Paper

INTERACTIVE RADIOEPIDEMIOLOGICAL PROGRAM (IREP): A WEB-BASED TOOL FOR ESTIMATING PROBABILITY OF CAUSATION/ASSIGNED SHARE OF RADIOGENIC CANCERS

David C. Kocher,* A. Iulian Apostoaei,* Russell W. Henshaw,† F. Owen Hoffman,* Mary K. Schubauer-Berigan,† Daniel O. Stancescu,‡ Brian A. Thomas,* John R. Trabalka,* Ethel S. Gilbert,§ and Charles E. Land§

Abstract—**The Interactive RadioEpidemiological Program (IREP) is a Web-based, interactive computer code that is used to estimate the probability that a given cancer in an individual was induced by given exposures to ionizing radiation. IREP was developed by a Working Group of the National Cancer Institute and Centers for Disease Control and Prevention, and was adopted and modified by the National Institute for Occupational Safety and Health (NIOSH) for use in adjudicating claims for compensation for cancer under the Energy Employees Occupational Illness Compensation Program Act of 2000. In this paper, the quantity calculated in IREP is referred to as "probability of causation/assigned share" (PC/AS). PC/AS for a given cancer in an individual is calculated on the basis of an estimate of the excess relative risk (ERR) associated with given radiation exposures and the relationship PC/AS = ERR/ERR+1. IREP accounts for uncertainties in calculating *probability distributions* of ERR and PC/AS. An accounting of uncertainty is necessary when decisions about granting claims for compensation for cancer are made on the basis of an estimate of the upper 99% credibility limit of PC/AS to give claimants the "benefit of the doubt." This paper discusses models and methods incorporated in IREP to estimate ERR and PC/AS. Approaches to accounting for uncertainty are emphasized, and limitations of IREP are discussed. Although IREP is intended to provide unbiased estimates of ERR and PC/AS and their uncertainties to represent the current state of knowledge, there are situations described in this paper in which NIOSH, as a matter of policy, makes assumptions that give a higher estimate of the upper 99% credibility limit of PC/AS than other plausible alternatives and, thus, are more favorable to claimants.**
Health Phys. 95(1):119–147; 2008

Key words: dose reconstruction; risk analysis; radiation risk; cancer

* *SENES* Oak Ridge, Inc., 102 Donner Drive, Oak Ridge, TN 37830; † National Institute for Occupational Safety and Health, 4676 Columbia Parkway, Cincinnati, OH 45226; ‡ SRA International, Inc., 2605 Meridian Parkway, Durham, NC 27713; § Radiation Epidemiology Branch, National Cancer Institute, 6120 Executive Boulevard, Bethesda, MD 28092-7335.

For correspondence contact: D. C. Kocher, *SENES* Oak Ridge, Inc., 102 Donner Drive, Oak Ridge, TN 37830, or email at dck@senes.com.

(*Manuscript accepted* 16 *September* 2007)
0017-9078/08/0

INTRODUCTION

The Interactive RadioEpidemiological Program (IREP) is a Web-based, interactive computer code that is used to estimate the probability that a given cancer in an individual was induced by given exposures to ionizing radiation. A defining characteristic of IREP is that it accounts for uncertainties in estimating cancer risks due to exposure to ionizing radiation and in evaluating causation of a given cancer in an individual.

IREP was developed by a Working Group of the National Cancer Institute (NCI) and Centers for Disease Control and Prevention (CDC) (NIH 2003) to provide an update of the 1985 National Institutes of Health (NIH) Radioepidemiological Tables (NIH 1985), which had been used to facilitate adjudication of claims for compensation for cancers that could have been caused by exposure to ionizing radiation. The Congressional mandate to develop the 1985 NIH Tables and their update in IREP are described in NIH (2003).

The Energy Employees Occupational Illness Compensation Program Act (EEOICPA) of 2000 specified that the 1985 NIH Tables, as updated, shall provide the basis for adjudication of claims for compensation for cancer under the Act (U.S. Congress 2000). Accordingly, the National Institute for Occupational Safety and Health (NIOSH) adopted IREP for use by the U.S. Department of Labor (DOL) in adjudicating claims under EEOICPA (U.S. DHHS 2002a). NIOSH has modified IREP in a number of ways since its adoption to address needs of the compensation program for energy workers.

This paper describes models and methods that are incorporated in IREP to estimate cancer risks and the probability that a given cancer in an individual was induced by given exposures to ionizing radiation. Unless

otherwise noted, all discussions of IREP apply to both versions of the code. Where distinctions are necessary, the version currently used by NIOSH, which is the primary focus of this paper, is referred to as NIOSH-IREP and the original version as NIH-IREP. The treatment of uncertainty in IREP is emphasized. Models and assumptions in the two versions of IREP are described in more detail in NIH (2003), NIOSH (2002), Kocher et al. (2002, 2005), and reports by NIOSH's Office of Compensation Analysis and Support (OCAS) that are available at www.cdc.gov/niosh/ocas/ocasirep.html. IREP includes descriptions of models and assumptions under View Model Details and in other help files, and NIOSH-IREP includes descriptions of recent changes to that version. NIOSH also has issued user's guides to NIOSH-IREP; the latest version was issued in January 2007 (*SENES* Oak Ridge 2007).

IREP is a work in progress. NIOSH has implemented various improvements since IREP was adopted for use under EEOICPA, and the need for further improvements is continually being evaluated. NIOSH applies all modifications of NIOSH-IREP retroactively—i.e., whenever changes in risk models are implemented, all previously denied claims that could be affected are reassessed. Modifications of NIOSH-IREP are documented at the OCAS Web site noted above. More generally, publication of the National Research Council's Biological Effects of Ionizing Radiation (BEIR) VII report (NRC 2006) will occasion a complete reevaluation and appropriate revisions of risk models in NIH-IREP (NIH 2003).

QUANTITIES CALCULATED IN IREP

In NIOSH-IREP, the estimated probability that a given cancer in an individual was induced by given exposures to ionizing radiation is referred to as "probability of causation" (PC), whereas the term "assigned share" (AS) is used in NIH-IREP. The NCI-CDC Working Group preferred the latter term because it indicates that the quantity calculated in IREP is based on estimates of cancer risks due to radiation that are obtained from epidemiologic studies of exposed populations (NIH 2003). Thus, the quantity calculated in IREP is a property of a population group to which an individual belongs that is assigned to that individual.** Further discussion on the meaning of the quantity calculated in IREP is given in NIH (2003).

In this paper, the quantity calculated in IREP is referred to as "probability of causation/assigned share" (PC/AS) to retain the more common term (PC) used in EEOICPA (U.S. Congress 2000) that indicates an application to specific individuals, and to explicitly acknowledge its basis in estimates of cancer risks in exposed populations. Use of the term PC/AS also was endorsed in a report by a committee of the National Research Council (NRC 2005). PC/AS is defined as

$$\mathrm{PC/AS} = \frac{\mathrm{R}}{\mathrm{R} + \mathrm{B}}, \tag{1}$$

where R is the excess risk of an individual's cancer due only to sources of radiation exposure of concern to an evaluation of causation and B is the baseline (background) risk of that cancer due to all other causes, including other radiation exposures (e.g., unavoidable exposures to natural background radiation, nonoccupational radiation exposures of energy workers who file claims for compensation under EEOICPA). R is often called the excess absolute risk (EAR).

PC/AS for a given cancer in an individual is calculated in IREP on the basis of an estimate of the excess relative risk (ERR) associated with given radiation exposures (NIH 2003). ERR is defined as RR−1, where RR is the relative risk (i.e., the total risk to that individual relative to the baseline risk) given by (R + B)/B. Thus, the relationship between ERR and R is

$$\mathrm{ERR} = \mathrm{R/B},\ \mathrm{R} = \mathrm{ERR} \times \mathrm{B}. \tag{2}$$

On the basis of the definition in eqn (1) and the relationship in eqn (2), PC/AS is calculated as

$$\mathrm{PC/AS} = \frac{\mathrm{ERR}}{\mathrm{ERR} + 1}. \tag{3}$$

PC/AS is a probability and, thus, has a value between 0 and 1.†† In IREP, however, PC/AS is expressed in percent (e.g., a PC/AS of 0.5 is expressed as 50%).

Although the primary output of IREP is an estimate of PC/AS, IREP is first and foremost a tool for estimating ERRs. All the effort in modeling that is incorporated in IREP is directed at estimating ERR for a specific cancer in an exposed individual and its uncertainty. As indicated by eqn (3), calculation of PC/AS is a trivial exercise once ERR is estimated.

** Concerns about the validity of using epidemiologic data to evaluate causation of a given cancer in a specific individual, including a concern that the true PC in an individual or the etiologic fraction in a population may be underestimated, are discussed by Greenland (1999), Robins and Greenland (1989a, 1989b), and Greenland and Robins (1988). These concerns also are recognized and discussed in NIH (2003) and NRC (2000).

†† The risk due to radiation, R, also is a probability. However, the essential difference is that, whereas R is the probability that radiation will induce a cancer at some time after exposure in an individual who is free of that cancer, PC/AS is conditional on the occurrence of cancer. ERR is not a probability and can be >1.

USE OF PC/AS IN ADJUDICATING CLAIMS FOR COMPENSATION

Part B of EEOICPA (U.S. Congress 2000) and its implementing regulations (U.S. DHHS 2002a) specify that eligible claims for compensation for cancer shall be granted when the upper 99% credibility limit of an uncertain PC/AS is at least 50%.[‡‡] A PC/AS of at least 50% represents a requirement that it must be "at least as likely as not" that an individual's cancer was caused by exposure to ionizing radiation. The legal requirement to adjudicate claims on the basis of an upper 99% credibility limit of PC/AS—i.e., by allowing that the chance that PC/AS is at least 50% can be as little as 1%—then gives claimants the "benefit of the doubt" in the presence of uncertainty. Additional discussion on requirements of EEOICPA is presented in another paper in this issue (Neton et al. 2008).

NIOSH-IREP includes a procedure to calculate an upper 99% credibility limit of PC/AS when a claim for compensation involves more than one primary cancer (U.S. DHHS 2002a). In all such cases, NIOSH-IREP is run for each primary cancer separately, and the upper 99% credibility limit of PC/AS for all cancers combined, PC/AS_{total}, is calculated as

$$PC/AS_{total} = 1 - \prod_{i=1}^{n}(1 - PC/AS_i), \qquad (4)$$

where PC/AS_i is the upper 99% credibility limit of PC/AS for the i^{th} primary cancer. The terms $(1-PC/AS_i)$ are the probabilities that each cancer was not caused by radiation, and their product is the probability that none of the cancers were caused by radiation. By using upper 99% credibility limits in eqn (4), all uncertain PC/AS_i are assumed to be perfectly correlated. Thus, PC/AS_{total} is higher, and more favorable to claimants, than an upper 99% credibility limit that would be calculated by assuming that all PC/AS_i are uncorrelated. A procedure to estimate PC/AS in cases of multiple primary cancers is not included in NIH-IREP.

BASIC ASSUMPTIONS ABOUT CANCER RISKS DUE TO RADIATION

A basic assumption in IREP is that the risk due to radiation (R), and therefore ERR, for any cancer is an increasing function of dose, without threshold. With the exception of models to estimate ERRs for leukemia under conditions of acute exposure to low linear energy transfer (low-LET) radiations (photons and electrons) and the model for lung cancer due to exposure to radon, risk models for all cancers are based on an assumption that ERR is a linear function of dose. Thus, ERR for most cancers can be represented by $\alpha^* \times d$, where d is a dose to the organ or tissue in which an individual's cancer was induced and α^* is the ERR per unit dose for that cancer, which can depend on several factors discussed in this paper.

Models for leukemia under conditions of acute exposure to low-LET radiations that are incorporated in IREP are based on an assumption that ERR is a linear-quadratic function of dose and, further, that ERR can be represented by $\alpha^*(d + d^2)$ (NIH 2003). This model is a simplification of the general formulation of a linear-quadratic model for ERR, represented by $\alpha^* d + \beta^* d^2$, in which the coefficients of the linear and quadratic terms are assumed to be equal. This simplification was adopted because estimates of β^*/α^* that were obtained by fitting the general model to data on dose-response for various types of leukemia in Japanese atomic-bomb survivors were statistically consistent with $\beta^*/\alpha^* = 1$ (NIH 2003).

Given the assumed dose-response relationships described above and the relationship in eqn (3), PC/AS for any cancer is a nonlinear function of dose, and the dose required to reach any PC/AS (e.g., 50%) increases nonlinearly as ERR at a unit dose decreases, and vice versa. These statements about nonlinearities in PC/AS also apply to the model for lung cancer due to exposure to radon, in which ERR is calculated on the basis of an estimate of exposure rather than dose.

TREATMENT OF UNCERTAINTY IN IREP

IREP accounts for many sources of uncertainty in estimating ERR for a specific type of cancer in an individual and PC/AS for that cancer. An accounting of uncertainty is necessary when the upper 99% credibility limit of PC/AS is used in adjudicating claims for compensation.

General approach to accounting for uncertainty

Each parameter in models used to estimate ERR that is assumed to be uncertain is treated as a random variable and is described by a *probability distribution*. Doses to an organ or tissue in which a given cancer was induced also can be described by probability distributions. As discussed in this paper, a variety of bounded and unbounded probability distributions are used to represent parameter uncertainty in IREP.

A probability distribution of PC/AS is calculated in IREP in the following way. A probability distribution of ERR is calculated by repeated random sampling of probability distributions that are assumed to represent uncertainties in all relevant parameters and propagation

[‡‡] Other requirements in Part E of EEOICPA are not considered in this paper.

of the randomly selected parameter values through the models to estimate ERR. A probability distribution of PC/AS then is calculated from the probability distribution of ERR using eqn (3). Any percentile of the probability distribution of PC/AS (e.g., the upper 99% credibility limit) is determined by the same percentile of the probability distribution of ERR.

The method of sampling from probability distributions of parameters used in IREP is a form of stratified random sampling referred to as midpoint (median) Latin hypercube sampling; Latin hypercube sampling is described by McKay et al. (1979). The use of stratified sampling ensures that the entire probability distribution of each parameter is sampled, which is important when the upper 99% credibility limit of the probability distribution of PC/AS calculated in IREP is used in adjudicating claims for compensation.[§§]

Many probability distributions of model parameters incorporated in IREP are subjective representations of uncertainty that were developed using scientific judgment; i.e., they represent judgments about the state of knowledge of parameters used to estimate ERR for a given cancer in a specific individual. Even parameters for which probability distributions were derived on the basis of statistical analyses of fits to data on dose-response for specific cancers in exposed populations are subjective to the extent that they depend on assumed formulations of cancer risk models. Therefore, probability distributions of ERR and PC/AS calculated in IREP are subjective representations of uncertainty. The importance of scientific judgment leads to the use of such terms as "*credibility* limit" to describe properties of a probability distribution, rather than the more familiar "confidence limit."

The importance of judgment in developing models to estimate ERR and its uncertainty also is reflected in a NIOSH policy on use of IREP to evaluate claims for compensation under EEOICPA. Whenever NIOSH-IREP incorporates alternative cancer risk models or there are alternative assumptions about conditions of exposure that are considered plausible, NIOSH generally uses the model or assumption that gives a higher upper 99% credibility limit of PC/AS and, thus, is more favorable to claimants. Situations in which NIOSH applies claimant-favorable assumptions as a matter of policy are described in this paper.

[§§] Probability distributions of PC/AS are calculated using 2,000 iterations per run and a random seed of 99 to initiate the random sampling process as defaults. At the default number of iterations, a change in the random seed can result in variations in the upper 99% credibility limit of PC/AS about a nominal value of 50% of about three percentage points; i.e., the calculated upper 99% credibility limit can vary between about 47% and 53%. Given this degree of statistical precision and to reduce the chance of denying a claim for compensation due to an arbitrariness in random sampling, a special version of NIOSH-IREP is run whenever the calculated upper 99% credibility limit of PC/AS is $\geq$45% and $<$52%. The number of iterations per run is increased to 10,000, NIOSH-IREP is run 30 times using a new random seed in each run, and the mean of the upper 99% credibility limits of PC/AS from the 30 runs is compared with 50% to determine the outcome of a claim.

Overview of uncertainties considered in IREP

The various uncertainties that are taken into account in calculating probability distributions of ERR and PC/AS in IREP can be categorized as follows:

- statistical uncertainties in ERRs, as estimated from best fits to data on dose-response in study populations, principally Japanese atomic-bomb survivors, using conventional parameterizations of dose-response relationships; and
- uncertainties in various corrections and adjustments to estimated ERRs in study populations (1) to account for random and systematic errors in dosimetry for individuals in those populations and the minimum latency period of each type of cancer and (2) to apply estimated ERRs in atomic-bomb survivors to the U.S. population and to conditions of exposure other than acute exposure to low-LET radiations at relatively high doses.

Uncertainties in estimated doses to an organ or tissue in which an individual's cancer was induced also are taken into account when they are specified in input to IREP.

