log-uniform distribution between 30 and 200 mGy;

the median and mean of that distribution are 77 and 90 mGy, respectively, and the 95% CI is (31, 191) mGy. Another feature of the approach in IREP is that a DDREF is phased in gradually as an acute dose decreases below a value sampled from the assumed probability distribution of D_L (Land et al. 2003a; Kocher et al. 2008), rather than introduced abruptly, and unrealistically, at doses just below D_L .

A.2.2 Microdosimetric Considerations

Microdosimetric arguments can be used to estimate an upper limit of a low acute dose. The estimate of 0.2 mGy by UNSCEAR (1993) given in Table A.1 corresponds to the average dose in an organ or tissue from exposure to ^{60}Co gamma rays at which there is an average of 0.2 radiation tracks through a cell nucleus. When the average number of energy deposition events per target is 0.2, <2% of all possible targets and <10% of the hit targets will experience more than one event (Goodhead 1988; NCRP 2001). An average number of tracks per cell nucleus of 0.2 was proposed by Goodhead (1988) to represent a conservatively low number of hits below which the initial biological effect (e.g., damage to DNA) should be fully proportional to dose; i.e., such effects should be produced solely as a result of the passage of a single radiation track through the target. This argument can be applied whenever multiple energy deposition events in the appropriate target are rare and the initial biological effect [e.g., DNA double-strand breaks (DSBs) or clustered damage] is a direct result of energy deposition in a single target (UNSCEAR 2000; NCRP 2001). At such low doses, it is axiomatic that dose-responses for initial damage at the level of the individual cell must be linear and independent of dose rate (Goodhead 1988).

Estimates of a low acute dose based on microdosimetric considerations depend on the assumed target size and vary inversely with the square of the target diameter. The low dose of 0.2 mGy estimated by UNSCEAR (1993) was based on an assumption that the nucleus of a typical cell with an average diameter of about 8 μm is the appropriate target. However, there is evidence that the biologically significant target could be much smaller than a cell nucleus, perhaps as small as a single nucleotide in DNA, or as large as an entire organ or tissue. If the target size is decreased to the volume of nuclear chromatin (DNA and associated proteins) in a cell nucleus with a diameter about 2 μm (NCRP 2001), a low acute dose would increase to about 3 mGy. On the other hand, if non-targeted and delayed effects (e.g., bystander effects and genomic instability) were important, the appropriate target could be a cluster of many cells, and a low acute dose would be much less than 0.2 mGy.

A complication in estimating a low acute dose based on microdosimetric considerations is that such a dose also depends on LET, which can vary by more than order of magnitude for low-LET radiations of different energies (NCRP 2001). For example, if the appropriate target is the volume of nuclear chromatin, a low dose of 25 kVp (mammography) x rays would be nearly a factor of seven higher than a

low dose of ^{60}Co gamma rays, and the increase would be a factor of about five if the appropriate target is a cell nucleus (NCRP 2001).

A further complication arises from analyses of track structure and biophysical models of radiation action, which indicate that the primary determinant of biological effects of low-LET radiation is damage to DNA produced by low-energy secondary electrons (about 0.1–5 keV) at the ends of radiation tracks; i.e., biological effects of low-LET radiation are due mainly to a clustering of energy deposition on a spatial scale on the order of nanometers, and the sparse ionizations and excitations along the rest of a track have little biological effect (Goodhead 1988). When energy depositions along a track are highly non-uniform, the assumption that a low acute dose can be defined as the dose at which the average number of tracks per cell nucleus is <0.2 should be overly conservative; i.e, a larger number of tracks would give the same number of significant energy deposition events per target. Since about 33% of the dose from ^{60}Co gamma rays is delivered by low-energy secondary electrons (Nikjoo and Goodhead 1991), estimates of a low acute dose from exposure to ^{60}Co gamma rays could be increased by a factor of about three (e.g., to about 10 mGy if the appropriate target is the volume of nuclear chromatin). In cases of exposure to 220 kVp x rays, about 50% of the total dose is delivered by low-energy secondary electrons (Nikjoo and Goodhead 1991), and the increase in a low acute dose would be a factor of about two.

While damage to DNA is expected to increase linearly with dose from low-LET radiations, as illustrated in Figure A.1, the probability of conversion of that damage to chromosome aberrations or mutations that could lead to cancer at low doses is thought by some to depend primarily on the probability of misrepair and the overall kinetics of repair (ICRP 2005). Translation of a linear dose-response for the initial insult to the dose-response for the endpoint of greatest concern, a radiation-induced cancer, depends on the likelihood that biological mechanisms for dealing with DSBs and associated clustered damage that can be produced by a single radiation track, even at the lowest doses, are 100% effective. As discussed in Sections 3.1 and 3.3 and by Bonner (2003), some such damage is considered impossible to repair. If misrepaired or unrepaired damage is sufficiently severe, however, the cell may not survive to become a cancerous clone or may survive but become senescent and unable to clone itself (Section 3.1).

Thus, a variety of cellular mechanisms (including DNA repair, cell cycle arrest, and apoptosis) could modify the dose-response for cancer induction (Section 3.1). It is not known whether processes that modify DNA damage or related cellular responses affect the shape of dose-responses for cancer at doses on the order of mGy or less, because information at very low doses and dose rates is lacking and results from studies at higher doses may not be representative of the progression of events at low doses. There are many steps between the initial biological events and development of a cancer, and it is not known if this progression is different at low doses than at higher doses where increases in risks of cancer have been observed (NCRP 2001).

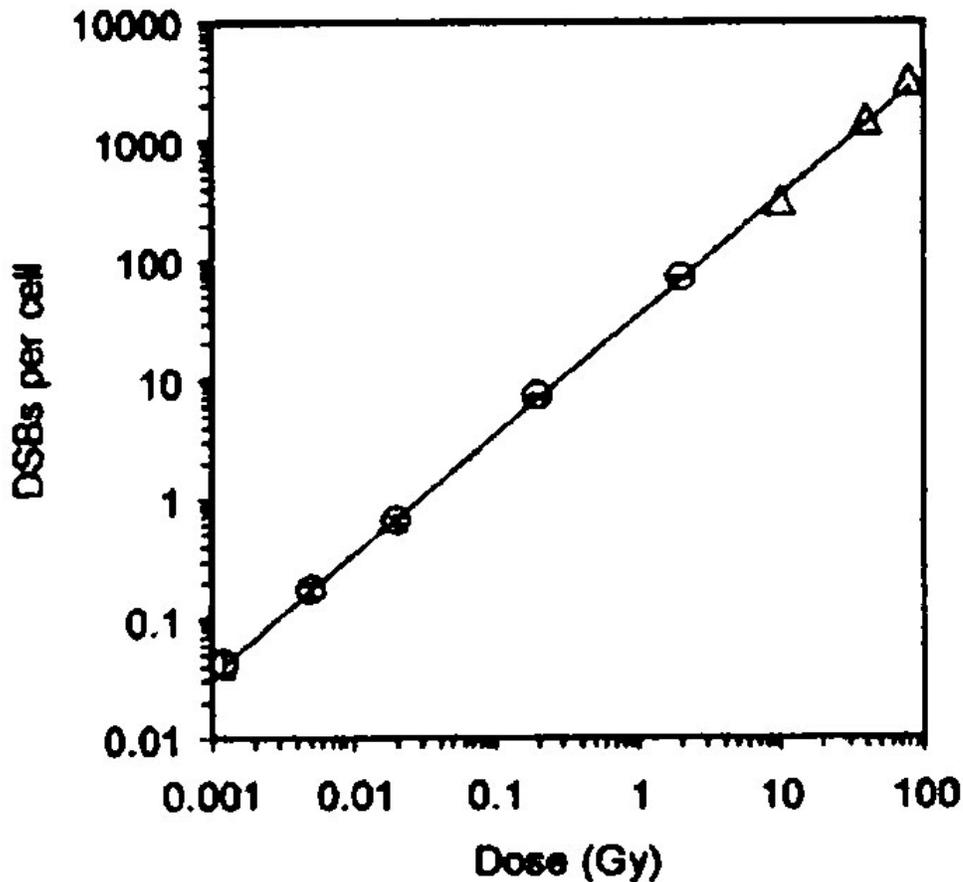


Figure. A.1. DNA double-strand break (DSB) induction in normal human fibroblasts, based on mean values of γ -H2AX foci counted 3 minutes after irradiation (circles) or data from pulsed-field gel electrophoresis analysis (triangles). Line is a linear fit to the data with slope of 35 DSBs per cell per Gy. Source: Rothkamm and Löbrich (2003).

The greatest uncertainty in microdosimetric calculations is associated with determining the appropriate target size (e.g., cell nucleus vs entire organ or tissue). Despite current uncertainties about the applicability of an LNT model, evidence for production of genomic instability as a direct effect of DNA damage rather than as a non-targeted effect indicates that microdosimetric considerations might still be relevant to estimating an upper limit of a low acute dose, D_L . In addition, because some form of primary DNA damage in a single cell nucleus can initiate the signaling cascade that leads to the production of non-targeted and delayed effects, 10 mGy could still represent a reasonable estimate of a low acute dose. Because DNA damage can be produced by irradiation of cytoplasm, presumably by the action of free

radicals generated by a radiation track outside the nucleus, it also could be reasonable to reduce a low dose to about 1–5 mGy to reflect the increased target size represented by the entire cell.

The effects of single-track action could still dominate the dose-response at doses as high as about 100–200 mGy if plausible repair mechanisms are assumed to be operable (Goodhead 1988; NCRP 2001). However, the uncertainty introduced by the proposed mechanism for low-dose hyper-radiosensitivity makes such extensions of the range of a low dose problematic. Another caution is that a linear risk coefficient may still exhibit a dependence on dose rate, as in the examples in Figure A.2 and in Figure 2.2 in Section 2.3 of the main text (Goodhead 1988). Thus, apparently linear dose-responses derived, for example, from epidemiological data for acute or fractionated acute exposures could still conceal some degree of dose-rate dependence that would justify application of a DDREF in cases of exposure at low dose rates, if not at high dose rates.

