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.

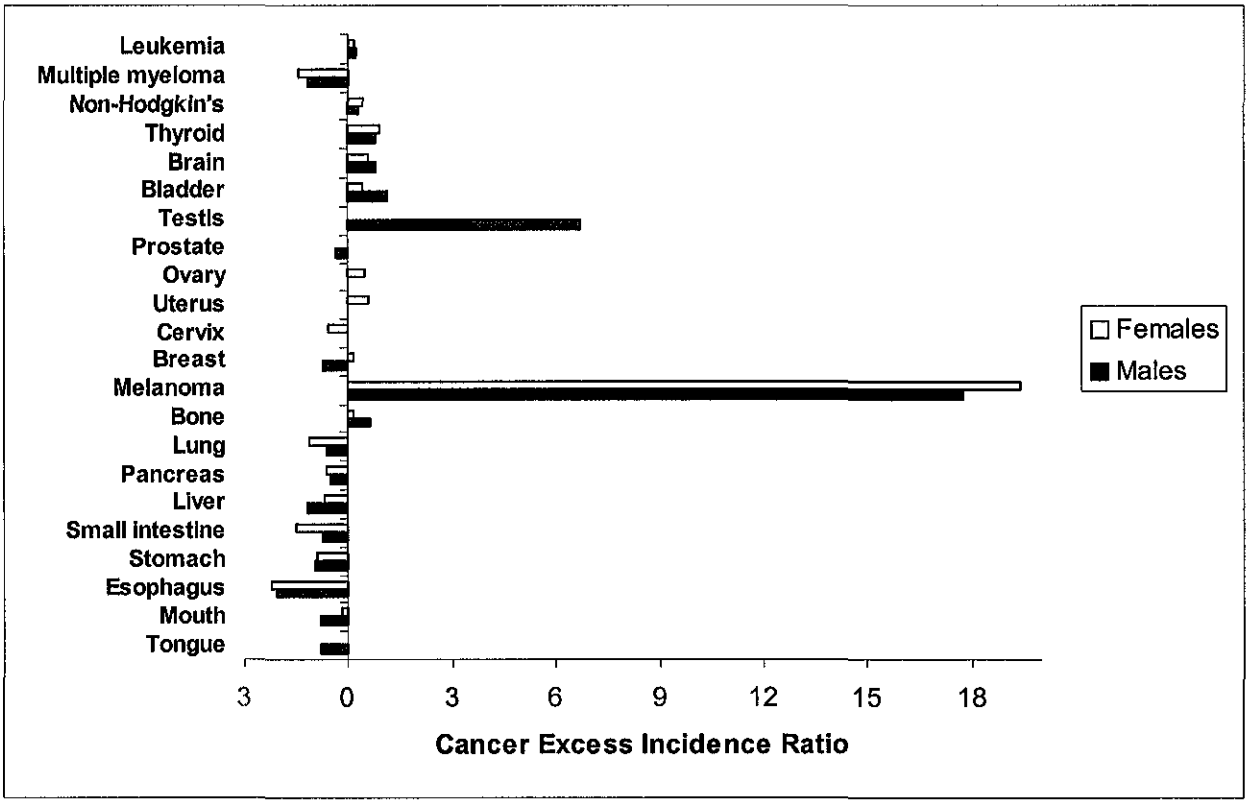
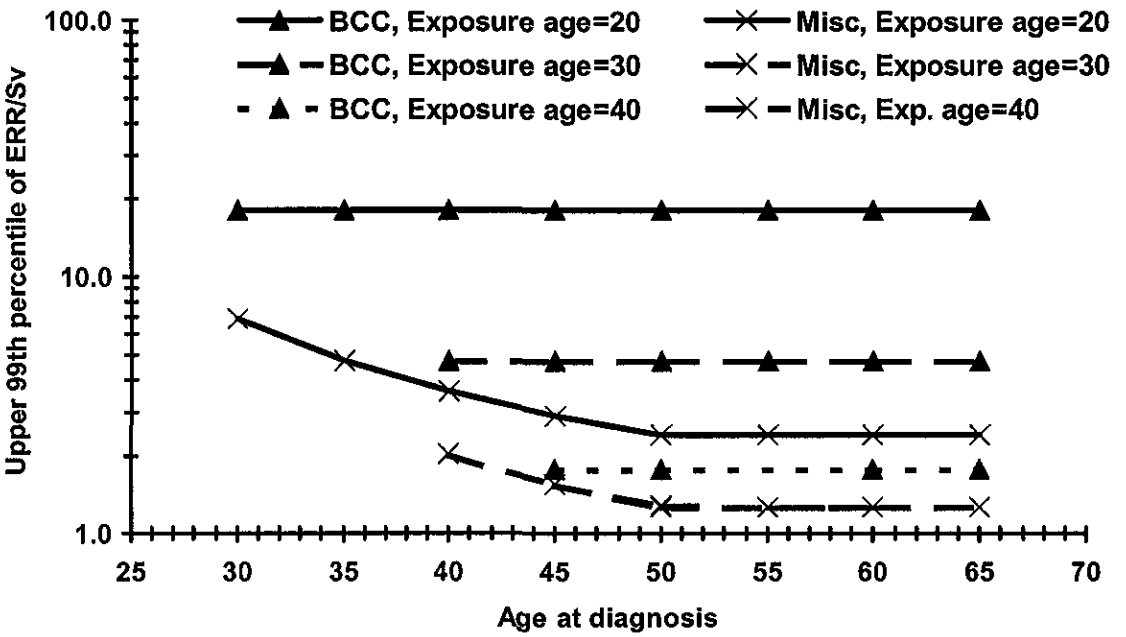