Two additional sources of uncertainty in estimating ERRs that had been considered by other investigators were not evaluated by the NCI-CDC Working Group (NIH 2003). The first involves diagnostic misclassification of cancers in atomic-bomb survivors (NCRP 1997; U.S. EPA 1999). The Working Group judged that it would be difficult to quantify uncertainties in estimated ERRs for specific types of cancer due to diagnostic misclassification, and that it is unlikely that this source of uncertainty would be important.

The second source of uncertainty involves extrapolation of estimated ERRs in study populations beyond the time period covered by the data, i.e., to the end of life for all members of those populations (NCRP 1997). This uncertainty was shown to be unimportant in a population of workers exposed at ages 20–65 y (NCRP 1997), which is similar to the population of concern to NIOSH in implementing EEOICPA. In addition, cancer risk models incorporated in IREP take into account an uncertain dependence of ERR on attained age or time since exposure, which accounts for this source of uncertainty to some extent.

INPUTS TO IREP

IREP calculates ERR and PC/AS on the basis of the following types of information related to an individual of concern that must be specified by the user:

- cancer type;
- sex, birth year, and year of diagnosis of cancer;
- number of exposures, year in which each exposure occurred, and radiation type and associated dose to the organ or tissue of concern in each exposure; and
- race or ethnicity (skin cancer only) or smoking history (lung cancer only).

Information on sex and age-related parameters is needed when ERR for most types of cancer is assumed to depend on sex, age at exposure, and attained age or time since exposure. The age at exposure must be ≥15 in NIOSH-IREP, whereas NIH-IREP can calculate ERR and PC/AS for any age at exposure. ERRs for skin or lung cancer are assumed to depend on race/ethnicity or smoking history, respectively.

Specification of cancer type

All cancers except chronic lymphocytic leukemia (CLL) are assumed to be radiogenic. In NIOSH-IREP, PC/AS can be calculated for 33 different cancer types, which are referred to as cancer "models" by NIOSH (2002); some of these types include cancers at more than one site. The different cancer types are placed in one of four groups, as indicated in Table 1; the basis for this grouping is described in a later section. Assumptions used by NIOSH to select the appropriate cancer model in specific cases, including assumptions about the primary cancer site when only a site of metastasis is known, are described in Section III of NIOSH (2002).

Specification of exposures

Information on exposures must be entered into IREP by radiation type—i.e., a single exposure is

Table 1. Cancer types (models) included in NIOSH-IREP.[a]

Category[b]	Cancer type (ICD-9 code)[c]	
Group 1	All digestive (150–159)[d]	Liver (155.0)
	Stomach (female only) (151)	Breast (174, 175)[e]
Group 2	Oral cavity and pharynx (140–149)	Connective tissue including other soft tissue not listed (171)[g]
	Esophagus (150)	Ovary (183)
	Stomach (male only) (151)	All male genitalia (including prostate) (185–187)
	Colon (153)	Bladder (188)
	Rectum (154)	Kidney and other urinary organs except bladder (189)
	Gallbladder (155.1, 156)	Eye (190)[g,h]
	Pancreas (157)	Nervous system (including brain) (191, 192)
	Lung including trachea and bronchus (162)[f]	Endocrine glands other than thyroid (194)[g]
	Respiratory other than lung (160, 161, 163–165)	Other and ill-defined sites (195)[g]
	Bone (170)[g]	Lymphoma and multiple myeloma (200–203)
Group 3	Lung including trachea and bronchus (162)[i]	All female genitalia except ovary (179–182, 184)
Group 4	Malignant melanoma (172)[j]	All leukemia, except chronic lymphocytic leukemia (204–208, except 204.1)
	Non-melanoma (173) — basal cell carcinoma	
	Non-melanoma (173) — non-basal cell carcinoma (squamous cell carcinoma)	Acute lymphocytic leukemia (204.0)
		Acute myeloid leukemia (205.0)
	Thyroid (193)	Chronic myeloid leukemia (205.1)
	Lung including trachea and bronchus (162)[k]	

[a] Adapted from Table 2 of NIOSH (2002); cancer types also are included in NIH-IREP (NIH 2003), except as noted.
[b] Cancer types in Groups 1–3 have a similar formulation of model to estimate ERRs; each cancer type in Group 4 has a unique model (see Table 2).
[c] International Classification of Diseases (ICD)-9 codes are given in U.S. DHHS (1991); see also Appendix II of NIOSH (2002). ICD-9 codes give cancer types for which ERR and PC/AS are estimated; codes also give cancer sites used as source of data to estimate ERRs associated with radiation exposure in study populations, except as noted.
[d] Model is intended to be applied to cancers of digestive tract other than esophagus, stomach, colon, or rectum. Cancer type is called "other digestive cancers" in NIH-IREP.
[e] Model for breast cancer was developed on the basis of data in females, and model is assumed to apply to males; only breast cancer in females is included in NIH-IREP.
[f] Model for lung cancer in Group 2 applies to sources of exposure other than radon. Model is used in NIH-IREP and is one of two alternatives in "combined" lung model used in NIOSH-IREP (see footnote i).
[g] Data for several cancer sites combined, referred to as "residual solid cancers," are used to estimate ERRs; those sites including bone and articular cartilage (170), connective and other soft tissue (171), male breast (175), eye (190), endocrine glands other than thyroid and related structures (194), and other and ill-defined sites (195).
[h] Eye cancer is not included in NIH-IREP; user must choose "other and ill-defined sites" or "nervous system."
[i] Alternative model for lung cancer in Group 3 applies to sources of exposure other than radon and is used in "combined" lung model in NIOSH-IREP (see footnote f); model is not used in NIH-IREP.
[j] Cancer type is not included in NIH-IREP. Model in NIOSH-IREP is based on data for basal cell carcinoma (173).
[k] Model for lung cancer in Group 4 applies to exposure to radon.

defined by a given dose to an organ or tissue of concern from a specific type of radiation, rather than a total dose from all radiation types combined. The different radiation types considered in IREP include photons, electrons, and neutrons of specified energy ranges and alpha particles of any energy produced in radioactive decay. As discussed in a later section, entering organ doses by radiation type and associated energy allows differences in their biological effectiveness to be taken into account in calculating ERR and PC/AS.

A single calculation of ERR and PC/AS in IREP can involve up to 1,000 separate exposures. In addition to the year in which each exposure occurred and the radiation type, required information on each exposure includes (1) the exposure rate (chronic or acute), (2) the assumed form of the probability distribution of the given dose to the organ or tissue of concern, and (3) values of parameters that define the selected probability distribution of dose.

Selection of the exposure rate can be based on an assumption that an exposure is chronic if the dose rate averaged over a period of a few hours is less than 6 mGy h^{-1} (UNSCEAR 1993; U.S. EPA 1994). In most cases, however, NIOSH assumes that all external exposures to photons or electrons are acute and that all external exposures to neutrons are chronic (NIOSH 2002; U.S. DHHS 2002b). As discussed in later sections, the resulting estimates of ERR and PC/AS are higher than estimates obtained using the alternative assumptions and, thus, are favorable to claimants. Use of these assumptions also obviates the need to make somewhat arbitrary judgments about whether external exposures of energy workers were acute or chronic. An exception is that all external exposures of energy workers to radionuclides in the environment are assumed to be chronic (NIOSH/OCAS 2002). All internal exposures are assumed to be chronic (NIOSH 2002).

Doses entered into IREP must be equivalent doses in cSv (i.e., in conventional units of rem commonly used in the U.S.). However, ERRs are calculated in IREP on the basis of estimates of the average *absorbed dose* to an organ or tissue of concern, D_T. As the first step in calculating an ERR, an equivalent dose, H_T, in cSv from a specific radiation type entered by the user is converted to the corresponding absorbed dose (Gy):

$$D_T\,(\mathrm{Gy}) = \frac{H_T\,(\mathrm{cSv})}{w_R \times 100}, \qquad (5)$$

where w_R is the radiation weighting factor for the specific radiation type (ICRP 1991). To ensure that the correct absorbed doses are used to calculate ERR and PC/AS, equivalent doses must be calculated using w_Rs assumed in IREP (ICRP 1991).

When the site of a primary cancer is known, equivalent doses in the organ or tissue in which that cancer occurred should be estimated. In cases of lymphoma, NIOSH evaluates alternative target organs and tissues and selects the plausible alternative in which the equivalent dose is the highest (NIOSH 2006a). Selection of a target organ or tissue for cancers at secondary sites when the primary cancer site is unknown is discussed in Section III of NIOSH (2002) and in another paper in this issue (Brackett et al. 2008).

IREP includes a menu of probability distributions that can be used to represent an uncertain equivalent dose. A constant distribution is used when no uncertainty is assigned.

Additional information in cases of skin or lung cancer

In estimating ERR and PC/AS for skin cancer, IREP requires that the user specify an individual's race or ethnic group. Racial and ethnic groups that can be selected in NIOSH-IREP include: American Indian or Alaskan native; Asian, native Hawaiian, or other Pacific Islander; Black; White-Hispanic; and White-Non-Hispanic. If no choice is made, "White-Non-Hispanic" is selected by default in NIOSH-IREP.***

In estimating ERR and PC/AS for lung cancer, two additional types of information must be specified by the user. The first is whether an exposure was due to radon, a source other than radon, or radon plus other source. If no choice is made, exposure to a source other than radon is selected by default. When exposure to radon is assumed, a cumulative exposure in Working Level Months (WLM)††† must be entered. The second is information on an individual's smoking history. Several smoking categories, which are determined by an individual's history of cigarette smoking, can be selected (NIH 2003; NIOSH 2002). The smoking category assumed by NIOSH is the category that applies at the date of diagnosis of a primary lung cancer (NIOSH 2002). If no choice is made, "never smoked" is selected by default in both versions of IREP.

*** NIH-IREP includes "All races/races not specified" as the default category. This category, which is not included in NIOSH-IREP, represents an average mix of racial and ethnic groups in the U.S. population and is intended to be used when an individual's race or ethnicity is not specified or is uncertain.

††† One Working Level Month (WLM) is a cumulative exposure, equivalent to exposure to one Working Level (WL) for a working month (170 h), where 1 WL = 2.08×10^{-5} J m^{-3} (1.3×10^5 MeV L^{-3}) of potential alpha energy in air due to short-lived decay products of radon.

MODELS TO ESTIMATE ERRS FOR SPECIFIC CANCER TYPES IN STUDY POPULATIONS AND THEIR UNCERTAINTIES

This section describes models that are incorporated in IREP to estimate ERRs for specific types of cancer in various study populations and their uncertainties. ERRs for nearly all cancers are estimated on the basis of modeled dose-responses in Japanese atomic-bomb survivors, who mainly received acute exposures to high-energy photons. Exceptions include thyroid cancer, for which data in groups exposed as children to medical x rays also are used, and lung cancer due to exposure to radon, for which ERRs are estimated on the basis of an analysis of pooled data from studies of U.S. uranium miners. Corrections and adjustments to modeled ERRs in study populations that are incorporated in IREP are described in the following section.

ERRs and their uncertainties are estimated on the basis of data on cancer *incidence* in study populations. Data on cancer incidence in Japanese atomic-bomb survivors obtained from information in cancer registries through the year 1987 (Thompson et al. 1994; Preston et al. 1994) and estimates of dose to individual survivors obtained using Dosimetry System 1986 (DS86) (Roesch 1987) provided the basis for estimates of ERR for most cancer types (NIH 2003). Only those survivors with DS86 doses (i.e., kerma in air from gamma rays and neutrons) <4 Gy were included, and age-specific baseline risks were estimated from incidence rates in survivors with weighted doses from gamma rays and neutrons of <10 mSv who were located within 2.5 km of the bombing at Hiroshima or within 10 km at Nagasaki (Thompson et al. 1994; Preston et al. 1994). The organ or tissue in which estimates of dose in atomic-bomb survivors were used to model ERRs for each type of solid cancer is listed in Table IV.C.1 of NIH (2003); a surrogate organ or tissue was used in many cases. Estimated doses to red bone marrow were used to model ERRs for leukemia, lymphoma, and multiple myeloma.

The following summaries of cancer risk models incorporated in IREP describe models that were developed by the NCI-CDC Working Group (NIH 2003), except as noted. The assumed risk models were similar to those that were used in other analyses (e.g., NRC 1990; Thompson et al. 1994; Preston et al. 1994). However, the NCI-CDC Working Group performed its own statistical analyses of data on dose-response independently of previous analyses. Other analyses were not designed for use in compensation programs, in which all cancer types are of concern, and careful attention needed to be paid to the effects of age- and time-related parameters on estimates of ERR and PC/AS.

The categorization of different cancer types (models) into four groups, as indicated in Table 1, was based on the number of cancers of each type in Japanese atomic-bomb survivors and assumptions about the dependence of ERRs on age- and time-related parameters. ERRs for cancer at a specific site were modeled only if there were at least 50 cases in atomic-bomb survivors who received doses ≥ 10 mSv (NIH 2003). Otherwise, with the exception of malignant melanoma, ERRs were modeled by merging data for cancers at several sites. For example, data for prostate cancer were merged with data for all other cancers of male genitalia because there were too few cancers of the latter type.

General model for most solid cancers

For all types of solid cancers, plus lymphoma and multiple myeloma, in Groups 1, 2, and 3 (Table 1), ERRs in Japanese atomic-bomb survivors were modeled by assuming a linear dose-response relationship of the general form:

$$\mathrm{ERR}(D, s, e, a) = \alpha D \exp\left[\beta I_s(\mathrm{sex}) + \gamma f(e) + \delta g(a)\right], \quad (6)$$

where D is a weighted dose in Sv, similar to an equivalent dose, calculated from a tissue-specific absorbed dose in Gy from photons (D_γ) and neutrons (D_n) as $D = D_\gamma + 10D_n$, $I_s(\mathrm{sex})$ is an indicator function for the opposite sex with the value 0 or 1, e is the age at exposure, a is the attained age (equal to the age at diagnosis in an individual with cancer), f and g are specified functions of e and a, respectively, and α, β, γ, and δ are the unknown parameters that are estimated from a statistical analysis of fits to cancer-specific data on dose-response. By restricting the coefficient α to positive values ($\alpha > 0$) on the basis of an assumption that any dose imposes some risk, eqn (6) can be written as

$$\mathrm{ERR}(D, s, e, a) = D \exp\left[\ln(\alpha) + \beta I_s(\mathrm{sex}) + \gamma f(e) + \delta g(a)\right]. \quad (7)$$

This general formulation is used for all solid cancers except thyroid cancer, skin cancers, and lung cancer due to exposure to radon; $\beta I_s(\mathrm{sex})$ is the only term that depends on sex.

The functions $f(e)$ and $g(a)$ in eqns (6) and (7) are given by:

$$f(e) = \begin{cases} -15 & \text{if} \quad e \le 15 \\ e - 30 & \text{if} \quad 15 < e \le 30, \\ 0 & \text{if} \quad e > 30 \end{cases} \tag{8}$$

$$g(a) = \begin{cases} \ln(a/50) & \text{if} \quad 0 < a < 50 \\ 0 & \text{if} \quad a \ge 50 \end{cases}. \tag{9}$$

The parameters γ and δ in eqns (6) and (7) were found to be negative in all cases. Thus, for most solid cancers, ERR at a fixed age at exposure is assumed to decrease linearly with increasing attained age to age 50 y at a rate independent of age at exposure and to remain constant thereafter, and ERR at a fixed attained age is assumed to decrease exponentially with increasing age at exposure between 15 and 30 at a rate independent of attained age and to remain constant outside that interval. An important implication of the general model for most solid cancers is that, at any age at exposure, there is no attained age beyond which ERR is reduced to zero. This result also applies to cancer types in Group 4, for which different risk models are assumed.

The formulations in eqns (8) and (9) apply when the difference between the attained age and age at exposure is sufficiently large that the minimum latency period of the cancer type of concern does not have a significant effect on estimates of ERR. Assumptions about minimum latency periods and their effects on ERRs are discussed in a later section.

Since the modifiers in eqns (8) and (9) are independent of sex, the parameter α in eqns (6) and (7) represents the sex-specific ERR per Sv at ages $e \ge 30$ and $a \ge 50$; at these ages, $f(e)$ and $g(a)$ are both zero. Therefore, at ages $e < 30$ or $a < 50$, or both, the sex-specific ERR per Sv, which is denoted by ERR/Sv (NIH 2003; NRC 2006), for most solid cancers can be expressed as

$$\text{ERR/Sv} = \alpha \times h(e, a; \gamma, \delta), \tag{10}$$

$$h(e, a; \gamma, \delta) = \exp[\gamma f(e) + \delta g(a)], \tag{11}$$

where α includes the term $\beta I_s(\text{sex})$ in eqns (6) and (7). In this formulation, the dependence of ERR on sex is no longer explicit, but is incorporated in the cancer-specific parameter α.

