NIOSH-Interactive RadioEpidemiological Program (NIOSH-IREP) Technical Documentation

Final Report

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I. Background

Under the Energy Employees' Occupational Illness Compensation Program Act of 2000 (EEOICPA), the National Institute for Occupational Safety and Health (NIOSH) is charged with the development of guidelines to determine whether a claimant's cancer meets the criterion for causation by workplace exposure to ionizing radiation (i.e., a 50% or greater probability of causation).

The basis for this determination, as specified in EEOICPA, is the set of radioepidemiological tables developed by a National Institutes of Health Ad Hoc working group in 1985 (NIH 1985), as they are updated periodically. These radioepidemiological tables serve as a reference tool providing probability of causation estimates for individuals with cancer who were exposed to ionizing radiation. Use of the tables requires information about the person's dose, gender, age of exposure, date of cancer diagnosis and other relevant factors. The tables are used by the Department of Veterans Affairs (DVA) to make compensation decisions for veterans with cancer who were exposed in the line of duty to radiation from atomic weapon detonations. The primary source of data for the 1985 tables is research on the occurrence of cancer-related deaths among Japanese atomic bomb survivors from World War II.

The 1985 tables have recently been updated by the National Cancer Institute (NCI) and the Centers for Disease Control and Prevention (CDC) to incorporate progress in research on the relationship between radiation and cancer risk, including the assessment of associated uncertainties. The draft update (NCI 2000) has been reviewed by the National Research Council (NAS/NRC 2000). The finalized update (NCI 2002) will be available soon for public release. HHS/NIOSH has

employed the finalized version of the NCI update, with certain modifications important to claims under EEOICPA, as a basis for determining probability of causation for employees covered under EEOICPA.

A scientific change achieved by the NCI update is the use of risk models developed from data on the occurrence of cancers (cases of illness) rather than the occurrence of cancer deaths among Japanese atomic bomb survivors. The risk models are based on more current data as well. Many more cancers have been modeled in the revised report. The new risk models also take into account factors that modify the effect of radiation on cancer, related to the type of radiation dose, the amount of dose, and the timing of the dose.

A major technological change accompanying this update, which represents a scientific as well as practical improvement, is the development of a computer software program for calculating assigned share. The assigned share is a term recommended in the NCI update of the radioepidemiological tables, instead of probability of causation, to properly reflect that these estimates are properties of groups of similar people, not of the individual. In other words, it is not possible to determine, for a given individual, whether his or her cancer resulted from a workplace exposure to ionizing radiation. The assigned share is used to estimate the probability of causation needed for determining eligibility for an award under EEOICPA, and these terms are used interchangeably in this document. It should also be noted that this software does not predict an individual's chances of getting cancer from workplace radiation exposure. Rather, it estimates (from epidemiological models combined with information on the individual's past exposure) the likelihood that an existing cancer resulted from that exposure.

The software program, named the Interactive RadioEpidemiological Program (IREP), allows the user to apply the NCI risk models directly to data on an individual claimant. This makes it possible to calculate probability of causation using better quantitative methods than could be incorporated into printed tables. In particular, IREP allows the user to take into account uncertainty concerning the information being used to calculate probability of causation. There typically is uncertainty about the radiation dose levels to which a person has been exposed, as well as uncertainty in the science relating levels of dose received to levels of cancer risk observed in study populations.

Accounting for uncertainty is important because it can have a large effect on the probability of causation estimates. DVA, in its use of the 1985 radioepidemiological tables, employs the value found in the tables at the upper 99 percentile of the probability of causation estimate. Similarly, as required by EEOICPA, the U.S. Department of Labor (DOL) will use the upper 99 percent credibility limit to determine whether the cancers of employees are at least as likely as not caused by their radiation doses. This will help minimize the possibility of denying compensation to claimants under EEOICPA for those employees with cancers likely to have been caused by radiation exposures.

The risk models developed by NCI and CDC for IREP (NCI 2002) provide the primary basis for developing guidelines for estimating probability of causation under EEOICPA. They directly address most cancers and most types of radiation exposure relevant to employees covered by EEOICPA. These models take into account the employee's cancer type, year of birth, year of cancer diagnosis, and exposure information such as years of exposure, as well as the dose received from gamma radiation, x rays, alpha radiation, beta radiation, and neutrons during each year. The risk model

for lung cancer takes into account smoking history as well. None of the risk models explicitly accounts for exposure to other occupational, environmental, or dietary carcinogens. Models accounting for these factors have not been developed and may not be possible to develop based on existing research. Moreover, DOL could not consistently or efficiently obtain the data required to make use of such models.

As stated above, the final draft of the National Cancer Institute's IREP software (NCI 2002) has formed the basis of the NIOSH-IREP software. The NCI's final draft has been updated from the version reviewed by the National Research Council in several ways. The updated draft includes a model for lung cancer resulting from radon exposure, developed from an analysis of U.S. uranium miner cohorts (RECA Committee, 1996), the development of models for non-melanoma skin cancer, the incorporation of a "miscellaneous cancer model", which they suggest should be used for bone cancer and male breast cancer, and the inclusion of models for non-melanoma skin cancer (squamous cell and basal cell carcinoma). Other changes include the incorporation of an uncertainty distribution for the latency of solid cancers, and the development of statistical distributions for the radiation effectiveness factors (REF) and dose and dose-rate effectiveness factor (DDREF) of different energies of photons, neutrons, and alpha particles (Kocher et al. 2002).

One important change in the NCI's methodology (which also constitutes the basis of NIOSH-IREP) is in the method of modeling solid cancer risk from the Japanese atomic bomb survivor study (NCI 2002, pp 27-31). Effects of gender, age at exposure and attained age were modeled for all solid cancers as a group. The risk modifications from these general models were then applied to the

site-specific models, unless there was a statistically-significant difference between these risk modifiers for the site-specific and general model. This approach has been recommended by an international expert committee (Pierce and Preston 1993; UNSCEAR 2000b, p. 208). The models show higher sensitivity (in general) for females compared to males. The general coefficients also show reductions in risk per unit dose between ages-at-exposure of 15 and 30 (if attained age is held constant). The ERR per Sv estimates do not change after age-at-exposure of 30. Thus, for most cancers NIOSH-IREP relies on direct evidence from the A-bomb survivors exposed as adults rather than as young children. This modulates the strong decline in risk with increasing age that is observed among those exposed as children in that study, and thus is more appropriate for modeling risks among those exposed as adults.

The modeling of risk from exposures as young as age 15 is a result of the Poisson regression procedure used to analyze the atomic bomb survivor cohort. This is a grouped data method; data are available for modeling within 5-year age-at-exposure categories; therefore, the modeled exposure classes for adults must begin at either age 15 or age 20. Because DOE employees may have begun working and accrued workplace radiation exposures before age 20, for EEOICPA it is necessary to model exposure categories beginning at age 15.

No age-at-exposure effect has been incorporated for acute myeloid leukemia, chronic myeloid leukemia, lung cancer (non-radon exposures), and female genital cancers other than ovary. The NCI models incorporate a trend of decreasing risk per unit dose with increasing age at exposure for acute lymphocytic leukemia, all leukemia other than chronic lymphocytic, basal cell carcinoma, and cancers of thyroid. For thyroid and non-melanoma skin cancer models, the age at exposure effects were modeled

using site-specific estimates, and generally decrease with increasing age at exposure. For the skin cancer model, a log-linear term is used to decrease risks for increasing ages at exposure between 10 and 40. Ideally, this model would include only adult exposures (as for other solid cancers); however, the data were not modeled in this way for NCI-IREP, and the data were not available to NIOSH researchers. Data were modeled categorically for a given age at exposure, and risk coefficients for intermediate ages at exposure were obtained through interpolation from values at surrounding age categories (Table IV.D.9 of NCI 2002).

For radon exposures and lung cancer, there is no direct adjustment for exposure age; risks are dependent on time since last exposure and on age at diagnosis. The effect of this adjustment is that, at a constant "time since last exposure", the risk decreases for increasing age at last exposure; however, for constant "age at diagnosis", the risk increases for increasing age at last exposure. For all other cancers, the NCI models incorporate a trend of decreasing risk per unit dose for exposure ages between 15 and 30, and assumes constancy thereafter.

These changes are detailed in the NCI IREP documentation being finalized by the NCI (NCI 2002). [It must be noted, however, that the NCI IREP is not finalized at the time of this writing. (May 2002) Any changes or modifications which occur as part of the finalization of the NCI-IREP which are not notes here must be evaluated for scientific merit and applicability under EEIOCPA.] Changes in the NCI IREP that are relevant to the evaluation of compensation claims under EEOICPA may be incorporated into future versions of NIOSH-IREP.

II. NIOSH-IREP and its implementation under EEOICPA

A. Dosimetry Issues

NIOSH-IREP includes twelve types of radiation exposure. For this purpose, radon is considered an exposure that may contribute to risk of lung cancer only, and the remaining eleven types of exposure, considered for any cancer type, are described in Table 1. These types of exposures are differentiated by the assumed radiation weighting factor (termed here the radiation effectiveness factors or REF) and in some cases, a factor accounting for reduced or enhanced effectiveness in producing cancers resulting from dose protraction (dose and dose rate effectiveness factor, or DDREF). The distributions assumed for these factors are described in Section II.D below. There are two classes of electron (beta particle) exposure within NIOSH-IREP: one class associated with exposure to tritium, and a second class for all other electrons. Three different photon energy classes exist within NIOSH-IREP: photons of energy greater than 250 keV (exemplified by high-energy gamma radiation that was the primary exposure of the Japanese atomic bomb survivors), photons of energy between 30 and 250 keV, which includes photofluorographic x rays used during the 1940s and 1950s at some Department of Energy (DOE) facilities (Cardarelli 2000), and photons of energy less than 30 keV, which includes photons emitted by certain transuranic radionuclides. There are five classes of neutrons differentiated by energy type. The most commonly encountered type of neutron exposure within the DOE workforce is fission neutrons, composed primarily of neutrons with energy between 100 keV and 2 MeV. However, neutrons of higher and lower energy are included because these exposures are relevant for certain DOE workers. Finally, a single class of radiation exposure is included for non-radon alpha

particles. The exposure units used in NIOSH-IREP are working level months (WLM) for radon, and cSv (rem) for all other radiation types.

For each type of exposure, the dose used in NIOSH-IREP will be based on the individual organ or tissue in which the primary cancer occurred, or, if unavailable, in the nearest relevant organ or tissue. For bone cancer, dose to the endosteal cells (the cells of the outer bone surface) will be calculated. For skin cancer, a more site-specific approach will be used. Because studies of medically-exposed persons have shown that radiation-induced skin cancers tend to occur within the field of radiation exposure (van Daal et al. 1983, Shore et al. 1984, Hildreth et al. 1985, Lichter et al. 2000), skin dose will be calculated only for the location where the cancer occurred, as reflected in the 9th Revision of the International Classification of Diseases (ICD-9) 4-digit nosology code (i.e., lip, eyelid, ear, other parts of face, scalp and neck, trunk, upper limb, lower limb). If the body location is unspecified, the maximum skin dose at any location will be calculated as input to NIOSH-IREP.

In determining the dose rate (i.e., acute or chronic) that should be assumed for use in NCI-IREP, the NCI working group referenced the definition used by the UNSCEAR (UNSCEAR 1993), which is that an acute dose is delivered at a dose rate of 6 mGy per hour or greater (NCI 2002, p. 37), averaged over several hours. This is equivalent to a dose rate of 0.1 mGy (10 mrem) per minute. Lower exposure rates should be considered chronic, according to this definition.

Work-related medical x-ray exposures are clearly acute, by this definition. Although likely to have been chronic, the true dose rate of these gamma and neutron exposures is unknown for any given worker within the badging period. *Therefore, the approach used in the NIOSH Dose*

Reconstruction methods and NIOSH-IREP is to make an assumption about duration of exposure that is most favorable to the claimant. This is consistent with the approach used elsewhere in NIOSH-IREP, of providing the benefit of doubt to the claimant where two or more plausible alternatives for input exist. This approach was, additionally, recommended by the NAS panel reviewing NCI-IREP: "... the officials responsible for adjudicating claims might routinely assume that the exposure aggregated over the smallest unit of time available (such as a quarter-year) was received as a single acute dose to provide a liberal estimate of risk" (NAS/NRC 2000, p. 13). In the case of gamma exposures, such a liberal assumption would be that the dose was acute. For neutron exposures, an assumption of chronic dose rate would produce the most liberal estimate of risk.

