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	Deoxyribonucleic acid
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 *in situ* hybridization
G	Giemsa (G-band, G-banding)
GM	Geometric mean
GSD	Geometric standard deviation

Gy	Gray
h	Hour
HM	Harmonic mean
hgprt	Hypoxanthine-guanine phosphorobosyl transferase
HPA	Health Protection Agency (U.K.)
HPRT	Hypoxanthine phosphorobosyl transferase
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	International Nuclear WORKers Study
IREP	Interactive RadioEpidemiological Program
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 *in situ* 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	Ribonucleic acid
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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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 $R_L = R_H/\text{DDREF}$, 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, $\Re$, from acute exposure at dose D (Gy) is estimated as $\Re = \alpha D + \beta D^2$, 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 ≡ 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., ^{60}Co 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–≥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 $\Re = (\alpha D + \beta D^2) \exp(-\gamma D)$. 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).

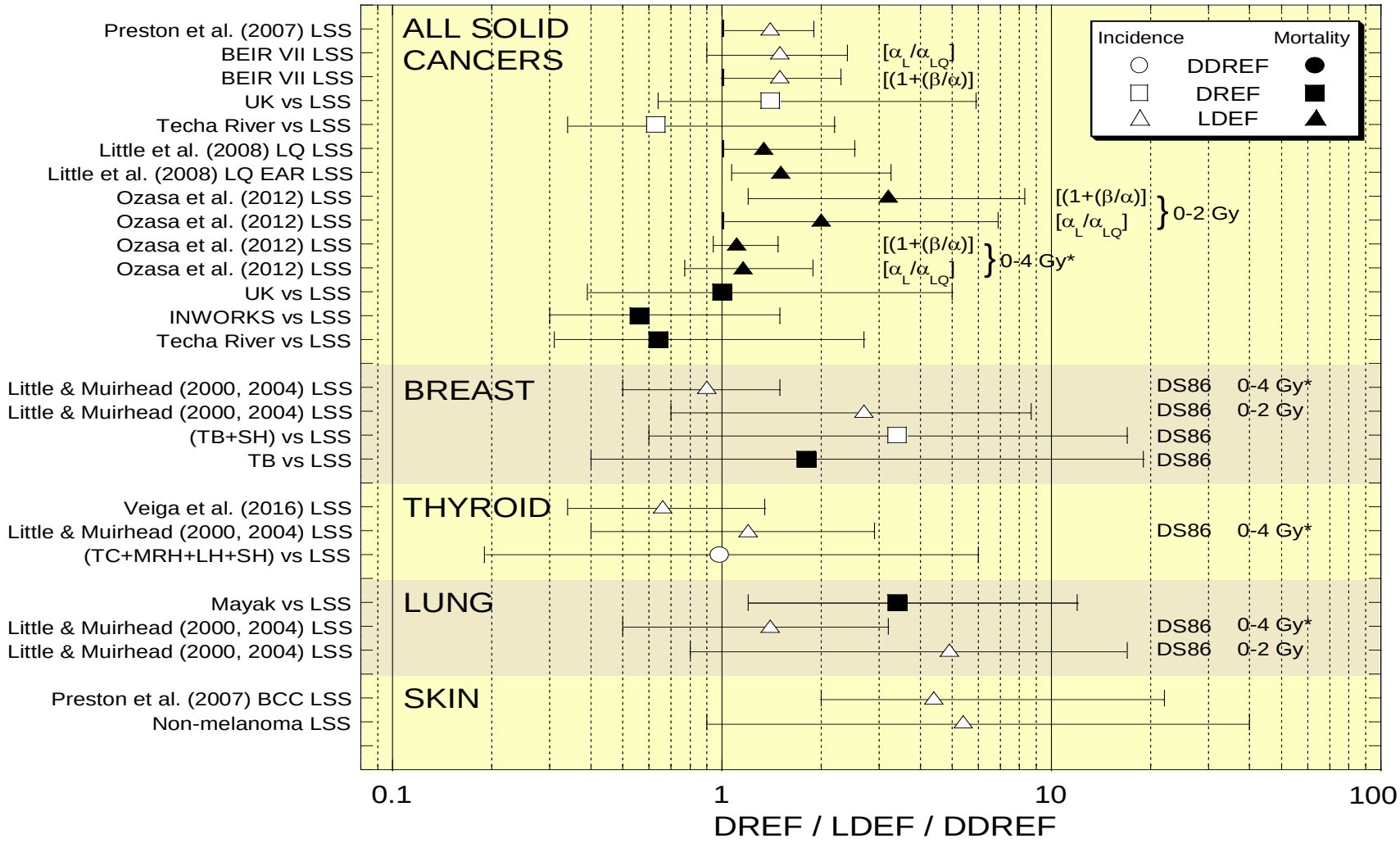

Figure ES.1. Estimates of 50th percentiles and 90% CIs of DREF, LDEF, or DDREF for all solid cancers or specific solid cancers based on selected epidemiological studies. Estimates are based on modeled ERRs and DS02 dosimetry in LSS cohort, except as noted. UK = United Kingdom workers; INWORKS = International 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] 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
	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) 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
	3.2 (1.2, 8.3)[c] 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
	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.