Cancer-specific estimates of the parameter β in the modifier for sex are used for stomach, colon, and liver cancer; for liver cancer, ERRs are assumed to be the same in males and females ($\beta = 0$). For all other cancer types in Groups 1, 2, and 3 that occur in both sexes, except the model for lung cancer in Group 2, a single value ($\beta = 0.843$) is assumed on the basis of the lack of evidence of significant departure from this common value. This assumption results in ERRs that are a factor of 2.3 higher in females than in males.

Application of the general formulation of the dose-response model described above to cancer types in Group 1, 2, or 3 and approaches to estimating uncertainties in ERR/Sv for cancer types in each group are described in the following three sections. The sections thereafter discuss (1) models for lung cancer in Groups 2 and 3 and (2) models for each cancer type in Group 4, which are not represented by the general formulation described above.

Model for cancer types in Group 1

Cancer types in Group 1 are distinguished from those in Group 2 by the larger number of cases in Japanese atomic-bomb survivors, which allowed a more detailed statistical analysis of data on dose-response. Fits to the data indicated that the parameters γ and δ in eqns (6) and (7) are cancer-specific. In addition, $\ln(\alpha)$ was found to be correlated with γ and δ, and these correlations were taken into account in fitting the data (NIH 2003).

The parameters $\ln(\alpha)$, γ, and δ that were estimated from a statistical analysis of fits to data on dose-response in atomic-bomb survivors are approximated by normal probability distributions. Mean values of $\ln(\alpha)$, γ, δ and their uncertainties (variances), and covariances of $\ln(\alpha)$ and γ, $\ln(\alpha)$ and δ, and γ and δ for each cancer type in Group 1 are given in Table IV.D.1 of NIH (2003). The resulting probability distributions of ERR/Sv were found to be approximately lognormal. Therefore, as also given in Table IV.D.1 of NIH (2003), ERR/Sv for each cancer type is assumed to be described by a lognormal probability distribution with a geometric mean (GM) given by $\alpha \times h(e, a; \gamma, \delta)$, where h is defined in eqn (11) and $f(e)$ and $g(a)$ are defined in eqns (8) and (9), respectively, and a geometric standard deviation (GSD) that is a function of $f(e)$, $g(a)$, variances of $\ln(\alpha)$, γ, and δ, and covariances of those parameters.

An example of how ERR/Sv in atomic-bomb survivors and its uncertainty depend on age at exposure (e) and attained age (a) for cancer types in Group 1 is provided by estimates for liver cancer shown in Fig. 1. Since the parameters γ and δ are cancer-specific, the dependencies at ages $15 < e \le 30$ and $a < 50$ are slightly different for other cancer types in this group. The 95% credibility intervals of ERR/Sv in Fig. 1 span an order of magnitude or less and correspond to GSDs of 1.5–1.8. Uncertainties in ERR/Sv for other cancer types in Group 1 are similar.

Breast cancer, which is a cancer type in Group 1, is treated differently in the two versions of IREP. The NCI-CDC Working Group analyzed data for breast cancer in female atomic-bomb survivors only, and ERRs for breast cancer in males are not calculated in NIH-IREP (NIH 2003). In NIOSH-IREP, the model for breast

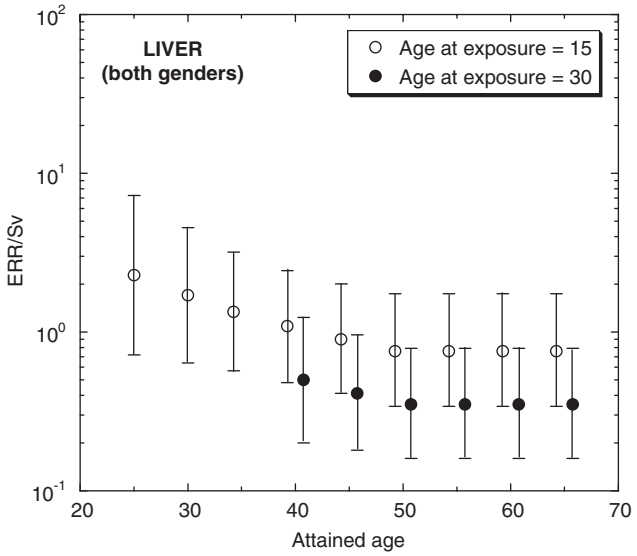

Fig. 1. Medians and 95% credibility intervals of lognormal probability distributions of ERR/Sv in linear dose-response for liver cancer in male or female Japanese atomic-bomb survivors at selected ages at exposure and attained ages in 5-y steps.

cancer in females is assumed to apply to males. This assumption, which is plausible on biological grounds, is used because it most often results in higher estimates of ERR and PC/AS in males than an alternative of applying the model for "residual solid cancers" in Group 2 (NIOSH 2002), which was developed on the basis of data in atomic-bomb survivors for several cancer types in Group 2 combined (Table 1, footnote g), including the few cases of male breast cancer.[‡‡‡] However, differences in baseline risks in the two sexes are taken into account in applying an ERR/Sv for female breast cancer in atomic-bomb survivors to males in the U.S. population.

Model for cancer types in Group 2

Cancer types in Group 2 include all other solid cancers, plus lymphoma and multiple myeloma, for which ERRs are estimated using the general formulation of the risk model in eqns (6–11). A variation of the general model is used for lung cancer due to sources of exposure other than radon in Group 2.

[‡‡‡] Since studies have shown that an early age at first full-term pregnancy reduces risks of breast cancer, an interaction between radiation and age at first full-term pregnancy also was considered in estimating ERRs for female breast cancer (NIH 2003). In a study of atomic-bomb survivors, a multiplicative model for the interaction between the two risk factors was found to be consistent with the data, and an additive interaction model could be rejected (Land et al. 1994). Thus, allowing for deviations from the multiplicative interaction model, which requires no adjustment of ERR/Sv to account for age at first full-term pregnancy, should contribute very little additional uncertainty to estimates of ERR/Sv for female breast cancer, and no adjustment was made to account for this risk factor (NIH 2003).

Since the number of cases of most cancer types in Group 2 in atomic-bomb survivors was less than the number of cases of Group 1 cancers, certain simplifications were used in modeling ERRs (NIH 2003). First, fits to the data on dose-response in atomic-bomb survivors indicated that, in contrast to Group 1 cancers, correlations between a sex-specific $\ln(\alpha)$ and the parameters γ and δ were modest. Therefore, α was assumed to be statistically independent of γ and δ. Second, as noted previously, the dependence of ERR on sex was found to be practically independent of cancer type, and a single value of the parameter β was used. Third, single values of γ and δ that were estimated from a statistical analysis of fits to the data for all solid cancers combined, including cancer types in Group 1 but excluding thyroid and skin cancers in Group 4, were used; i.e., these parameters were assumed to be independent of cancer type. This simplification was justified on the grounds that cancer-specific estimates of γ and δ did not differ significantly from the values that were assumed for all cancer types in Group 2.

Group 2 includes a cancer type referred to as "residual solid cancers" (Table 1, footnote g). ERRs for residual solid cancers are used to estimate ERRs for cancers at several sites where there were too few cases in atomic-bomb survivors to establish a dose-response model; these sites include bone, connective tissue, eye, endocrine glands other than the thyroid, and other and ill-defined sites. Thus, cancers at all these sites are assumed to have the same ERR/Sv in atomic-bomb survivors. However, cancer-specific baseline risks are taken into account in applying an ERR/Sv for residual solid cancers in atomic-bomb survivors to estimate ERR/Sv for cancers at these sites in the U.S. population.

In the model for lung cancer in Group 2, which was developed for use in NIH-IREP (NIH 2003), α also was found to be statistically independent of β. Therefore, for that cancer type, independence was assumed between $\ln(\alpha)$ and the modifier

$$h^*(s, e, a; \beta, \gamma, \delta) = \exp[\beta s + \gamma f(e) + \delta g(a)], \quad (12)$$

where $s = -0.5$ for males and $+0.5$ for females. As with all other cancer types in Group 2, the resulting ERRs for lung cancer are a factor of 2.3 higher in females than in males.

For each cancer type in Group 2, probability distributions of ERR/Sv were calculated using the model in eqns (10) and (11), except eqn (11) was replaced by eqn (12) in the case of lung cancer. The quantities h and h^* were assumed to be described by lognormal probability distributions with GMs and GSDs given in Section

IV.D.1 of NIH (2003). For each cancer type except lung cancer, selected quantiles of the sex-specific probability distribution of α are given in Table IV.D.2 of NIH (2003); those quantiles also represent probability distributions of ERR/Sv at ages at exposure (e) $\geq$ 30 and attained ages (a) $\geq$ 50. Selected quantiles of the probability distribution of α in the model for lung cancer in Group 2 are given in Table IV.D.3 of NIH (2003); that distribution applies to never smokers and both sexes. Methods used in IREP to interpolate between tabulated quantiles of α for the purpose of facilitating random sampling of probability distributions are described in Appendix D of NIH (2003).

At ages $e < 30$ or $a < 50$, or both, where the modifiers for age at exposure and attained age are nonzero [eqns (8) and (9)], there is some bias associated with an assumption of statistical independence of the parameter α and the parameters γ and δ [eqns (10–12)] for cancer types in Group 2. However, an analysis discussed in Section IV.D.1 and Appendix C of NIH (2003) indicates that this bias is small and has an insignificant effect on estimated upper 99% credibility limits of ERR and PC/AS.

For a majority of cancer types in Group 2, the probability distribution of α includes negative values as a consequence of the few excess cancers in atomic-bomb survivors who received doses $\geq$10 mSv. Since any exposure is assumed to impose some risk, all negative values in tabulated quantiles of α are set to zero in IREP. As a result, means of probability distributions of ERR and PC/AS for those cancer types are higher than would be calculated by allowing negative values of α. However, setting all negative values of α to zero has no effect on estimated upper 99% credibility limits of ERR and PC/AS.

For all cancer types in Group 2, the dependencies of ERR/Sv in atomic-bomb survivors and its uncertainty on age at exposure (e) and attained age (a) are similar to those for liver cancer (Group 1) shown in Fig. 1. However, in contrast to Group 1 cancers, the dependencies at ages $15 < e \leq 30$ and $a < 50$ are the same for all Group 2 cancers as a consequence of an assumption that the parameters γ and δ are independent of cancer type. In addition, probability distributions of ERR/Sv for Group 2 cancers are not lognormal and are not well described by any commonly used distribution. Uncertainties in ERR/Sv for most cancer types in Group 2 are larger than uncertainties for Group 1 cancers at all ages at exposure and attained ages. For example, at ages $e \geq 30$ and $a \geq 50$, the ratio of the upper 97.5% credibility limit of ERR/Sv to the median for many cancer types in Group 2 is between 2.4 and 8, compared with a range of about 1.6 to 2.2 for Group 1 cancers.[§§§] However, uncertainties in ERR/Sv for lung, urinary tract, and residual solid cancers are comparable to uncertainties for Group 1 cancers. As described in a later section, the model for lung cancer is based on updated data on cancer incidence in atomic-bomb survivors and, thus, an increase in the number of cases. The other two cancer types in Group 2 for which uncertainties in ERR/Sv are relatively small include cancers at multiple sites with larger numbers of total cases in atomic-bomb survivors.

Model for cancer types in Group 3

For the two cancer types in Group 3, fits to data on dose-response in atomic-bomb survivors indicated that the parameters γ and δ in eqn (11) are approximately zero. Thus, ERRs are assumed to be independent of age at exposure and attained age, and ERR/Sv for each cancer type in Group 3 is completely specified by the parameter α, which is sex-specific in the model for lung cancer. The model for lung cancer in Group 3 is not used in NIH-IREP.

Quantiles of the probability distribution of ERR/Sv for all cancers of female genital organs except the ovary are given in Table IV.D.3 of NIH (2003); the 50th percentile (median) is negative, which indicates a weak association with radiation exposure in atomic-bomb survivors. Sex-specific quantiles of the probability distribution of ERR/Sv in the model for lung cancer in Group 3 are given in Table B.1 of Apostoaei and Trabalka (2004); the 95% credibility intervals span nearly an order of magnitude for males but less than a factor of 3 for females.

Discussion of models for lung cancer—exposure to sources other than radon

As indicated in Table 1 and discussed above, two models to estimate ERRs for lung cancer due to sources of exposure other than radon are incorporated in NIOSH-IREP: the model for cancer types in Group 2, in which ERR/Sv depends on age at exposure and attained age, and the model for cancer types in Group 3, in which ERR/Sv does not depend on those parameters. In addition, the model for lung cancer in Group 3 is based on data in a population that included smokers and nonsmokers (Apostoaei and Trabalka 2004), whereas the model in Group 2 is based on data in never smokers only (NIH 2003). In both models, ERR/Sv is assumed to depend on

[§§§] For all cancer types in Group 2, the median of any credibility interval of ERR/Sv that includes positive values only is shifted toward the upper bound of that credibility interval compared with lognormal distributions of ERR/Sv for all Group 1 cancers; i.e., the ratio of the upper bound to the median is less than the ratio of the median to the lower bound.

sex, but the female/male ratio is higher in the model in Group 3 (Apostoaei and Trabalka 2004).

Development of a "combined" lung model in NIOSH-IREP. When NIOSH adopted IREP in 2002, only the model for lung cancer in Group 3 was incorporated in the code; that model was developed by the NCI-CDC Working Group on the basis of data in atomic-bomb survivors through 1987 (Thompson et al. 1994) and certain assumptions about the interaction between radiation and smoking. Shortly after NIOSH adopted IREP, however, the NCI-CDC Working Group replaced the model for lung cancer in Group 3 with the model in Group 2 and documented that model in its final report (NIH 2003). The model in NIH-IREP was developed on the basis of an analysis by Pierce et al. (2003) of data on lung cancer incidence through 1994 in a subcohort of atomic-bomb survivors for whom data on radiation dose and smoking history were available. That data set allowed a more rigorous investigation of the interaction between radiation and smoking.

On 28 February 2006, NIOSH adopted the model for lung cancer in Group 2, as incorporated in NIH-IREP (NIOSH 2006b). However, NIOSH also retained the previous model in Group 3, mainly on the grounds that use of the model in Group 2 may not fully account for uncertainties in the interaction between radiation and smoking. Now that NIOSH-IREP incorporates both models, which are referred to as the "combined" lung model, PC/AS is calculated using both models and the higher upper 99% credibility limit is used in adjudicating a claim (NIOSH 2006b).

An evaluation of past claims for lung cancer by energy workers indicated that use of the combined lung model resulted in an increase in the upper 99% credibility limit of PC/AS in about 10% of all cases (NIOSH/OCAS 2006, 2007)—i.e., in about 90% of claims evaluated, the model used only in NIOSH-IREP (Group 3) resulted in a higher upper 99% credibility limit of PC/AS than the model in NIH-IREP (Group 2). Therefore, adoption by NIOSH of the combined lung model should be more favorable to claimants in some cases and cannot result in a reduced upper 99% credibility limit of PC/AS in any case.

Modeling of interaction between radiation and smoking. Both models to estimate ERRs for lung cancer due to sources of exposure other than radon in NIOSH-IREP take into account an interaction between radiation and smoking. Analyses of data on lung cancer in atomic-bomb survivors and uranium miners discussed in NIH (2003) indicated that there is uncertainty about whether this interaction can be described by an additive or a multiplicative model.**** Therefore, ERR/Sv unadjusted for smoking is multiplied by a factor that depends on smoking history and accounts for an uncertain interaction between radiation and smoking. This adjustment factor depends on whether the model for lung cancer in Group 2 or Group 3 is used.

When ERR/Sv is calculated using the model for lung cancer in Group 3, the adjustment for the interaction between radiation and smoking, denoted by W_S, is given by

$$W_S = x + (1 - x)W_S^*, \tag{13}$$

where x represents an uncertain mixture of additive and multiplicative interaction models and W_S^* is a factor given in Table IV.I.1 of NIH (2003) that decreases with increasing use of cigarettes. The random variable x is described by a triangular probability distribution with a minimum at 0, mode at 1, and maximum at 1.1, denoted by T(0, 1, 1.1); the values $x = 0$ and 1 correspond to assumptions of a purely additive and a purely multiplicative interaction, respectively. Thus, x is weighted more toward an assumption of a multiplicative interaction (i.e., a lesser influence of smoking on reducing ERR/Sv); this assumption is supported by studies in uranium miners (NRC 1988, 1999). The median x of 0.74 corresponds to an assumption that ERR/Sv in never smokers is about twice the value in present and former smokers as a group, in agreement with analyses of data in uranium miners (NRC 1999). The small weight of about 0.1 given to a super-multiplicative interaction ($x > 1$) represents an assumption that ERR/Sv is higher in smokers than in nonsmokers. This assumption can increase upper 99% credibility limits of ERR and PC/AS by nearly 10% in the heaviest smokers (40+ cigarettes per day) if the uncertainty in dose is relatively small, but increases are less in other categories of smokers. When the model for lung cancer in Group 3 is used, the parameter α (ERR/Sv in this case) is a value that applies to an assumed distribution of smoking histories in a population.