For these reasons, in the dose reconstruction process, gamma and x ray doses will be considered acute over the smallest period of time during which the exposure measurement occurred. As a practical matter, this means that the exposure rate will be categorized as acute for each badge reading, and each will be specified separately within a given year in NIOSH-IREP. For example, if a claimant's dosimetry badges were exchanged and read on a quarterly basis, each of the four badge results would be entered as a separate acute dose (or dose distribution) in NIOSH-IREP. In contrast, photon exposures resulting from the intake of an internal emitter will be assumed to be chronic, as the decay path of the alpha particle (which is a known physical quantity) produces a chronic exposure. For reasons outlined above, neutron doses will be assumed to be chronic over the badge reading period. This assumption will have the effect of increasing the probability of causation for neutron exposures, because of the use of a protraction enhancement factor (e.g., see Section II.D and Kocher et al. 2002).

B. Cancers added to NIOSH-IREP

The final NCI-IREP program (NCI 2002) includes more cancer models than the draft NCI-IREP program reviewed by the NAS panel (NCI 2000). Cancer models for squamous cell carcinoma of skin and basal cell carcinoma of skin have been added, based on new analyses conducted by researchers at the Radiation Effects Research Foundation (RERF), in Japan (see discussion of "skin cancer models" in Sec. II.B.2, below). Certain cancer models have been added to NIOSH-IREP. These include malignant melanoma of skin, and cancers of the male breast, bone, connective tissue, eye, and endocrine glands other than thyroid. The NCI version of IREP includes the last four of these in a general "miscellaneous" cancer model, but they are explicitly separated in NIOSH-IREP. The scientific basis of these models and their implementation in NIOSH-IREP are described below.

In summary, NIOSH-IREP incorporates three different models for skin cancer. For non-melanoma skin cancer, basal cell and squamous cell carcinoma models are based on different sets of risk coefficients. In claims for which the non-melanoma skin cancer type is indeterminate, the model for basal cell carcinoma is to be used in estimating the probability of causation. Both basal cell and non-basal cell carcinoma models are modified by race-specific background incidence rates for combined non-melanoma skin cancers. A third skin cancer model, for malignant melanoma, uses basal cell carcinoma risk coefficients, modified by background incidence rates for malignant melanoma. All three skin cancer models use the "general" risk transfer uncertainty distribution (developed for all solid cancers save breast and thyroid). For other cancer types, the sites used to produce excess relative risk

(ERR) per Sv estimates for each risk model, and the cancer groupings to which these models were applied, are given in Table 2.

1. Bone cancer:

Exposure to plutonium has been found in numerous animal studies to cause bone cancer (NAS 1988). There is also a large body of literature regarding the induction of bone cancer from occupational exposure to radium, in the form of Thorotrast (see NAS/NRC 1988 and IARC 2001, for summary). Most U.S. worker studies are based on relatively low exposures and small numbers of workers exposed to plutonium, and have thus been inconclusive with respect to bone cancer induction. However, a recent study of the Russian Mayak facility (Koshurnikova et al. 2000) found elevated rates of bone cancer among workers with positive plutonium body burdens, after adjusting for cumulative external dose (RR = 7.9; 95% confidence interval = 1.6-32). Unfortunately, this study cannot be used for quantitative assessment of risk, because of serious limitations in the plutonium dosimetry for these workers (Koshurnikova et al. 2000); however, it does provide strong qualitative evidence for an association between plutonium exposure and bone cancer in humans.

For the purposes of NIOSH-IREP, two sources of risk coefficients were considered: data from the risk analysis conducted for plutonium exposures among Rocky Flats workers (Grogan et al. 2000, 2001), and the miscellaneous cancer model used in NCI-IREP. The risk coefficients from Grogan and colleagues' analysis are based on three sources: mortality data from the Japanese atomic bomb survivors studies (modified by the uncertain radiation

effectiveness factors for alpha particles as compared to low-energy photons and by the dose-and-dose rate effectiveness factor); studies of humans exposed to other alpha-emitters; and studies of animals exposed to plutonium. A subjectively weighted combination of these risk estimates for plutonium exposure was then used to produce estimates of lifetime risk per unit dose and per unit intake of plutonium.

The approach of Grogan and colleagues is quite difficult to incorporate into IREP, however, because of the need of IREP to incorporate risks from many types of radiation exposure, not just plutonium and other alpha-emitting radionuclides. The problem with using human and animal studies of alpha-exposed groups as a source of risk coefficients in IREP is that, in the former, the risk per unit dose is expressed as a function of the initial (rather than the committed dose), while in the latter, the risk per unit dose is expressed on an incremental basis as dose is received by the target organ. In other words, in the studies upon which the risk models are based, the radionuclide is deposited in the target organ (e.g., the bone surfaces), and the dose to bone surfaces is delivered throughout the life of the individual. The expression of risk in these studies is based on the initial exposure to the bone surface, which is an underestimate of the total dose received by the organ. While this is not an inconsistent approach for evaluating the risks of plutonium or other transuranic radionuclides, it is incompatible with the approach used throughout IREP, which is concerned with both these radionuclides and external ionizing radiation exposures. The model implemented by Grogan and colleagues that is most compatible with the approach of IREP is the bone cancer model

obtained from Japanese atomic bomb survivors, modified by relevant distributions of REF and DDREF for different types of radiation. Use of this approach is also consistent with that adopted by NCI for other tissues in which transuranic radionuclides tend to accumulate (e.g., liver).

The study of cancer incidence among atomic bomb survivors (Thompson et al. 1994) does not quantify bone cancer risks; however, the Grogan model uses excess risk estimates from the latest mortality study (Pierce et al. 1996) for its cancer incidence model. This model was not deemed appropriate by NCI for IREP because the extreme rarity of this cancer, particularly in the exposed group, would have resulted in a model that was inconsistent with the methods used for other cancers (which were based on risk coefficients for groups of similar cancers that numbered at least 50 in the population exposed to 0.5 cSv or greater).

The final NCI-IREP program includes bone cancer among the grouping of miscellaneous cancers includes bone cancer (NCI 2002). The primary argument against the use of the miscellaneous cancer risk coefficients for bone cancer claims is that the model includes many disparate types of cancers, including those of bone, connective tissue, eye, male breast cancer, non-thyroid endocrine glands, and ill-defined sites. The alternative, however, of using highly uncertain risk coefficients (from the bone cancer mortality series) without modification from other information sources, seems less defensible, and inconsistent with the approach used for other cancers in this class. The point estimates for the two models are quite similar. Therefore, we concur with the NCI that the most appropriate source of risk coefficients

for use at this time in the bone cancer models is the miscellaneous cancer model from NCI-IREP. As is the case for other cancers in this category, the risk coefficients are modified by the background incidence rates for the specific cancer.

2. Non-melanoma skin cancer:

Some expert groups consider skin cancer risk in establishing low-level skin radiation exposure limits (ICRP 1991a), as several studies have provided evidence that non-melanoma skin cancers, particularly basal cell carcinoma (BCC), are related to exposure to ionizing radiation (Shore 2001). These include studies of radiologists, uranium miners, and patients exposed during treatment for medical conditions, as well as the Japanese atomic bomb survivors (Sevcova et al. 1978, van Daal et al. 1983, Hildreth et al. 1985, Thompson et al. 1994, Ron et al 1998). Many studies suggest that, of the two types comprising non-melanoma skin cancer, BCC is much more radiosensitive than squamous cell carcinoma and other non-melanoma skin cancers (SCC; van Daal et al. 1983, Ron et al. 1998, Shore 2001); however, others do not specify the relative radiosensitivity of these two skin cancer types (Hildreth et al. 1985), or found similar radiosensitivity of the two types (Lichter et al. 2000).

Within NIOSH-IREP, only skin cancer has an adjustment for race and/or ethnicity in determining the probability of causation. Unlike other cancers, the biological justification for this adjustment is very strong: skin cancer incidence rates vary by a factor of 20 or more for individuals of different racial or ethnic groups, while most other cancers that show racial

variation in incidence differ by a factor of two or less (Fig. 1). For malignant melanoma, incidence rates are 18-20 times greater among non-Hispanic U.S. whites than among African-Americans. Skin cancer incidence rates for Asian-Americans and Native Americans are similar to African-Americans (Miller and Gaudette 1996), and rates for Hispanic whites are intermediate between those of African-Americans and whites (Scotto et al. 1996). For most cancers, the reasons for disparity in incidence by race are not known, but probably include factors such as differences in tobacco use, dietary factors, and access to health care. In contrast, the reasons for racial and ethnic differences in skin cancer incidence rates appear strongly related to the damage produced by exposure to ultraviolet radiation (UV) in susceptible individuals. Non-whites are thought to be at less risk of cancer from exposure to UV through the protective effect of melanin, which absorbs harmful UV radiation in the skin (Kaidbey et al. 1979, Altman et al. 1987, Kollias et al. 1991). The net effect of incorporating the background incidence rate of skin cancer is to properly reflect the increased probability of causation for radiation-induced skin cancer for non-white claimants, compared to whites exposed to the same doses under the same conditions, if a sub-multiplicative relationship exists between radiation exposure and sensitivity to UV radiation exposure. Not incorporating the ethnic differences in background risk would have the effect of underestimating the probability of causation of radiation-induced skin cancers among non-whites.

The true form of the interaction between ionizing and UV radiation exposure is unclear. On theoretical grounds, ionizing radiation might be expected to interact additively with

background risk (caused primarily by exposure of susceptible skin to UV radiation; UNSCEAR 2000b, p. 200), if melanin is not similarly protective of its effects. However, some studies have suggested that melanin provides protection from radiation-induced skin cancer as well (Harley et al. 1983, Shore et al. 1984, Davis et al. 1989). Unfortunately, few studies have evaluated formally the interaction of ionizing radiation exposure with skin pigmentation. A meta-analysis of twelve epidemiologic studies of UV and ionizing radiation exposed individuals could not distinguish between an additive and multiplicative interaction, due to the lack of controls with ionizing radiation exposure alone (Shore 1990; UNSCEAR 2000b). Without the capability to formally test for the form of interaction within a study, the United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) recommends careful comparison of the relative risks among different populations in comparable studies (UNSCEAR 2000c, p. 310). The ICRP evaluated existing studies, and, given the findings of several studies that excess absolute risk from ionizing radiation exposure is greatest among white populations (and is still higher in areas of the skin usually exposed to greater UV radiation), suggested an interaction that is more than additive (Harley et al. 1983, Shore et al. 1984; ICRP 1991a, pp. 75-78). However, a recent analysis of non-melanoma skin cancer among the Japanese atomic bomb survivors found excess relative risks per unit dose nearly ten times higher for areas of the body unexposed to UV radiation (Ron et al. 1998). This finding strongly suggests a submultiplicative interaction between ionizing and UV radiation exposures. An authoritative

UNSCEAR report (UNSCEAR 2000b) suggests that a sub-multiplicative model should be employed for risk modeling, based on the totality of evidence.

The uncertainty in the appropriate form of interaction between UV and ionizing radiation exposure is expected to be most critical in determining the role of race or ethnicity in modifying the excess relative risk estimates produced from the Japanese atomic bomb survivor study. Because of this large uncertainty, the method of risk transfer from the Japanese to the U.S. racial/ethnic groups, built into the NIOSH-IREP program, should incorporate the possibility of an additive or multiplicative interaction (or a mixture of these). Given the conflicting evidence regarding the appropriateness of any specific interaction model between UV and ionizing radiation exposure, the IREP program uses the same uncertainty distribution for risk transfer as was used for all other solid cancers (except breast and stomach cancer). This distribution is trapezoidal, equally weighting the probabilities for an additive and multiplicative interaction, with slight probabilities of sub-additive or super-multiplicative interactions.

In order to apply the risk transfer function referenced above, background cancer incidence rates in Japan and the U.S. (by race/ethnicity categories) are required. Incidence rates for non-melanoma skin cancer are available for Japan, but not for the U.S., as this is not a reportable cancer among U.S. registries. However, a survey of non-melanoma skin cancer rates was carried out by researchers at the National Cancer Institute in the early 1980s, reflecting rates across a wide area within the U.S. for 1977-1980 (Scotto et al. 1983). In

Japan, non-melanoma skin cancers are reportable, and incidence rates are available both for 1990 (Parkin et al. 1977) and for 1978-1982 (Muir et al. 1987). Therefore, to more accurately reflect comparative rates in both countries, incidence rates for the late 1970s (age-adjusted to the 1970 U.S. standard population) were used from both countries for NIOSH-IREP. For the U.S. population of non-Hispanic whites, these data were obtained from Tables 5 (males) and 6 (females) of Scotto et al. (1983). For Hispanic whites and African-Americans (Hispanic and non-Hispanic), these data were obtained from Scotto et al. (1996). The age-adjusted background incidence rates used in NIOSH-IREP are shown here in Table 3. Incidence rates for Asian or Native Americans have not been estimated in the special surveys of non-melanoma skin cancer incidence (Scotto et al. 1983, 1996). Based on literature reporting low rates of non-melanoma skin cancer risk among these groups (Miller and Gaudette 1996), as well as the similarity in malignant melanoma incidence among Native Americans, Asian-Americans and African-Americans (Table 3), the non-melanoma skin cancer incidence for the former two ethnic groups is assumed to be the same as for African-Americans, for purposes of NIOSH-IREP. While the background incidence rates for most cancers are based on relatively current rates (i.e., circa 1990), the rates for non-melanoma skin cancer for both the Japanese and U.S. populations are based on data from the late 1970s. More recent studies show that incidence rates have likely increased since that time (Miller and Weinstock 1994). This is not likely to be an unacceptable source of error for calculation of probability of causation within the DOE workforce, since claims are to be considered for any cancer

occurring since the worker began employment at a facility (i.e., a time period extending from the 1940s through the present day).

