Response to Subject Matter Expert Review Comments on NIOSH-IREP

(1) Use of the upper 99% subjective confidence interval estimate for the probability of causation as an adjudication level.

Comments: Several reviewers (R. Shore, D. Stram, R. Hornung) questioned whether this practice would be more likely to result in a claim award for "less-radiogenic" cancers, which presumably have higher error estimates about the ERR/Sv, than for cancers acknowledged to be strongly associated with cancer. D. Stram recommended the use of random effects models to reduce the tendency for rarer cancers to be compensated.

Response: The relevance of these comments depends on several factors, including the method by which radiogenicity is defined, and the intent of the EEOICPA in addressing the role of uncertainty in awarding claims. While the latter issue results from a mandate of Congress, the former issue may be addressed explicitly, by considering the uncertainties in risk coefficients from the Japanese A-bomb cohort for various cancers. The radiogenicity of many cancers has been classified (somewhat informally) by Boice et al. (1996), into four groupings, based on the totality of the epidemiologic evidence regarding their association with ionizing radiation exposure. The four cancer groupings are:

1. "Cancers frequently associated with radiation with authoritative risk estimates"
Leukemia (except CLL), thyroid, female breast

2. "Cancers occasionally associated with radiation with valid risk estimates"
Lung, stomach, colon, esophagus, bladder, ovary, multiple myeloma

3. "Cancers rarely associated with radiation with uncertain risk estimates"
Brain and nervous system, kidney, liver, salivary glands, non-Hodgkin's lymphoma, skin, rectum, uterus, bone, connective tissues

4. "Cancers never or sporadically associated with radiation with no risk estimates"
Chronic lymphocytic leukemia, pancreas, Hodgkin's disease, prostate, testis, cervix, retinoblastoma, Wilms' tumor, and others of embryonic origin, muscles, tendons, and synovial membranes of joints

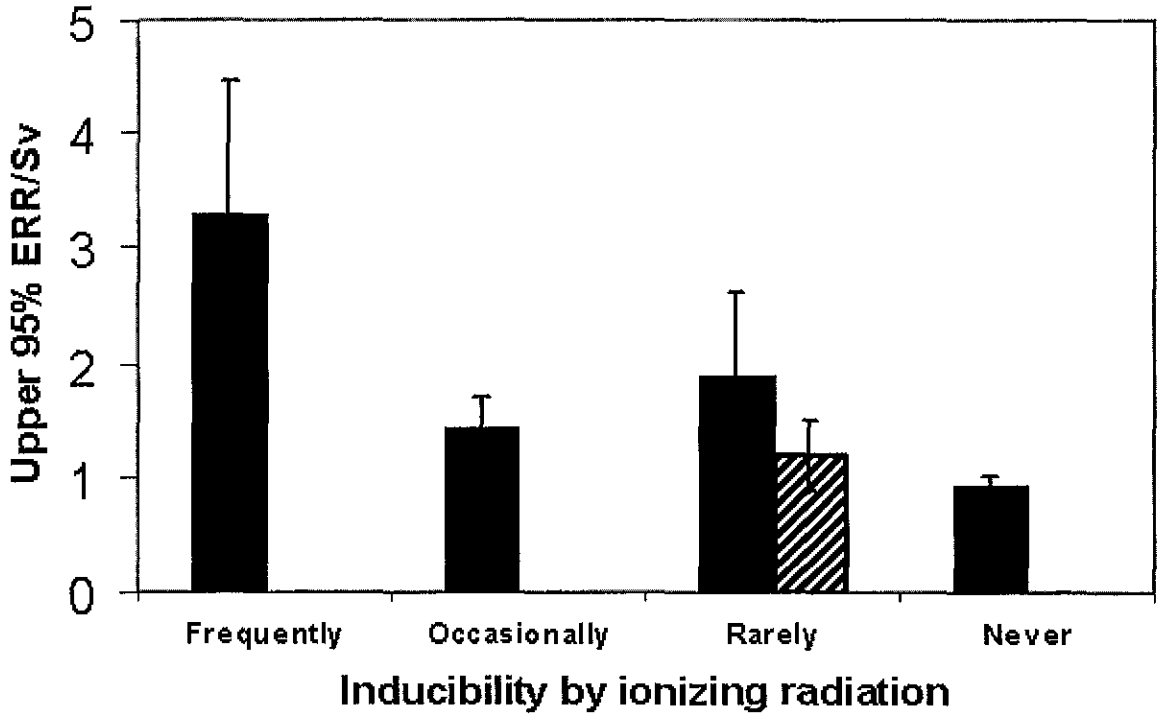
It can be seen that upper tail estimates of the distribution of the ERR/Sv for "less inducible" cancers classified by the method of Boice et al. (1996) *are not* in general higher than those of "more inducible" cancers (Table 1, Fig. 1). This tendency is strengthened, in particular, when salivary cancer (a rare cancer with high risk coefficients in the A-bomb cohort analysis) is excluded from the comparison (Fig. 1).