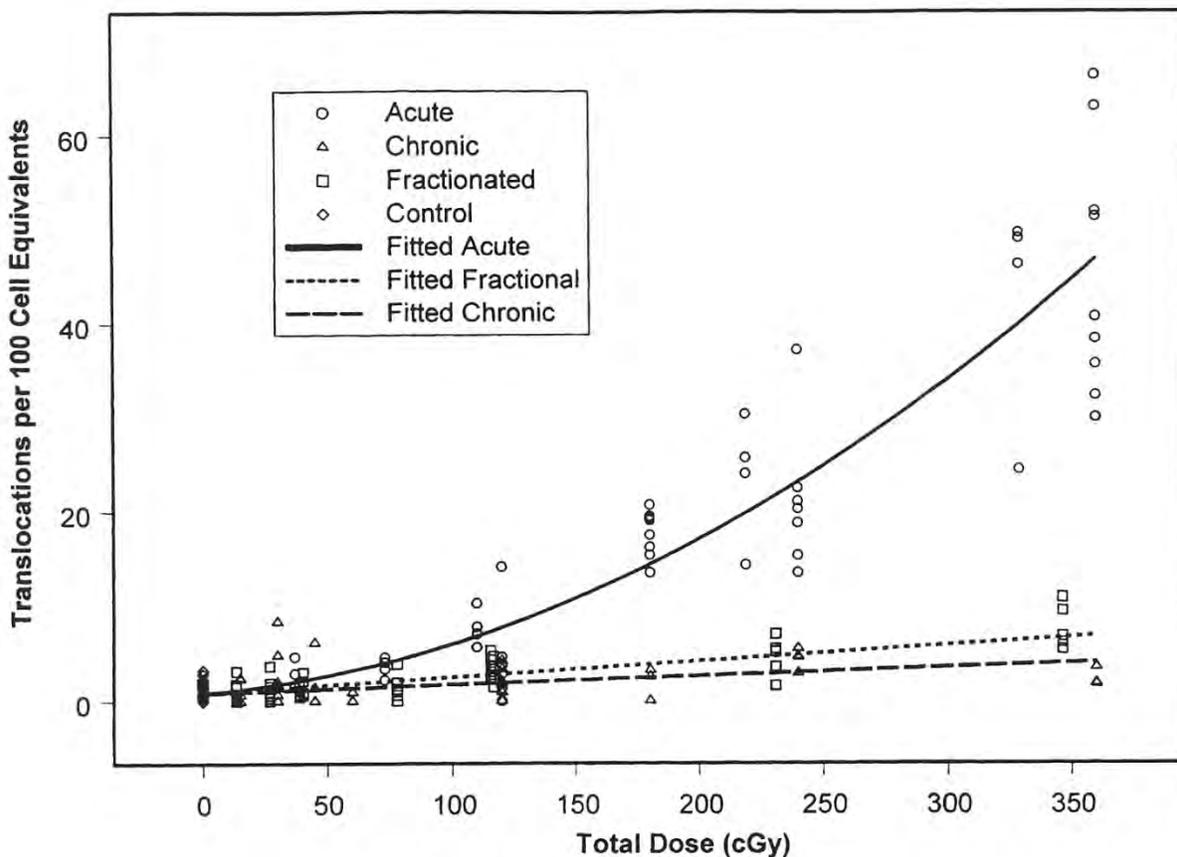


Figure A.2. Effect of dose and dose rate on frequency of translocations in mouse lymphocytes following acute, chronic, or fractionated exposures to gamma rays *in vivo*. Source: Sorensen et al. (2000).

In summary, microdosimetric considerations suggest that an upper limit of a low acute dose from exposure to low-LET radiation is on the order of 10 mGy. This estimate is based on three assumptions:

- An acute dose is low when the average number of biologically damaging tracks per target is <0.2 , in which case the dose-response at lower doses must be linear.
- The appropriate target in which biological damage occurs is the volume of nuclear chromatin.
- Biological damage is due primarily to low-energy secondary electrons at the ends of radiation tracks.

However, any such estimate is highly uncertain, due to such factors as uncertainties in the appropriate target size and the importance of non-targeted and delayed effects. A more general concern is that microdosimetric calculations are based on physics only, and it may be naïve to assume that there are simple relationships between such calculations and biological effects (Nikjoo and Lindborg 2010).

A.2.3 Analyses of Data in Cells

As summarized in Table A.1, an upper limit of a low acute dose can be estimated on the basis of studies of dose-responses for dicentric chromosome aberrations in human lymphocytes reviewed by the BEIR VII committee (NRC 2006), a study of dose-responses for dicentric chromosome aberrations in human fibroblasts (Cornforth et al. 2002), and studies of oncogenic transformation in rodent cells reviewed by NCRP (2001). Estimates of an upper limit of a low acute dose based on those studies range from 10 to 160 mGy. Each upper limit is the lowest dose at which an increase in responses was observed. In studies of oncogenic cell transformation, the estimated upper limit of 10 mGy was the lowest dose used in the irradiations.

The applicability of data on dose-responses from studies in cells to cancer induction in humans is uncertain. For example, it is questionable whether data on dicentric chromosome aberrations, which are nontransmissible, are relevant to induction of cancer. Another concern is that oncogenic transformation in rodent cells occurs at frequencies per Gy many orders of magnitude higher than transformation frequencies per cell in whole organisms (NCRP 2001), which indicates the potential importance of homeostatic mechanisms in intact tissues in controlling cancer outcomes (Barcellos-Hoff and Brooks 2001). Nonetheless, estimates of an upper limit of a low acute dose obtained from studies in cells are consistent with estimates based on other studies, including analyses of dose-responses for cancer mortality or incidence in the LSS cohort.

A.2.4 Analyses of Data in Laboratory Animals

As indicated in Table A.1, an upper limit of a low acute dose in the range of about 10 to 100 mGy can be estimated on the basis of data on dose-responses for tumor induction in laboratory animals. Studies on which the estimated range is based involved induction of mammary carcinomas in female BALB/c mice that received acute, fractionated, or chronic exposures to ^{137}Cs gamma rays at total doses of 0.1, 0.2, or 0.25 Gy (Ullrich et al. 1987) or induction of mammary tumors in female WAG/Rij rats that were treated with estrogen and received fractionated exposures to ^{60}Co gamma rays at a dose per fraction as low as 2.5 or 10 mGy at intervals of 12 or 24 hours and total doses of 1 or 2 Gy (Barstra et al. 2000).

In the study by Ullrich et al. (1987), the incidence of mammary tumors at a total dose of 0.25 Gy was about the same under conditions of acute exposure at a dose rate of 0.35 Gy min^{-1} or fractionated exposures at doses per fraction of 50 mGy delivered over five consecutive days at a high dose rate (50 mGy min^{-1}). A finding that the effect of five daily doses delivered acutely was almost additive—i.e., that the effect was nearly the same as the effect of a single acute dose—suggests that an upper limit of a low acute dose is not much higher than the dose per fraction of 50 mGy (but could be lower). When the same total dose was delivered at a lower daily dose per fraction of 10 mGy and the same dose rate (50 mGy min^{-1}), the incidence of mammary tumors was reduced by a factor of about two to three; i.e., the effects of the daily dose fractions were no longer additive. This finding suggests that an upper limit of a low acute dose could be as low as about 10 mGy (but could be higher).

In the study by Bartstra et al. (2000), the incidence of mammary tumors was reduced by about a factor of four when the dose per fraction was decreased from 40 to 10 mGy, but there was no further reduction in effects when the dose per fraction was decreased to 2.5 mGy. This finding suggests that an upper limit of a low acute dose could be as low as about 10 mGy (but could be somewhat higher).

Taken together, and also taking into account that there is substantial uncertainty in estimates of the incidence of mammary tumors, the two studies summarized above suggest that an upper limit of a low acute dose is in the range of about 10 to 100 mGy.

A.2.5 Analyses of Epidemiological Data

Analyses of dose-response relationships obtained in epidemiologic studies can provide estimates of an upper limit of a low acute dose. Analyses of dose-responses in the LSS cohort provided the basis for the more recent estimates of an upper limit of a low acute dose by expert groups.

A.2.5.1 Analyses of data in LSS cohort

Recent analyses of dose-responses for all cancers combined, excluding leukemias, in the LSS cohort can be used to estimate an upper limit of a low acute dose. Such a dose can be defined as the dose at which the contribution from the quadratic term in an assumed non-linear dose-response reaches a minimum level of significance. At doses below that level, the modeled dose-response is essentially linear.

In an analysis of the dose-response for all fatal cancers, excluding leukemias, in the LSS cohort by UNSCEAR (1993), which gave the low acute dose of 200 mGy listed in Table A.1, the minimum level of significance of the quadratic term in the dose-response was assumed to be a contribution to the modeled risk of about 20% of the contribution from the linear term. i.e., a dose of about $0.2 (\beta/\alpha)^{-1}$ Gy. In the other entries in Table A.1 that were based on analyses of dose-responses for incidence or mortality of all cancers combined, excluding leukemias, in the LSS cohort, a minimum level of significance of the quadratic term is assumed to be reached when the contribution from that term to the modeled risk is 5% of the contribution from the linear term. Those estimates of a low acute dose also are based on the current dosimetry system (DS02) and a longer period of follow-up of the LSS cohort.