While many studies have found an association between ionizing radiation exposure and skin cancer, the appropriate form of dose-response model for skin cancer is highly uncertain (ICRP 1991a, p. 52). Some researchers advocate the use of a threshold model, on the basis of observations about dose-response relationships for such deterministic endpoints as skin dermatitis, desquamation and erythema, and upon evidence for a nonlinear dose-response relationship observed in some animal studies (reviewed in ICRP 1991a, pp 52-55). However, no evidence of a dose threshold was observed in a meta-analysis of twelve UV and ionizing radiation-exposed groups (Shore 1990, UNSCEAR 2000b). A recent study evaluated various forms of the dose-response relationship for the atomic bomb survivors, and concluded that the best-fitting model for non-melanoma skin cancer is proportional to the fourth power of dose (Little and Charles 1997). However, a more recent analysis found no significant model improvement (over linearity) using a linear-quadratic model (Ron et al. 1998). A linear dose-response relationship for non-melanoma skin cancer has been advocated by others as well (e.g., Scotto et al. 1996). The mechanisms in skin carcinogenesis that might lead to a threshold, not observed for most other organs in these studies, are unclear (ICRP 1991a, pp. 54-55).

Skin doses are poorly estimated in most studies of risks associated with ionizing radiation exposure, making quantitative dose-response analysis difficult. As for other cancer sites, an exception is the Japanese atomic bomb survivors study. The final version of NCI-

IREP includes separate risk coefficients for BCC and other non-melanoma skin cancers (mainly SCC), based on new analyses of skin cancer incidence among atomic bomb survivors conducted by researchers at the Radiation Effects Research Foundation in Japan (NCI 2002, p. 34). The method used to develop risk coefficients for these separate models is quite consistent with that for other cancers. The results of this modeling effort support the use of substantially different risk coefficients for the two non-melanoma skin cancer types. However, it should be noted that ICD-9 (and its revision, ICD-10) does not distinguish between SCC and BCC within the non-melanoma skin cancer category. In cases where it is not possible to determine which cancer cell type applies to a given claimant, DOL is instructed to use the risk models for basal cell carcinoma.

The risk coefficients developed for non-melanoma skin cancer in the finalized NCI-IREP were incorporated into the final NIOSH-IREP. The excess relative risk coefficients for BCC vary by age at exposure but not by gender or attained age, and are linear in dose. The coefficients for SCC do not vary by gender, age at exposure, or attained age. No adjustment is made for time since exposure (except the latency adjustment used for all other cancers between 0 and 5 years after exposure). This is supported by evidence from several studies which indicate that radiation-related skin cancer risks remain elevated for many years following exposure (van Daal et al. 1983; Ron et al. 1998).

3. Malignant melanoma

The association between malignant melanoma and radiation is not clear. Few studies have been conducted with sufficient power to detect increases in the relative risk of melanoma. This problem is exacerbated by the fact that background incidence rates are very low for some populations in which radiation-related risks have been evaluated. For example, the point estimate of radiation excess relative risk among atomic bomb survivors is high, but with a wide confidence interval, due to the very small number of cases (Ron et al. 1998). No significant excess of malignant melanoma was observed among the primarily African and Asian cohort of children exposed to radiation for the treatment of tinea capitis (scalp ringworm) in Israel (Ron et al. 1991). However, a small study of Israeli children exposed to x rays during cardiac catheterization showed elevated incidence of malignant melanoma (Modan et al. 2000). The radiation-related relative risk point estimate for melanomas was very similar to that for non-melanoma skin cancer in an irradiated North American population; however, the melanoma estimate was based on sparse data (Hildreth et al. 1985).

Most studies of DOE workers have shown no association between malignant melanoma and radiation exposure. However, early studies of workers at the Lawrence Livermore National Laboratory showed elevated incidence of malignant melanoma compared to the adjacent community, although risk was not associated with recorded doses to ionizing radiation (Austin et al. 1981). This finding has been attributed by some to potentially increased surveillance among this population, and to important related factors, such as skin pigmentation

and sunlight exposure patterns, which were not considered in the initial study (Hiatt et al. 1986, Moore et al. 1997). Other recent studies have concluded that, while surveillance bias may have partially contributed to the observed excess in malignant melanoma, an association with employment exposures including ionizing radiation persists after adjusting for confounding factors (Hiatt et al. 1993, Schwartzbaum et al. 1994, Austin and Reynolds 1997). Among other nuclear worker cohorts, skin cancer mortality (predominantly malignant melanoma) was found to be associated with external ionizing radiation dose in the U.K. National Registry of Radiation Workers cohort (Carpenter et al. 1994), although that finding was not significant in a later study of that cohort (Muirhead et al. 1999).

Direct quantitative estimates of radiation risk for malignant melanoma are not generally available. The risk estimates from the Japanese atomic bomb survivor data have very wide confidence intervals, as they are based on only ten cases; however, they are consistent with the rates for basal cell carcinoma (Ron et al. 1998). There is great need for future studies of malignant melanoma in radiation-exposed populations, in order to better estimate risk coefficients for this cancer. However, in the absence of direct information, three reasonable potential sources of risk coefficients are those developed in IREP for non-melanoma skin cancer (one model each for basal cell and squamous cell carcinoma) and the miscellaneous site cancer model. Using the model producing the highest ERR/Sv risk coefficients would be consistent with HHS policy decisions about selecting the most claimant-favorable among equally-valid alternatives in determining probability of causation in EEOICPA.

Both the basal cell carcinoma and the miscellaneous cancer models have higher ERR/Sv estimates than the squamous cell carcinoma model (NCI 2002). Of these two, the basal cell carcinoma model produces higher ERR/Sv estimates for men at all combinations of age at exposure and attained age, and for women at younger ages of exposure (Fig. 2). At ages of exposure above about 35, the miscellaneous cancer model produces slightly greater ERR/Sv estimates (but these are both quite low, considering typical exposure patterns at DOE facilities). Therefore, it would in general be most favorable to the claimant to use the basal cell carcinoma model to provide excess relative risk estimates for malignant melanoma. These estimates should be applied to the background incidence rates for malignant melanoma in Japan and the U.S., and the same risk transfer model as for other skin cancers, as discussed earlier (i.e., the distribution favoring neither the additive nor the multiplicative interaction model).

For these reasons, the ERR per Sv estimates for basal cell carcinoma were used to evaluate probability of causation for malignant melanoma. The sources of background incidence rates used in NIOSH-IREP for malignant melanoma of the skin are the same as for other cancers: Japanese incidence data were obtained from Parkin et al. (1997), and U.S. rates (race- and ethnicity-specific) were obtained from the U.S. Surveillance Epidemiology and End Results (SEER) program.

4. Male breast cancer

Breast cancer is extremely rare among men: the age-adjusted incidence is 0.7 per 100,000 among white males, compared to 90.7 per 100,000 for white females in the U.S. (Parkin et al. 1997). As a result, this cancer is very difficult to study directly in men, and little is known about risk factors for male breast cancer, with the exception of Klinefelter syndrome, a known major risk factor (Hultborn et al. 1997). A few sporadic cases among men given medical radiation treatment have been reported (Greene et al. 1983, Olsson and Ranstam 1988). However, the following lines of evidence (summarized in Henderson et al. 1996) suggest that male breast cancer may have similar hormonally-related cancer promotion risk factors as female breast cancer: 1) Breast cancer in males, as in females, increases greatly with age 2) Male breast cancer is associated with overweight in early adulthood, a finding that is true for post-menopausal women as well. 3) Gynecomastia (a factor related to excess estrogen) is a risk factor for breast cancer in men 4) Evidence from mathematical modeling of breast tissue aging in men and women suggests that differences in predicted tissue concentrations of estrogen are sufficient to explain the differences in breast cancer incidence among the sexes (Casagrande et al. 1988, Bernstein et al. 1989, Thomas et al. 1992, Hsing et al. 1998). Hormonally-related risk factors have been found to interact multiplicatively with radiation, in studies of female Japanese atomic bomb survivors (Land et al. 1994, NCI 2002). Thus, the excess relative risk of radiation-induced male breast cancer (applied to the background rates of males) may be similar to that of female breast cancer. An alternative

approach that was considered was the use of the miscellaneous cancer model, which includes male breast cancer incident cases from the Japanese atomic bomb survivor cohort. In the absence of scientific information to determine which of two or more alternative methods should be used, a consistent policy throughout the development of the HHS methods for determining probability of causation under EEOICPA has been to use the approach that is most favorable to the claimant. The female breast is considered among the most radiosensitive tissues in the body (Boice et al. 1996); however, sensitivity of the breast decreases greatly with increasing age at exposure. Therefore, it is not immediately clear which source of risk coefficients provides the most claimant-favorable estimate of probability of causation. Examination of the upper 99th percentile ERR/Sv estimates for both models (Fig. 3) shows that the use of the female breast cancer model provides the most claimant-favorable estimates, at most combinations of exposure and diagnosis ages.

Within NIOSH-IREP, therefore, for the male breast cancer model, ERR per Sv coefficients from female breast cancer models were modified by the background incidence rates for male breast cancer in the U.S. and Japan (Parkin et al. 1997; NCI 2000, 2002). There is no data to support the use of any particular risk transfer model between the Japanese and U.S. populations. In the absence of such information, the approach developed for all cancers other than female breast and stomach was employed in NIOSH-IREP. This transfer function is trapezoidal, which equally weights additive and multiplicative transfer models (with small probabilities of sub-additive and super-multiplicative models; NCI 2002).

5. Connective tissue cancer, eye cancer, other endocrine cancer, and other and ill-defined sites

There is very little specific information about the radiogenicity of the following cancer groups:

(1) connective and other soft tissue cancers (ICD-9 171),

(2) cancer of the eye (ICD-9 190),

(3) cancer of the endocrine glands other than thyroid (ICD-9 194), or

(4) cancers of other, ill-defined and unspecified sites (ICD-9 196 and 199).

The NCI-IREP program contains a set of "miscellaneous" ERR per Sv coefficients derived from analysis of these and a few other sites, namely bone cancer and male breast cancer. To implement probability of causation models for the four groups above, the miscellaneous-site ERR per Sv model was applied to the background cancer incidence rates (U.S. and Japan) for each of the four groupings defined above, using data from Parkin et al. (1997). Thus, there are four additional models within NIOSH-IREP, for each of the four groupings described above (Table 2, 4).

C. Cancers excluded from NIOSH-IREP

1. Chronic lymphocytic leukemia (ICD-9 204.1).

No dose-response model was developed for chronic lymphocytic leukemia (CLL) by either the NIH Working Group (NIH 1985) or the NCI/CDC working group to update these tables (NCI 2000). This is because no elevation of CLL incidence was observed among Japanese atomic bomb survivors (Preston et al 1994). Because CLL is very rare among non-Western populations (implying, therefore, that the power to detect small excess relative risks is poor in the atomic bomb survivors study), it is necessary to evaluate the relationship observed between radiation and CLL in other populations. No association of radiation exposure with CLL was observed among 14,000 British ankylosing spondylitis patients treated with x rays (a total of 2 CLL deaths; Darby et al. 1987). No elevation of CLL risk has been observed among U.S., Canadian and European women exposed to radiation during treatment for uterine cancer (a total of 57 CLL deaths; Curtis et al. 1994), nor has a relationship been observed in a large study of over 124,000 nuclear workers in the U.K. (Muirhead et al. 1999). Finally, no relationship was observed between external radiation dose and CLL in the first combined international nuclear workers study (a total of 27 CLL deaths; Cardis et al 1995). Studies of people exposed to internal sources of radiation have also not shown increased risks of CLL. For example, no increased risk was found for CLL among patients in Denmark exposed to Thorotrast, a ^{232}Th-containing contrast medium (Andersson et al. 1993, IARC 2001)

In addition to these individual studies, most expert committees have listed CLL as a cancer that appears non-radiogenic. The BEIR V Committee report (NAS/NRC 1990) excluded CLL from the group of leukemias for which risk models were produced, based on the lack of an association found among the studies reviewed. The UNSCEAR 2000 report states that CLL appears to be non-inducible by radiation exposure (UNSCEAR 2000c, p. 308). In summary, chronic lymphocytic leukemia is strongly associated with attained age. No evidence has been found in published studies that ionizing radiation is associated with increased risk of CLL. This approach will be revisited in future versions of NIOSH-IREP, as new scientific information becomes available.