Figure 2. ERR/Sv estimates (at the upper 99th percentile of the credibility distribution) for basal cell carcinoma (triangle) and for miscellaneous cancer (X) models, from NCI (2002), for (a) males and (b) females.

(a) Males



(b) Females

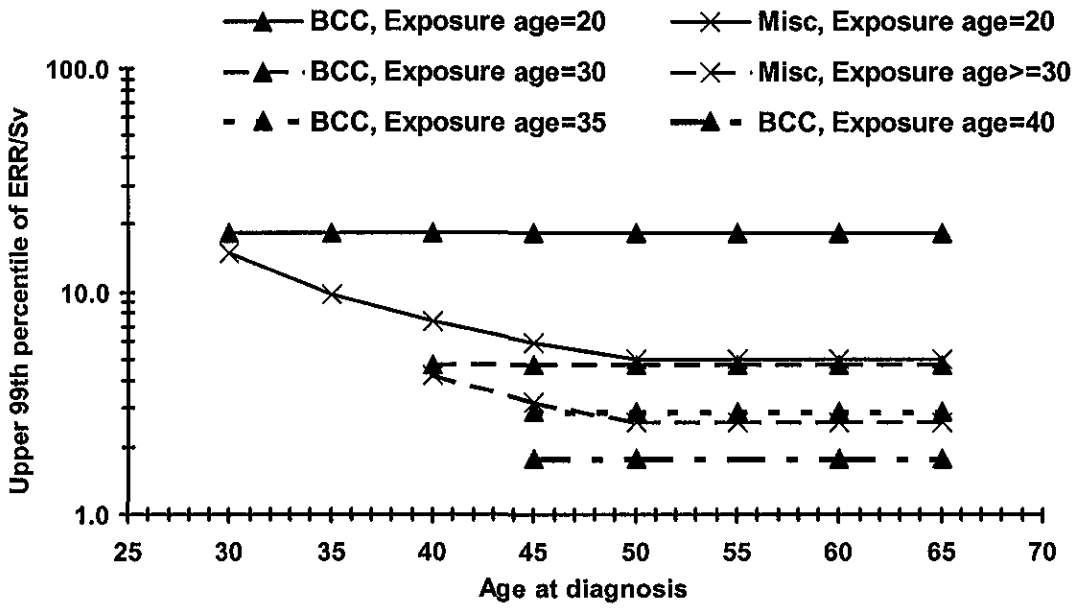


Figure 3. ERR/Sv estimates (at the upper 99th percentile of the credibility distribution) for female breast cancer (FBC, triangle) and for male miscellaneous cancer (M Misc, X) models, from NCI (2002).