The pooling of biologically-similar cancers by NCI for the derivation of radiation risk estimates (NCI 2001) should further reduce concern about this issue.

Table 1. Upper 95% confidence interval estimate (two-sided) of ERR/Sv, from analysis of cancer incidence in Japanese A-bomb survivors (Thompson et al. 1994 and Preston et al. 1994). Inducibility category was classified by Boice et al. (1996).

Cancer	n	Upper 95%CL of ERR/Sv	Inducibility category
Leukemia, excluding CLL	141	5.6	1
Female breast	289	2.2	1
Thyroid	129	2.1	1
Bladder	115	2.1	2
Ovary	66	2.3	2
Lung (incl. trachea and bronchus)	449	1.4	2
Colon	223	1.3	2
Stomach	1305	0.5	2
Oesophagus	84	1	2
Non-melanoma skin	91	1.9	3
Kidney	34	2.2	3
Rectum	179	0.75	3
Uterus	349	0.1	3
Salivary gland	13	6	3
Liver	283	0.92	3
Nervous system	69	1.3	3
Prostate	61	1.2	4
Oral & pharynx	64	0.93	4
Pancreas	122	0.82	4
Gall-bladder	143	0.72	4

Figure 1. Group mean (± 1 standard error) upper 95% confidence interval estimate of the ERR at 1 Sv (from Table 1), by cancer inducibility category (as classified by Boice et al. 1996). Cross-hatched bar shows result excluding salivary cancers.



(2) Use of female breast cancer ERR/Sv coefficients for male breast cancer model

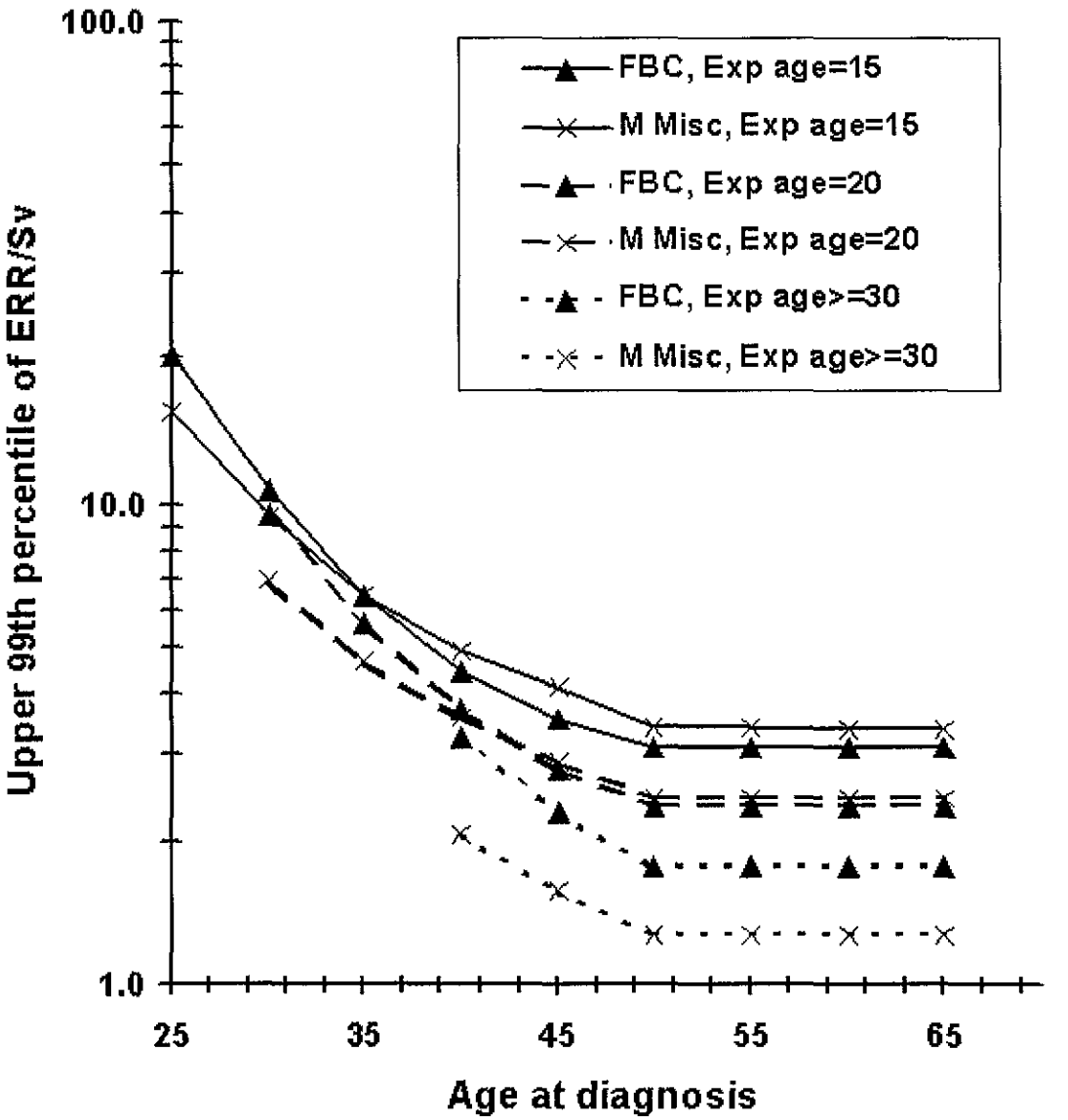
Comment: One reviewer (D. Hoel) questioned whether sufficient scientific evidence supports the assumption that male breast cancer is hormonally-related, which underlies the decision to use risk coefficients from female breast cancer for male breast cancer models within NIOSH-IREP. This reviewer suggests that the residual cancer model be used to derive risk estimates.