When ERR/Sv is calculated using the model for lung cancer in Group 2, a modification of the adjustment for smoking history in eqn (13) is used in cases of exposure to photons, electrons, or neutrons. On the basis of an analysis of data in atomic-bomb survivors by Pierce

**** If radiation dose D and another risk factor F are multiplicative in effect, the increase in cancer risk (R) due to both factors is the product of the increases in risk due to each factor separately, and the ERR associated with radiation exposure is independent of F. If D and F are additive in effect, the increase in risk due to both factors is the sum of the increases in risk due to each factor separately, and the conditional ERR associated with radiation exposure given an exposure to F, denoted by ERR($D|F$), is given by ERR($D|F$) = ERR(D)/[1 + ERR(F)] (NIH 2003). Thus, if the interaction is additive (or submultiplicative), ERR associated with radiation exposure is reduced compared with ERR in the absence of the risk factor F.

et al. (2003), which indicated that the interaction between low-LET radiation and smoking is statistically inconsistent with a multiplicative model, 50% weight is given to an assumption that x is described by the triangular probability distribution T(0, 1, 1.1) used with the model for lung cancer in Group 3 and 50% weight is given to an assumption that $x = 0$ (i.e., that the interaction is additive). Thus, the effect of smoking on reducing ERR/Sv is greater than when the model for lung cancer in Group 3 is used, due to the greater weight given to the additive interaction model. In addition, the parameter α in the model for lung cancer in Group 2 applies to never smokers, rather than a population with a distribution of smoking categories. Therefore, the applicable values of W_S* are obtained by normalizing the values in Table IV.I.1 of NIH (2003) to 1.0 for never smokers by dividing by 4.74 for males and 3.90 for females.

In cases of exposure to alpha particles, however, the model for the interaction between radiation and smoking that gives greater weight to an additive interaction, as described above, is not used with the model for lung cancer in Group 2. Rather, the interaction model in eqn (13) is used without adjustment; i.e., no additional weight is given to the additive interaction model. This assumption is consistent with data in uranium miners (NRC 1988, 1999) who were exposed to alpha particles emitted by short-lived radon decay products. As noted above, those data indicated that greater weight should be given to a multiplicative interaction.

In neither model for the interaction between radiation and smoking is an uncertainty assigned to the value of W_S* for a given smoking category. All uncertainty is assigned to the parameter x that defines the weights given to the additive and multiplicative interaction models.

Models for cancer types in Group 4

Each cancer type in Group 4 (Table 1) has a unique risk model. These models are described in the following sections.

Lung cancer—exposure to radon. ERRs for lung cancer due to exposure to radon are modeled on the basis of data described in Section IV.D.5 of NIH (2003) that represent risks of lung cancer in U.S. uranium miners and their uncertainties. ERR is assumed to be a function of cumulative exposure to short-lived, alpha-emitting decay products in WLM:

$$\mathrm{ERR}(\mathrm{WLM}, a, t) = \alpha \times \mathrm{WLM}^{\beta} \times \exp[\gamma f(a) + \delta g(t)], \quad (14)$$

where a is the age at diagnosis, t is the time since last exposure (y), and α, β, γ, and δ are the unknown parameters that are estimated from fits to the data. Thus, ERRs are assumed to be proportional to a power of the cumulative exposure in WLM. Although the risk model is based on data in male miners only, ERRs are assumed to be independent of sex. The model applies at cumulative exposures $\leq$3,200 WLM; at higher exposures, effects of cell killing reduce the risk of lung cancer due to radiation.

The functions $f(a)$ and $g(t)$ in eqn (14) are given by

$$f(a) = \begin{cases} 0 & \text{if} \quad a \leq 45 \\ a - 45 & \text{if} \quad 45 < a \leq 75, \\ 30 & \text{if} \quad a > 75 \end{cases} \quad (15)$$

$$g(t) = \begin{cases} 0 & \text{if} \quad t \leq 5 \\ t - 5 & \text{if} \quad 5 < t \leq 25. \\ 20 & \text{if} \quad t > 25 \end{cases} \quad (16)$$

The parameters γ and δ were found to be negative. Thus, ERR at a fixed time since last exposure is assumed to decrease exponentially with increasing age at diagnosis between 45 and 75 y and to remain constant outside that interval, and ERR for a given age at diagnosis is assumed to decrease exponentially with increasing time since last exposure between 5 and 25 y and to remain constant outside that interval.

The estimated value of the parameter β is 0.82. Thus, ERR per WLM increases as the cumulative exposure decreases. This relationship, which implies that ERR is a nonlinear function of absorbed dose from alpha particles emitted by short-lived radon decay products, represents an inverse dose-rate effect for exposure to high-LET radiations discussed in a later section. No uncertainty is assigned to β.

ERRs for lung cancer due to exposure to radon also are assumed to depend on smoking history. However, only two smoking categories are used—smokers and nonsmokers—and the model in eqn (13) that gives greater weight to a multiplicative interaction model, with no additional weight given to an additive model, is assumed. Quantiles of probability distributions of ERR at 1 WLM in smokers and nonsmokers at ages at diagnosis (a) $\leq$ 45, 63, and $\geq$75 and times since last exposure (t) $\leq$ 5, 15, and $\geq$25 y are given in Table IV.D.10 of NIH (2003); ERRs are a factor of 3.8 higher in nonsmokers than in smokers. ERRs at 1 WLM at other ages at diagnosis and times since last exposure are estimated by interpolation. The 95% credibility intervals of ERR at 1 WLM span a factor of about 27–50.

Thyroid cancer. ERRs for thyroid cancer are estimated on the basis of an analysis of a pooled set of data assembled by Ron et al. (1995), including data in Japanese atomic-bomb survivors and various groups

exposed as children to x rays during medical treatment; ages at exposure in the latter groups of children were ≤15, and the average age in each group ranged from <1 to 7 y. The various study populations, which represent several nationalities, may have different baseline risks, B, and risks due to radiation, R.

Fits to the pooled data indicated that there was no statistically significant dependence of ERR for thyroid cancer on sex or attained age, and that the common attained-age parameter δ used in the model for solid cancers in Group 2 was statistically inconsistent with the data. Therefore, the parameters β and δ in eqns (6) and (7) were both set to zero, and ERR was modeled as a linear function of dose, D, and an exponential function of age at exposure (e) as

$$\mathrm{ERR}(D, e) = D \exp(\theta_1 I_1 + \ldots + \theta_n I_n + \gamma e), \quad (17)$$

where $I_1, \ldots, I_n$ are indicator functions for the different study populations and $\theta_1, \ldots, \theta_n$ are assumed to be normally distributed random variables with a common mean, θ.

The method used to estimate $\theta_1, \ldots, \theta_n$, θ, and γ is described in Section IV.D.3 of NIH (2003). The resulting probability distributions of ERR/Sv are lognormal, with GMs and GSDs at various ages at exposure given in Table IV.D.8 of NIH (2003). GMs and GSDs at other ages <50 are estimated by interpolation, and values at age 50 are assumed to apply at all ages >50, where the number of thyroid cancers in atomic-bomb survivors was judged to be too small to establish a dependence of ERR on age at exposure. Although atomic-bomb survivors were the only study population to include adults, estimates of ERR/Sv in adults and their uncertainties are heavily influenced by the estimates in children exposed at ages ≤15. Estimates of ERR/Sv in adults used in IREP are positive and statistically significant, even though estimates in adult atomic-bomb survivors are not statistically significant (Thompson et al. 1994).

Estimates of ERR/Sv and their uncertainty for thyroid cancer at selected ages at exposure are shown in Fig. 2. The uncertainty is seen to increase with increasing age at exposure to age 50 y, and the 95% credibility interval spans more than two orders of magnitude at ages ≥50.

In pooling data in atomic-bomb survivors and various groups of children exposed to medical x rays, high-energy gamma rays from the atomic bombs and medical x rays were assumed to be equal in biological effectiveness. This assumption was made even though, as discussed in a later section, IREP incorporates an assumption that x rays are about twice as effective as high-energy gamma rays in inducing cancer under the same conditions of exposure. However, since exposures to medical x rays were fractionated, a dose and dose-rate effectiveness factor (DDREF) should be applied to reduce ERRs from those exposures compared with ERRs for acute exposure. The NCI-CDC Working Group considered that no correction to modeled ERRs was required because, 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 (NIH 2003). Thus, ERR/Sv for thyroid cancer in cases of fractionated exposures to medical x rays is assumed to be the same as ERR/Sv in cases of acute exposure to high-energy gamma rays in atomic-bomb survivors. No additional uncertainty is included to account for the possibility that this assumption is incorrect.

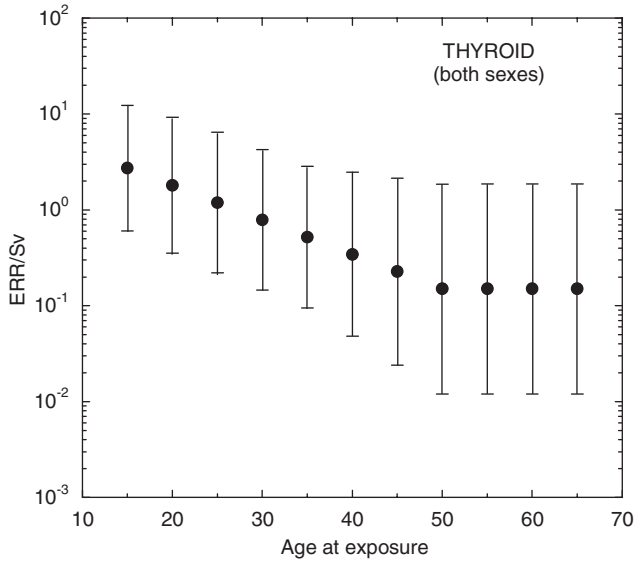

Fig. 2. Medians and 95% credibility intervals of lognormal probability distributions of ERR/Sv in linear dose-response for thyroid cancer in males or females in study populations at selected ages at exposure in 5-y steps. ERR/Sv is independent of attained age.

Skin cancers. ERRs for skin cancers are estimated on the basis of data on dose-response in Japanese atomic-bomb survivors that were used in a previous analysis by Ron et al. (1998). Three types of skin cancer are considered in NIOSH-IREP—malignant melanoma, basal cell carcinoma, and other non-melanoma skin cancers, principally squamous cell carcinoma—and a different model is used for each type.

ERRs for skin cancers in Japanese atomic-bomb survivors are assumed to be independent of sex. However, differences in baseline risks in males and females are taken into account in applying estimates of ERR/Sv in atomic-bomb survivors to the U.S. population.

Basal cell carcinoma is the only type of skin cancer for which a significant dose-response was seen in atomic-bomb survivors (Ron et al. 1998). Fits to data using the general model formulation in eqn (7) indicated, first, that ERR is independent of attained age (a) and, second, that ERR declines steeply with increasing age at exposure (e) beyond age 30 and is otherwise different from the common trend for cancer types in Groups 1 and 2. Therefore, the parameter δ in eqn (7) was set to zero and $f(e)$ in eqn (8) was replaced by

$$f(e) = \begin{cases} -30 & \text{if} \quad e \le 10 \\ e - 40 & \text{if} \quad 10 < e < 40. \\ 0 & \text{if} \quad e \ge 40 \end{cases} \qquad (18)$$

Since the parameter γ in eqn (7) was found to be negative, ERR is assumed to decrease exponentially with increasing age at exposure between 10 and 40 y and to remain constant outside that interval. The resulting quantiles of the probability distribution of ERR/Sv for basal cell carcinoma at ages at exposure (e) of 0–10, 20, 30, and ≥40 are given in Table IV.D.9 of NIH (2003). The 95% credibility intervals span a factor of about 6–50.

For non-melanoma skin cancers other than basal cell carcinoma, principally squamous cell carcinoma, data in atomic-bomb survivors did not indicate an association with radiation exposure, and ERR/Sv tended to be negative. Given the lack of statistical significance indicated by fits to the data, ERR/Sv is assumed to be independent of age at exposure and attained age, as in the model for cancer types in Group 3. Thus, ERR/Sv for this cancer type is completely specified by the parameter $\ln(\alpha)$ in eqn (7). Selected quantiles of the probability distribution of ERR/Sv are given in Table IV.D.9 of NIH (2003); the 50th percentile is negative.

Malignant melanoma is not modeled in NIH-IREP because there were too few cases in atomic-bomb survivors who received doses ≥10 mSv (NIH 2003). In NIOSH-IREP, ERR/Sv for malignant melanoma is estimated using the model for basal cell carcinoma described above. That model is used, rather than the model for squamous cell carcinoma or the model for solid cancers at other and ill-defined sites in Group 2, because it most often gives higher estimates of ERR/Sv than those alternatives and, thus, should be favorable to claimants in most cases (NIOSH 2002). However, differences in baseline rates of malignant melanoma and basal cell carcinoma are taken into account in applying the model for basal cell carcinoma in atomic-bomb survivors to estimate ERR/Sv for malignant melanoma in the U.S. population.

As noted previously, estimates of ERR/Sv for skin cancers in atomic-bomb survivors are applied to the U.S. population by taking into account an individual's race or ethnicity. The possibility of including an interaction between ionizing and ultraviolet (UV) radiation to account for the fact that baseline rates of basal cell carcinoma are greater in lighter-skinned than in darker-skinned populations also was considered by the NCI-CDC Working Group (NIH 2003). However, data discussed in NIH (2003) did not clearly indicate whether an additive or multiplicative interaction model is more appropriate. Therefore, in applying estimates of ERR/Sv for skin cancers in atomic-bomb survivors to the U.S. population, effects of different levels of skin pigmentation are taken into account by using baseline rates in specific racial or ethnic groups and an "uninformed" assumption discussed in a later section that gives equal weight to an additive or multiplicative risk-transfer model and any linear combination of the two.

Leukemia. As noted previously, all types of leukemia except CLL, which is not considered to be radiogenic, are modeled in IREP by assuming that ERR is a linear-quadratic function of dose from acute exposure to high-energy photons, and that the coefficients of the linear and quadratic terms are equal. Further, a linear dose-response from exposure to neutrons (high-LET radiation) was assumed in fitting data in Japanese atomic-bomb survivors.

The model to estimate ERRs for leukemia in atomic-bomb survivors due to absorbed doses of photons (D_γ) and neutrons (D_n) is formulated in terms of the modifying factors sex (s), age at exposure (e), attained age (a), and time since exposure (t) as

$$\mathrm{ERR}(D_\gamma, D_n, e, a) = \alpha(D_\gamma + 10D_n + D_\gamma^2) \exp(\beta e + \gamma t + \delta e t), \qquad (19)$$

where $t = a - e$ and α, β, γ, and δ are the unknown parameters, which may be sex-specific. The parameters β, γ, and δ were estimated from fits to data on dose-response, except they were set to zero if their inclusion did not contribute significantly to an improvement in the fits. Similarly, all parameters were assumed to be sex-specific only if the fits were improved significantly.

Since fits to the data indicated that β, γ, and δ are negative, the general model for leukemia in eqn (19) assumes that ERR at a fixed age at exposure (e) decreases exponentially with increasing time since exposure (t) and that ERR at a fixed time since exposure decreases exponentially with increasing age at exposure. In addition, rates of decrease of ERR depend on the value of the fixed parameter (e or t), because the model includes the term $e \times t$.

In cases of chronic exposure to low-LET radiations, ERRs for any type of leukemia are assumed to be a linear function of dose and the term D_γ^2 in eqn (19) is omitted. This assumption is in accordance with the usual interpretation of the linear-quadratic model that the slope of the dose-response at any dose under conditions of chronic exposure is the same as the slope as an acute dose approaches zero (NRC 2006). Therefore, at 1 Sv, an ERR from chronic exposure to low-LET radiations is assumed to be half the ERR from acute exposure. In cases of exposure to high-LET radiations at any dose rate, the dose-response is assumed to be linear.

On the basis of fits to data in atomic-bomb survivors, the general formulation of the model in eqn (19) is applied to specific types of leukemia as summarized below:

- All types of leukemia as a group (except CLL)—ERR decreases exponentially with increasing age at exposure (e) to age 55 and remains constant thereafter, and ERR decreases exponentially with increasing time since exposure (t) between 5 and 50 y and remains constant thereafter. The rate at which ERR decreases with increasing time since exposure decreases with increasing age at exposure. ERR is independent of sex;
- Acute lymphocytic leukemia (ALL)—A distinction is made between ages at exposure (e) < 20 and ≥ 20, but ERR is independent of age at exposure in those two age groups. At $e < 20$, ERR decreases exponentially with increasing time since exposure (t) between 5 and 50 y and remains constant thereafter, whereas at $e \geq 20$, ERR is independent of time since exposure. ERR is independent of sex;
- Acute myelogenous leukemia (AML)—ERR is independent of age at exposure (e), and ERR decreases exponentially with increasing time since exposure (t) between 5 and 50 y and remains constant thereafter. ERR is independent of sex; and
- Chronic myelogenous leukemia (CML)—The dependence of ERR on age at exposure (e) and time since exposure (t) is the same as in the model for AML. ERR depends on sex such that ERR is higher in males than in females at $t < 13$ y and ERR in males decreases much more rapidly with increasing t than in females.