In the estimates of an upper limit of a low acute dose based on analyses of dose-responses in the LSS cohort and an assumption that the contribution from the quadratic term in a modeled dose-response is minimally significant if it is 5% of the contribution from the linear term, estimates based on data for cancer incidence tend to be higher than estimates based on data for cancer mortality; the former give a central estimate of about 170 mGy, whereas the latter give central estimates of about 12 to 140 mGy. However, uncertainties in estimates based on data for either disease outcome, which are based on reported confidence intervals of the curvature parameter β/α , are large, and there is considerable variability in the estimates based on data for cancer mortality, especially estimates based on the different forms of the dose-response relationship assumed by Little et al. (2008). Furthermore, the slope of the linear term in best fits to the data on dose-response depends on the high-dose cutoff used to identify members of the LSS cohort to be included in an analysis, which varies in the different studies; the high-dose cutoff is 1.5 Gy in analyses by the BEIR VII committee (NRC 2006) and Pierce et al. (2008), 2 Gy in analyses by Preston et al. (2004, 2007), and >3 Gy in the analysis by Little et al. (2008).

Another potential complication is that the data on cancer mortality reported by Preston et al. (2004) show elevated risks at doses from photons and neutrons less than about 300 mGy, compared with risks based on a linear extrapolation to zero dose of risks at doses above 300 mGy, which are not seen in the data on cancer incidence (Preston et al. 2007). Such elevated risks at the lowest doses also are seen in the more recent analysis of data on cancer mortality by Ozawa et al. (2012). This difference in dose-responses for cancer mortality and cancer incidence at low doses, which would affect a comparison of estimates of

an upper limit of a low acute dose based on data for the two disease outcomes, could be due to the influence of contributions from neutrons to the risks to lightly shielded organs, such as the breast and thyroid. Those contributions would be more important to the risk of cancer incidence than to the risk of cancer mortality. It also has been suggested that the biological effectiveness of neutrons in lightly shielded organs could be underestimated substantially (Kellerer et al. 2006), which also could affect differences in dose-responses for cancer incidence and cancer mortality at doses of about 300 mSv and below. These potential complications make it more difficult to conclude with confidence that there is a significant difference in an upper limit of a low acute dose estimated on the basis of data for the two disease outcomes in the LSS cohort.

A.2.5.2 Information from other epidemiological studies

Results from other epidemiological studies summarized in Table A.1 and described below can inform a judgment about an upper limit of a low acute dose.

Analyses of the dose-response for childhood cancers following *in utero* exposure of pregnant women to diagnostic x rays (Doll and Wakeford 1997; Ron 2003; UNSCEAR 2000) suggested an increased risk of all cancers, excluding leukemias, at doses as low as about 10 to 20 mGy.

A pooled analysis by Ron et al. (1995) of data from the five largest cohort studies of thyroid cancer incidence in children who were exposed to external radiation at ages <15 suggested that the risk increased linearly with dose at doses >75 mGy.

An analysis by Preston et al. (2002) of data on breast cancer incidence in tuberculosis patients in Massachusetts who received x-ray fluoroscopy treatments showed an excess risk when many low-dose fractions of about 10 mGy per fraction separated by about two weeks were delivered at a high dose rate (>10 mGy min⁻¹). This result suggests that an upper limit of a low acute dose could be as low as 10 mGy. However, since the total doses of about 0.5 to 2 Gy were much higher than the dose per fraction and risks associated with a range of doses per fraction could not be studied, an upper limit of a low acute dose in those patients could be substantially higher than 10 mGy.

In a study of patients in Great Britain without previous cancer diagnoses who received computed tomography (CT) scans as children or young adults, Pearce et al. (2012) found a statistically significant increase in the incidence of brain tumors at cumulative doses to the brain as low as 50 to 74 mGy (mean dose about 60 mGy). This result suggests an upper limit of a low acute dose of about 50 mGy.

In a study of children exposed at age <1 year to ¹³¹I in fallout from nuclear weapons testing, Gilbert et al. (1998) found a positive association of thyroid cancer mortality or incidence with dose at estimated doses as low as about 10 to 100 mGy. However, there was no statistically significant association with the

total dose at all ages or the dose at ages of 1 to 15. These results, which were confirmed in a follow-up study (Gilbert et al. 2010), were not consistent with results from an analysis by Ron et al. (1995) of data on thyroid cancer in children who received external exposure, as described above. Gilbert et al. (2002; 2010) noted that their study had limitations and biases inherent in ecological studies, such as errors in estimated doses and case ascertainment in a mobile population. Given these limitations, an estimate of a low acute dose based on the studies by Gilbert et al. (1998, 2010) is not included in Table A.1.

Estimates of an upper limit of a low acute dose summarized above and given in Table A.1 are consistent with estimates based on data for all cancers combined, excluding leukemias, in the LSS cohort discussed in the previous section.

A.2.6 Conclusions About Upper Limit of Low Acute Dose

Analyses of dose-responses for all cancers combined, excluding leukemias, in the LSS cohort should be the most valid approach to estimating an upper limit of a low acute dose. At acute doses below the upper limit, a DDREF should be applied in estimating risks of all cancers other than leukemias from exposure to low-LET radiation on the basis of estimated risks per unit dose at higher acute doses in the LSS cohort assuming linear dose-responses. A DDREF is not applied in estimating risks of leukemia at low acute doses on the basis of data in the LSS cohort when a linear-quadratic dose-response, which incorporates a dose-dependent DDREF implicitly, is assumed.

Analyses of recent data on mortality or incidence of all cancers, except leukemias, in the LSS cohort summarized in Table A.1 suggest an upper limit of a low acute dose in the range of about 10 to 200 mGy. Those estimates were based on the current dosimetry system (DS02) and recent follow-up of that cohort. The upper limit of this range may be more reliable than the lower limit, since the lowest dose at which a statistically significant excess risk is observed in the LSS cohort is about 100 mGy (NRC 2006). Differences in the various estimates of an upper limit of a low acute dose based on data in the LSS cohort probably are due to several factors, including:

- possible differences in the dose-responses for cancer mortality and incidence at doses less than about 300 mGy;
- differences in the choice of a high-dose cutoff used to identify members of the LSS cohort to be included in an analysis, which affects modeled dose-responses at lower doses; and
- the effect of assuming a different form of the dose-response (linear-quadratic-exponential vs linear-quadratic).

Other epidemiological data summarized in Table A.1 support the suggested range of an upper limit of a low acute dose based on data in the LSS cohort, especially the suggestion that the upper limit could be as low as about 10 mGy.

A variety of other information obtained from radiobiological studies in laboratory animals and cells and considerations of microdosimetry provides support for an upper limit of a low acute dose in the range of about 10 to 200 mGy. For example, if the appropriate target is assumed to be the volume of nuclear chromatin in a cell, a low acute dose from ^{60}Co gamma rays of about 9 mGy is estimated on the basis of microdosimetric calculations. Although the applicability of estimates based on radiobiological data and microdosimetry to cancer induction in humans can be questioned, the consistency of estimates based on the different lines of evidence is noteworthy.

A.3 SPECIFICATION OF LOW DOSE RATE

A dose rate below which protracted exposures to low-LET radiation should be considered chronic (an upper limit of a low dose rate) can be estimated based on studies of cancer induction in animals, studies of chromosome aberrations, and microdosimetric considerations. At such low dose rates, a DDREF should be applied in estimating risks of all cancers except leukemias at any total dose on the basis of risk coefficients at high acute doses in the LSS cohort, and risks of leukemias should be estimated by assuming that only the linear term in an assumed linear-quadratic dose-response in the LSS cohort contributes. A recent epidemiological study of the association of childhood leukemias with exposure to natural background radiation (Kendall et al. 2013) described in Section 5.8.3.6 also may be informative. Estimates of an upper limit of a low dose rate are summarized in Table A.2 and discussed in the following sections. All estimates should be interpreted as approximate values.

A.3.1 Recommendations by Expert Groups

Recommendations on an upper limit of a low dose rate from exposure to low-LET radiation have been developed by UNSCEAR, ICRP, and the BEIR VII committee. Compared with recommendations on an upper limit of a low acute dose by expert groups summarized in Table A.1, recommendations on an upper limit of a low dose rate are more variable, ranging from $0.01 \text{ mGy min}^{-1}$ (NRC 2006) to 2 mGy min^{-1} (ICRP 1991). Not included in Table A.2 is an early estimate of $10^{-4} \text{ mGy min}^{-1}$ by NCRP (1980), which was based on the dose limit for occupational exposure at that time (a limit on annual dose equivalent from uniform whole-body irradiation of 50 mSv).

Table A.2. Estimates of upper limit of low dose rate from protracted exposure to low-LET radiation^a

Source or basis	Low dose rate (mGy min ⁻¹)
UNSCEAR (1986)	0.05
UNSCEAR (1993)	0.1 ^b
ICRP (1991)	2 ^c
IREP (Land et al. 2003a)	0.1 ^d
BEIR VII report (NRC 2006)	0.01 ^e
Tumor induction in laboratory animals	0.06 ^f
Chromosome aberrations	
Human lymphocytes	1–2 ^g
Human fibroblasts	≈0.5–1 ^g
Microdosimetric considerations	— ^h
Epidemiological study of childhood leukemias from exposure to natural gamma radiation (Kendall et al. 2013)	— ⁱ

^a Dose rate below which protracted exposures should be considered chronic. At low dose rates, DDREF should be applied at any total dose in estimating risks of all cancers except leukemias on the basis of risk coefficients at high acute doses in LSS cohort, and risks of leukemias should be estimated by assuming that only linear term in assumed linear-quadratic dose-response contributes.

^b Dose rate averaged over about one hour, whatever the total dose.

^c Estimate based on recommended upper limit of low dose rate of 0.1 Gy h⁻¹. Recommendation was specified without justification and was not retained in ICRP (2007).

^d Adopted value recommended by UNSCEAR (1993) applies to dose rate averaged over period of a few hours. Any protracted exposure over period of more than one day is assumed to be chronic.

^e Value specified without justification.