Response: As acknowledged by the NIOSH-IREP technical documentation, little epidemiological evidence exists about the etiology of male breast cancer. After further review of the relevant literature, particularly in an authoritative review of the etiology of breast cancer (Henderson et al. 1996), it appears the "mainstream" scientific view is that male breast cancers are hormonally-mediated. The evidence for this hormonal linkage is manifold: 1) Breast cancer in males, as in females, increases greatly with age 2) Male breast cancer is associated with overweight in early adulthood (Casagrande et al. 1988), 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 (Bernstein et al. 1989). A further question, then, is whether excess relative risk (ERR) from radiation exposures is higher among young than older males, as is the case for females. No quantitative studies have estimated such risks directly. Two reasonable surrogate approaches to estimate the radiation-related risks for male breast cancer would be to use either the female breast cancer or the residual cancer ERR/Sv coefficients, applied to the male background cancer risks for Japan and the U.S. However, no information exists in the literature to choose between these two models. This determination has been confirmed by discussion with experts at NCI (Charles Land, personal communication).

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 rule on Probability of Causation 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. 2) shows that the use of the female breast cancer model provides the most claimant-favorable estimates, at most combinations of exposure and diagnosis ages. The female breast cancer model risk coefficients, therefore, will be employed in the NIOSH-IREP models.

There is, similarly, no data to support the use of a 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 will be employed in NIOSH-IREP (NCI 2001). This transfer function is trapezoidal, with no preference for an additive over a multiplicative model.

Figure 2. 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 (2001).



(3) Selection of risk coefficients for squamous cell carcinoma and malignant melanoma.

Criticism: One reviewer (R. Shore) argued against the use of the basal cell carcinoma risk coefficients for malignant melanoma. This reviewer suggested that malignant melanoma is only inducible at high doses. Another reviewer (D. Hoel) asserted that evidence is weak for dose-related increases in malignant melanoma among nuclear workers, and that the basal cell carcinoma (BCC) risk coefficients should not be used for squamous cell carcinoma or other non-melanoma skin cancers (SCC), which showed much lower risk estimates. The NCI also discouraged the use of BCC risk coefficients for SCC, and developed a separate model for the two forms of non-melanoma skin cancer.

Response:

Upon further review of the arguments for the use of separate SCC risk coefficients, we determined that it is both appropriate and feasible to employ separate models for BCC and SCC within NIOSH-IREP. The development of risk coefficients for these separate models for the finalized NCI-IREP 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) do 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 will be instructed to use the risk models for basal cell carcinoma. Background incidence rates for non-melanoma skin cancer remain based on the combined rates of these and other non-melanoma skin cancers, as separate Japanese rates for BCC and SCC are not available.