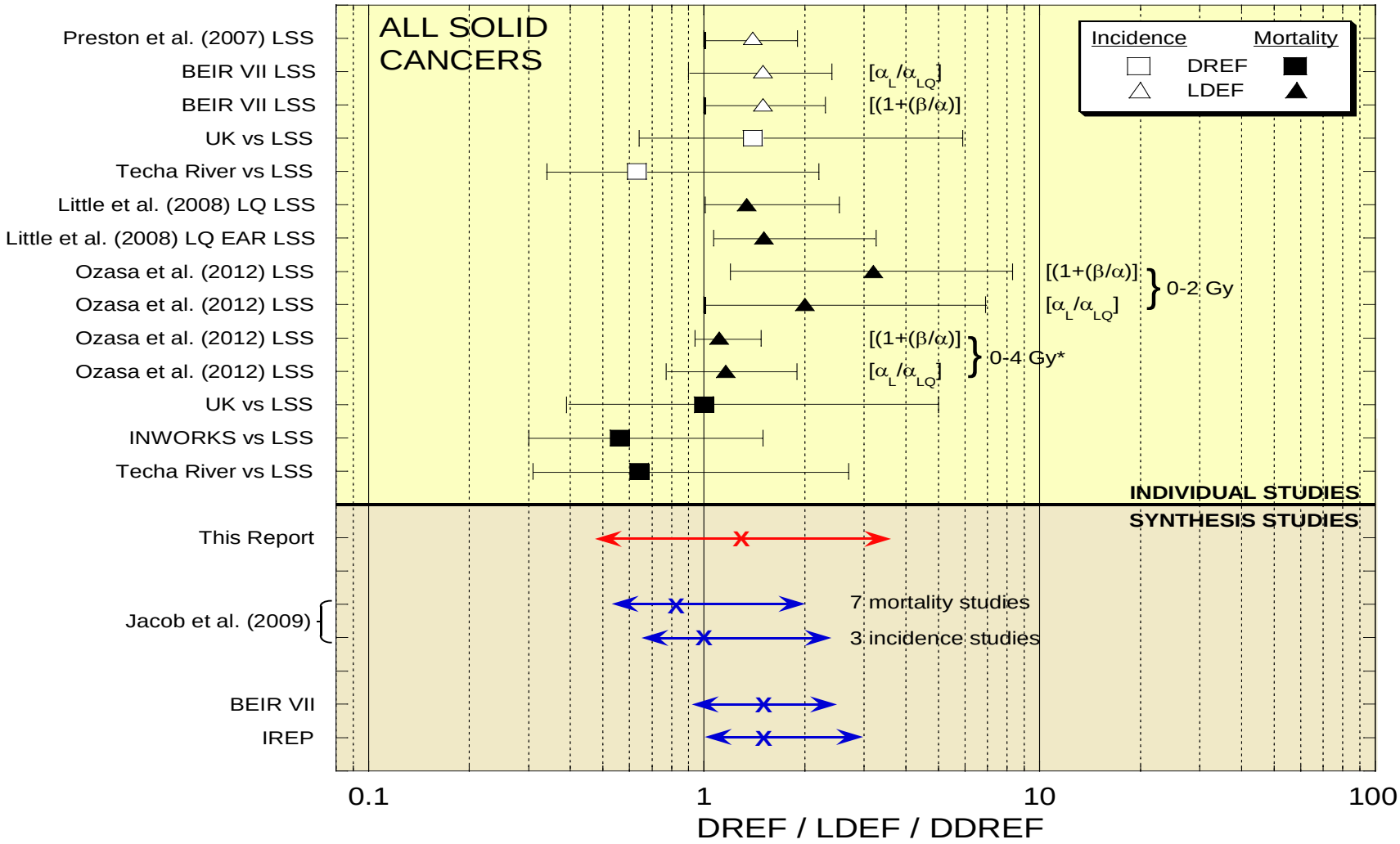

Figure ES.2. Estimates of 50th percentiles and 90% CIs of DREF or LDEF for solid cancer incidence or mortality used to develop probability distribution of DDREF for all solid cancers in this report (top) and comparison of our preferred distribution with DDREF distributions developed by Jacob et al. (2009) 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.