^f Value reported by UNSCEAR (1993) was lowest dose rate in studies of cancer induction in animals by Ullrich and Storer (1978, 1979b, 1979c).

^g Dose rate below which dose-response in cell culture studies reported by Cornforth et al. (2002) was linear and independent of dose rate.

^h UNSCEAR (1993) suggested that low dose rate based on allowing only a single track to traverse cell nucleus over cell lifetime of about 60 years would be about 10⁻⁸ mGy min⁻¹ or, alternatively, that low dose rate based on allowing only single track per cell nucleus during period of perhaps a few hours during which DNA repair could take place would be about 10⁻³ mGy min⁻¹.

ⁱ Statistically significant increase in risk of childhood leukemias associated with exposure to natural gamma radiation and similarity of risk estimates with estimates based on data in LSS cohort suggest that low dose rate is about 10⁻⁶ mGy min⁻¹. This estimate would apply only for the purpose of estimating a dose rate below which risks of leukemias should be estimated by assuming that only the linear term in assumed linear-quadratic dose-response in LSS cohort contributes.

Of the recommendations by expert groups in Table A.2, only those by UNSCEAR (1986, 1993), which were reiterated in a later report (UNSCEAR 2000), were justified by discussions of potentially relevant information. The recommendation by UNSCEAR (1993) was adopted for use in IREP (Land et al. 2003a). Recommendations by ICRP (1991) and the BEIR VII committee (NRC 2006) were not explained, and their basis is unknown.

Recommendations by UNSCEAR (1986, 1993) were based on studies of cancer induction in laboratory animals exposed to ^{137}Cs gamma rays, especially studies in RFM and BALB/c mice by Ullrich and Storer (1978, 1979b, 1979c). Dose rates in those studies were as low as 0.06 to 0.07 mGy min^{-1} . At those dose rates, the dose-response was linear and the response per unit dose was substantially lower than the response per unit dose at higher dose rates. Low dose rates used in the animal studies were rounded up to derive the recommendation of 0.1 mGy min^{-1} by UNSCEAR (1993).

A.3.2 Data on Cancer Induction in Laboratory Animals

Data on cancer induction in laboratory animals used by UNSCEAR (1986, 1993) should be relevant for the purpose of estimating an upper limit of a low dose rate. As summarized below, however, there is uncertainty about whether those data define such an upper limit.

- Only a limited number of widely separated dose rates were used in animal studies to investigate the effects of dose rate on cancer induction. Consequently, there is considerable uncertainty about whether the lowest dose rates used in those studies define an upper limit of a low dose rate. As noted by UNSCEAR (1993), the yield of tumors per unit dose could have been about the same at dose rates a few times higher than the lowest dose rates used in those studies.
- Given that total doses of several gray were required to observe excess cancers at low dose rates in the animal studies, a dose rate of 0.06 to 0.07 mGy min^{-1} was close to the lowest dose rate that could be used and complete the exposures well within the normal lifetime of the study animals (Edwards 1992). The response per unit dose could have been substantially lower at lower dose rates that could not be investigated in those studies.
- In a study of fatal cancers in beagle dogs that were given continuous, duration-of-life exposures to ^{60}Co gamma rays (Seed et al. 2002), the occurrence of fatal solid tumors was highest at the lowest dose rate of 3 mGy d^{-1} (0.002 mGy min^{-1}) and decreased to zero at the highest dose rate of 128 mGy d^{-1} (0.09 mGy min^{-1}). This result does not conform to the usual assumption about responses at low dose rates compared with responses at higher dose rates. In contrast, the incidence of myeloid leukemias was highest at an intermediate dose rate of 37.5 mGy d^{-1}

(0.026 mGy min⁻¹) and decreased to zero at the lowest dose rate (Fritz et al. 1986; Seed et al. 2002). At higher dose rates, other responses were more important than myeloid leukemias.

- In studies of bone sarcomas in beagle dogs or mice that received total doses to bone in the range of about 2 to 30 Gy, thresholds in responses were observed at doses of about 10 to 20 Gy under conditions of chronic exposure to ⁹⁰Sr beta particles at dose rates one to two orders of magnitude lower than 0.06 mGy min⁻¹ (Boecker et al. 1994; Finkel et al. 1959; Mays and Finkel 1980; Miller and Buster 1986; NCRP 1990; White et al. 1993). However, a concern with the apparent threshold responses in those studies is the lack of statistical power when dose rates and the numbers of exposed animals probably were too low to produce observable effects within the lifetimes of the animals.

The first two observations about the studies of cancer induction in animals used by UNSCEAR (1986, 1993) indicate that the uncertainty in an upper limit of a low dose rate estimated on the basis of those studies (a dose rate of about 0.1 mGy min⁻¹) would be at least several-fold. Results of other studies of cancer induction in animals noted above suggest that the effects of dose rate may be more complex in some cases than would be predicted on the basis of a linear-quadratic dose-response model.

Other studies in laboratory animals provide support for an upper limit of a low dose rate of about 0.1 mGy min⁻¹. In studies of life shortening in mice exposed daily throughout life to ⁶⁰Co gamma rays, as reported by Grahn (1970) and Sacher (1973) and summarized in Figure. 8.27 of NCRP (2001), the mortality rate increased linearly with dose rate at dose rates of about 0.003 to 0.2 Gy d⁻¹ (0.002 to 0.1 mGy min⁻¹) and increased more rapidly at higher dose rates. Life shortening in those studies was due primarily to solid cancers.

A.3.3 Analyses of Data in Cells

Data on induction of dicentric chromosome aberrations in human lymphocytes indicated that there should be no effect of dose rate on the response per unit dose at dose rates less than 50 to 100 mGy h⁻¹ (1 to 2 mGy min⁻¹) (Cornforth et al. 2002). A similar estimate of an upper limit of a low dose rate was obtained in studies of chromosome aberrations in normal human fibroblasts (Cornforth et al. 2002).

Estimates of an upper limit of a low dose rate based on studies in cells were obtained by assuming that a linear-quadratic dose-response model applied to induction of chromosome aberrations that were scored using conventional Giemsa staining (IAEA 2001). However, that method of scoring did not distinguish between simple and complex aberrations, a distinction which studies using mFISH have shown to be critical in assessing the dependence of the dose-response on dose rate. The assumption of a

linear-quadratic model for simple and complex aberrations combined masked important differences in dose-responses for those endpoints, including that simple aberrations are important at any dose but complex aberrations are important only at high doses—i.e., the apparently linear-quadratic dose-response was an artifact of combining dose-responses for multiple endpoints, none of which is linear-quadratic. More importantly, studies of chromosome aberrations in human fibroblasts using mFISH (Loucas et al. 2004) showed that (1) the acute dose-response for simple aberrations was nearly linear at all doses and (2) the dose-response under conditions of chronic exposure at low dose rates also was linear but the slope of the dose-response was much lower than the slope at high dose rates. This difference was contrary to an expectation based on an assumption of a linear-quadratic model that the slope of the linear dose-response for simple chromosome aberrations should be independent of dose rate. Results of the studies using mFISH cast considerable doubt on the validity of estimates of an upper limit of a low dose rate obtained in earlier studies of chromosome aberrations.

A.3.4 Microdosimetric Considerations

UNSCEAR (1993) used two different criteria based on microdosimetric considerations to estimate an upper limit of a low dose rate. An assumption that a low dose rate could be defined as a dose rate at which only a single radiation track would traverse a cell nucleus during a cell's lifetime of about 60 years gave an estimate of about 10^{-8} mGy min⁻¹. Alternatively, an assumption that a low dose rate could be defined as a dose rate at which only a single track would traverse a cell nucleus during a time characteristic of DNA repair (a time of perhaps a few hours) gave an estimate of about 10^{-3} mGy min⁻¹. The lower of these estimates is about two orders of magnitude less than the average dose rate from exposure to natural background radiation, excluding radon.

Neither of the upper limits of a low dose rate calculated by UNSCEAR (1993) on the basis of microdosimetric considerations was adopted as a recommendation. Rather, as discussed in Section A.3.1, UNSCEAR (1993) recommended an upper limit of a low dose rate of about 0.1 mGy min⁻¹ on the basis of studies of cancer induction in laboratory animals.

A.3.5 Epidemiological Study of Childhood Leukemias

In a study to investigate possible associations of childhood cancers with exposure to natural background radiation in Great Britain, Kendall et al. (2013) found a statistically significant increase in the risk of childhood leukemias at cumulative doses to bone marrow from external gamma radiation of about 4 mGy or higher. That study had a greater statistical power to detect an effect than previous studies of an

association of childhood leukemias with exposure to natural background. Furthermore, estimated cumulative risks of leukemias at attained ages of 1 to 14 years were consistent with estimates based on data in the LSS cohort (NRC 2006; UNSCEAR 2008). These findings suggest that a dose rate from chronic exposure below which only the linear term in an assumed linear-quadratic dose-response for leukemias in the LSS cohort would contribute could be as low as the dose rate from natural gamma radiation of about 1 mGy y^{-1} , or about $10^{-6} \text{ mGy min}^{-1}$. This estimate is uncertain, however, due to uncertainties in estimated risks of leukemias in the LSS cohort and children in Great Britain.

Kendall et al. (2013) did not find an association between all childhood cancers excluding leukemias and exposure to natural gamma radiation at cumulative doses up to 15 mGy.

A.3.6 Conclusions About Upper Limit of Low Dose Rate

Available data to estimate an upper limit of a low dose rate from protracted exposure to low-LET radiation appear to be less definitive than data reviewed in Section A.2 to estimate an upper limit of a low acute dose. Since estimates based on analyses of the effect of dose rate on dose-responses for chromosome aberrations that were scored using conventional Giemsa staining probably are invalid, studies of cancer induction in laboratory animals provide the only documented basis for estimating an upper limit of a low dose rate. Consequently, there is little reason to depart from the recommendation by UNSCEAR (1993) that an upper limit of a low dose rate is about 0.1 mGy min^{-1} . Such an upper limit defines a dose rate below which a DDREF should be applied in estimating risks of all cancers except leukemias at any total dose on the basis of risk coefficients at high acute doses in the LSS cohort. It also defines a dose rate below which risks of leukemias should be estimated by assuming that only the linear term in an assumed linear-quadratic dose-response in the LSS cohort contributes. However, the uncertainty in the estimated upper limit of a low dose rate is substantial (probably several-fold).