The argument that malignant melanoma may be inducible only at high doses, and that, therefore, no risk models should be developed, is inconsistent with the approach used for other cancers for which such arguments have been made (e.g., bone cancer, squamous cell carcinoma, cancer of the uterus). The approach used in IREP for these types of cancers takes into account the full uncertainty distribution–including the possibility of great attenuation of effect at low doses–of the risk coefficient. We acknowledge that the evidence for radiogenicity of malignant melanoma is weak. In the Japanese A-bomb survivor study, only 13 cases of malignant melanoma were observed, which is far below the level at which risk estimates were derived independently by NCI for the IREP program. Point estimates for risk coefficients in this study are consistent with the risks observed for basal cell carcinoma. There is also (weak) evidence from nuclear worker studies that malignant melanoma may be related to ionizing radiation dose (although, as indicated by D. Hoel, the confidence intervals on the risk coefficients are wide; Muirhead et al. 1999).

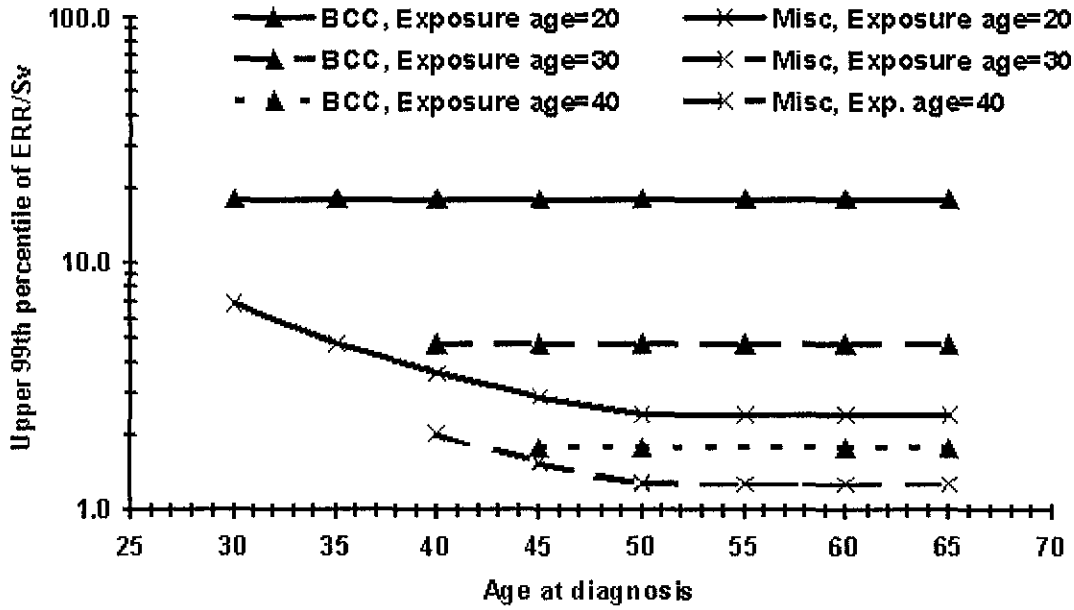
There is great need for future studies of malignant melanoma in radiation-exposed populations, in order to better estimate risk coefficients for this cancer. However, in the absence of direct information, three reasonable potential sources of risk coefficients are those developed for non-melanoma skin cancer (one model each for basal cell and squamous cell carcinoma) and the miscellaneous site cancer model. As discussed for male breast cancer, above, using the model producing the highest ERR/Sv risk coefficients would be consistent with HHS policy decisions about selecting among equally-valid alternatives in the Probability of Causation rule.

Both the basal cell carcinoma and the miscellaneous cancer models have higher ERR/Sv estimates than the squamous cell carcinoma model (NCI 2001). 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. 3). 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 claimant-favorable 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 below (i.e., the distribution favoring neither the additive nor the multiplicative interaction model).