D. Dose and dose-rate effectiveness factors

As indicated in Section I of this report, changes in the DDREF and REF distributions adopted in the final NCI program were used in NIOSH-IREP. These changes include substantial modifications of the uncertainty distributions for the REF, described in detail in the accompanying document (Kocher et al. 2002).

For DDREF, the NCI-IREP program has modified an uncertainty distribution used by Grogan et al. (2000), p. 6-23, for low linear energy transfer (LET) radiation (NCI 2002). The uncertainty distribution is similar to that recommended in NCRP (1997), except that it is discrete, more heavily weights a DDREF of one, and it incorporates a small probability of a DDREF less than one (i.e., it allows the possibility of an inverse dose-rate effect for low-LET radiation). The justification for this

change, reflecting a preference for the use of epidemiological data to estimate low-dose effects, is the latest analyses of the Japanese atomic bomb survivor data (Pierce and Preston 2000), upon which the majority of IREP models are based. This analysis strongly supports a linear over a sublinear (e.g., linear-quadratic) model, even within the lowest dose categories. The A-bomb survivor study (the epidemiological study deemed most informative in the development of other risk modifiers, such as gender and age at exposure) does not support the use of a DDREF of much larger than one, for low-dose acute exposures. [The DDREF in NCI-IREP is phased-in at acute doses lower than 0.2 Sv – well above levels found to be linear in studies of incidence (Pierce and Preston 2000) and mortality (Pierce et al. 1996) in the A-bomb survivor cohort].

The recent strong evidence for a linear (or, more weakly, for a supralinear) dose-response relationship for all solid *incident cancers* in the dose range of 0.05 to 0.1 Sv in the A-bomb study is made more compelling because it avoids the potential biases for which the finding in the mortality series has been criticized. On the other hand, there is substantial evidence from animal studies supporting a DDREF of greater than two (summarized on pp. 60-66 of NCRP 1997 and on p 23 in BEIR V 1990) for low-LET exposures. Moreover, most expert committees, including the NCRP, the ICRP, and UNSCEAR, recommend a DDREF of about 2 (NCRP 1997, p 66; ICRP 1991b; UNSCEAR 2000c, p 358).

However, in light of the new analysis of cancer incidence in low-dose ranges of the Japanese A-bomb study referenced above, the NCI has shifted the DDREF distribution for all solid cancers in IREP to more heavily weight a DDREF of one, and to include a small probability for a DDREF of less

than one (i.e., a supralinear effect at low doses). This distribution, more similar to that used by the U.S. EPA (USEPA 1999), and the recent report by Grogan and colleagues (Grogan et al. 2000), is also the basis for the revised NIOSH-IREP (Fig. 4a). To make the DDREF distribution consistent for breast and thyroid cancers, NCI has added a small probability of supralinear effects at low doses (i.e., a DDREF of less than one; Fig. 4b). This has also been adopted for use in NIOSH-IREP.

The uncertainty distribution used in both NCI's and NIOSH's IREP is consistent with the large body of laboratory studies that demonstrate a reduced effect with dose protraction for most cancers (IARC 2000, pp 301-304; UNSCEAR 2000a, pp 116-119), together with the latest analysis of the Japanese atomic bomb survivors, which suggests no reduction (and possibly, an enhancement) of carcinogenic effects at low doses. This DDREF distribution is used for chronic exposures, and is invoked for acute exposures below 0.2 Sv, according to the probability distribution used in NCI's original IREP methodology (NCI 2000).

It should be noted that at present IREP (both NCI and NIOSH versions) assumes the quadratic term in the leukemia dose-response relationship is fixed. Ideally, this term should have some uncertainty associated with it (this was also mentioned by the NAS panel reviewing the draft NCI-IREP); however, it is not clear what that uncertainty distribution should be.

E. Radiation (type) effectiveness factors (REFs)

The REF distributions used in IREP vary for each different type of radiation (Tables 5A, 5B, and 5C). The assumptions underlying these distributions are detailed in Kocher et al. (2002). In

summary, the approach used to estimate the REF for each type of radiation was to review the relevant literature comparing the REF for the specific exposure type as compared to high-dose, high-energy photon radiation (i.e., the same exposure type as experienced by the Japanese atomic bomb survivors). Evidence from neoplastic endpoints was preferentially considered.

The REF was assumed to be unity for photons of energy greater than 250 keV, as this is the primary exposure in the Japanese atomic bomb survivors studies, upon which the majority of the risk estimates are based. Two sets of distributions, having an increased REF compared to >250 keV photons, were established for photons of lower energy, based on reviews of the relevant radiobiological literature. The REF distributions assumed for electrons are also based on values obtained from review of the relevant literature (Kocher et al. 2002; Table 5A). For alpha radiation, the estimated REF for chronic alpha exposure compared to low-dose-rate, low-LET exposure was also much greater than one (Kocher et al. 2002, Table 5B).

For neutrons, the REF distribution was estimated first for fission neutrons (those of energy between 100 keV and 2 MeV). For neutrons of higher or lower energy, an REF reduction factor was applied (Table 5, ICRP 1991b). The neutron REFs include an adjustment for a possible inverse dose-rate relationship for chronic exposures (Kocher et al. 2002; Table 5C). This factor increases the effect of a given dose for a chronic relative to an acute exposure. A direct adjustment is also made within NIOSH-IREP for a possible inverse dose rate relationship for all alpha radiation exposure except radon (as discussed below). The inverse dose-rate phenomenon has been observed for many in vitro and animal studies, but it is thought to apply to a rather narrow range of LET and total dose (Brenner et

al. 1992, 1993). An inverse dose-rate effect has also been observed in studies of radon-exposed workers (Hornung and Meinhardt 1987, Xuan et al. 1993, Tomasek et al. 1994); however, it has not been observed at doses below approximately 50 working level months (Lubin et al. 1995), nor has it been adopted in expert panel assessments of low-dose radon risk (NAS/NRC 1999). Such an inverse dose-rate effect was not incorporated for models of lung cancer risk from radon exposure, because it is implicitly included in the form of the dose-response relationship for that exposure.

F. Definitions of smoking categories for lung cancer claims

The NCI IREP program includes an adjustment to the probability of causation estimate for primary lung cancer, based on an assumed submultiplicative relationship between smoking and lung cancer (NCI 2000, pp. 48-50). There are seven smoking categories included in the NCI model (Table 6). No adjustments were made to this model for NIOSH-IREP; however, the definitions of the cancer categories require clarification for use under EEOICPA. The first clarification needed is that only cigarette smoking history is considered. This is a result of precedent established in the first NIH Radioepidemiological Tables (NIH 1985), based on the strong, unambiguous, and quantifiable relationship between cigarette smoking and lung cancer (Baron and Rohan 1996). In addition, all smoking categories are defined *as of the date of the primary cancer diagnosis*. Lastly, additional clarification is given for the definitions of "never smoker" and "former smoker." For EEOICPA, a "never smoker" is defined as a person who has smoked fewer than 100 cigarettes throughout his or her lifetime (prior to cancer diagnosis). Most epidemiologic studies define the "never smoker" category as

never, rare or highly infrequent smokers (e.g., Rogot and Murray 1980, McLaughlin et al. 1995). This quantitative classification is currently in use by the CDC in several national surveys of smoking behavior (Anonymous 1994). A "former smoker" is an individual who ceased smoking cigarettes at least five years before the date of primary lung cancer diagnosis. This definition is adopted from the original NIH radioepidemiological tables, and is based on the observation that lung cancer background risks are not reduced for the first five years following smoking cessation (Rogot and Murray 1980).

III. Cancer model selection

The model to be used in NIOSH-IREP for each primary cancer is given in Table 4. For some cancers (e.g., certain leukemias) more than one IREP model will be employed. In this case, the model producing the highest probability of causation at the upper 99% credibility limit is to be used as a basis for the compensation decision.

IREP models do not specifically include cancers as defined in their early stages: carcinoma in situ (CIS). These neoplasms are becoming more frequently diagnosed, as the use of cancer screening tools, such as mammography, has increased in the general population. Thus, many cancers of epithelial origin are now being detected before they have spread to the basement membrane of the affected tissue. The risk factors and treatment for CIS are frequently similar to those for malignant neoplasms. While controversial, there is growing evidence that CIS represents the earliest detectable phase of malignancy (Correa 1996, Kerlikowske et al. 1997, Grippo and Sandgren 2000), and they have been included in some evaluations of radiation-related cancer risks (Ron et al. 1998). It is uncertain what

proportion of these would proceed to invasive malignant neoplasms without intervention, and it is impossible to determine this at the level of the individual claimant. A policy consistently used in NIOSH-IREP is to provide the benefit of doubt to the claimant, and to assume that a carcinoma in situ is a malignant neoplasm. No distinction is made among the sites at which the CIS might develop with regard to this policy. Therefore, within NIOSH-IREP, CIS will be treated as a malignant neoplasm of the specified site.

Cancers identified by their secondary sites (sites to which a malignant cancer has spread), when the primary site is unknown, raise another issue for the application of IREP. This situation will most commonly arise when death certificate information is the primary source of a cancer diagnosis. It is accepted in medicine that cancer-causing agents such as ionizing radiation produce primary cancers. This means, in a case in which the primary site of cancer is unknown, the primary site must be established by inference to estimate probability of causation.

An evaluation of the relationship between primary and secondary cancer sites using the National Center for Health Statistics (NCHS) Mortality Database for years 1995-1997 was used to infer the primary site when only the site of metastasis is known. Because national cancer incidence databases (e.g., the National Cancer Institute's Surveillance, Epidemiology and End Results program) do not contain information about sites of metastasis, the NCHS database was considered the best available data source to assign the primary site(s) most likely to have caused the spread of cancer to a known secondary site. For each secondary cancer, the set of primary cancers producing approximately 75% of that secondary cancer among the U.S. population was identified (males and females were considered

separately; Table 7). Therefore, for secondary cancers with unknown primary site, this table will be consulted to select likely primary sites, which will each then be evaluated using NIOSH-IREP.

If no primary or secondary cancer site is specified (i.e., the cancer is identified as ICD-9 199, with no secondary cancer site specified), then the model for "Other and ill-defined sites" should be used (Table 2, 4).

IV. Limitations of NIOSH-IREP

As stated previously, the basis of NIOSH-IREP is the set of methods and models developed by the National Cancer Institute, which updated the 1985 Radioepidemiological Tables developed by a National Institutes of Health working group. The National Research Council (NAS/NRC 2000) identified some limitations to the methods used in the first draft of NCI-IREP (NCI 2000), many of which were addressed by NCI in the version that is the basis of NIOSH-IREP (NCI 2002). The revised NCI report (NCI 2002) considers the current IREP software to be an interim product that may require substantial revision after the publication of the consensus of the BEIR VII committee.

Several limitations existing in the revised NCI methods could not be addressed in NIOSH-IREP, due to the very short time frame established by EEOICPA. The following list describes some of these limitations. It is anticipated that these and other limitations will be remedied in future versions of NIOSH-IREP.

A. For EEOICPA, the ideal source population from which to develop risk estimates for probability of causation calculation is the DOE workforce itself, particularly for exposures

to alpha radiation. Despite the finding of excess cancers among some DOE populations, at present it is difficult to use these findings in a quantitative risk assessment, because of uncertainties about confounding exposures (like chemical exposures), complex patterns and timings of exposure and disparate findings among different populations. It is likely that current research studies underway and future research will provide a better basis for quantitative risk assessment using data that relates directly to the DOE workforce, particularly for cancers found to be weakly associated with radiation exposure in the Japanese atomic bomb survivor cohort (or not at all associated, such as chronic lymphocytic leukemia).

B. Consideration of the appropriateness of various methods of incorporating the modification of cancer risk from radiation exposure by time-dependent factors such as age at exposure, time since exposure and attained age. The NCI-IREP modeling approach, in particular, requires further evaluation in future versions of NIOSH-IREP, as there are alternative ways of modeling the data. For example, a recent re-analysis of the A-bomb survivors suggests that, excluding the hormonally-related cancers (such as breast and thyroid), no variation by age-at-exposure is indicated for remaining cancers after accounting for attained age (Pierce and Mendelsohn 1996). Models that provide equivalent fit to the source data (e.g., the Japanese atomic bomb survivor cohort) could produce quite different estimates of assigned share for a given claimant; however, the current NCI models (adopted for NIOSH-IREP) use a fixed modeling approach to incorporate these factors.