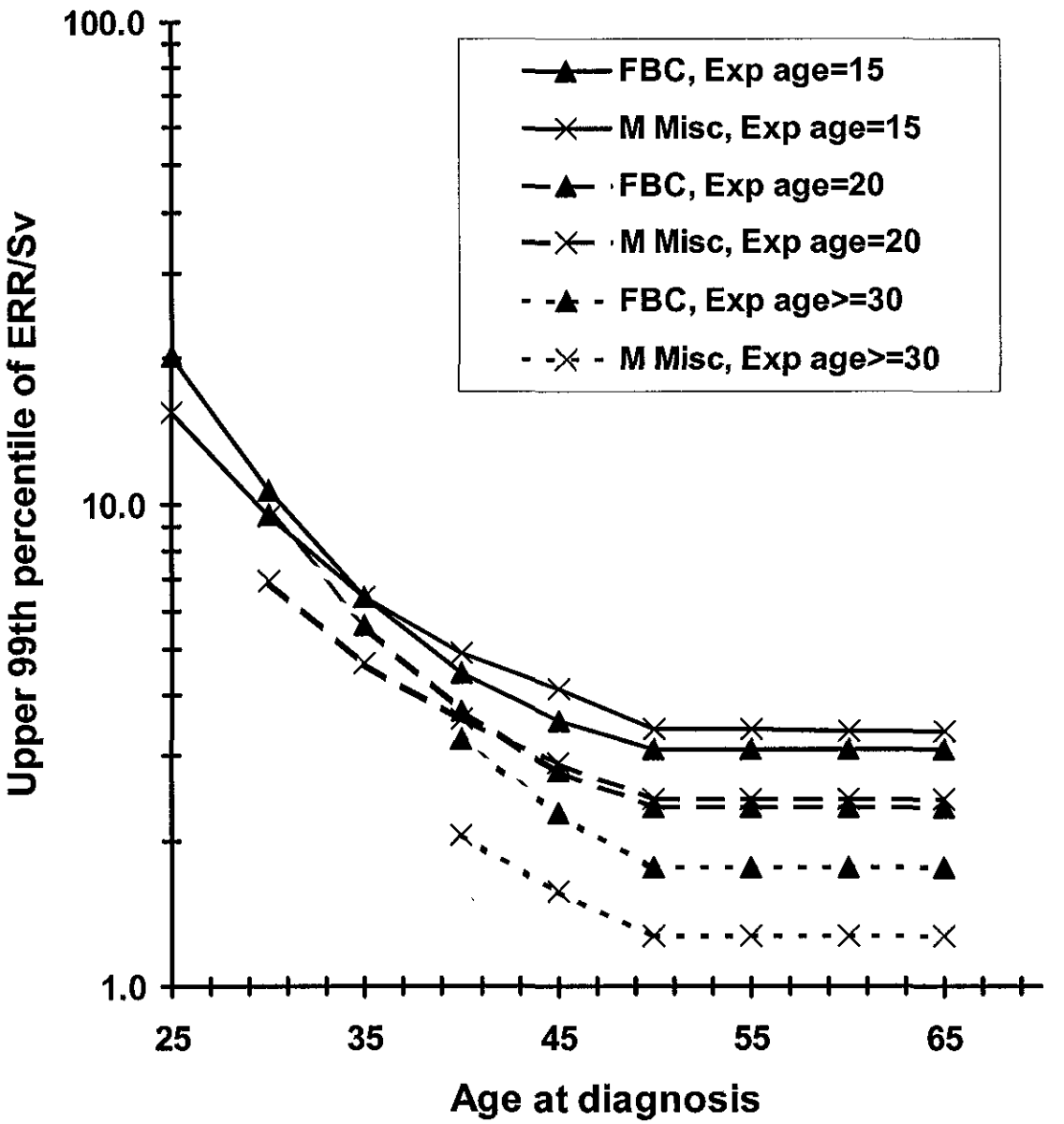
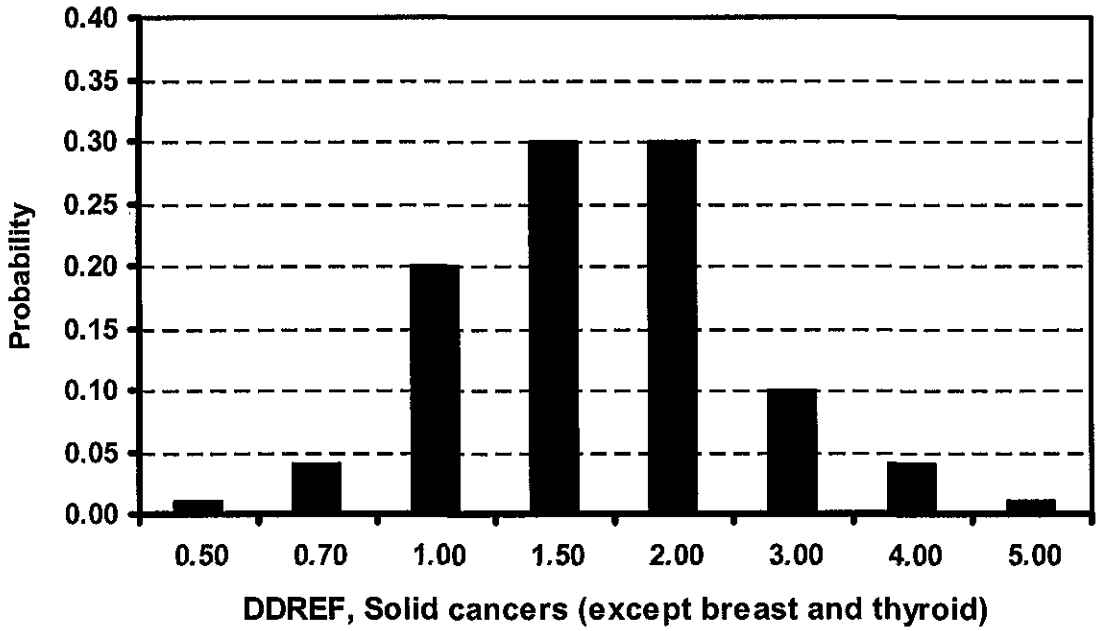