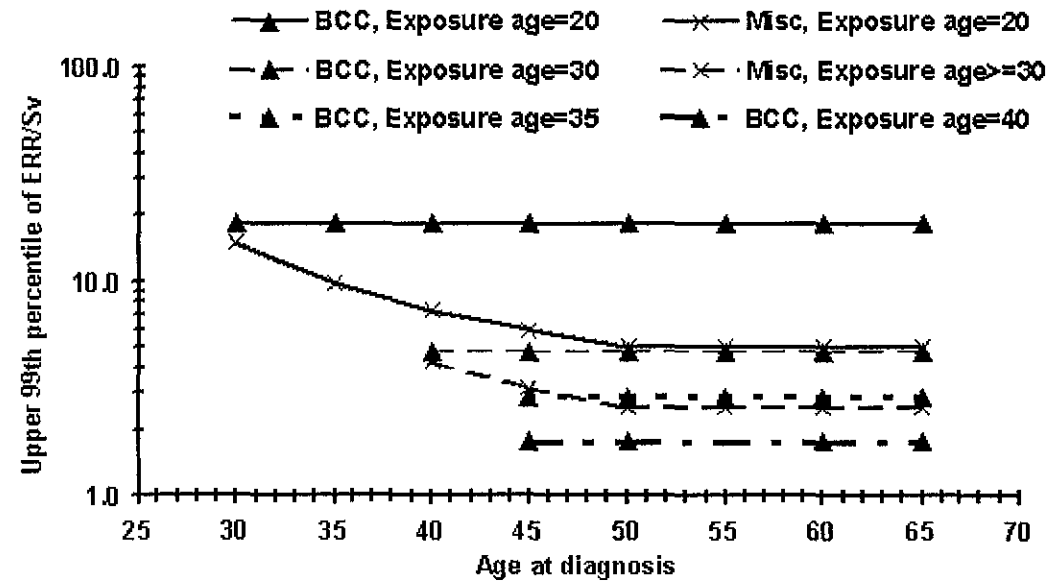
In summary, NIOSH-IREP incorporates three different skin cancer models. For non-melanoma skin cancer, basal cell and squamous cell carcinoma models are based on different sets of risk coefficients. In claims where the non-melanoma skin cancer type is indeterminate, the model for basal cell carcinoma will be used. Both basal cell and squamous cell carcinoma models are modified by race-specific background incidence rates for all 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).

Figure 3. 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 (2001), for (a) males and (b) females.

(a) Males



(b) Females



(4) Appropriate risk transfer method (from Japanese to U.S. population) for skin cancers

Comment: Two reviewers (R. Shore and D. Hoel) asserted that the evidence of the tinea capitis study, in which relative risks were similar for white and black subjects, supports the use of a multiplicative over an additive risk transfer model.

Response: There is substantial scientific uncertainty regarding the appropriate risk transfer model to be used for skin cancer. As acknowledged in the NIOSH-IREP technical documentation, the tinea capitis study referenced by the reviewers tends to support the use of a multiplicative interaction; however, observations of greater *relative* risks from ionizing radiation in sun-protected, compared to sun-exposed, skin among the Japanese A-bomb survivors strongly suggests that an additive (or other sub-multiplicative) interaction with ultraviolet (UV) radiation sensitivity is warranted. The UNSCEAR report (UNSCEAR 2000, pp. 177-295) states that a sub-multiplicative model should be employed for risk modeling, based on the totality of evidence, including the studies mentioned above.

The uncertainty distribution for the generic risk transfer model in NIOSH-IREP is designed to incorporate this sort of scientific uncertainty. It assigns a uniform distribution to a multiplicative vs. an additive interaction model (with small probabilities associated with sub-additive and super-multiplicative interactions). Based on consideration of the opinions of the expert reviewers, we concur with NCI that there is insufficient information to favor an additive over a multiplicative interaction between ionizing and UV radiation exposure for skin cancers. *Thus, the revised version of NIOSH-IREP reverts to the default risk transfer function used for all cancers other than stomach and female breast.*

(5) Use of Japanese atomic bomb data as source of radiation risk coefficients.

Comments: D. Hoel commented on quality differences between the A-bomb survivor cancer incidence and mortality that recommend the use of the former. D. Richardson argued that the A-bomb survivor study is inadequately adapted as a source of risk coefficients for DOE workers. A number of limitations were enumerated, including the lack of adjustments for a "healthy survivor effect", for some types of random and systematic error in dose estimation from the study, and for other sources of bias described in the NCRP Report 126 (NCRP 1997).

Response: Cancer incidence data from the Japanese A-bomb survivor study are the basis for the risk estimates for all cancers except lung cancer from exposures to radon, and thyroid cancer. The bias and random error sources considered in NCRP Report include selection bias, misspecification of the true dose-response function, errors in the classification of cancers, and dosimetry errors. Many of these biases were considered by NCI in establishing the risk models used in IREP. The potential for bias in risk coefficients resulting from a "healthy survivor effect" in the Japanese A-bomb cohort has been described (Stewart and Kneale 1990, 2000, NCRP 1997). In a formal evaluation (Little and Charles 1990), its magnitude appeared relatively weak, appeared negligible beyond a few years after exposure, and may be attributable to errors in the (T65D) dosimetry system employed. While it is not clear at this time how a potential selection bias should be incorporated into NIOSH-IREP, this issue should be addressed systematically in future versions of IREP.