C. Large changes in cancer incidence over time exist for many cancers (e.g., breast, lung, prostate); however, the background rates have been fixed at a single point in time (usually, 1990). Failing to incorporate these changes could lead to an overestimation or underestimation of a claimant's probability of causation.

D. Some of the source models for risk coefficients have unquantified uncertainty related to the latency between exposure and cancer incidence. For example, the excess relative risk of leukemia between 2 and 5 years following exposure is unknown, because the follow-up time for the Japanese atomic bomb survivors began 5 years after the exposure. Excess relative risks between 2 and 5 years after exposure may be different than those 5 or more years after exposure. This limitation is less likely to exist for other cancer types because of the generally longer latency for most cancers.

E. The assumed form of interaction between UV radiation exposure or susceptibility (as reflected by racial and ethnic differences in background skin cancer risk) and radiation exposure is highly uncertain, and has not been evaluated formally through a thorough assessment (or meta-analysis) of the relevant literature. Similarly, formal evaluations of the risk factor interactions for many cancers (e.g., breast and stomach) could further elucidate the appropriate form of risk transfer between the Japanese and U.S. populations.

F. The uncertainty distribution of the adjustment factor for low-dose, low dose-rate exposure (i.e., the DDREF) used in NCI's and NIOSH's IREP currently has a large influence on the calculated probability of causation values. This factor merits further attention with respect

to the appropriate weighting to use for various values (including less than one), for low-dose, chronic photon exposures, and to the incorporation of uncertainty associated with the quadratic term of the dose-response relationship for leukemia.

Figure 1. U.S. White and African-American cancer excess incidence ratio (calculated as higher rate divided by lower rate, minus 1), for cancers showing heterogeneity by race (data from Parkin et al. 1997). Bars extending to the left indicate cancers that have higher incidence rates among African-Americans, and bars extending to the right indicate cancers with higher incidence rates among whites.

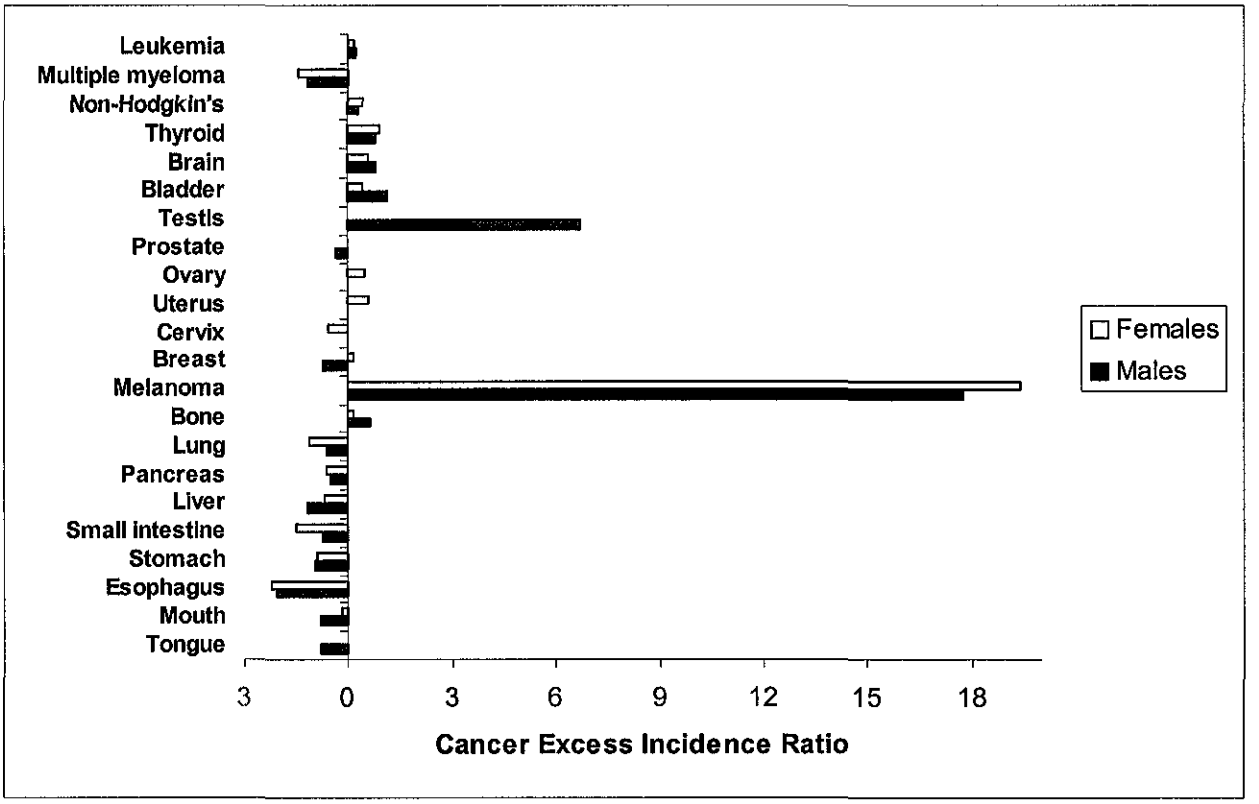
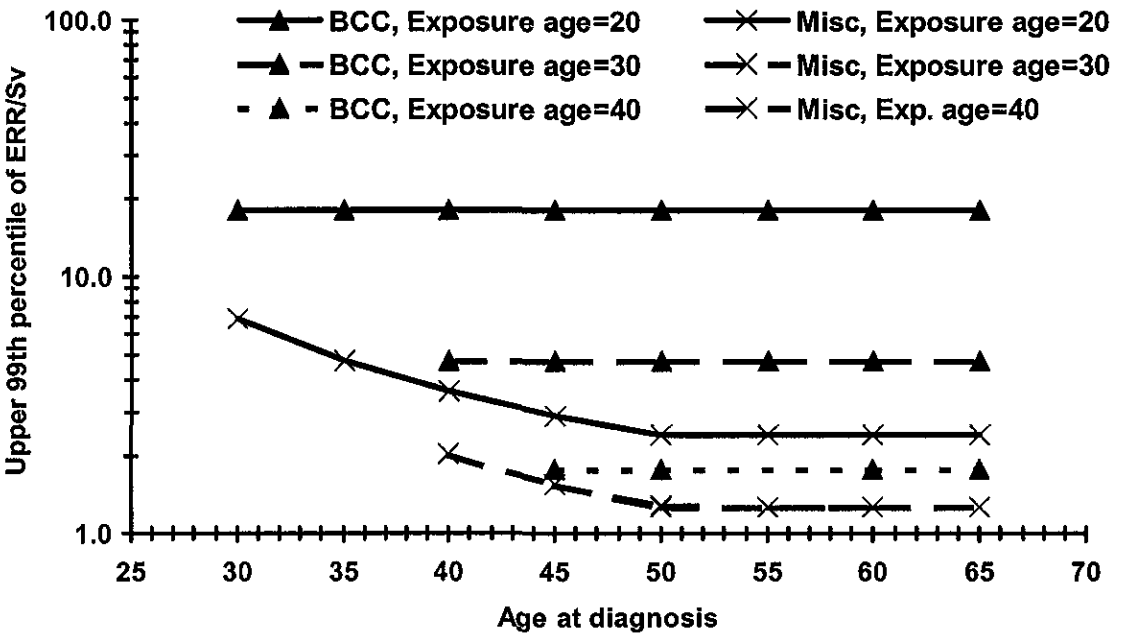


Figure 2. ERR/Sv estimates (at the upper 99th percentile of the credibility distribution) for basal cell carcinoma (triangle) and for miscellaneous cancer (X) models, from NCI (2002), for (a) males and (b) females.

(a) Males



(b) Females

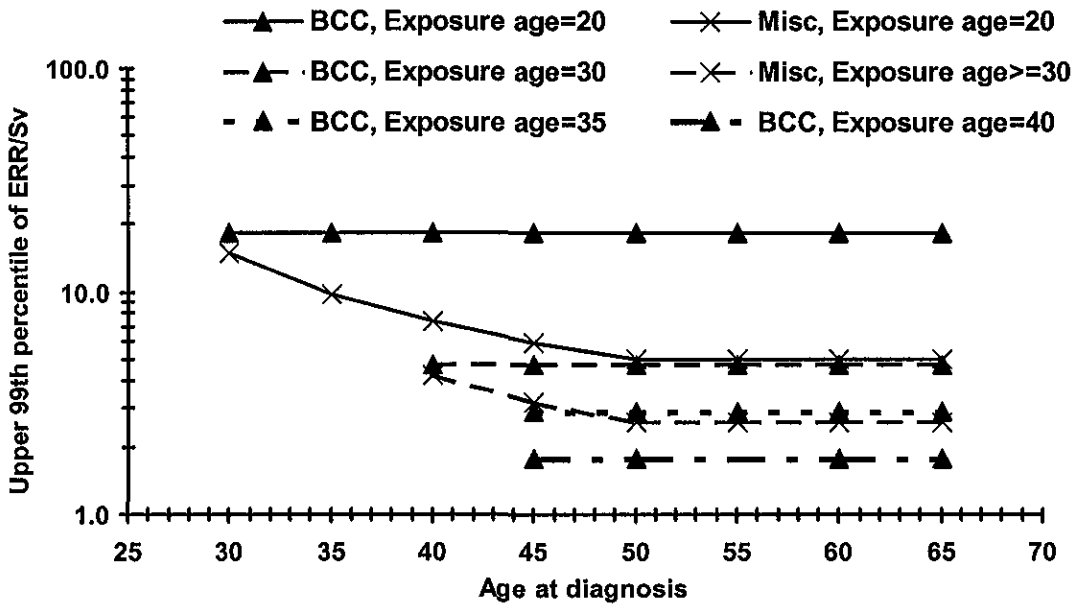


Figure 3. ERR/Sv estimates (at the upper 99th percentile of the credibility distribution) for female breast cancer (FBC, triangle) and for male miscellaneous cancer (M Misc, X) models, from NCI (2002).