Recommendations on an upper limit of a low dose rate of 2 mGy min^{-1} by ICRP (1991) and $0.01 \text{ mGy min}^{-1}$ by the BEIR VII committee (NRC 2006) differ by about an order of magnitude from the recommendation of about 0.1 mGy min^{-1} by UNSCEAR (1993). However, in the absence of justifications of the recommendations by ICRP and the BEIR VII committee, neither their validity nor their uncertainties can be evaluated.

APPENDIX B

ESTIMATION OF DDREF IN BEIR VII REPORT

B.1 APPROACH TO ESTIMATION OF DDREF BY BEIR VII COMMITTEE

This appendix presents a review and critique of the approach used by the BEIR VII committee (NRC 2006) to estimate a DDREF based solely on analyses of dose-responses from acute exposure of the Japanese atomic-bomb survivors (LSS cohort) and laboratory animals. We accept the LDEF the committee derived from its analysis of the dose-response for solid tumor incidence in the LSS cohort, as summarized in Table 5.2 in the main report, despite our reservations about whether an LDEF derived from an acute dose-response can be characterized as a DDREF, i.e., that an LDEF accounts for the effects of dose and dose rate on dose-responses (Sections 2.2 and 5.2.1.4). The discussion in this appendix focuses is on how the BEIR VII committee used animal data in conjunction with data in the LSS cohort to estimate a DDREF and whether the animal data used in the committee's analysis were appropriate for the purpose of quantifying a DREF of relevance to cancer induction in humans.

As discussed in Sections 2.3 and 4.3 in the main report, a wide variety of dose-response relationships were observed in studies of radiation carcinogenesis in laboratory animals. The BEIR VII committee (NRC 2006) dealt with the complexity of dose-responses observed in animals by:

- eliminating from consideration all studies of cancer induction in animals other than studies at the barrier facility at Oak Ridge National Laboratory using specific-pathogen-free mice from the RFM and BALB/c strains;
- restricting the data used in an analysis to dose-responses from acute whole-body exposures to ¹³⁷Cs gamma rays at doses of 0–2 Gy or, for studies of life-span shortening, to dose-responses from acute whole-body exposures of RFM female mice at doses of 0–1.5 Gy;
- excluding data for induction of thymic lymphomas, ovarian cancer, reticulum cell carcinoma, and non-myeloid leukemias on the grounds that they were thought to arise by atypical mechanisms (e.g., some require large doses for initiation and, thus, involve apparent threshold responses) or they represented an ill-defined combination of cancer types; and
- fitting all acute dose-responses with a linear-quadratic (LQ) model even though, as shown in Figure B.1, data for the majority of cancers suggested other patterns of dose-response.

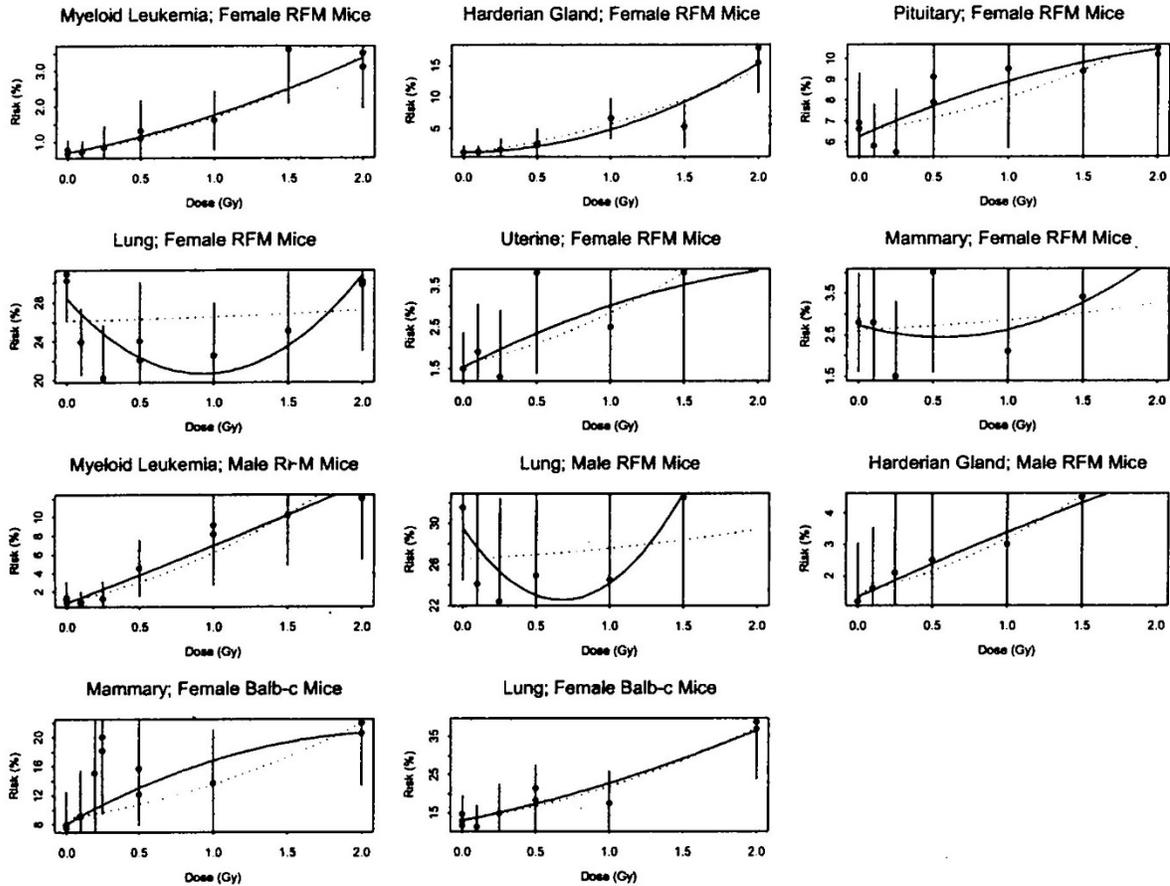


Figure B.1. Estimated risks of cancer induction in specific-pathogen-free mice vs dose from acute exposure in studies conducted in barrier facility at Oak Ridge National Laboratory. Vertical bars extend two standard errors above and below each estimate. Solid curves are based on fits to each data set without constraints on the form of the dose-response. Dotted curves are best linear-quadratic (LQ) fits when curvature parameter is constrained to be the same in all data sets. Source: NRC (2006), Figure 10 B-2.

The BEIR VII committee justified its choice of an LQ dose-response model based on a study of induction of lung adenocarcinomas in female BALB/c mice, which indicated that a large number of small acute dose fractions (100 mGy each), separated in time by 24 hours, produced the same reduction in risk, compared with the risk from a single acute exposure, as chronic exposure at a dose rate of about $0.06 \text{ mGy min}^{-1}$, as predicted by the linear slope from an LQ model fit to the dose-response from acute exposure. In addition, several data sets used by the committee were pooled results from as many as three studies conducted at different times. All the data used by the committee had been compiled by Edwards (1992) for an analysis of DDREFs based on data on radiation-induced cancer in animals.⁸³ However, as

⁸³ The report by Edwards (1992) was a major source for the evaluation of DDREFs by UNSCEAR (1993).

discussed below, Edwards (1992) reached different conclusions about the applicability of the animal data to estimation of DDREFs in humans.

In only three of the 11 sets of tumor data in animals selected by the BEIR VII committee and shown in Figure B.1 were the dose-responses best fitted with an LQ dose-response that showed some evidence of upward curvature; these fits are the solid curves for myeloid leukemia in female RFM mice, Harderian gland tumors in female RFM mice, and lung adenocarcinomas in female BALC/c mice. However, even for these cancers, linear fits to the data by the authors of the studies were superior to or equally as valid from a statistical standpoint as LQ fits (Ullrich and Storer 1979a, 1979b, 1979c; Ullrich 1983). NCRP (1993a) was referring to such data when it concluded that “[i]n animal experiments, significant dose-rate effects have been noted for the response of certain tissues in which a linear fit to the data obtained at a high dose rate was considered the best fit” and “[t]he fact that the linear fit appears appropriate for the data over a broad range of doses does not preclude a dose-rate effect.” One difference is that responses at 3 Gy for the first two cancer types noted above were omitted by the committee; this was a subjective choice that the committee recognized would result in different dose-response relationships (NRC 2006). This choice was used to support the committee’s decision to assume LQ rather than linear dose-response relationships for those cancer types.

As indicated by the solid curves in Figure B.1, fitted dose-responses for myeloid leukemia in male RFM mice and Harderian gland tumors in male RFM mice were essentially linear, while best fits for pituitary tumors in female RFM mice, uterine tumors in female RFM mice, and mammary tumors in female BALB/c mice exhibited some degree of downward curvature.⁸⁴ However, Ullrich and Storer (1979b, 1979c) and Edwards (1992) showed that a linear fit to the data for pituitary tumors was superior to an LQ fit when data at 3 Gy were included, and the dose-response for mammary tumors is complex for biological reasons summarized in Section B.2.2. Dose-responses for lung adenocarcinomas in male and female RFM mice and mammary tumors in female RFM mice were U- or J-shaped, which could indicate a hormetic response. We think it is significant that most of the data on lung tumors in RFM mice at intermediate doses could be artifacts of tumor ascertainment (Ullrich and Storer 1979b, Ullrich et al. 1979), so the applicability of the data on lung tumors in RFM mice to the committee’s analysis appears questionable. When female RFM mice were given localized x-ray exposures to the thoracic region, incidence of lung tumors was best described by a threshold model with a quadratic response above the threshold dose (Section B.2.1); i.e., that dose-response was different from any fitted dose-responses for RFM mice shown in Figure B.1.