Estimates of ERR at 1 Sv and its uncertainty for all types of leukemia as a group (excluding CLL) at selected ages at exposure and times since exposure are shown in Fig. 3. The dependence on time since exposure decreases as the age at exposure increases as a consequence of the term $e \times t$ in the risk model (eqn 19). Uncertainties increase with time since exposure at $t > 15$, and the 95% credibility interval of ERR at 1 Sv spans more than two orders of magnitude in the worst case.

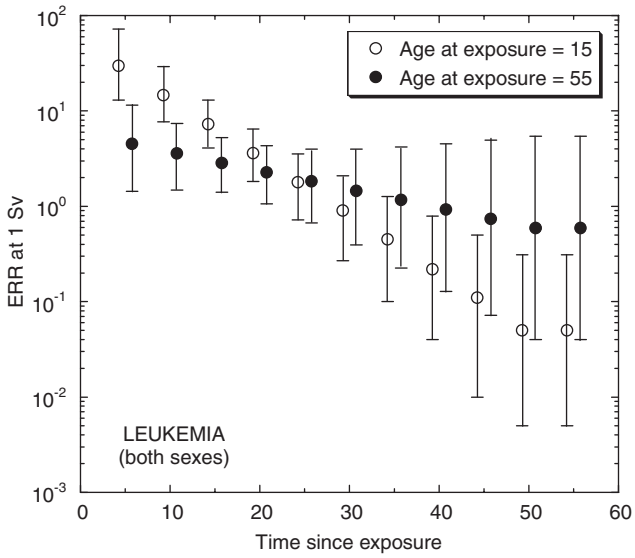

Fig. 3. Medians and 95% credibility intervals of probability distributions of ERR at 1 Sv in linear-quadratic dose-response for all types of leukemia as a group (excluding CLL) in male or female Japanese atomic-bomb survivors at selected ages at exposure and times since exposure in 5-y steps. Probability distributions are not lognormal.

Quantiles of the parameter α in eqn (19) for different types of leukemia, corrected as appropriate for the effects of age at exposure and time since exposure, are given in Tables IV.D.4–IV.D.7 of NIH (2003). Those results give quantiles of the probability distribution of ERR/Sv for chronic exposure to low-LET radiations, and twice the tabulated values give quantiles of the probability distribution of ERR at 1 Sv for acute exposure to those radiations. Uncertainties are higher for ALL, AML, and CML than for all types of leukemia as a group (excluding CLL). Two-dimensional interpolations between tabulated quantiles of α and the selected times since exposure for the purpose of facilitating random sampling of probability distributions of α are performed as described in Appendix D of NIH (2003).

In evaluating claims for compensation for ALL, AML, or CML, for most diagnostic categories NIOSH runs IREP for the diagnosed type of leukemia and for all types of leukemia as a group (excluding CLL) (Table 4 of NIOSH 2002). In those cases, the higher upper 99% credibility limit of PC/AS is reported as the value of record. This procedure, which is favorable to claimants, is based on the consideration that there may be uncertainty in the diagnosis of a particular type of leukemia. When a diagnosis cannot be made with any degree of certainty, a calculation of PC/AS for all types of leukemia as a group is used.

Summary of risk models

In IREP, ERRs for all solid cancers, plus lymphoma and multiple myeloma, are assumed to increase linearly with dose, whereas a linear-quadratic model with equal coefficients of the linear and quadratic terms is assumed for all types of leukemia. Models for the different cancer types in study populations used in IREP incorporate a variety of assumptions about the dependence of ERR on the modifying factors sex (*s*), age at exposure (*e*), attained age (*a*), and time since exposure (*t*). These assumptions are summarized in Table 2.

CORRECTIONS AND ADJUSTMENTS TO MODELED ERRS IN STUDY POPULATIONS AND THEIR UNCERTAINTIES

Models to estimate ERRs and their uncertainties discussed in the previous section are based on statistical analyses of fits to data on dose-response in study populations, principally the Japanese atomic-bomb survivors. Various corrections and adjustments to modeled ERRs in study populations are applied in IREP to obtain estimates of ERR for given conditions of exposure of an individual of concern. These corrections and adjustments consider:

- random and systematic errors in dosimetry;
- the minimum latency period of each cancer type;
- transfer of ERRs in Japanese atomic-bomb survivors to the U.S. population;
- reductions in ERR/Sv for all solid cancers, plus lymphoma and multiple myeloma, at low doses or low dose rates of low-LET radiations compared with estimates at higher acute doses of high-energy photons in atomic-bomb survivors; and
- radiation effectiveness factors (REFs) for different radiation types, which represent their effectiveness in inducing cancer in humans relative to high-energy photons.

These adjustments and their uncertainties are described in the following sections. Also described is an option to allow the user to account for any other uncertainties not considered in IREP.

Corrections to account for random and systematic errors in dosimetry

Several corrections to modeled ERRs in atomic-bomb survivors to account for random and systematic errors in dosimetry are included in IREP (NIH 2003; NCRP 1997). These corrections and their uncertainties are summarized below.

Random errors in doses to individuals. Random errors in dosimetry for individual atomic-bomb survivors result from uncertainty in their position and shielding at the time of exposure. Such errors bias ERRs downward (i.e., the true dose-response is flattened). This source of error is incorporated in uncertain bias correction factors $1 + F_L$ and $1 + F_Q$ for cancer types with linear and linear-quadratic dose-responses, respectively. F_L and F_Q are assumed to be lognormally distributed with a GM of 0.088 and 0.0556, respectively, with a common GSD of 1.22. This correction thus increases ERRs, but by less than 10%.

A correction to account for random errors in estimates of cumulative exposure (WLM) in U.S. uranium miners is used to adjust ERRs for lung cancer due to exposure to radon. On the basis of an analysis by Stram et al. (1999), this correction is assumed to be described by a triangular distribution T(1, 1.3, 1.5). Thus, on average, ERRs are increased by 27%.

Random error in biological effectiveness of neutrons. Doses to atomic-bomb survivors were estimated by assuming an average quality factor of 10 for neutrons, which contributed a small fraction of the total absorbed doses. The uncertainty in a factor to represent the random error in the average neutron quality factor is assumed to be described by a triangular distribution T(0.9, 1.0, 1.1). This error factor does not result in a bias correction to ERRs.

Systematic bias in estimates of kerma in air from gamma rays. Comparisons with measurements using thermoluminescence dosimetry indicated that calculations of kerma in air from gamma rays used in DS86 (Roesch 1987) systematically underestimated true values. The uncertainty in the error factor to represent this systematic bias is assumed to be described by a triangular distribution T(1.0, 1.1, 1.4). This bias factor is applied to estimated doses to all organs and tissues, and it results in a decrease in ERRs for all cancer types by 17% on average.

Systematic bias in estimates of absorbed dose from neutrons at Hiroshima. Comparisons of measurements of ^{60}Co produced by neutron activation with calculations of neutron fluence used in DS86 (Roesch 1987) indicated that absorbed doses from neutrons at Hiroshima were underestimated. The uncertainty in the error factor to represent this systematic bias is assumed to be described by a triangular distribution T(1.0, 1.1, 1.3). This bias factor results in a decrease in ERRs for all cancer types by 13% on average.

Overall corrections. The overall corrections to modeled ERRs in atomic-bomb survivors to account for random and systematic errors in dosimetry are obtained

Table 2. Summary of assumed dependencies of ERR for specific cancer types on sex, age at exposure, attained age, and time since exposure in NIOSH-IREP.

Cancer type[a]	Sex	Age at exposure (e)	Attained age (a)[b]	Time since exposure (t)[b]
Group 1 (all)	No, except for all digestive cancers[c]	Decreases exponentially for $15 < e \leq 30$[d] Constant for $e \leq 15$ and $e > 30$	Decreases linearly for $a < 50$[d] Constant for $a \geq 50$	No explicit dependence[e]
Group 2 (all)	Yes[f]	Decreases exponentially for $15 < e \leq 30$[g] Constant for $e \leq 15$ and $e > 30$	Decreases linearly for $a < 50$[g] Constant for $a \geq 50$	No explicit dependence[e]
Group 3 (all)	Yes[f]	Constant at all ages	Constant at all ages	Constant at all times[h]
Group 4[i]				
Lung—exposure to radon	No	Constant at all ages	Decreases exponentially for $45 < a \leq 75$ Constant for $a \leq 45$ and $a > 75$	Decreases exponentially with time since last exposure for $5 < t_{last} \leq 25$ Constant for $t_{last} \leq 5$ and $t_{last} > 25$
Thyroid	No	Decreases exponentially for $e \leq 50$ Constant for $e > 50$	Constant at all ages	Constant at all times[h]
Malignant melanoma	No	Decreases exponentially for $10 < e < 40$ Constant for $e \leq 10$ and $e \geq 40$	Constant at all ages	Constant at all times[h]
Non-melanoma—basal cell carcinoma	No	Decreases exponentially for $10 < e < 40$ Constant for $e \leq 10$ and $e \geq 40$	Constant at all ages	Constant at all times[h]
Non-melanoma—squamous cell carcinoma	No	Constant at all ages	Constant at all ages	Constant at all times[h]
All leukemia, except chronic lymphocytic leukemia (CLL)	No	At fixed t, decreases exponentially for $e \leq 55$ Constant for $e > 55$	No explicit dependence[j]	At fixed e, decreases exponentially for $5 \leq t \leq 50$ Constant for $t > 50$
Acute lymphocytic leukemia (ALL)	No	Dependence on time since exposure is different for $e < 20$ and $e \geq 20$ Constant for $e < 20$ and $e \geq 20$	No explicit dependence[j]	For $e < 20$, decreases exponentially for $5 \leq t \leq 50$ and constant for $t > 50$ For $e \geq 20$, constant at all times
Acute myelogenous leukemia (AML)	No	Constant at all ages	No explicit dependence[j]	Decreases exponentially for $5 \leq t \leq 50$ Constant for $t > 50$
Chronic myelogenous leukemia (CML)	Yes	Constant at all ages	No explicit dependence[j]	Decreases exponentially for $5 \leq t \leq 50$ Constant for $t > 50$

[a] Cancer types in Groups 1, 2, and 3 are listed in Table 1.
[b] Dependence does not take into account effect of minimum latency period, which is a cancer-specific adjustment applied separately.
[c] Model for stomach cancer in Group 1 applies to females only; model for stomach cancer in males is in Group 2.
[d] Rate of decrease depends on cancer type.
[e] Dependence is modeled implicitly based on assumed dependencies on age at exposure and attained age and relationship $t = a - e$.
[f] Some cancers in this group occur in one sex only.
[g] Rate of decrease is the same for all cancer types in this group.
[h] Dependence is not modeled explicitly.
[i] Each cancer type in this group has a unique model.
[j] Dependence is modeled implicitly based on assumed dependencies on age at exposure and time since exposure and relationship $a = e + t$.

by multiplying the correction factors described above (NIH 2003). The resulting probability distributions of the overall corrections to modeled ERRs are described by the normal distributions N(0.83, 0.08) for solid cancers and N(0.81, 0.08) for leukemia, where the two parameters are the mean and standard deviation. Thus, on average, random and systematic errors in dosimetry reduce estimates of ERR for all cancer types in atomic-bomb survivors by nearly 20%, and the standard deviation of this correction is about 10% of the mean. In the case of

lung cancer due to exposure to radon, only the correction to account for random errors in estimates of exposure of uranium miners, which increases ERRs by nearly 30% on average, is applied.

Minimum latency period of specific cancer types

Models to estimate ERRs for all cancer types in study populations described previously do not take into account the time delay between exposure to ionizing radiation and the earliest diagnosis of a radiation-induced cancer. In IREP, the risk model for any cancer type is modified by a function that is assumed to represent the effect of a minimum latency period on reducing ERRs at early times since exposure.

To avoid an abrupt increase in ERRs from zero at times since exposure less than a minimum latency period to their maximum values at times when the minimum latency period is exceeded, the effect of latency on ERR is represented by a sigmoid ("S-shaped") function

$$F_{\text{latency}}(t) = \frac{1}{1 + e^{-\frac{(t-\mu)}{S}}}, \quad (20)$$

where t is the time since exposure (y), μ is the time since exposure at the inflection point where $F_{\text{latency}} = 0.5$, and S is a shape parameter that defines the steepness of the function as it increases from values near zero to values near the maximum of 1.0. Three assumptions about the adjustment to account for a minimum latency period are used, depending on the cancer type.

For all solid cancers (including lymphoma and multiple myeloma) except thyroid and bone cancer, the nominal value of the midpoint of the sigmoid function, μ, is assumed to be 7.5 y, and the shape parameter S is set so that the latency adjustment in eqn (20) attains values of approximately 0.01 and 0.99 at $t = 4$ and 11 y, respectively. Thus, ERRs are assumed to be very small (close to zero) at $t < 4$ y and to attain their full value at $t > 11$ y. This adjustment to represent the effect of the minimum latency period on reducing ERRs for most solid cancers is given by the solid curve in Fig. 4.

Thyroid and bone cancer are assumed to have a shorter minimum latency period than all other solid cancers. In NIOSH-IREP, the nominal value of μ is assumed to be 4.5 y, and the parameter S is set so that the latency adjustment attains values of approximately 0.01 and 0.99 at $t = 2$ and 7 y, respectively. A slightly longer minimum latency period for thyroid and bone cancer is assumed in NIH-IREP; the nominal value of μ is 5 y, and the latency adjustment attains values of approximately 0.01 and 0.99 at $t = 2.5$ and 7.6 y, respectively.

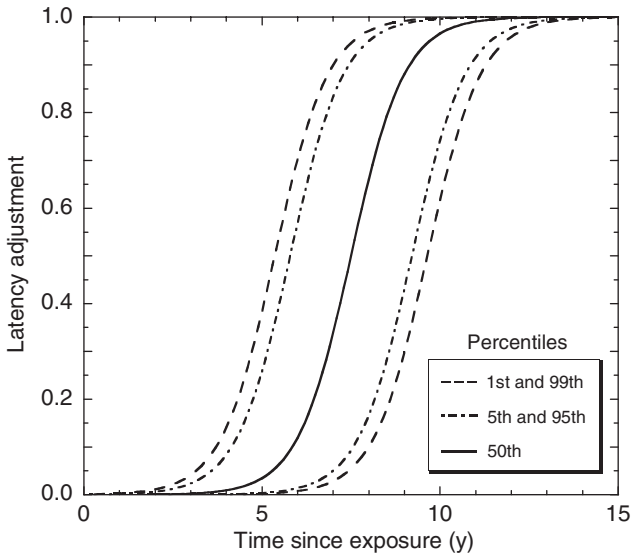

Fig. 4. Sigmoid (S-shaped) function to represent effect of minimum latency period on reducing ERRs for all solid cancers (including lymphoma and multiple myeloma) except thyroid and bone cancer at early times since exposure and its uncertainty as represented by 98% and 90% credibility intervals of triangular probability distribution of midpoint of sigmoid function.

All types of leukemia are assumed to have a shorter minimum latency period than solid cancers. The nominal value of μ is assumed to be 2.25 y, and the latency adjustment attains values of approximately 0.01 and 0.99 at $t = 0.4$ and 4.1 y, respectively.

To represent uncertainty in the effects of the minimum latency period on estimates of ERR, the midpoint, μ, is described by the following triangular probability distributions: all solid cancers except thyroid and bone cancer, T(5, 7.5, 10); thyroid and bone cancer, T(4, 4.5, 5.5) in NIOSH-IREP and T(3, 5, 7) in NIH-IREP; all types of leukemia, T(2, 2.25, 2.5). The effect of uncertainty in μ on the adjustment for minimum latency for all solid cancers except thyroid and bone cancer is indicated by the various percentiles (credibility intervals) of the latency adjustment shown in Fig. 4. For all cancers, the greatest effect of this uncertainty is to increase ERRs by a substantial factor at times since exposure $t < \mu$; effects on ERRs are smaller at $t > \mu$.

Transfer of ERRs in Japanese atomic-bomb survivors to U.S. population

When modeled ERRs for specific cancer types in Japanese atomic-bomb survivors are used to estimate ERRs in the U.S. population, differences in baseline risks in the two populations and a possible dependence of the risk due to radiation (R) on the baseline risk (B) must be taken into account. The importance of baseline risks and the dependence of ERR on B are indicated by the

relationships in eqns (1) and (2). The fundamental issue in modeling transfer of ERRs from a Japanese to the U.S. population is that the biological relationship between R and B is unknown.