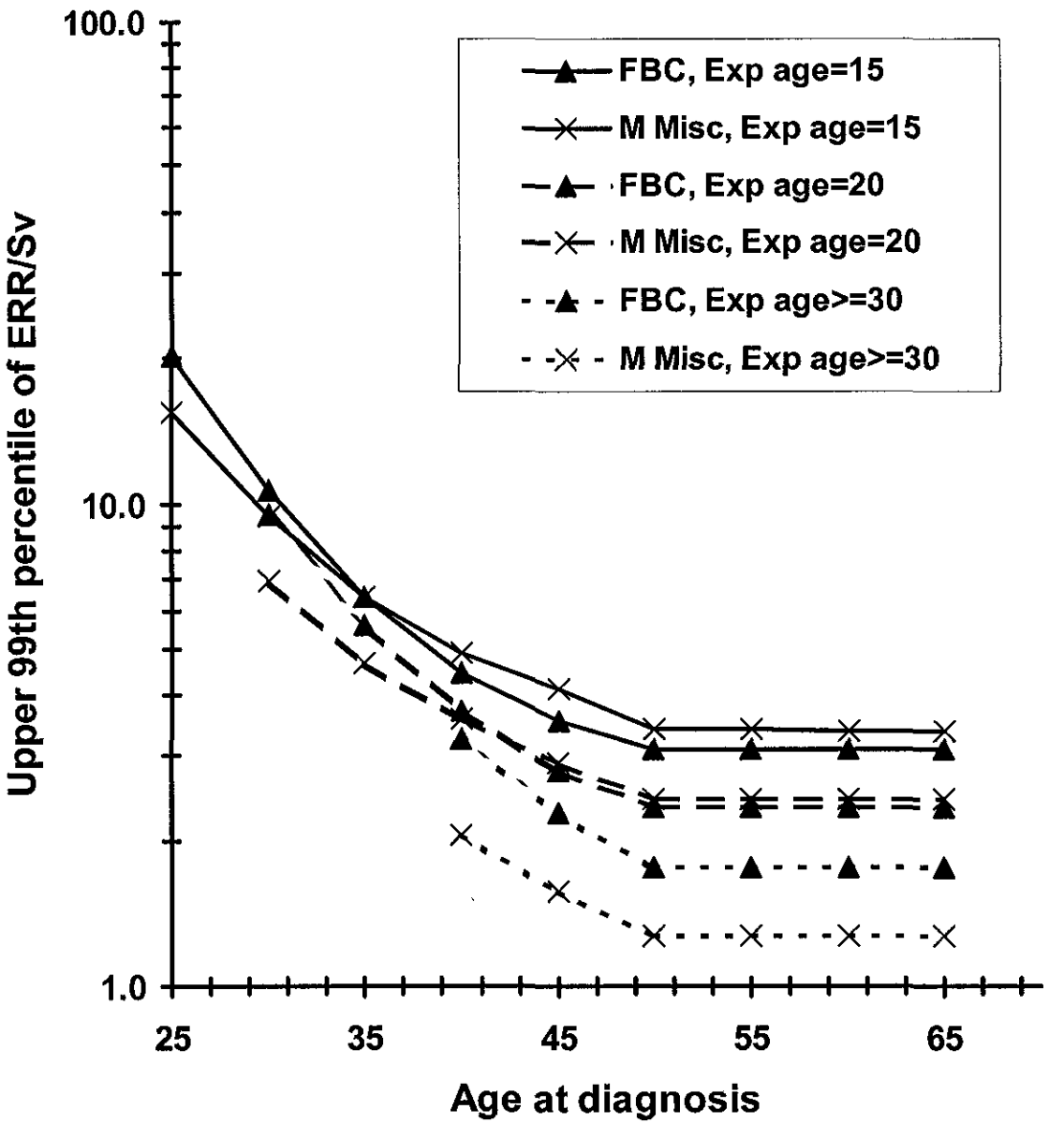
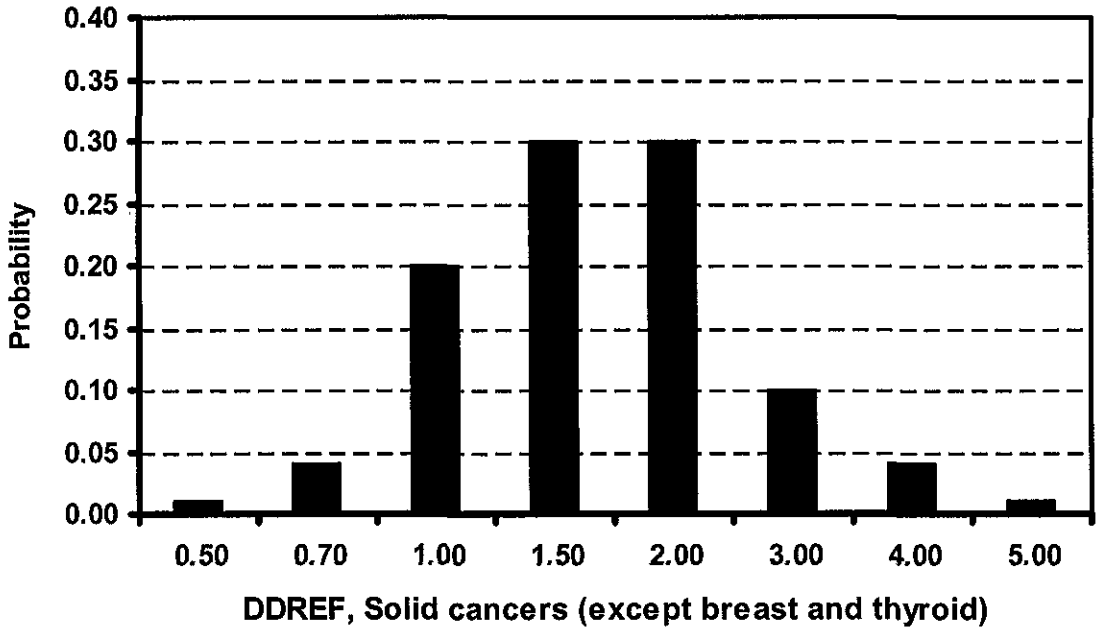


Figure 4. Draft and final DDREF distribution used in NIOSH-IREP for (a) all solid cancers except breast and thyroid and (b) breast and thyroid cancer.

(a)



(b)

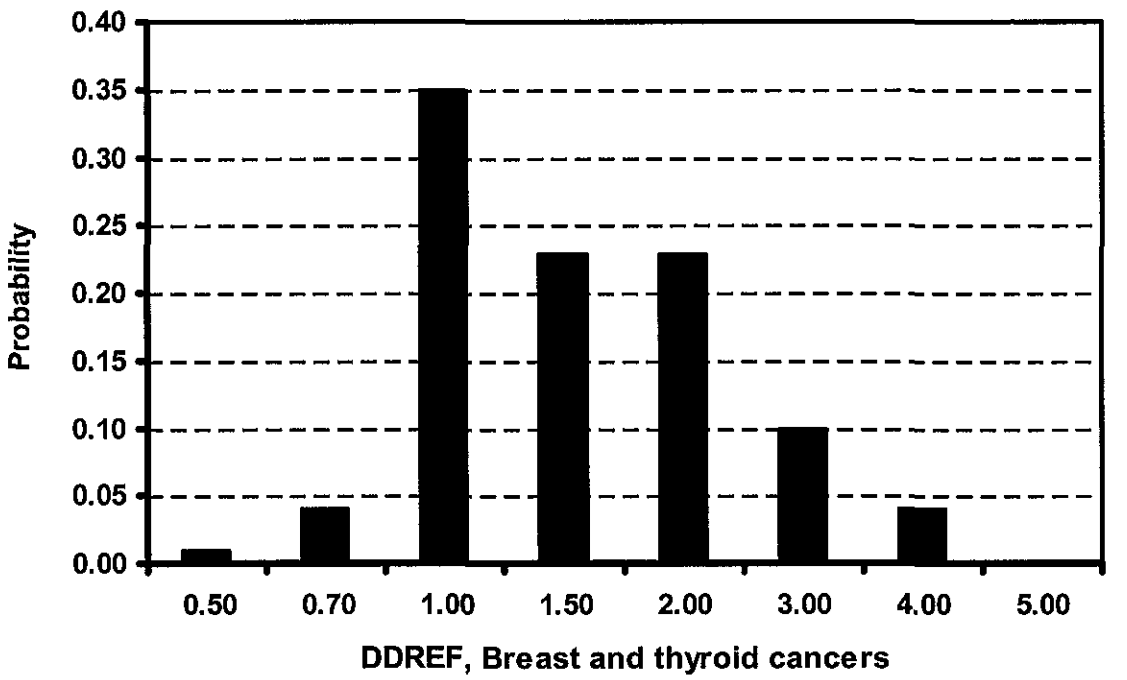


Table 1. Radiation exposure types in NIOSH-IREP

Exposure type	Energy range	Typical exposure scenario
Radon (lung cancer only)	All	Exposure occurs near large sources of radium-bearing material such as the K-65 material at Fernald, or storage of radium in drums.
Electron (source other than tritium)	> 14 keV	Exposure typically results from processing and/or handling of fission products, such as Sr-90, or activation products, such as Co-60. Exposure can also result from uranium handling or processing operations.
Electron (tritium)	$E_{\beta max}$ = 14 keV	Exposure typically occurs around tritium production facilities such as Savannah River and Mound, but can also result from nuclear reactor operations or nuclear weapons assembly or research.
Photon	<30 keV	Low-energy x rays from transuranic isotopes such as plutonium.
Photon	30-250 keV	Medium-energy photons are typically encountered from scatter of higher energy photons. These photons can also result from gamma emissions of certain transuranic isotopes such as americium, and are the primary energy found in early stereoscopic x rays.
Photon	>250 keV	High-energy photons are the most common of the three categories listed. These are typically encountered from work with the nuclear fuel cycle from fuel manufacturing, reactor operations, spent nuclear fuel processing, decontamination and decommissioning activities and waste monitoring and storage.
Neutron	<10 keV	Low-energy neutrons exposures include thermal neutrons commonly found around nuclear reactors.
Neutron	10-100 keV	Intermediate-energy neutron exposure can occur around nuclear reactors as neutrons are moderated from high energy to thermal energies.
Neutron (fission)	100 keV-2 MeV	Neutron exposure typically encountered during the operation of a nuclear reactor. This energy of neutron exposure can also be encountered from work with californium neutron sources.
Neutron	2-20 MeV	Reactions between alpha particles from materials such as plutonium or polonium and light materials such as beryllium resulting the production of neutrons. These reactions are commonly called (α,n) reactions. This range also includes 14 MeV neutrons from fusion reactions.
Neutron	>20 MeV	Exposure to neutrons greater than 20 MeV can result from work around accelerators.
Alpha	All	Primary exposure hazard is internal radiation following the inhalation or ingestion of an alpha emitting radionuclides such as plutonium, uranium, americium, polonium, actinium, and thorium.

Table 2. Cancer sites as source for excess relative risk (ERR) per Sv coefficients for risk models in NIOSH-IREP, and cancer group to which model should be applied.

Cancer models in NIOSH-IREP	Cancer site used as source of ERR/SV (ICD-9 code)	ICD - codes of background rates
Oral Cavity and Pharynx (140-149)	140-149	140-149
Esophagus (150)	150	150
Stomach (151)	151	151
Colon (153)	153	153
Rectum (154)	154	154
All digestive (150-159)	150-159	150-159
Liver (155.0)	155.0	155.0
Gallbladder (155.1, 156)	155.1, 156	155.1, 156
Pancreas (157)	157	157
Trachea, Bronchus and Lung (162)	162	162
Other respiratory (nasal cavity, larynx and other, 160, 161, 163-165)	160, 161, 163-165	160, 161, 163-165
Bone (170)	170, 171, 175, 190, 194, 195	170
Connective tissue (171)	170, 171, 175, 190, 194, 195	171
Malignant melanoma (172)	173 (basal cell carcinoma only)	172
Non-melanoma skin (173) -basal cell carcinoma	173 (basal cell carcinoma only)	173 (all combined)
Non-melanoma skin (173)-non basal cell carcinoma	173 (non-basal cell carcinoma only)	173 (all combined)
Breast-female (174)	174	174
Breast-male (175)	174	175

Table 2 (continued). Cancer sites as source for excess relative risk (ERR) per Sv coefficients for risk models in NIOSH-IREP, and Cancer group to which model should be applied

Cancer models in NIOSH-IREP	Cancer site used as source of ERR/SV (ICD-9)	ICD-9 codes of background rates
Ovary (183)	183	183
Female genitalia less ovary (179-182, 184)	179-182, 184	179-182, 184
All male genitalia (185-187)	185-187	185-187
Bladder (188)	188	188
Kidney and other urinary organs (188-189)	188-189	189
Eye (190)	170, 171, 175, 190, 194, 195	190
Nervous system (191, 192)	191, 192	191, 192
Thyroid (193)	193	193
Other endocrine glands (194)	170, 171, 175, 190, 194, 195	194
Other and ill-defined sites (195, 199)	170, 171, 175, 190, 194, 195	195
Lymphoma and Multiple Myeloma (200-203)	200-203	200-203
Leukemia, less chronic lymphocytic leukemia (204-208, less 204.1)	204-208, less 204.1	204-208, less 204.1
Acute lymphocytic leukemia (204.0)	204.0	204.0
Acute myelogenous leukemia (205.0)	205.0	205.0
Chronic myelogenous leukemia (205.1)	205.1	205.1

Table 3. U.S. skin cancer incidence rates used in NIOSH-IREP. 1990 Malignant melanoma incidence rates for Japan are adapted from Parkin et al. (1997) and for the U.S. are from SEER program (April 1999 public use datafile). 1978-1982 non-melanoma skin cancer incidence rates for Japan are from Parkin et al. (1997), and for three U.S. ethnic groups are from Scotto et al. (1983, 1996).

	Age-adjusted incidence rate, per 100,000 persons annually (standard error)					
	Japanese[1]	**U.S. Native American**	**U.S. Asian and Pacific Islander**	**U.S. African-American**	**U.S. White Hispanic**	**U.S. White Non-Hispanic**
Malignant melanoma[2], 1990 rates						
Males	0.48 (0.09)	0.66 (0.30)	1.01 (0.11)	0.82 (0.10)	2.29 (0.15)	16.4 (0.15)
Females	0.43 (0.08)	1.26 (0.33)	0.77 (0.09)	0.55 (0.07)	2.44 (0.14)	11.9 (0.13)
Non-melanoma skin cancer[3], 1978-1982 rates						
Males	6.05 (0.65)	N/A[4]	N/A	4.1 (1.3)	61.6 (4.8)	312 (2.4)
Females	4.42 (0.48)	N/A	N/A	4.5 (0.76)	45.1 (3.5)	173 (1.6)

[1]Japanese rates are weighted rates from Hiroshima (2/3) + Nagasaki (1/3) Prefectures

[2]Rates are age-adjusted to 1940 World standard population

[3]Rates are age-adjusted to 1970 U.S. standard population

[4]N/A: not available

Table 4. Cancer models to be used in calculation of probability of causation. Derivation of NIOSH-IREP models is described in Section II-B. Abbreviations. MN (malignant neoplasm), CIS (carcinoma in situ), NUB (neoplasm of uncertain behavior), NUN (neoplasm of unspecified nature).