⁸⁴ The BEIR VII committee’s inclusion of data on pituitary tumors in RFM mice is puzzling when the committee suggested that those data could be compromised by effects associated with the sensitivity of the mouse ovary and disruption of pituitary and ovarian hormone functions (NRC 2006). Although we think that such data should be included, the committee’s position appears to be inconsistent.

Because statistical uncertainties in the animal data often were large, the BEIR VII committee was able to fit LQ dose-responses with the same curvature parameter ($\beta/\alpha \approx 0.4 \text{ Gy}^{-1}$) to all data sets, with the assumption that only the linear (α) coefficients varied; these fits are the dotted curves in Figure B.1. Although the actual curvature in the 11 dose-responses was not the same, the committee's LQ model with a common curvature explained 97% of the variability in responses, while a model that allowed a variable curvature explained 98% of the variability. However, inspection of the 11 data sets suggests that a linear dose-response also would fit most, if not all, of the data sets with similar (or superior) results with respect to explaining the variability. However, use of a linear dose-response model would not have permitted an estimate of DDREF without access to data on responses at lower dose rates or the committee's application of a Bayesian analysis to the data in animals and the LSS cohort.

In a separate analysis, the BEIR VII committee judged that the dose-response for life shortening in female RFM mice could be fitted with an LQ model with a curvature parameter, β/α , of about 1 Gy^{-1} . By combining this curvature parameter with the common curvature parameter in the LQ fits to tumor data in animals given above and accounting for uncertainties in both estimates, the committee estimated a β/α of 0.5 [95% CI: (0.1, 3.2)] Gy^{-1} , which yielded a DDREF of 1.5 [95% CI: (1.0, 4.4)]. A Bayesian analysis that combined the committee's estimated curvature in the dose-response for incidence of all solid tumors in the LSS cohort at neutron-weighted colon doses of 0–1.5 Gy of $\beta/\alpha = 0.3$ [95% CI: (-0.1, 1.5)] Gy^{-1} , which yielded the DDREF of 1.3 [95% CI: (0.8, 2.6)] given in Table 5.2 in the main report, with the estimated curvature based on the animal data resulted in a DDREF of 1.5 [95% CI: (1.1, 2.3)]. This DDREF would be applied to estimated cancer risks based on data in the LSS cohort.

The BEIR VII committee acknowledged that the probability distribution of DDREF with a 95% CI of (1.1, 2.3) probably understated the uncertainty in the state of knowledge of DDREF based on data in the LSS cohort, because of the many subjective judgments involved. The committee concluded that further study “could possibly lead to a better summarization of radiobiological information ... [but] would be similarly obstructed by the subjectivity involved in the choice of dose range upon which [LQ] models are fit, by the inconsistency of animal experiment results, and by the difficulty in translating mouse results to human cancer rates” (NRC 2006).

The committee then inflated the variance of the distribution of the logarithm of DDREF by 50% for use in estimating uncertainties in cancer risks based on data in the LSS cohort. The committee justified the inflated variance on the grounds that “the DDREF analysis is necessarily rough and the variance of the uncertainty analysis described [in Annex 10B] is, if anything, misleadingly small” (NRC 2006). However, the committee did not provide a quantitative rationale for the assumed increase in the variance of the logarithm of DDREF.

The result of the BEIR VII committee's analysis was a DDREF of 1.5 [95% CI: (0.8, 2.7)]. This CI is essentially the same as the 95% CI of (0.8, 2.6) that was based solely on the committee's analysis of data in the LSS cohort, as given above and in Table 5.2 in the main report.

B.2 CRITIQUE OF APPROACH IN BEIR VII REPORT

B.2.1 Basic Assumptions

The BEIR VII committee's approach to derivation of a DDREF, including the approach to selecting relevant data in animals, raises important concerns. First, the committee's reliance on estimates of DDREF derived from analyses of curvature in fits to acute dose-responses in animals that were assumed to be universally LQ in nature, despite the variety of patterns observed in the original data as indicated in Figure B.1, is at odds with results from previous analyses of the animal data (NCRP 1980; Edwards 1992; Fry 1992; UNSCEAR 1993; Cox et al. 1995; see Section 4.2). In addition, because the parameters β and α in an LQ model fit are negatively correlated (Kellerer and Brenot 1974; Edwards 1992), it seems unlikely that the curvature parameter, β/α , would be constant when the range of variation in α coefficients indicated by the data in Figure B.1 is between one and two orders of magnitude. On the basis of these considerations, we believe that the committee's assumption of an LQ dose-response relationship with a fixed curvature parameter may compromise the committee's analysis of the data in animals.

Second, given that the linear risk coefficients for induction of solid cancers in humans derived by the BEIR VII committee were based on data on dose-responses in the LSS cohort at neutron-weighted organ doses as high as about 4 Gy, depending on the cancer type, we believe that a DDREF that is intended to be applied to those risk coefficients should be based on an analysis of data over the same dose range, rather than the more restricted dose ranges of 0–1.5 Gy in the LSS cohort and 0–2 Gy in the animal data; i.e., data in the LSS cohort or animals at doses exceeding 1.5 or 2 Gy should not be excluded from an analysis. However, inclusion of such data could be problematic when data at higher doses include effects of cell sterilization that are not accommodated by the LQ model that was used by the committee to estimate a DDREF.

Finally, it is puzzling that the BEIR VII committee used data on radiation-induced leukemia in animals in its analysis to estimate a DDREF to be applied in estimating risks of solid tumors in humans when the committee used human data on solid tumors only.

B.2.2 Influence of Biological Factors on Tumor Responses

By pooling data in animals and restricting the curvature parameter in fitted LQ dose-responses to a single value, the BEIR VII committee seemingly discounted known and potential differences in the etiology and biology of different cancers, e.g., leukemias compared with solid tumors. The idea that differences in the shapes of dose-responses for different cancer types do not convey useful information because of the statistical uncertainties associated with individual data points is not universally accepted (e.g., Fry 1992; NCRP 2001). Others have concluded, for example, that there are marked differences in the shapes of acute dose-responses for different tumors in the same animal strain (Edwards 1992; UNSCEAR 1993; NCRP 2001), and that there is no common value of DDREF that can be applied to all tumors (NCRP 1980; Edwards 1992; Fry 1992). By discounting substantial differences in best fits to dose-responses for different tumors in animals, the BEIR VII committee seems to imply that biological differences in specific cancer types can be ignored. We do not agree that such a conclusion is valid.

In addition, dose-responses for lung adenocarcinomas in female BALB/c mice, which the BEIR VII committee used to justify its assumption that an LQ model is universally applicable to the data in animals, seem to us to be exceptional, rather than commonplace. In addition, estimates of DDREF based on comparisons of dose-responses for lung adenocarcinomas in female BALB/c mice from acute and either chronic or fractionated exposures were 2.1, 3.2, and 4.2 at doses of 1, 2, and 3 Gy, respectively (UNSCEAR 1993), all of which are higher than the central estimate of 1.5 derived by the BEIR VII committee based on the combined animal data.⁸⁵ Although this comparison suggests that DDREFs derived from data from acute exposures may be underestimates, they are inconclusive when uncertainties in the various estimates and the expected increase in DDREF with increasing dose are taken into account.

It also is important to note that the BALB/c mouse is exceptional in the following respects:

- It carries a genetic defect in one of the key repair pathways for DNA DSBs that results in inefficient repair of radiation-induced DSBs, and it is susceptible to induction of genomic instability, in contrast to less radiosensitive strains of mice.⁸⁶

⁸⁵ A DREF of about 0.5 for lung adenocarcinomas in BALB/c mice was derived based on a Bayesian statistical analysis of archived data from the Oak Ridge barrier facility under conditions of acute and chronic exposure at a dose of 2 Gy (NCRP 2005). However, the complete set of data in the BALB/c mice indicates that DREF should be ≥ 2 [see Table 4.2 in the main report and Figure 10B-1 in NRC (2006), which was based on a more extensive study of the effects of dose protraction and fractionation by Ullrich et al. (1987) that was not considered by the authors of the study cited in NCRP (2005)].

⁸⁶ Only one mutational event was required to transform the cancer-prone BALB/c strain into the SR/CR strain, which is virtually immune to cancer development. If this mutational event represents reversion to the wild type, most of the results from radiobiological research involving the BALB/c strain might have little relevance to estimating a DDREF. To our knowledge, studies of radiation effects in the SR/CR strain have not been carried out.

- It is one of the most radiosensitive strains of mice (Okayasu et al. 2000).
- The sparing effect of reduced dose rates on the lethal effects of radiation is greatly reduced when compared with the less radiosensitive C57BL/6 black mouse (Kallman 1962). Lack of a sparing effect also was found to be typical of radiosensitive cell lines that exhibited major defects in the repair of DNA DSBs. The lower the sparing effect, the lower the level of curvature in an LQ dose-response.

On the basis of these characteristics, we would expect that dose-responses in this mouse strain typically would exhibit less curvature than dose-responses in other mouse strains and, therefore, that estimates of LDEF would be lower. In addition, patterns of induction of mammary cancers in female BALB/c mice were different from those for lung cancers, as discussed below.