Two approaches can be used to describe the transfer of ERRs in a Japanese population to a comparable U.S. population: a multiplicative and an additive risk-transfer model. In a multiplicative model, R is assumed to be proportional to B, and ERR = R/B transfers directly without adjustment. In an additive model, R is assumed to be independent of B, and R (but not ERR) transfers directly. Both models are plausible on biological grounds (NIH 2003), but they can lead to very different estimates of ERR in the U.S. population when baseline risks in Japanese and U.S. populations differ greatly (e.g., stomach, liver, and female breast cancer).

Information about which risk-transfer model might be correct for a specific cancer type often is lacking. To account for this uncertainty, risk transfer is modeled in IREP by assuming that a cancer-, sex-, and age-specific probability distribution of ERR/Sv in the U.S. population (or ERR at 1 Sv for leukemia) can be described by a random linear combination of distributions that are obtained by using a multiplicative or additive risk-transfer model as

$$(\mathrm{ERR/Sv})_{\mathrm{US}} = [y \times (\mathrm{ERR/Sv})_{\mathrm{mult}}] + [(1 - y) \times (\mathrm{ERR/Sv})_{\mathrm{add}}], \quad (21)$$

where y is the random variable, $(\mathrm{ERR/Sv})_{\mathrm{mult}}$ is the ERR/Sv in atomic-bomb survivors adjusted for random and systematic errors in dosimetry as described previously, which would apply to the U.S. population if risk transfer obeyed a purely multiplicative model, and $(\mathrm{ERR/Sv})_{\mathrm{add}}$ is the same ERR/Sv adjusted for the ratio of baseline risks in the two countries as

$$(\mathrm{ERR/Sv})_{\mathrm{add}} = (\mathrm{ERR/Sv})_{\mathrm{mult}} \times \left(\frac{\mathrm{B_{Japan}}}{\mathrm{B_{US}}}\right), \quad (22)$$

which would apply if risk transfer obeyed a purely additive model. In IREP, baseline risks are estimated using recent data on cancer incidence rates in the populations of Hiroshima and Nagasaki and the U.S. population (NIH 2003). When a cancer type occurs in both sexes, the ratio of baseline risks in eqn (22) is sex-specific. However, baseline risks in each country used in the risk-transfer model are age-averaged values, rather than age-specific (NIH 2003).

The value of the random variable y in eqn (21) determines the weights given to the additive and multiplicative risk-transfer models. For most cancer types, y is assumed to be described by the following trapezoidal probability distribution:[††††]

$$f(y) = 0.9091 \times \begin{cases} (10 \times y) + 1 & \text{if } -0.1 < y < 0 \\ 1 & \text{if } 0 \le y \le 1.0. \\ 11 - (10 \times y) & \text{if } 1.0 < y < 1.1 \end{cases} \quad (23)$$

This distribution represents an "uninformed" assumption about the relative importance of the additive and multiplicative risk-transfer models, in that it gives equal weight to any linear combination of the two. The probability distribution in eqn (23) also gives a small weight of 4.5% each to values $y < 0$ and $y > 1$ to allow for the possibility, judged to be unlikely, that the risk due to radiation, R, is negatively correlated with the corresponding baseline risk, B.

The "uninformed" risk-transfer model in eqn (23) is assumed to apply to all cancer types except breast, thyroid, stomach, and one of the models for lung cancer due to exposure to sources other than radon. The following assumptions are used in those cases (NIH 2003):

- Breast cancer—A weight of 50% is given to the additive model, and a weight of 50% is given to the "uninformed" model. Thus, greater weight is given to the additive model;
- Thyroid cancer—A purely multiplicative model is assumed, and ERRs obtained from the analysis of pooled data in several study populations are applied to the U.S. population. This assumption is based on an argument that ERRs obtained from an analysis of data on dose-response in groups representing several nationalities (Ron et al. 1995) account for possible differences in risks due to radiation and baseline risks in different countries and, therefore, that probability distributions of ERR incorporate an uncertainty in risk transfer;
- Stomach cancer—A weight of 33% is given to the multiplicative model, and a weight of 67% is given to the "uninformed" model. Thus, greater weight is given to the multiplicative model; and
- Lung cancer—In the model for lung cancer due to exposure to sources other than radon in Group 2 (Table 1), transfer of ERRs in atomic-bomb survivors to the U.S. population is described by the same mixture of additive and "uninformed" models used in cases of breast cancer. This assumption is based on data in atomic-bomb survivors which indicated that the interaction between radiation and smoking was closer to

[††††] The probability distribution of y given in Section IV.G of NIH (2003) is incorrect and does not represent the distribution that is incorporated in either version of IREP.

additive than multiplicative (Pierce et al. 2003) and the strong dependence of baseline rates of lung cancer on cigarette consumption. In the risk model for lung cancer in Group 3, which is used in NIOSH-IREP only, the "uninformed" trapezoidal probability distribution that applies to most solid cancers is used. No risk-transfer model is applied to ERRs for lung cancer due to exposure to radon (Group 4), because uranium miners in which ERRs were estimated are members of the U.S. population.

Reduction of ERR/Sv at low doses or low dose rates of low-LET radiations

In IREP, ERR/Sv for all solid cancers, plus lymphoma and multiple myeloma, is assumed to be reduced at low doses or low dose rates of low-LET radiations compared with estimates of ERR/Sv at higher acute doses of high-energy gamma rays in atomic-bomb survivors. This reduction is described by an uncertain dose and dose-rate effectiveness factor (DDREF). A DDREF for low-LET radiations is applied as

$$(\mathrm{ERR/Sv})_{\gamma,\mathrm{L}} = \frac{(\mathrm{ERR/Sv})_{\gamma,\mathrm{H}}}{\mathrm{DDREF}}, \qquad (24)$$

where $(\mathrm{ERR/Sv})_{\gamma,\mathrm{H}}$ is the ERR/Sv at higher acute doses (H) of high-energy photons (γ) in atomic-bomb survivors, where the dose-response for all solid cancers is assumed to be linear, and $(\mathrm{ERR/Sv})_{\gamma,\mathrm{L}}$ is the ERR/Sv at low doses or low dose rates (L). DDREF accounts for a possible curvature in the dose-response at lower doses under conditions of acute exposure, and it assumes that the slope of the dose-response at any dose under conditions of chronic exposure is the same as the slope as an acute dose approaches zero.

A DDREF is not applied to an assumed linear dose-response for high-LET radiations (alpha particles and neutrons). However, as described in the following section, an assumption that ERRs under conditions of chronic exposure to high-LET radiations are higher than ERRs under conditions of acute exposure at the same dose is incorporated in IREP.

A DDREF also is not used explicitly in estimating ERRs for leukemia. However, the assumption of a linear-quadratic dose-response for leukemia under conditions of acute exposure to low-LET radiations incorporates a DDREF implicitly. Since the coefficients of the linear and quadratic terms are assumed to be equal, DDREF = 2 at an acute dose of 1 Sv. Thus, for all types of leukemia, ERRs at acute doses well below 1 Sv and ERRs under conditions of chronic exposure at any dose are assumed to be half the values obtained by linear extrapolation to zero of ERR at an acute dose of 1 Sv. No uncertainty is assigned to the implicit DDREF for leukemia.

For all cancer types except leukemia, the assumed probability distribution of DDREF for low-LET radiations depends on whether an exposure is chronic or acute. Assumptions under the two conditions of exposure are described below. NIOSH's assumptions about whether an exposure to low-LET radiations is acute or chronic are described previously.

Under conditions of *chronic* exposure to low-LET radiations, a probability distribution of DDREF is applied at any dose. Two probability distributions are specified in IREP: one for breast and thyroid cancer, and one for all other solid cancers. These probability distributions, which are discrete, are shown in Fig. 5. The mean DDREF is 1.6 for breast and thyroid cancer

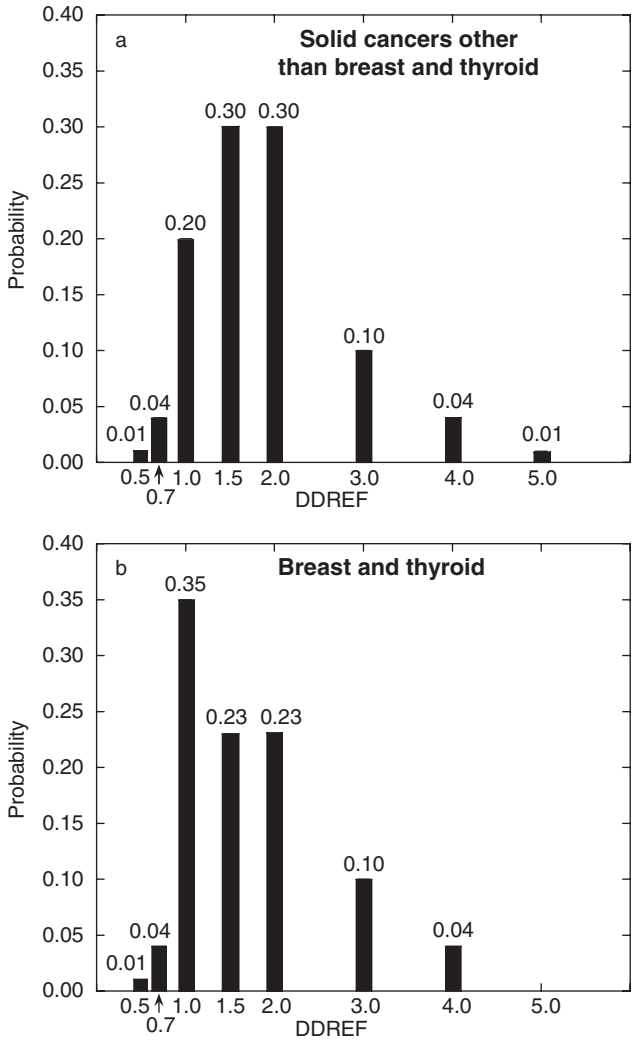

Fig. 5. Discrete probability distributions of dose and dose-rate effectiveness factor (DDREF) for low-LET radiations for (a) solid cancers other than breast and thyroid and (b) breast and thyroid cancer.

and 1.8 for all other solid cancers. Both distributions give a small weight of 5% to the possibility that ERR/Sv is higher at low doses or low dose rates of low-LET radiations than at high doses and dose rates, i.e., that the dose-response is supra-linear with DDREF <1.

Under conditions of *acute* exposure, a DDREF is applied only when a given equivalent dose from photons or electrons is less than an uncertain reference dose, D_L. At doses $>D_L$, DDREF is assumed to be unity on the basis of the observed linearity in the dose-response for cancer mortality in atomic-bomb survivors (Pierce et al. 1996). The uncertain dose, D_L, below which a DDREF is applied, is assumed to be described by a loguniform probability distribution between 0.03 and 0.2 Sv. Thus, a DDREF is never applied at acute doses >0.2 Sv, is always applied at acute doses <0.03 Sv, and is applied at acute doses between 0.03 and 0.2 Sv only if the equivalent dose is less than the randomly selected value of D_L.

By considering that application of the full DDREF for chronic exposure described above to an acute exposure should not be abrupt at doses just below the uncertain reference dose, D_L, DDREF is phased in gradually. 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 for chronic exposure at zero dose. This smooth change is assumed to be described by a logistic function of dose, D, as

$$\mathrm{DDREF}_{\mathrm{acute}} = \frac{1}{1 - \left\{ \dfrac{1 - \dfrac{1}{\mathrm{DDREF}_{\mathrm{chronic}}}}{1 + e^{\frac{(D - D_1)}{S}}} \right\}} \quad \text{if } D < D_L, \quad (25)$$

where D_I is the inflection point on the curve of $\mathrm{DDREF}_{\mathrm{acute}}$ as a function of 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 $\mathrm{DDREF}_{\mathrm{chronic}}$ at zero dose. That value of S also ensures that $\mathrm{DDREF}_{\mathrm{acute}} > 0.99$ at a dose D_L.

The phasing in of $\mathrm{DDREF}_{\mathrm{acute}}$ as the equivalent dose, D, decreases below the uncertain reference dose, D_L, is depicted in Fig. 6. At a fixed D_L, the probability distribution of $\mathrm{DDREF}_{\mathrm{acute}}$ at a given dose has the same form as one of the probability distributions of $\mathrm{DDREF}_{\mathrm{chronic}}$ shown in Fig. 5, except discrete values of the distribution are compressed toward the value 1.0 in accordance with the logistic function in eqn (25), with the degree of compression increasing as the ratio D/D_L increases. Thus, since D_L is a random variable, $\mathrm{DDREF}_{\mathrm{acute}}$ is a nearly continuous probability distribution at $D < 0.2$ Sv, which is the assumed upper bound of D_L, even though it is calculated from a discrete probability distribution of $\mathrm{DDREF}_{\mathrm{chronic}}$.

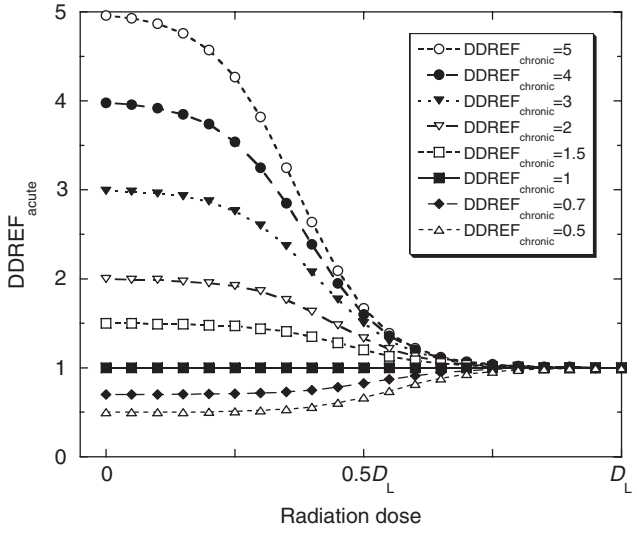

Fig. 6. Dependence of dose and dose-rate effectiveness factor (DDREF) under conditions of acute exposure to low-LET radiations, $\mathrm{DDREF}_{\mathrm{acute}}$, on dose for given DDREF under conditions of chronic exposure, $\mathrm{DDREF}_{\mathrm{chronic}}$, and reference dose, D_L, above which the acute dose-response for all solid cancers is assumed to be linear. Uncertain D_L is represented by loguniform probability distribution between 0.03 and 0.2 Sv.

Radiation effectiveness factors for different radiation types

As discussed previously, radiation doses are entered into IREP by radiation type, and a given equivalent dose to an organ or tissue from a given radiation type in cSv (i.e., rem) is converted to an average absorbed dose in Gy (eqn 5). The absorbed dose then is modified in IREP by an uncertain radiation effectiveness factor (REF), which represents the biological effectiveness of the given radiation type in inducing cancer in humans relative to high-energy (>250 keV) photons, to obtain a biologically significant dose used in estimating ERRs.

Probability distributions of REFs for different radiation types (photons, electrons, and neutrons of specified energy ranges; alpha particles of any energy produced in radioactive decay) were developed by Kocher et al. (2002, 2005); these probability distributions also are given in Tables IV.H.1–IV.H.3 of NIH (2003) and Tables 5A–5C of NIOSH (2002). The resulting 95% credibility intervals of REFs are summarized in Tables 3 and 4.

Table 3. Summary of probability distributions of radiation effectiveness factors (REFs) for neutrons and alpha particles in IREP.[a]

Neutrons and solid cancers[b]		95% credibility interval of REF_H[c]		
Energy	Exposure	2.5th percentile	50th percentile	97.5th percentile
0.1–2 MeV	Acute	2.0	7.7	30
	Chronic	2.4	10	47
10–100 keV; 2–20 MeV	Acute	1.2	3.8	18
	Chronic	1.4	4.7	28
<10 keV; >20 MeV	Acute	1.1	1.9	11
	Chronic	1.1	2.4	16
Neutrons and leukemia[b]		**95% credibility interval of REF_L[d]**		
Energy	Exposure	2.5th percentile	50th percentile	97.5th percentile
0.1–2 MeV	Acute	2.0	11	60
	Chronic	2.5	14	91
10–100 keV; 2–20 MeV	Acute	1.3	5.6	36
	Chronic	1.5	7.1	55
<10 keV; >20 MeV	Acute	1.1	2.8	22
	Chronic	1.2	3.4	34
Alpha particles[e]		**95% credibility interval of REF_L[d]**		
Cancer type	Exposure	2.5th percentile	50th percentile	97.5th percentile
Solid cancers	All	3.4	18	100
Leukemia	All	1.0	4.1	42

[a] Adapted from Table 14 of Kocher et al. (2005). Many probability distributions are not described by commonly used continuous distributions (e.g., lognormal).
[b] Probability distributions are described in Table 5 of Kocher et al. (2005); distributions under conditions of chronic exposure include enhancement factor to represent inverse dose-rate effect.
[c] REF_H is REF at high doses and high dose rates of reference high-energy (>250 keV) photons.
[d] REF_L is REF at low doses and low dose rates of reference high-energy (>250 keV) photons.
[e] Probability distributions are described in Table 7 of Kocher et al. (2005) and apply to alpha particles of any energy produced in radioactive decay; all distributions include enhancement factor to represent inverse dose-rate effect.