Primary neoplasm	ICD-9 code	NIOSH-IREP model for calculating PC
Malignant neoplasm (MN) of lip, oral cavity and pharynx	140-149	Oral cavity and pharynx
MN of esophagus	150	Esophagus
MN of stomach	151	Stomach
MN of small intestine	152	All digestive
MN of colon	153	Colon
MN of rectum and anus	154	Rectum
MN of liver	155.0, 155.2	Liver
MN of gall bladder and bile ducts	155.1, 156	Gall bladder
MN of pancreas	157	Pancreas
MN of retroperitoneum and peritoneum	158	All digestive
MN of other digestive	159	All digestive
MN of nasal cavities, middle ear, and sinuses	160	Other respiratory
MN of larynx	161	Other respiratory
MN of trachea, bronchus and lung	162	Lung
MN of pleura	163	Other respiratory
MN of thymus, heart and mediastinum	164	Other respiratory
MN of other respiratory organs	165	Other respiratory
MN of bone	170	Bone
MN of connective tissue	171	Connective tissue

Table 4 (continued). Cancer models to be used in calculation of probability of causation. Derivation of NIOSH-IREP models is described in Section II-B. Abbreviations: NM (malignant neoplasm), CIS (carcinoma in situ), NUB (neoplasm of uncertain behavior), NUN (neoplasm of unspecified nature.

Primary neoplasm	ICD-9 code	NIOSH-IREP model for calculating PC
Malignant melanoma	172	Malignant melanoma
Basal cell carcinoma of skin	173	Non-melanoma skin-Basal cell
Other (non-basal cell, non-melanoma) carcinoma of skin	173	Non-melanoma skin-Squamous cell
MN of breast	174, 175	Breast
MN of uterus or uterine cervix	179, 180, 182	Female genitalia less ovary
MN of ovary	183	Ovary
MN of other female genital	181, 184	Female genitalia less ovary
MN of male genital	185-187	All male genitalia
MN of urinary bladder	188	Bladder
MN of kidney and other urinary organs	189	Urinary organs less bladder
MN of eye	190	Eye
MN of brain and other nervous system	191, 192	Nervous system
MN of thyroid gland	193	Thyroid
MN of other endocrine glands	194	Other endocrine glands
MN of other and ill-defined sites	195	Other and ill-defined sites
Non-Hodgkin's lymphoma and other lymphoid tissue, Hodgkin's disease	200-202	Lymphoma and multiple myeloma
Multiple myeloma and other immunoproliferative diseases	203	Lymphoma and multiple myeloma
Acute and unspecified lymphocytic leukemia	204.0, 204.9	Acute lymphoid leukemia

Table 4 (continued). Cancer models to be used in calculation of probability of causation. Derivation of NIOSH-IREP models is described in Section II-B. Abbreviations: MN (malignant neoplasm), CIS (carcinoma in situ), NUB (neoplasm of uncertain behavior), NUM (neoplasm of unspecified nature).

Primary neoplasm	ICD-9 code	NIOSH-IREP model for calculating PC
Subacute and other (not chronic) lymphoid leukemia	204.2, 204.8	Leukemia, less CLL
Acute and unspecified myelogenous leukemia	205.0, 205.9	Leukemia, less CLL AND Acute myeloid leukemia
Chronic myelogenous leukemia	205.1	Leukemia, less CLL AND Chronic myeloid leukemia
Subacute myelogenous leukemia, myeloid sarcoma, and other myeloid leukemia	205.2, 205.3, 205.8	Leukemia, less CLL
Monocytic leukemia, other specified leukemia	206, 207	Leukemia, less CLL
Acute leukemia of unspecified cell type	208.0	Leukemia, less CLL AND Acute lymphoid leukemia, AND Acute myeloid leukemia
Chronic leukemia of unspecified cell type	208.1	Leukemia, less CLL AND Chronic myeloid leukemia
Carcinoma in situ (CIS) of lip, oral cavity and pharynx	230.0	Oral cavity and pharynx
CIS of esophagus	230.1	Esophagus
CIS of stomach	230.2	Stomach
CIS of colon	230.3	Colon
CIS of rectum, anal canal, and anus	230.4, 230.5, 230.6	Rectum
CIS of liver and biliary system	230.8	Liver
CIS of other and unspecified intestine, digestive organs	230.7, 230.9	All digestive

Table 4 (continued). Cancer models to be used in calculation of probability of causation. Derivation of NIOSH-IREP models is described in Section II-B. Abbreviations: MN (malignant neoplasm), CIS (carcinoma in situ), NUB (neoplasm of uncertain behavior), NUM (neoplasm of unspecified nature).

Primary neoplasm	ICD-9 code	NIOSH-IREP model for calculating PC
CIS of larynx and other respiratory	231.0, 231.8, 231.9	Other respiratory
CIS of lung	231.1, 231.2	Lung
CIS of skin	232	Malignant melanoma AND non-melanoma skin
CIS of breast	233.0	Breast
CIS of cervix uteri or other and unspecified parts of uterus	233.1, 233.2	Female genitalia, less ovary
CIS of other and unspecified female genital organs	233.3	Female genitalia, less ovary AND Ovary
CIS of prostate, penis or other and unspecified male genital organs	233.4	All male genitalia
CIS of bladder	233.7	Bladder
CIS of other and unspecified urinary organs	233.9	Urinary organs less bladder
CIS of eye	234.0	Eye
CIS of other and unspecified sites	234.8, 234.9	Other and ill-defined sites
Neoplasm of uncertain behavior (NUB) of salivary gland, lip, oral cavity or pharynx	235.0, 235.1	Oral cavity and pharynx
NUB of stomach	235.2	Stomach
NUB of colon	235.2	Colon
NUB of rectum and anus	235.2	Rectum

Table 4 (continued). Cancer models to be used in calculation of probability of causation. Derivation of NIOSH-IREP models is described in Section II-B. Abbreviations: MN (malignant neoplasm), CIS (carcinoma in situ), NUB (neoplasm of uncertain behavior), NUM (neoplasm of unspecified nature).

Primary neoplasm	ICD-9 code	NIOSH-IREP model for calculating PC
NUB of liver and biliary passages	235.3	Liver
NUB of retroperitoneum and peritoneum, and other and unspecified digestive organs	235.4, 235.5	All digestive
NUB of larynx, pleura, thymus, mediastinum, and other and unspecified respiratory organs	235.6, 235.8, 235.9	Other respiratory
NUB of trachea, bronchus and lung	235.7	Lung
NUB of uterus, and other and unspecified female genital organs	236.0, 236.1, 236.3	Female genitalia, less ovary
NUB of ovary	236.2	Ovary
NUB of prostate, testis and other male genital	236.4, 236.5, 236.6	All male genitalia
NUB of bladder	236.7	Bladder
NUB of other and unspecified urinary tract, and suprarenal gland	236.9, 237.2	Urinary organs less bladder
NUB of pituitary, pineal and other and unspecified endocrine glands	237.0, 237.1, 237.4	Thyroid
NUB of paraganglia, brain and spinal cord, and other nervous system	237.3, 237.5, 237.6, 237.7, 237.9	Nervous system
NUB of bone and articular cartilage	238.0	Bone
NUB of connective and other soft tissue	238.1	Connective tissue
NUB of skin	238.2	Malignant melanoma AND Non-melanoma skin-Basal cell

Table 4 (continued). Cancer models to be used in calculation of probability of causation. Derivation of NIOSH-IREP models is described in Section II-B. Abbreviations: MN (malignant neoplasm), CIS (carcinoma in situ), NUB (neoplasm of uncertain behavior), NUM (neoplasm of unspecified nature).

Primary neoplasm	ICD-9 code	NIOSH-IREP model for calculating PC
NUB of breast	238.3	Breast
NUB of other lymphatic and hematopoietic	238.5-238.7	Lymphoma and multiple myeloma
NUB of other specified and unspecified sites	238.8, 238.9	Other and ill-defined sites
Neoplasm of unspecified nature (NUN) of digestive system	239.0	All digestive
NUN of respiratory system	239.1	Lung AND Other respiratory
NUN of bone and soft tissue	239.2	Bone
NUN of skin	239.2	Non-melanoma skin-Basal cell
NUN of breast	239.3	Breast
NUN of bladder	239.4	Bladder
NUN of other genitourinary organs	239.5	Female genital less ovary AND Ovary AND All urinary organs (if female) All male genital AND All urinary organs (if male)
NUN of brain and other parts of nervous system	239.6, 239.7	Nervous system
NUN of endocrine glands	239.7	Thyroid AND Other endocrine glands
NUN of other specified or unspecified sites	239.8, 239.9	Other and ill-defined sites

Table 5A. Photons and electrons: Probability distributions of radiation effectiveness factors (REFs) to be used in estimating risks and probability of causation of cancers

Radiation type	Exposure	Probability distribution of radiation effectiveness factor (REF_L)	95% Confidence Interval		
Photons	Chronic or acute[a]		2.5th	50.0th	97.5th
E > 250 keV		Single-valued at 1.0 (higher-energy photons are assumed reference radiation)	----	1.0	----
E = 30-250 keV		Hybrid distribution with – 25% probability assigned to value 1.0; 75% probability assigned to lognormal distribution with 95% confidence interval between 1.0 and 5.0	1.0	1.9	4.7
E < 30 keV		Product of two distributions – (1) hybrid distribution for E_γ = 30-250 keV; and (2) triangular distribution with minimum of 1.0, mode of 1.3, and maximum of 1.6	1.1	2.4	6.1
Electrons	Chronic or acute[a]				
E > 15 keV		Single-valued at 1.0 (assumed to be same as value for reference higher-energy photons)	----	1.0	----
E < 15 keV		Lognormal distribution with 95% confidence interval between 1.2 and 5	1.2	2.4	5.0

[a]For solid tumors, DDREF is always applied under conditions of chronic exposure. At acute doses greater than 0.2 cGy, DDREF is assumed to be 1.0. At acute doses less than 0.2 cGy, a DDREF that can exceed 1.0 is applied, and the distribution of possible values approaches the probability distribution of DDREF that applies to all chronic exposures as the dose approaches zero.

Table 5B. Alpha particles: Probability distributions of radiation effectiveness factors (REFs) to be used in estimating risks and probability of causation of cancers

Cancer type	Probability distribution of radiation effectiveness factor (REF_L)	95% Confidence Interval		
Leukemias		2.5th	50.0th	97.5th
All energies of alpha particles	Hybrid distribution with – 25% probability assigned to value 1.0; 50% probability assigned to lognormal distribution with 95% confidence interval between 1.0 and 15; 25% probability assigned to lognormal distribution with 95% confidence interval between 2.0 and 60[d]	1.0	4.1	42[b]
Solid tumors				
All energies of alpha particles	Lognormal distribution with 95% confidence interval between 3 and 80	3.4	18	101[b]
[a]Correction for inverse dose-rate effect for all exposures to alpha particles: Discrete distribution with – 70% probability assigned to value 1.0; 20% probability assigned to value 1.5; 7.5% probability assigned to value 2.0; 2.5% probability assigned to value 3.				

[a]Acute exposures to alpha particles emitted by radionuclides generally should not occur; correction factor to account for inverse dose-rate effect under conditions of chronic exposure to alpha particles is applied in all cases.

[b]Distribution includes the correction for inverse dose-rate effect.

Table 5C. Neutrons: Probability distributions of radiation effectiveness factors (REFs) to be used in estimating risks and probability of causation of cancers

Cancer type	Probability distribution of radiation effectiveness factor (REF_L)	Exposure	95% Confidence Interval		
Leukemia[a]			2.5th	50.0th	97.5th
Neutron energies					
E = 0.1-2 MeV[b]	Lognormal distribution with 95% confidence interval between 2.0 and 60	Acute Chronic[c]	2.0 2.5	11 14	60 91
E = 10-100 keV; E = 2-20 MeV	Stepwise uniform distribution with – 30% probability assigned to values from 1.0 to 4.0; 50% probability assigned to values from 4.0 to 8.0; 20% probability assigned to values from 8.0 to 40	Acute Chronic	1.3 1.5	5.6 7.1	36 55
E < 10 keV; E > 20 MeV	Stepwise uniform distribution with – 30% probability assigned to values from 1.0 to 2.3; 50% probability assigned to values from 2.3 to 3.5; 20% probability assigned to values from 3.5 to 25	Acute Chronic	1.1 1.2	2.8 3.4	22 34

(Table is continued on following page)

Table 5C (continued). Neutrons: Probability distributions of radiation effectiveness factors

Cancer type	Probability distribution of radiation effectiveness factor (REF_H)	Exposure	95% Confidence Interval		
Solid tumors			2.5th	50.0th	97.5th
Neutron energies					
E = 0.1-2 MeV[b]	Lognormal distribution with 95% confidence interval between 2.0 and 30	Acute Chronic	2.0 2.4	7.7 10	30 47
E = 10-100 keV; E = 2-20 MeV	Stepwise uniform distribution with – 30% probability assigned to values from 1.0 to 3.0; 50% probability assigned to values from 3.0 to 5.0; 20% probability assigned to values from 5.0 to 20	Acute Chronic	1.2 1.4	3.8 4.7	18 28
E < 10 keV; E > 20 MeV	Stepwise uniform distribution with – 30% probability assigned to values from 1.0 to 1.6; 50% probability assigned to values from 1.6 to 2.4; 20% probability assigned to values from 2.4 to 12	Acute Chronic	1.1 1.1	1.9 2.4	11 16
Correction for inverse dose-rate effect for chronic exposures to neutrons – Discrete distribution with – 50% probability assigned to value 1.0; 30% probability assigned to value 1.5; 15% probability assigned to value 2.0; 5% probability assigned to value 3.0					

[a]Assumed probability distributions apply to leukemias, lymphomas, and lymphocytic cancers.
[b]Energy range includes spectrum of fission neutrons.
[c]Under conditions of chronic exposure only, correction factor to account for the inverse dose-rate effect is applied.