Based on linear fits to dose-responses from acute and chronic exposure at doses of 0–2 Gy, Edwards (1992) estimated DREFs for Harderian gland tumors in female RFM mice of $3.8_{-1.1}^{+1.5}$ and $4.2_{-1.5}^{+2.1}$ using equations that did or did not account for second-order error terms, respectively, where the uncertainties are ± 1 SE. Using Monte Carlo uncertainty propagation techniques, we estimated a DREF of 3.8 [95% CI: (1.8, 11)] for incidence of Harderian gland tumors in female RFM mice based on the linear coefficients for tumor incidence derived by Edwards (1992), but without accounting for second-order error terms (Table 4.2). All three estimates appear to be inconsistent with the DDREF derived by the BEIR VII committee from the animal data in Figure B.1, and the inclusion of two data sets for this tumor in the committee's analysis raises additional concerns about the suitability of DDREFs derived from acute exposure data only and the applicability of data for Harderian gland tumors, which are found only in animals that have a third eyelid, to humans.

If the acute dose-responses for myeloid leukemia and Harderian gland tumors are excluded from consideration, only one of the seven remaining data sets shown in Figure B.1, i.e., the dose-response for lung adenocarcinomas in female BALB/c mice, exhibits an apparent LQ response at doses of 0–2 Gy. We think that an analysis of those seven data sets would yield a significantly larger estimate of DDREF with substantially greater uncertainty than the DDREF and its uncertainty derived by the BEIR VII committee (e.g., Edwards 1992; UNSCEAR 1993).

Additional support for such a conclusion is provided by an observation that dose-responses for several tumors were reduced essentially to the level of controls when doses that produced the maximum tumor response from acute exposure were delivered chronically at a dose rate of about $0.06 \text{ mGy min}^{-1}$. This behavior, which indicates the potential for very high DREFs (UNSCEAR 1993), was observed in data for myeloid leukemia in female RFM mice at doses of 0–3 Gy, which gave a DREF with a 95% CI

of (9.7, ∞), data for pituitary tumors in female BALB/c mice at doses of 0–2 Gy, which gave a DREF in the range of 4.6–25 (Edwards 1992), and data for mammary tumors in female BALB/c mice at doses of 0–0.25 Gy, which gave a DREF of 12, with an upper limit of ∞ . The estimated DREFs for myeloid leukemia and mammary tumors are given in Table 4.2 in the main report.

Curve-fitting exercises using a limited set of animal data with large uncertainties have been used by some to justify an assumption of an LQ dose-response for leukemias, for example, whereas the totality of the data, including the effects of low dose rates discussed above, led UNSCEAR (1993) to conclude that there was no consistent pattern in dose-responses for myeloid leukemia in animals. We make this point to illustrate that ignoring data on the effects of dose rate can lead to erroneous conclusions about the nature of dose-responses and the magnitude of a DDREF.

Suppression of ovulation in mice and rats at acute doses ≥ 0.5 Gy, e.g., by extensive killing of oocytes in mice (NCRP 1980; Shellabarger et al. 1986), leads to reduced secretion of estrogens and an underestimate of the risk from irradiation of the mammary gland. Administration of estrogen to animals was used to eliminate possible effects of radiation-induced variations in plasma estrogen levels, because hormonal factors are crucial to the development of mammary tumors in humans and animals (Bartstra et al. 1998b, 2000). Because the human ovary is much less sensitive to ionizing radiation than the rodent ovary (NCRP 1980; ICRP 2005; NRC 2006), we think that a DREF of about 12 for mammary cancer derived from responses in BALB/c mice at lower doses up to 0.25 Gy and an LDEF of about 10 derived from responses in rats irradiated at higher doses but supplemented with estrogen (see Table 4.2 in the main report) should be considered to fall within the range of possible values of DDREF for breast cancer in human females irradiated at doses up to about 3 Gy or higher, as in the LSS cohort. These estimates may be contrasted with values of 1–2 that are obtained from analyses of responses in mice under conditions of acute exposure at doses of 0–2 Gy, but which neglect the fine structure in the dose-response at low doses, and analyses of responses in rats not given estrogen supplements under conditions of acute and fractionated exposures up to 3 Gy.

Our conclusion is supported by the BEIR VII committee's review of epidemiological studies of breast cancer incidence that showed either the absence of risk or significant reductions in risk associated with cessation or reduction of ovarian function in women who received 5 Gy or more of x rays to the ovaries or whose therapy advanced the onset of menopause (NRC 2006; see also UNSCEAR 2008). The committee's risk model for breast cancer incidence, which was derived from the pooled analysis by Preston et al. (2002) discussed in Section 5.3.1 of the main report, also incorporates a reduction in the effect of attained age starting at age 60 to reflect the reduced risk of breast cancer after the onset of menopause: the exponent η in the relationship $(\text{attained age}/60)^\eta$ in the risk model changes from 3.5 to 1 at age 60 (NRC 2006). In the model developed by Preston et al. (2002), this change occurs at age 50.

Because laboratory mice and rats were much more sensitive to induction of mammary tumors than humans, we think that fractionation of doses in 10 mGy increments at intervals of 1–2 weeks, as in exposures of the Massachusetts tuberculosis fluoroscopy cohorts, is likely to have produced effects similar to those resulting from doses delivered chronically to animals at rates $<0.1 \text{ mGy min}^{-1}$. Indeed, when a higher RBE for medical x rays was taken into account, the effects of protracted doses of x rays delivered in such an incremental manner on induction of breast cancer in humans were similar to the effects of gamma radiation delivered chronically at somewhat higher dose rates, as in the Swedish skin hemangioma cohorts (Section 5.3.2).

B.2.3 Use of Life-Span Shortening As Endpoint for Solid Tumor Incidence

The BEIR VII committee's use of data on life-span shortening to estimate a DDREF to be applied in estimating risks of solid tumors is as puzzling as the use of data on leukemia for the same purpose when the committee assumed an LQ dose-response for leukemia in humans (NRC 2006). The spectrum of tumor types induced by protracted exposures at low dose rates in laboratory animals is different from the spectrum of tumor types induced by acute exposures. In mice, for example, high acute doses induce more thymic lymphomas and myeloid leukemias, which kill at a relatively young age, whereas lymphomas and ovarian tumors induced by protracted exposures at low dose rates occur late in life, with much less loss of life span (Fry 1992). The dominant neoplasms in hematopoietic tissues in mice are lymphocytic in origin (thymic lymphoma and reticulum cell carcinoma), whereas those neoplasms in humans are more frequently of myelocytic origin (Carnes et al. 2003). Life-span studies of irradiated rats also revealed a marked inverse relationship between radiation dose and the latency of mammary neoplasms (NRC 1990). Finally, not all tumors are a cause of life shortening in animals or humans (NCRP 1993a; Ron et al. 1994; UNSCEAR 2000; NRC 2006). Use of such an integrated measure as life shortening, which should be influenced appreciably by the occurrence of hematopoietic cancers, could introduce significant errors in estimating a DDREF for solid tumors. DDREFs derived from data on life shortening in mice would be determined mainly by dose-responses for hematopoietic cancers rather than solid tumors, and the types of hematopoietic tumors induced by ionizing radiation in mice are different from those induced in humans.

The BEIR VII committee's approach to selection of data on life-span shortening raises additional concerns. The high susceptibility of RFM mice to hematopoietic cancers suggests that those mice might not have been a good model of a life-shortening effect of ionizing radiation even in mice. The highly variable dose-responses for individual cancers in female RFM mice shown in Figure B.1 further suggests that the dose-response for life-shortening—like the dose-response for solid tumors in BALB/c mice—may be exceptional and perhaps even aberrant due to the contributions from hematopoietic cancers.

The BEIR VII committee's choice of a dose range of 0–1.5 Gy in analyzing data on life-span shortening, in contrast to a dose range of 0–2 Gy in analyzing data on cancer induction, and the committee's use of an LQ model to represent the data on life-span shortening from acute exposure is puzzling for several reasons. Storer et al. (1979) showed that no simple model could be used to represent the entire data set on life shortening that the committee evaluated. As indicated in Figure B.2, a quadratic dose-response relationship provided the best fit to the data from acute exposure at doses up to about 0.5 Gy (Storer et al. 1979; NCRP 1980), whereas the data at higher doses up to 4 Gy showed an approximately linear trend with a shallower slope. Indeed, the data and dose range the committee selected could not yield a statistically significant fit using an LQ model when the committee's plotted curve did not intersect the 95% CI of the responses estimated by Storer et al. (1979) at 0.5 or 0.75 Gy (the two points labeled A in Figure B.2 that lie well above the fitted LQ curve). An LQ model that fit all the data should exhibit a greater degree of curvature than shown in the committee's model fit. A greater degree of curvature would result in a higher estimate of DDREF. The low-dose slope the committee derived also is not consistent with the slope of the dose-response at a low dose rate shown in Figure B.2; a lower slope indicated by the data at a low dose rate also would increase the estimated DDREF.

The study by Storer et al. (1979) also provided data on life shortening from acute exposure in male RFM and female BALB/c mice and data from acute and chronic exposures of female RFM and BALB/c mice that could be used to estimate a DREF for that endpoint. In the studies of acute and chronic exposure, total doses of 0.5–2 Gy of ^{137}Cs gamma radiation were delivered at dose rates of 0.40 Gy min^{-1} (two exposure groups) or $0.069 \text{ mGy min}^{-1}$ (three exposure groups). Those data gave estimated DREFs for life shortening of about 2–3 in female RFM mice and about 2–4 in female BALB/c mice. NCRP (1980) estimated DREFs of 2.1 and 2.0, respectively, from the same data based on comparisons of the linear slopes of dose-responses in acutely and chronically exposed animals. However, the BEIR VII committee did not provide reasons for not including such data in its analysis.

Estimated LDEFs for life shortening in B6CF₁ (C57BL/6 x BALB/c) mice that received single weekly doses of ^{60}Co gamma radiation for 60 weeks were 2.9 in males and 3.5 in females (see discussion of data from the JANUS study in Section 4.3.6). When the animals were chronically exposed for 5 days each week and 22 h d^{-1} for 59 weeks at dose rates of $0.8\text{--}3.7 \text{ mGy min}^{-1}$, a higher DREF of 5.1 in male B6CF₁ mice was reported. That DREF was reduced by half when chronic exposures were terminated after 23 weeks. A comparison of results from the studies of acute and chronic exposure suggests that a quantitative distinction can be made between an LDEF and a DREF.