Figure 4. Draft and final DDREF distribution used in NIOSH-IREP for (a) all solid cancers except breast and thyroid and (b) breast and thyroid cancer.

(a)



(b)

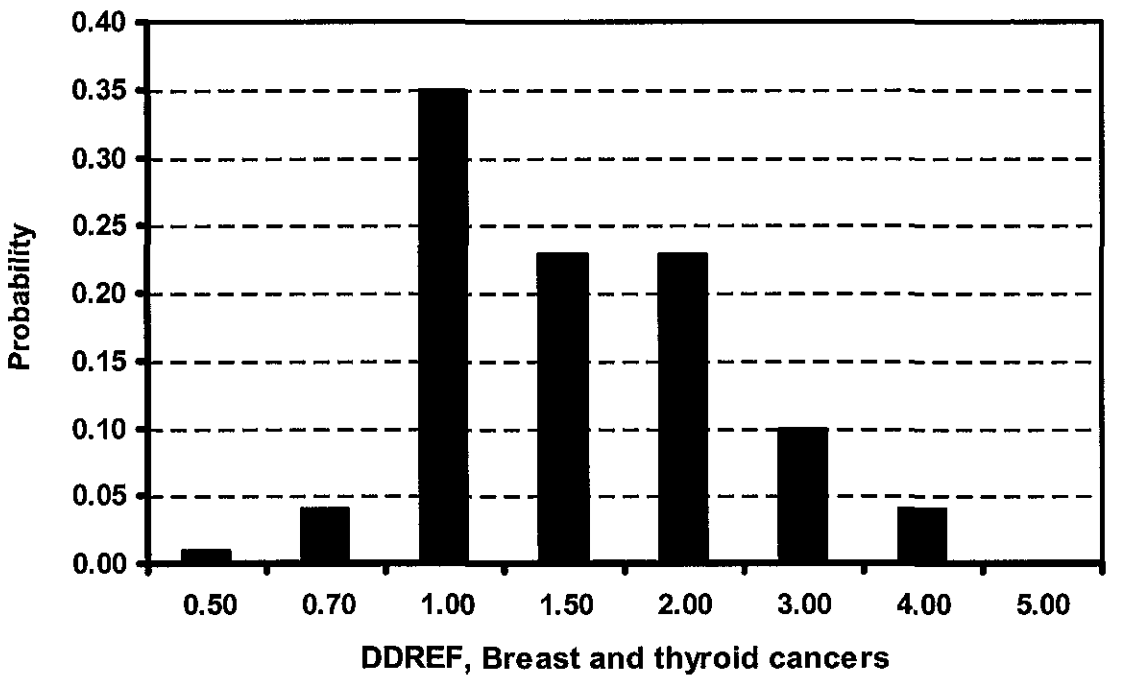


Table 1. Radiation exposure types in NIOSH-IREP

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