Table 6. Smoking category definitions for lung cancer claims under NIOSH-IREP

Smoking category	Definition
Never	Smoked fewer than 100 cigarettes (throughout lifetime) prior to cancer diagnosis
Former	Quit smoking five years or more before date of cancer diagnosis
Current (? cig/day)	Smoked at time of cancer diagnosis (or quit fewer than 5 years before), quantity unknown
Current (<10 cig/day)	Smoked at time of cancer diagnosis (or quit fewer than 5 years before), average of fewer than 10 cigarettes per day
Current (10-19 cig/day)	Smoked at time of cancer diagnosis (or quit fewer than 5 years before), average of 10-19 cigarettes per day
Current (20-39 cig/day)	Smoked at time of cancer diagnosis (or quit fewer than 5 years before), average of 20-39 cigarettes per day
Current (40+ cig/day)	Smoked at time of cancer diagnosis (or quit fewer than 5 years before), average of 40 or more cigarettes per day

Table 7. Primary cancers (ICD-9 codes[1]) for which probability of causation is to be calculated, if only a secondary cancer site is known. "M" indicates cancer site should be used for males only, and "F" indicates cancer site should be used for females only. Whenever "173" is indicated, the "non-melanoma skin-basal cell" model should be used.

Secondary cancer	ICD-9 code of likely primary cancers
Lymph nodes of head, face and neck (196.0)	141, 142 (M), 146 (M), 149 (F), 161 (M), 162, 172, 173, 174 (F), 193 (F)
Intrathoracic lymph nodes (196.1)	150 (M), 162, 174 (F)
Intra-abdominal lymph nodes (196.2)	150 (M), 151 (M), 153, 157 (F), 162, 174 (F), 180 (F), 185 (M), 189, 202 (F)
Lymph nodes of axilla and upper limb (196.3)	162, 172, 174 (F)
Inguinal and lower limb lymph nodes (196.5)	154 (M), 162, 172, 173 (F), 187 (M)
Intrapelvic lymph nodes (196.6)	153 (M), 154 (F), 162 (M), 180 (F), 182 (F), 185 (M), 188
Lymph nodes of multiple sites (196.8)	150 (M), 151 (M), 153 (M), 162, 174 (F)
Lymph nodes, site unspecified (196.9)	150 (M), 151, 153, 162, 172, 174 (F), 185 (M)
Lung (197.0)	153, 162, 172 (M), 174 (F), 185 (M), 188 (M), 189
Mediastinum (197.1)	150 (M), 162, 174 (F)
Pleura (197.2)	150 (M), 153 (M), 162, 174 (F), 183 (F), 185 (M), 189 (M)
Other respiratory organs (197.3)	150, 153 (M), 161, 162, 173 (M), 174 (F), 185 (M), 193 (F)
Small intestine, including duodenum (197.4)	152, 153, 157, 162, 171, 172 (M), 174 (F), 183 (F), 189 (M)
Large intestine and rectum (197.5)	153, 154, 162, 174 (F), 183 (F), 185 (M)
Retroperitoneum and peritoneum (197.6)	151, 153, 154 (M), 157, 162 (M), 171, 174 (F), 182 (F), 183 (F)
Liver, specified as secondary (197.7)	151 (M), 153, 154 (M), 157, 162, 174 (F)

[1]The International Classification of Diseases Clinical Modification (9th Revision) Volumes I&II. [1991] Department of Health and Human Services Publication No. (PHS) 91-1260, U.S. Government Printing Office, Washington, D.C.

Table 7 (continued). Primary cancers (ICD-9 codes) for which probability of causation is to be calculated, if on a secondary cancer site is known. "M" indicates cancer site should be used for males only, and "F" indicates cancer site should be used for females only. Whenever "173" is indicated, the "non-melanoma skin-basal cell" model should be used.

Secondary cancer	ICD-9 code of likely primary cancers
Other digestive organs (197.8)	150 (M), 151, 153, 157, 162, 174 (F), 185 (M)
Kidney (198.0)	153, 162, 174 (F), 180 (F), 185 (M), 188, 189, 202 (F)
Other urinary organs (198.1)	153, 174 (F), 180 (F), 183 (F), 185 (M), 188, 189 (F)
Skin (198.2)	153, 162, 171 (M), 172, 173 (M), 174 (F), 189 (M)
Brain and spinal cord (198.3)	162, 172 (M), 174 (F)
Other parts of nervous system (198.4)	162, 172 (M), 174 (F), 185 (M), 202
Bone and bone marrow (198.5)	162, 174 (F), 185 (M)
Ovary (198.6)	153 (F), 174 (F), 183 (F)
Suprarenal gland (198.7)	153 (F), 162, 174 (F)
Other specified sites (198.8)	153, 162, 172 (M), 174 (F), 183 (F), 185 (M), 188 (M)

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Appendix I: NIOSH-IREP program output

NIOSH-Interactive RadioEpidemiological Program
Probability of Causation Results

Date of Run: 06/12/2002
Time of Run: 12:00:05 PM
NIOSH ID #: 123456
Claimant Name: John Q. Doe
DOL District Office: DE
NIOSH-IREP version: 5.2
Claimant SSN: 123-45-6789

Claimant Cancer Diagnoses:

Primary Cancer #1:	*Prostate (ICD-9 185)*	*Date of Diagnosis:*	*10/20/1988*
Primary Cancer #2:	N/A	Date of Diagnosis:	N/A
Primary Cancer #3:	N/A	Date of Diagnosis:	N/A
Secondary Cancer #1:	Lung (ICD-9 197.0)	Date of Diagnosis:	03/13/1994
Secondary Cancer #2:	N/A	Date of Diagnosis:	N/A
Secondary Cancer #3:	N/A	Date of Diagnosis:	N/A

Claimant Information Used In Probability of Causation Calculation:

Gender: Male
Birth Year: 1920
Race (skin cancer only): N/A
Year of Diagnosis: 1988
Cancer Model: All Male Genitalia (185-187)
Should alternate cancer model be run?: No
Smoking history (trachea, bronchus, or lung cancer only): N/A

NIOSH-IREP Assumptions and Settings:

User Defined Uncertainty Distribution: Lognormal (1,1)
Number of Iterations: 2000
Random Number Seed: 99

Appendix I (continued): NIOSH-IREP program output

GENERAL EXPOSURE INFORMATION:

Exposure #	Exposure Year	Organ Dose (cSv)	Exposure Rate	Radiation Type
1	1955	Lognormal (0.5,1.8)	acute	photons E=30-250keV
2	1955	Lognormal (0.7,1.8)	acute	photons E>250keV
3	1956	Lognormal (0.1,1.8)	chronic	neutrons E=100keV-2MeV
4	1956	Lognormal (0.4,2.5)	acute	photons E>250keV
5	1957	Uniform (0.1,4)	chronic	alpha
6	1957	Lognormal (1.3,1.8)	acute	photons E>250keV
7	1958	Uniform (0.05,5.6)	chronic	alpha
8	1958	Lognormal (0.2,1.8)	acute	photons E>250keV
9	1959	Lognormal (0.5,2.5)	chronic	neutrons E=100keV-2MeV
10	1959	Lognormal (0.1,1.8)	acute	photons E>250keV
11	1960	Lognormal (0.5,1.8)	acute	photons E>250keV
12	1960	Lognormal (0.1,2.5)	chronic	neutrons E=100keV-2MeV
13	1961	Lognormal (0.3,1.8)	acute	photons E>250keV
14	1961	Lognormal (0.2,2.5)	chronic	neutrons E=100keV-2MeV
15	1962	Lognormal (0.1,1.8)	acute	photons E>250keV

Radon Exposure Information:

N/A (applies only to cases of Lung Cancer with Radon Exposures)

Appendix I (continued): NIOSH-IREP program output

Results of NIOSH-IREP
Probability of Causation:

1st percentile	0.0%
5th percentile	0.0%
50th percentile	0.81%
95th percentile	5.29%
99th percentile	**10.22%**

Name of Analyst:
Title:
Signature:
Date:

Name of Reviewer:
Title:
Signature:
Date:

Appendix II: Glossary of ICD-9 codes and their cancer descriptions[1]

ICD-9 code	Cancer description
140	Malignant neoplasm of lip
141	Malignant neoplasm of tongue
142	Malignant neoplasm of major salivary glands
143	Malignant neoplasm of gum
144	Malignant neoplasm of floor of mouth
145	Malignant neoplasm of other and unspecified parts of mouth
146	Malignant of neoplasm of oropharynx
147	Malignant neoplasm of nasopharynx
148	Malignant of neoplasm of hypopharynx
149	Malignant of neoplasm other and ill-defined sites within the lip, oral cavity, and pharynx
150	Malignant of neoplasm of esophagus
151	Malignant of neoplasm of stomach
152	Malignant of neoplasm of small intestine, including duodenum
153	Malignant of neoplasm of colon
154	Malignant of neoplasm of rectum, rectosigmoid junction, and anus
155	Malignant neoplasm of liver and intrahepatic bile ducts
156	Malignant neoplasm of gall bladder and extrahepatic bile ducts
157	Malignant neoplasm of pancreas
158	Malignant neoplasm of retroperitoneum and peritoneum
159	Malignant neoplasm of other and ill-defined sites within the digestive organs and peritoneum

[1]The International Classification of Diseases Clinical Modification (9th Revision) Volumes I&II. [1991] Department of Health and Human Services Publication No. (PHS) 91-1260, U.S. Government Printing Office, Washington, D.C.

Appendix II (continued): Glossary of ICD-9 codes and their cancer descriptions

ICD-9 code	Cancer description
160	Malignant neoplasm of nasal cavities, middle ear, an accessory sinuses
161	Malignant neoplasm of larynx
162	Malignant neoplasm of trachea, bronchus an lung
163	Malignant neoplasm of pleura
164	Malignant neoplasm of thymus, heart, and mediastinum
165	Malignant neoplasm of other and ill-defined sites within the respiratory system and intrathoracic organs
170	Malignant neoplasm of bone and articular cartilage
171	Malignant neoplasm of connective and other soft tissue
172	Malignant melanoma of skin
173	Other malignant neoplasm of skin
174	Malignant neoplasm of female breast
175	Malignant neoplasm of male breast
179	Malignant neoplasm of uterus, not otherwise specified
180	Malignant neoplasm of uterine cervix
181	Malignant neoplasm of placenta
182	Malignant neoplasm of uterine corpus (body of uterus)
183	Malignant neoplasm of ovary and other uterine adnexa
184	Malignant neoplasm of other and unspecified female genital organs
185	Malignant neoplasm of prostate
186	Malignant neoplasm of testis
187	Malignant neoplasm of penis and other male genital organs
188	Malignant neoplasm of urinary bladder
189	Malignant neoplasm of kidney and other and unspecified urinary organs
190	Malignant neoplasm of eye

Appendix II (continued): Glossary of ICD-9 codes and their cancer descriptions

ICD-9 code	Cancer description
191	Malignant neoplasm of brain
192	Malignant neoplasm of other an unspecified parts of nervous system
193	Malignant neoplasm of thyroid gland
194	Malignant neoplasm of other endocrine glands and related structures
195	Malignant neoplasm of other and ill-defined sites
196	Secondary and unspecified neoplasms of the lymph nodes
197	Secondary neoplasms of the respiratory and digestive organs
198	Secondary neoplasms of other tissue and organs
199	Malignant neoplasm without specification of site
200	Lymphosarcoma and reticulosarcoma
201	Hodgkin's disease
202	Other malignant neoplasms of lymphoid and histiocytic tissue
203	Multiple myeloma and other immunoproliferative diseases
204	Lymphoid leukemia
205	Myeloid leukemia
206	Monocytic leukemia
207	Other specified leukemia
208	Leukemia of unspecified cell type