Probability distributions of REFs for different radiation types, along with the probability distribution of DDREF for low-LET radiations under conditions of acute or chronic exposure discussed previously, are used in IREP to estimate ERRs at absorbed dose D in accordance with the following equations (Kocher et al. 2002, 2005; NIH 2003):

Solid cancers (including lymphoma and multiple myeloma) —

$$\mathrm{ERR} = \mathrm{REF_L} \times \frac{\mathrm{R_{\gamma,H}}}{\mathrm{DDREF}} \times D, \quad (26)$$

$$\mathrm{ERR} = \mathrm{REF_H} \times \mathrm{R_{\gamma,H}} \times D. \quad (27)$$

Leukemia —

$$\mathrm{ERR} = \alpha \times [(\mathrm{REF_L} \times D) + (\mathrm{REF_L} \times D)^2], \quad \text{acute exposure}, \quad (28)$$

$$\mathrm{ERR} = \alpha \times \mathrm{REF_L} \times D, \text{ chronic exposure}. \quad (29)$$

In these equations:

- $R_{\gamma,H}$ is the ERR per Gy for a given solid cancer at high acute doses (H) of high-energy photons (γ), as estimated from studies of atomic-bomb survivors and other study populations in the case of thyroid cancer;[‡‡‡‡]
- the subscript L or H with an REF indicates that it was derived from estimates of relative biological effectiveness (RBE) at low doses and low dose rates or at high doses and high dose rates of reference high-energy photons, respectively; and
- α is the coefficient of the linear and quadratic terms in the linear-quadratic dose-response for leukemia under conditions of acute exposure to high-energy photons.

The equation used to estimate ERR depends on the radiation and cancer types of concern. For solid cancers, eqn (26) is used in cases of exposure to photons, electrons, or alpha particles, and eqn (27) is used in cases of exposure to neutrons. The different approach for neutrons compared with alpha particles is based on the consideration that REFs for neutrons and solid cancers

[‡‡‡‡] Equivalent doses in Sv in atomic-bomb survivors, which were calculated as a weighted sum of contributions from high-energy photons and neutrons as $D_\gamma + 10D_n$ (NIH 2003), are assumed to be equivalent biologically to the same absorbed dose in Gy from photons only.

Table 4. Summary of probability distributions of radiation effectiveness factors (REFs) for photons and electrons in IREP.[a]

Photons[b]		95% confidence interval of REF_L[c]		
Energy	Exposure	2.5th percentile	50th percentile	97.5th percentile
>250 keV[d]	All	—	1.0	—
30–250 keV	All	1.0	1.9	4.7
<30 keV	All	1.1	2.4	6.1
Electrons[e]		**95% confidence interval of REF_L[c]**		
Energy	Exposure	2.5th percentile	50th percentile	97.5th percentile
>15 keV[f]	All	—	1.0	—
<15 keV[g]	All	1.2	2.4	5.0

[a] Adapted from Table 15 of Kocher et al. (2005). REFs apply to any cancer type.
[b] Probability distributions are described in Table 11 of Kocher et al. (2005); distributions are not described by commonly used continuous distributions (e.g., lognormal).
[c] REF_L is REF at low doses and low dose rates of reference high-energy (>250 keV) photons.
[d] Reference radiation with defined REF of unity.
[e] Probability distributions are described in Table 13 of Kocher et al. (2005); distribution for electrons of energy >15 keV is lognormal.
[f] An REF_L for 15–60 keV electrons consistent with REF_L for 30–250 keV photons is indicated on theoretical grounds, but is not adopted; see Kocher et al. (2005), Table 13, footnote c.
[g] Auger-emitting radionuclides incorporated into DNA are excluded. Beta particles produced in radioactive decay are included if average energy of continuous spectrum of electrons is <15 keV.

were derived from data on RBE at high acute doses of high-energy photons and, thus, a DDREF for photons is not needed to estimate ERRs from exposure to neutrons at any dose *D* and any dose rate (Kocher et al. 2002, 2005). However, since the REF for alpha particles and solid cancers was derived from data on RBE at low doses and low dose rates, $R_{\gamma,H}$ must be adjusted by DDREF to estimate ERRs from exposure to alpha particles at any dose.

For leukemia, eqn (28) is used in cases of acute exposure to photons or electrons, and eqn (29) is used in cases of chronic exposure to photons or electrons and any exposures to alpha particles or neutrons. The latter equation applies to alpha particles and neutrons because a linear dose-response for leukemia is assumed at any dose and dose rate of high-LET radiations.

As noted previously, NIOSH assumes that external exposures of energy workers to neutrons are chronic in the absence of information on conditions of exposure. That assumption results in upper 99% credibility limits of PC/AS that are higher than estimates obtained by assuming acute exposure to neutrons and, thus, is favorable to claimants. The higher PC/AS under conditions of chronic exposure to neutrons is the consequence of an assumption of an inverse dose-rate effect, whereby the biological effectiveness of neutrons at a given dose is assumed to be higher at low dose rates than at high dose rates (Kocher et al. 2002, 2005). The uncertain increase in REFs under conditions of chronic exposure to neutrons to account for an inverse dose-rate effect is 40% on average. An uncertain adjustment to account for an inverse dose-rate effect is also applied in cases of exposure to alpha particles, because all such exposures are assumed to be chronic; the increase in REFs is 22.5% on average.

User-defined uncertainty

IREP includes an option to allow the user to define an additional uncertainty in estimating ERR and PC/AS. This user-defined uncertainty can be invoked to account for any sources of uncertainty not considered in IREP.

The NCI-CDC Working Group emphasized that this option should be used only when an additional uncertainty not accounted for in IREP has been documented and justified by an authoritative review panel (NIH 2003). In practice, NIOSH has not seen the need to invoke a user-defined uncertainty in evaluating claims for compensation under EEOICPA.

UNCERTAINTY IN ERR IN CASES OF MULTIPLE EXPOSURES

Previous discussions on models to estimate ERRs for specific cancer types describe how ERR and its uncertainty are calculated for a single exposure. In cases of multiple exposures, which are especially common in energy workers, an ERR from all exposures combined, ERR_{total}, is the sum of ERRs from each exposure. Multiple exposures include exposures to the same radiation type in different years, exposures to different radiation types in the same year, and any combination of the two. As noted previously, a single calculation in IREP can involve up to 1,000 exposures. PC/AS in cases

of multiple exposures is determined by ERR_{total}, in accordance with eqn (3), but it is not the sum of PC/AS from each exposure.

In IREP, the uncertainty in ERR_{total} is calculated by assuming that probability distributions of ERR/Sv (or ERR at 1 Sv in cases of leukemia) for each exposure are perfectly correlated. This procedure, which is favorable to claimants, was adopted on the grounds that if an individual is more (or less) sensitive to radiation than other like individuals, the greater (or lesser) sensitivity should apply to all exposures of that individual. If doses received in each exposure are assumed to be constant, with no uncertainty, probability distributions of ERR from each exposure also are perfectly correlated and, in this case, the i^{th} percentile of the probability distribution of ERR_{total} is the sum of the i^{th} percentiles of the probability distributions of ERR from each exposure. However, when probability distributions of uncertain doses are entered into IREP, those distributions are assumed to be uncorrelated and, in this case, probability distributions of ERR from each exposure are only partially correlated to the extent that the uncertainty in ERR_{total} is determined by uncertainties in each ERR/Sv. The assumption about correlations of ERR/Sv from each exposure generally results in upper 99% credibility limits of ERR_{total} and PC/AS that are higher than values obtained by assuming that probability distributions of ERR/Sv from each exposure are uncorrelated or partially correlated.

LIMITATIONS OF IREP

The following sections discuss a number of limitations of IREP; some of these limitations also are discussed in NIOSH (2002) and NIH (2003). These discussions should not be interpreted as implying that IREP is unsuitable for use in compensation programs, or that individuals with claims are treated unfairly. Many of these limitations are present but not addressed in other cancer risk assessments, including those conducted by such authoritative groups as the BEIR committees (e.g., NRC 1990, 2006), the U.S. Environmental Protection Agency (U.S. EPA 1994, 1999), the International Commission on Radiological Protection (ICRP 2005), the National Council on Radiation Protection and Measurements (NCRP 1997), the United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR 1993, 2000), and Radiation Effects Research Foundation (e.g., Pierce et al. 1996; Preston et al. 1994, 2004, 2007; Thompson et al. 1994). Indeed, no single assessment addresses all potential limitations in estimating cancer risks and PC/AS.

Alternative assumptions about dependence of cancer risks on dose

In IREP, the linear, nonthreshold dose-response model for all solid cancers (including lymphoma and multiple myeloma), the linear-quadratic model for leukemia under conditions of acute exposure to low-LET radiations, and the model for lung cancer due to exposure to radon, which is a nonlinear function of cumulative exposure (WLM), are assumed to be correct, and no weight is given to alternative dose-response models that might describe risks at doses below limits of epidemiologic detection. Thus, no uncertainty is assigned to the basic model structure. This approach is consistent with assumptions used, for example, by the BEIR VII committee (NRC 2006) in estimating risks from exposure to low-LET radiation.

Assigning nonzero weights to alternative models that predict lower risks than models incorporated in IREP, such as models that include a threshold or represent a hormetic effect of radiation, would result in lower estimates of ERR at a given dose (Land 2002; ICRP 2005), and a higher dose would be required to give a PC/AS of 50% at the upper 99% credibility limit. Thus, ignoring the plausibility of alternative models that predict lower risks is favorable to claimants. However, this possible bias is taken into account to some extent by means of probability distributions of DDREFs for solid cancers in cases of exposure to low-LET radiations (Fig. 5). In addition, DDREFs used in IREP give a small weight to an assumption that the linear model underestimates ERRs at low doses or low dose rates, and an inverse dose-rate effect is incorporated in ERRs for all cancers in cases of chronic exposure to high-LET radiations.

Data sets used to model ERRs in atomic-bomb survivors

Except for the model for lung cancer due to sources of exposure other than radon in Group 2 (Table 1), all models to estimate ERRs in Japanese atomic-bomb survivors that are incorporated in IREP were developed using data on cancer incidence through 1987 and estimates of dose based on DS86. However, updated data on cancer incidence in atomic-bomb survivors through 1998 are available (RERF 2007), and DS86 has been replaced by a new dosimetry system, DS02 (Young and Kerr 2005). Updated data on cancer incidence and mortality and doses estimated using DS02 have been used in recent assessments of health risks from exposure to ionizing radiation (NRC 2006; Preston et al. 2007). Use of more recent data would result in changes in modeled ERRs for all cancer types in atomic-bomb survivors.

Selection of atomic-bomb survivors

A source of uncertainty not considered in IREP is the effect on modeled ERRs of excluding atomic-bomb survivors with DS86 doses (kerma in air) >4 Gy (Thompson et al. 1994; Preston et al. 1994). Recent analyses of data for all solid cancers (ICRP 2005) and leukemia (Preston et al. 2004) suggest that inclusion of survivors with estimated doses >4 Gy could have a significant effect on uncertainties in ERRs at much lower doses, even when cell killing at high doses is taken into account. Thus, uncertainties in ERRs at low doses in atomic-bomb survivors could be misrepresented. An additional uncertainty not considered in IREP is the effect on modeled ERRs at low doses of using a control group of survivors other than those who received doses <10 mSv to estimate baseline risks or including survivors at greater distances from the bombings (>2.5 km at Hiroshima or >10 km at Nagasaki) in the control group (ICRP 2005).

Sources of data used to develop estimates of ERR

For purposes of EEOICPA, the ideal study population for obtaining estimates of ERR is the cohort of energy workers themselves. At the time IREP was developed, however, data in energy workers did not provide an adequate basis for a quantitative risk assessment that could be incorporated in IREP. Ongoing studies (e.g., Shilnikova et al. 2003; Cardis et al. 2007) could provide information on several important issues, including the dependence of risk on age- and time-related parameters, risks due to exposure to alpha particles, the minimum latency period for different cancer types, DDREFs for low-LET radiations, and risks of cancers that are weakly associated with radiation in atomic-bomb survivors (e.g., multiple myeloma).

ERRs for lung cancer in females due to exposure to radon

ERRs for lung cancer due to exposure to radon are estimated on the basis of data in males only, and ERRs in males are assumed to apply to females. However, in the models for lung cancer due to sources of exposure other than radon in Groups 2 and 3 (Table 1), ERRs are substantially higher in females, which suggests that ERRs for lung cancer in females due to exposure to radon could be underestimated.

Effects of smoking on cancers other than lung cancer

In IREP, an interaction between radiation and smoking is taken into account in estimating ERRs for lung cancer only. It is plausible that a similar interaction could be important in estimating ERRs for cancers in other organs or tissues that are exposed to tobacco smoke, such as tissues lining the oral and nasal cavities, larynx, esophagus, and stomach. If data on lung cancer are a reliable indicator, other interactions between radiation and smoking should tend to be sub-multiplicative and, thus, should tend to reduce ERRs associated with radiation exposure.

Changes in baseline risks of cancer over time

In IREP, ERRs in the U.S. population are estimated on the basis of modeled ERRs in study populations, principally the Japanese atomic-bomb survivors, by assuming a linear combination of multiplicative and additive risk-transfer models [eqns (21) and (22)]. For a given cancer type, the contribution from the additive model is estimated using baseline risks of cancer incidence that are assumed to be constant in time; the assumed baseline risks represent data in Japanese and U.S. populations during the period from the late 1980's to the mid-1990's. However, incidence rates for many cancers (e.g., female breast, lung, skin, and prostate) have changed substantially in recent decades. By not accounting for these changes, ERR and PC/AS for a given cancer in an individual could be over- or underestimated when diagnosis occurred outside the period over which the assumed baseline risks apply.

Assumptions about baseline risks in modeling risk transfer

In the model to represent an uncertain transfer of ERRs in Japanese atomic-bomb survivors to the U.S. population [eqns (21) and (22)], age-averaged baseline risks are used to estimate the contribution from an additive risk-transfer model for all cancer types except thyroid cancer (NIH 2003). If the ratio B_{Japan}/B_{US} for a given cancer type is highly age-specific, use of age-averaged baseline risks could misrepresent the uncertainty in risk transfer in some cases. In addition, if the ratio of age-specific baseline risks for a given cancer type is much larger than the ratio of age-averaged risks and $B_{Japan}/B_{US} \approx 1$ or greater, the upper 99% credibility limit of ERR could be underestimated.

Treatment of the minimum latency period

There are at least two limitations to assumptions used in IREP to model the effect of a minimum latency period on estimated ERRs for a given cancer type. First, the representation of this effect in eqn (20) is based on judgment, especially in regard to the value of the shape parameter, *S*, to describe the rate at which that function increases during the first decade or less after exposure. Second, there is additional uncertainty in modeling the effect of a minimum latency period for leukemia due to the fact that data in Japanese atomic-bomb survivors

were not collected until 5 y after exposure. Thus, the effect on estimated ERRs for leukemia at shorter times since exposure in atomic-bomb survivors could not be ascertained. Assumptions about the minimum latency period for leukemia in IREP are based on other radiation studies and general knowledge of cancer progression.

Probability distributions of DDREF

Probability distributions of DDREF incorporated in IREP (Fig. 5) were based largely on subjective judgment and took into account recommendations by experts. These distributions, especially the weight given to values <1, can be important in estimating upper 99% credibility limits of ERR and PC/AS. Thus, further consideration of probability distributions to represent data on DDREF in humans and animals, including new data that could be obtained from ongoing studies of energy workers, is warranted.

Correlations of uncertain doses

Possible correlations of uncertain doses from multiple exposures are not taken into account in IREP. Such correlations are plausible in certain cases of internal exposure, including (1) doses received in each year following an intake of a radionuclide with a long retention time in the body, which are calculated in dose reconstructions for energy workers (U.S. DHHS 2002b) and constitute multiple exposures for purposes of running IREP, (2) annual doses from intakes of the same radionuclide in different years, or (3) annual doses from intakes of different radionuclides with similar biokinetic behavior in the body. Correlations also are plausible in certain cases of external exposure, such as when an unmonitored individual was located mostly in areas with unusually high (or low) radiation levels during periods of exposure. Correlations of uncertain doses from multiple internal or external exposures should be unimportant, however, unless uncertainties in estimated doses are comparable to or greater than uncertainties in ERR/Sv for each exposure.