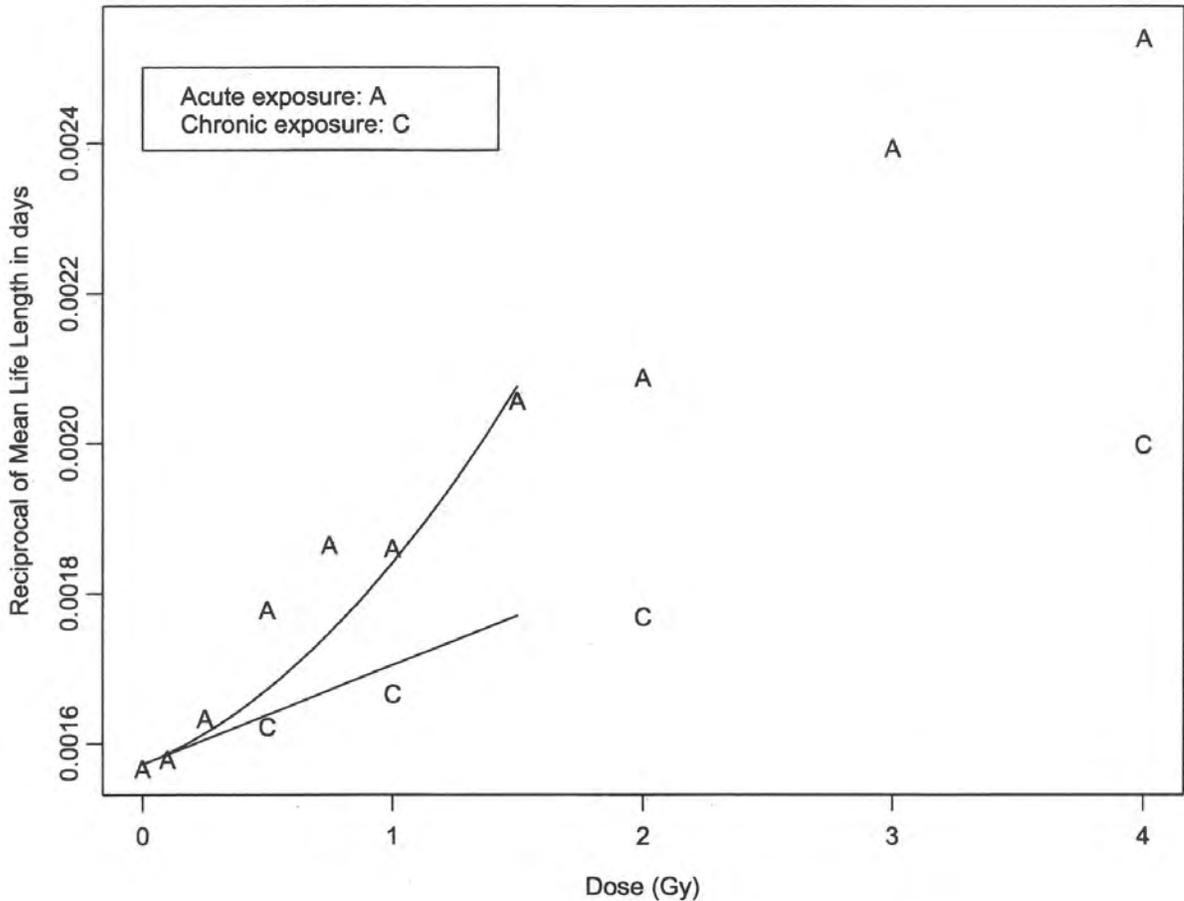


Figure B.2. Data on life-span shortening due to radiation exposure used by BEIR VII committee. Plotted curves are based on linear-quadratic (LQ) model for age-specific mortality rate fitted to data from acute exposure at doses of 0–1.5 Gy, with straight line determined by linear term in LQ dose-response. Source: NRC (2006), Figure 10 B-3.

B.2.4 Application of Animal Data in BEIR VII Committee’s Bayesian Analysis

The BEIR VII committee analyzed the combination of the probability distribution of an estimated curvature parameter that was based on the dose-response for all solid tumors combined in the LSS cohort and the probability distribution of an estimated curvature parameter that was based on dose-responses for various cancers in animals (the Bayesian prior distribution), which resulted in a Bayesian posterior distribution of DDREF with a smaller uncertainty than the uncertainty based on either data set alone (NRC 2006). For several reasons, we have concerns about the manner in which the Bayesian approach was used to analyze those data sets with respect to combining data on life-span shortening and cancer induction in animals or combining the data in animals and humans. Our reasons include (1) the genetic

uniqueness of BALB/c mice, (2) the differential susceptibilities of RFM and BALB/c mice to hematopoietic and solid tumors, (3) the inclusion of data for tumors of the Harderian gland, which is not found in humans, and (4) the high likelihood that the susceptibility to radiation-induced tumors in both of the inbred strains of mice is substantially different from susceptibility in most other strains of mice and members of the LSS cohort. For example, because of the strongly modifying effects of genetic background in animals that carry genetic variants that correspond to the familial human cancer syndromes, the BEIR VII committee concluded that rodent homologues are unlikely to provide a quantitatively reliable representation of radiation tumorigenesis in humans (NRC 2006).

Rather than reducing the overall uncertainty in an estimate of DDREF, we think that combining the different data sets used by the BEIR VII committee should have increased the uncertainty. Unless members of the LSS cohort had genetic defects in DNA repair genes similar to those in BALB/c mice and other aspects of their genetic makeup were similar to both inbred mouse strains with respect to susceptibility to radiation-induced tumors, we think that use of a prior distribution that represented the data in mice to reduce the uncertainty in the combined posterior distribution is questionable.

We note again that the BEIR VII committee concluded that the DDREF distribution with a 95% CI of (1.1, 2.3) that was obtained by combining estimates based on data in the LSS cohort and in animals probably understated the uncertainty in the current state of knowledge of the DDREF in the LSS cohort, because of the many subjective judgments involved. The committee then inflated the variance of its DDREF distribution for use in estimating uncertainties in cancer risks derived from data in the LSS cohort, but without providing a rationale. As a result, the 95% CI of the committee's estimate of DDREF increased to (0.8, 2.7), which is essentially identical to the 95% CI of the DDREF based on the LSS data alone prior to combining it with the animal data. This is essentially the result that would have been obtained if the Bayesian analysis had employed an "uninformative" prior distribution.

B.2.5 Summary and Conclusions

Given that the DDREF derived by the BEIR VII committee was based on data from acute exposures of the LSS cohort and animals, the quantity so derived is an LDEF, which may not properly account for effects of dose rate, i.e., a DREF. The committee began its evaluation of cancer risks in the LSS cohort by noting that "[study of the cohort] provides no information on dose-rate effects since all exposure is at high dose rates" (NRC 2006). However, based on an expectation that an LQ dose-response model applied to radiation-induced cancer and life shortening, the committee assumed that data from acute exposure in humans and animals provided information on effects of dose and dose rate on responses per unit dose; i.e., the committee assumed that the effects of dose and dose rate are the same.

If an LDEF and a DREF are not the same, the BEIR VII committee's decision not to use DREFs derived from studies in mice, rats and the beagle dog, such as data summarized in Table 4.2 in the main report, is important. Data on effects of dose rate on life-span shortening in mice and the beagle dog also are available and have been used in assessing commonalities in patterns of relative risk in different animal species and humans (UNSCEAR 2000; Carnes et al. 2003). Although the BEIR VII committee used animal data compiled by Edwards (1992) in its analysis, the committee did not heed Edwards' caution that data from acute exposure alone were inadequate to estimate a DDREF, and that data from chronic exposures were required. UNSCEAR (1993) and NCRP (1993a) reached conclusions similar to the caution by Edwards (1992).

In estimating a DDREF, the BEIR VII committee did not use epidemiological data other than data for all solid tumors combined in the LSS cohort. The large uncertainties in cancer-specific data were used to justify this decision (NRC 2006). However, the committee did use results from two earlier pooled studies of several exposed populations to estimate risks of breast and thyroid cancer (Preston et al. 2002; Ron et al. 1995), rather than data in the LSS cohort alone. As discussed in Sections 5.3 and 5.4, data in the different populations were pooled in those two studies without considering the potential effects of differences in the biological effectiveness of x rays and high-energy gamma rays or differences in the effects of a DDREF. It also is noteworthy that Preston et al. (2002) were unable to develop a model that adequately described radiation-related risks of breast cancer in all study populations. A possible reason for this noted by Preston et al. (2002) was differences in the nature of exposures (acute vs protracted). The BEIR VII committee concluded that an inability to identify the reasons for the differences in patterns of dose-responses for breast cancer in different populations and to model them effectively should "remind us that our understanding of radiation risks is incomplete and that models used to describe radiation risks are likely to be oversimplifications." We agree with this view and believe that it applies when attempting to estimate a DDREF and its uncertainty.

With regard to the observation of nearly linear dose-responses for solid cancers in the LSS cohort, NCRP (1993a) concluded that "[t]he fact that the linear fit appears appropriate for the data over a broad range of doses does not preclude a dose-rate effect. In animal experiments, significant dose-rate effects have been noted for the response of certain tissues in which a linear fit to the data obtained at a high dose rate was considered the best fit." We think that this conclusion is still valid, and that it indicates that the approach used by the BEIR VII committee did not yield an estimate of DDREF that reflects the current state of knowledge of the modifying effects of low doses or low dose rates on estimated risks of solid cancers from exposure to ionizing radiation.

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