SUMMARY AND CONCLUSION

IREP is a Web-based computer code that was developed by the NCI-CDC Working Group (NIH 2003) and then adopted and modified by NIOSH for use in adjudicating claims for compensation for cancer by energy workers under EEOICPA (U.S. DHHS 2002a). This paper has described models and other assumptions that are incorporated in IREP to estimate ERR and PC/AS for a given cancer in an individual. A defining characteristic of IREP is that it accounts for many sources of uncertainty in estimating ERR and PC/AS for any exposure situation. No other cancer risk assessments, including those conducted by authoritative groups, account for uncertainty as comprehensively as IREP does. An accounting of uncertainty is necessary when decisions about granting claims for compensation are made on the basis of an estimate of the upper 99% credibility limit of PC/AS (U.S. DHHS 2002a).

Statistical uncertainties in ERRs in study populations that are estimated on the basis of best fits to data on dose-response using conventional formulations of models in terms of age- and time-related parameters generally are important in estimating the uncertainty in ERR and PC/AS for any cancer type and exposure situation of concern. There also are uncertainties that generally are of minor importance including, for example, uncertainties in corrections to modeled ERRs in study populations to account for random and systematic errors in dosimetry.

The importance of other uncertainties often depends on the particular cancer type and conditions of exposure. The examples described below illustrate this point:

- The uncertainty in transfer of ERRs in Japanese atomic-bomb survivors to the U.S. population can be important when an "uninformed" model to describe the uncertain weights given to additive and multiplicative risk-transfer models is assumed and baseline risks in the two populations differ greatly (eqns 21–23). However, the uncertainty in assumptions about risk transfer is unimportant whenever baseline risks in the two populations are nearly the same;
- The uncertainty in DDREF, which is used in modeling ERRs for all cancer types except leukemia, can be important when the dose to an organ or tissue of concern is dominated by chronic exposure to low-LET radiations or acute exposure to those radiations at low doses, but this uncertainty is unimportant in cases of acute exposure to low-LET radiations at high doses. The uncertainty in DDREF for low-LET radiations also can be important in estimating ERRs from exposure to alpha particles on the basis of ERRs at high, acute doses of photons, but a DDREF is not used in estimating ERRs from exposure to neutrons (eqns 26 and 27 and following discussion); and
- Uncertainties in REFs (Tables 3 and 4) can be important when radiation types other than high-energy (>250 keV) photons or electrons of energy >15 keV contribute significantly to the total absorbed dose to an organ or tissue of concern, but uncertainties in REFs are unimportant when the dose is due primarily to exposure to high-energy photons or higher-energy electrons with a defined REF of unity.

The importance of the uncertainty in a parameter to the uncertainty in an estimate of ERR and PC/AS, as

summarized above, may not indicate the same degree of importance in determining an upper 99% credibility limit of ERR and PC/AS. That is, there can be a significant difference in uncertainties in ERR and PC/AS for two exposure situations, due to differences in the importance of uncertainties in various parameters, but little difference in their upper 99% credibility limits. Consider, for example, the sum of ERRs from two exposures. If the two doses differ greatly, a large uncertainty in the smaller dose has little effect on the upper 99% credibility limit of ERR from both exposures combined. Another example involves the model in eqns (21–23) to describe risk transfer from a Japanese to the U.S. population. A change in the assumption about the weight given to an additive risk-transfer model would have little effect on the upper 99% credibility limit of ERR in the U.S. population if substantial weight is given to a multiplicative risk-transfer model and $B_{Japan}/B_{US} < 1$, because the upper 99% credibility limit in such cases would still be determined mainly by the assumption that a multiplicative model is plausible. However, a change in the weight given to an additive model could be important in determining the upper 99% credibility limit of ERR if $B_{Japan}/B_{US} > 1$.

As a tool for use in adjudicating claims for compensation for cancer,[§§§§] IREP operates at the interface of science and public policy. Although IREP is intended to provide unbiased estimates of ERR and PC/AS and their uncertainties to represent the state of knowledge and reasonable efforts have been made to incorporate the best science and scientific judgment available at the time the code was developed or modified, its use in the compensation program for energy workers requires that NIOSH be mindful of the policy implications of choices of models and assumptions. An important example is the general NIOSH policy to use a model or assumption that gives the higher estimate of the upper 99% credibility limit of PC/AS when a choice can be made but there is little basis for selecting one alternative over the other. This policy, which is favorable to claimants, is an important means by which NIOSH gives claimants the "benefit of the doubt" in the presence of uncertainty.

REFERENCES

Apostoaei AI, Trabalka JR. Differences in the estimation of lung cancer risk between NIOSH-IREP and NIH-IREP. Oak Ridge, TN: *SENES* Oak Ridge, Inc.; 2004. Available at: http://www.cdc.gov/niosh/ocas/pdfs/irep/1005mod/enclose2.pdf. Accessed 28 April 2008.

[§§§§] NIOSH-IREP also is used by the U.S. Department of Veterans Affairs in adjudicating claims for compensation for cancer by veterans of military services who participated in radiation-related activities while in service (Mansfield 2005).

Brackett EM, Allen DE, Siebert SR, La Bone TR. Internal dose reconstruction under Part B of the Energy Employees Compensation Act. Health Phys 95:69–80; 2008.

Cardis E, Vrijheid M, Blettner M, Gilbert E, Hakama M, Hill C, Howe G, Kaldor J, Muirhead CR, Schubauer-Berigan M, Yoshimura T, Bermann F, Cowper G, Fix J, Hacker C, Heinmiller M, Thierry-Chef I, Utterback D, Ahn Y-O, Amoros E, Ashmore P, Auvinen A, Bae J-M, Bernar J, Biau A, Combalot E, Deboodt P, Diez Sacristan A, Ekloef M, Engels H, Engholm G, Gulis G, Habib RR, Holan K, Hyvonen H, Kerekes A, Kurtinaitis J, Malker H, Martuzzi M, Mastauskas A, Monnet A, Moser M, Pearce MS, Richardson DB, Rodriguez-Artalejo F, Rogel A, Tardy H, Telle-Lamberton M, Turai I, Usel M, Veress K. The 15-country collaborative study of cancer risk among radiation workers in the nuclear industry: estimates of radiation-related cancer risks. Radiat Res 167:396–416; 2007.

Greenland S. The relation of the probability of causation to the relative risk and the doubling dose: a methodological error that has become a social problem. Am J Public Health 89:1166–1169; 1999.

Greenland S, Robins JM. Conceptual problems in the definition and interpretation of attributable fractions. Am J Epidemiol 128:1185–1197; 1988.

International Commission on Radiological Protection. 1990 recommendations of the International Commission on Radiological Protection. Oxford: Pergamon Press; ICRP Publication 60, Ann ICRP 21(1–3); 1991.

International Commission on Radiological Protection. Low-dose extrapolation of radiation-related cancer risk. Oxford: Pergamon Press; ICRP Publication 99, Ann ICRP 35(4); 2005.

Kocher DC, Apostoaei AI, Hoffman FO. Radiation effectiveness factors (REFs) for use in calculating probability of causation of radiogenic cancers. Oak Ridge, TN: *SENES* Oak Ridge, Inc.; 2002. Available at: http://www.cdc.gov/niosh/ocas/pdfs/irep/irepref.pdf. Accessed 28 April 2008.

Kocher DC, Apostoaei AI, Hoffman FO. Radiation effectiveness factors for use in calculating probability of causation of radiogenic cancers. Health Phys 89:3–32; 2005.

Land C. Uncertainty, low-dose extrapolation and the threshold hypothesis. J Radiol Protect 22:A129–A135; 2002.

Land CE, Hayakawa N, Machado S, Yamada Y, Pike MC, Akiba A, Tokunaga M. A case-control interview study of breast cancer among Japanese A-bomb survivors: II. Interactions between epidemiological factors and radiation dose. Cancer Causes Control 5:167–176; 1994.

Mansfield GH. Letter to M Strehlow and HD Royal, Veterans Advisory Committee on Environmental Hazards. Washington, DC: The Deputy Secretary of Veterans Affairs; 22 April 2005.

McKay MD, Conover WJ, Beckman RJ. A comparison of three methods for selecting values of input variables in the analysis of output from a computer code. Technometrics 21:239–245; 1979.

National Council on Radiation Protection and Measurements. Uncertainties in fatal cancer risk estimates used in radiation protection. Bethesda, MD: National Council on Radiation Protection and Measurements; NCRP Report No. 126; 1997.

National Institute for Occupational Safety and Health. NIOSH-Interactive RadioEpidemological Program (NIOSH-IREP) technical documentation. Cincinnati, OH: Office of Compensation Analysis and Support, National Institute of Occupational Safety and Health; 2002. Available at: http://

www.cdc.gov/niosh/ocas/pdfs/irep/irepfnl.pdf. Accessed 28 April 2008.

National Institute for Occupational Safety and Health. Changes to the dose reconstruction target organ selection for lymphoma under the Energy Employees Occupational Illness Compensation Act of 2000. Fed Reg 71:7969–7970; 2006a.

National Institute for Occupational Safety and Health. Changes to the NIOSH-IREP lung cancer risk model under the Energy Employees Occupational Illness Compensation Program Act of 2000. Fed Reg 71:14896–14897; 2006b.

National Institute for Occupational Safety and Health/Office of Compensation Analysis and Support. External dose reconstruction implementation guideline. Cincinnati, OH: Department of Health and Human Services; OCAS-IG-001; 2002. Available at: http://www.cdc.gov/niosh/ocas/pdfs/dr/oc-ig-001-r2.pdf. Accessed 28 April 2008.

National Institute for Occupational Safety and Health/Office of Compensation Analysis and Support. Program Evaluation Plan: Modification of the NIOSH-IREP lung cancer risk model: impact of "combined" lung model on non-compensable lung cancer claims; OCAS-PEP-008; 2006. Available at: http://www.cdc.gov/niosh/ocas/pdfs/peps/oc-pep8-r0.pdf. Accessed 28 April 2008.

National Institute for Occupational Safety and Health/Office of Compensation Analysis and Support. Program Evaluation Report: Modification of the NIOSH-IREP lung cancer risk model: impact of "combined" lung model on non-compensable lung cancer claims; OCAS-PER-008; 2007. Available at: http://www.cdc.gov/niosh/ocas/pdfs/pers/oc-per8-r0.pdf. Accessed 28 April 2008.

National Institutes of Health. Report of the National Institutes of Health ad hoc working group to develop radioepidemological tables. Washington, DC: National Institutes of Health; NIH Publication No. 85-2748; 1985.

National Institutes of Health. Report of the NCI-CDC working group to revise the 1985 NIH radioepidemological tables. Washington, DC: National Institutes of Health, National Cancer Institute; NIH Publication No. 03-5387; 2003.

National Research Council. Health risks of radon and other internally deposited alpha-emitters. Washington, DC: National Academy Press; BEIR IV; 1988.

National Research Council. Health effects of exposure to low levels of ionizing radiation. Washington, DC: National Academy Press; BEIR V; 1990.

National Research Council. Health effects of exposure to radon. Washington, DC: National Academy Press; BEIR VI; 1999.

National Research Council. A review of the draft report of the NCI-CDC Working Group to review the "1985 radioepidemiological tables." Washington, DC: National Academy Press; 2000.

National Research Council. Assessment of the scientific information for the radiation exposure screening and education program. Washington, DC: The National Academies Press; 2005.

National Research Council. Health risks from exposure to low levels of ionizing radiation. Washington, DC: The National Academies Press; BEIR VII Phase 2; 2006.

Neton JW, Howard J, Elliott LJ. Radiation Dose Reconstruction Program of the National Institute for Occupational Safety and Health: overview. Health Phys 95:6–13; 2008.

Pierce DA, Shimizu Y, Preston DL, Vaeth M, Mabuchi K. Studies of the mortality of atomic bomb survivors. Report 12, Part 1. Cancer: 1950–1990. Radiat Res 146:1–27; 1996.

Pierce DA, Sharp GB, Mabuchi K. Joint effects of radiation and smoking on lung cancer risk among atomic bomb survivors. Radiat Res 159:511–520; 2003.

Preston DL, Kusumi S, Tomonaga M, Izumi S, Ron E, Kuramoto A, Kamata N, Dohy H, Matsui T, Nonaka H, Thompson DE, Soda M, Mabuchi K. Cancer incidence in atomic bomb survivors. Part III: Leukemia, lymphoma and multiple myeloma, 1950–1987. Radiat Res 137:S68–S97; 1994.

Preston DL, Pierce DA, Shimizu Y, Cullings HM, Fujita S, Funamoto S, Kodama K. Effect of recent changes in atomic bomb survivor dosimetry on cancer mortality risk estimates. Radiat Res 162:377–389; 2004.

Preston DL, Ron E, Tokuoka S, Funamoto S, Nishi N, Soda M, Mabuchi K, Kodama K. Solid cancer incidence in atomic-bomb survivors: 1958–1998. Radiat Res 168:1–64; 2007.

Radiation Effects Research Foundation. Life span study cancer incidence data, 1958–1998. Hiroshima, Japan: Radiation Effects Research Foundation; 2007. Available at: http://www.rerf.or.jp/library/dl_e/lssinc07.html. Accessed 28 April 2008.

Robins JM, Greenland S. Estimability and estimation of excess and etiological fractions. Stat Med 8:845–859; 1989a.

Robins JM, Greenland S. The probability of causation under a stochastic model for individual risks. Biometrics 46:1125–1138; 1989b.

Roesch WC, ed. Final report on the reassessment of atomic bomb radiation dosimetry in Hiroshima and Nagasaki. Hiroshima, Japan: Radiation Effects Research Foundation; 1987.

Ron E, Lubin JH, Shore RE, Mabuchi K, Modan B, Pottern LM, Scheider AB, Tucker MA, Boice JD Jr. Thyroid cancer after exposure to external radiation: a pooled analysis of seven studies. Radiat Res 141:259–277; 1995.

Ron E, Preston DL, Kishikawa M, Kobuke T, Iseki M, Tokuoka S, Tokunaga M, Mabuchi K. Skin tumor risk among atomic-bomb survivors in Japan. Cancer Causes Control 9:393–401; 1998.

SENES Oak Ridge, Inc. User's guide for the Interactive Radio Epidemiological Program (NIOSH-IREP), version 5.5.1. Oak Ridge, TN: *SENES* Oak Ridge, Inc.; 2007. Available at: http://www.cdc.gov/niosh/ocas/pdfs/irep/irepug0607.pdf. Accessed 28 April 2008.

Shilnikova NS, Preston DL, Ron E, Gilbert ES, Vassilenko EK, Romanov SA, Kuznetsova IS, Sokolnikov ME, Okatenko PV, Kreslov VV, Koshurnikova NA. Cancer mortality risk among workers at the Mayak nuclear complex. Radiat Res 159:787–798; 2003.

Stram DO, Langholz B, Huberman M, Thomas D. Measurement error corrections for the analysis of lung cancer mortality in the Colorado Plateau uranium miners cohort. In: Ron E, Hoffman FO, eds. Uncertainties in radiation dosimetry and their impact on dose-response analyses. Washington, DC: National Institutes of Health, National Cancer Institute; NIH Publication No. 99-4541; 1999: 192–195.

Thompson DE, Mabuchi K, Ron E, Soda M, Tokunaga M, Ochikubo S, Sugimoto S, Ikeda T, Terasaki M, Izumi S, Preston DL. Cancer incidence in atomic bomb survivors. Part II: Solid tumors, 1958–1987. Radiat Res 137:S17–S67; 1994.

United Nations Scientific Committee on the Effects of Atomic Radiation. Sources, effects, and risks of ionizing radiation. New York: United Nations; No. E.94.IX.2; 1993.

United Nations Scientific Committee on the Effects of Atomic Radiation. Sources and effects of ionizing radiation. Vol. II: Effects. New York: United Nations; No. E.00.IX.4; 2000.

U.S. Congress. Energy Employees Occupational Illness Compensation Program Act of 2000, as amended. 42 USC 7384 et seq.; 2000.

U.S. Department of Health and Human Services. The international classification of diseases clinical modification, ninth edition. Washington, DC: U.S. Government Printing Office; Department of Health and Human Services Publication No. 91-1260; 1991.

U.S. Department of Health and Human Services. 42 CFR Part 81—Guidelines for determining the probability of causation under the Energy Employees Occupational Illness Compensation Program Act of 2000; final rule. Fed Reg 67:22296–22314; 2002a.

U.S. Department of Health and Human Services. 42 CFR Part 82—Methods for radiation dose reconstruction under the Energy Employees Occupational Illness Compensation Program Act of 2000; final rule. Fed Reg 67:22314–22336; 2002b.

U.S. Environmental Protection Agency. Estimating radiogenic cancer risks. Washington, DC: U.S. Environmental Protection Agency; EPA 402-R-93-076; 1994.

U.S. Environmental Protection Agency. Estimating radiogenic cancer risks. Addendum: Uncertainty analysis. Washington, DC: U.S. Environmental Protection Agency; EPA 402-R-99-003; 1999.

Young RW, Kerr GD, eds. Reassessment of the atomic bomb radiation dosimetry for Hiroshima and Nagasaki. Hiroshima, Japan: Radiation Effects Research Foundation; Vol. 1 and 2; 2005.

■ ■