No direct adjustment is made in IREP for dose-response misspecification. However, the use of an uncertainty distribution for the dose and dose-rate effectiveness factor (DDREF) for solid cancers indirectly modifies the dose-response relationship. The use of a distribution encompassing values above and below unity ensures that the possibility of supra-linear, linear, or sub-linear dose-response relationships for these cancers are represented in the risk models. For non-CLL leukemia, the dose-response relationship is fixed as linear-quadratic. The need to adapt this approach for leukemia is discussed further below (See Item #7).

Some of the epidemiological biases discussed in NCRP Report 126 are more pertinent to the use of cancer mortality than cancer incidence data (NCRP 1997, p. 16 Charles Land, personal communication). For example, bias or error resulting from the use of cancer mortality data to estimate dose-related increases in cancer incidence would not be relevant if cancer incidence data were modeled directly. Biases due to misclassification of cancer cases are not as serious a problem for cancer incidence as for mortality data (NCRP 1997, p. 16-19). Underascertainment of incident cancers due to migration would be expected to affect absolute, not relative, risk coefficients, since it appears independent of radiation exposures (NCRP 1997, p. 19). The NCRP Report 126 declined to adjust risk coefficients based on cancer incidence data for epidemiologic bias and random error (NCRP 1997, p. 22). We believe that these potential epidemiologic biases are not of substantial concern for IREP, since cancer incidence data are the direct source of risk coefficients in NIOSH-IREP.

Dr. Richardson criticized IREP for failing to account for random errors in the A-bomb dosimetry. This criticism appears to stem from a misunderstanding about the way the random dosimetry error coefficient is applied. For solid cancers and non-CLL leukemias, the ERR/Sv coefficient is multiplied (not divided) by a value selected by the uncertainty distribution shown in in equations (1) and (2), respectively. This serves to increase, not decrease, the risk coefficients

applied to the models in IREP. For solid cancers, the multiplier has an expected value of 1.088, and a 95% confidence interval of 1.060-1.130. For leukemia, the expected value is 1.056, and the 95% confidence interval is 1.038-1.082.

$$R_{E(solid)} \sim 1 + \text{lognormal}(GM_S, GSD_S) \quad (1)$$

where GM_S = geometric mean for solid tumors = 0.088

GSD_S = geometric standard deviation for solid tumors = 1.22

$$R_{E(leukemia)} \sim 1 + \text{lognormal}(GM_L, GSD_L) \quad (2)$$

where GM_L = geometric mean for leukemia = 0.0556

GSD_L = geometric standard deviation for leukemia = 1.22

In summary, we concur that more evaluation is needed of additional sources of bias and random error in the epidemiologic factors relating to the risk coefficients developed for NIOSH-IREP. However, it is not clear what magnitude or uncertainty distributions would be appropriate for incorporating this error. Moreover, as mentioned by Dr. Richardson, it is likely that the dose estimates for the A-bomb survivors may change in the near future; hence, it seems prudent to consider these issues more fully in future revisions of IREP. This issue is equally germane to the NCI's IREP program, which is used by the Department of Veterans' Affairs for determining assigned share from radiation exposures. Thus, the uncertainty distributions for NIOSH-IREP should be developed in conjunction with those used for NCI-IREP. More important, we believe, is the need to incorporate information from other epidemiological studies, particularly those of DOE workers, into the risk models developed for NIOSH-IREP.

(6) Modeling the influence of age at exposure on radiation risk estimates

Comments: One reviewer (D. Richardson) argued that the dose-response models used in NIOSH-IREP should be changed in several ways: first, the models should based on adult (not childhood) exposures, and second, the models should include a possibility of higher cancer risks (per unit dose) at older ages, based upon findings among some DOE populations.

Response: There is substantial evidence from several key studies in addition to those of the A-bomb cohort that suggests radiation risk for many cancers decreases with increasing age at exposure. These include studies of breast cancer among x-ray tuberculosis patients (Boice et al. 1991), of thyroid cancer among medically- and occupationally-exposed populations (summarized in UNSCEAR 2000, pp. 338-343), and of skin cancer (UNSCEAR 2000, p. 402).

The NCI approach to adjusting radiation risk estimates for different exposure ages was adopted for NIOSH-IREP. The models used in the revised NCI-IREP were developed using a somewhat novel procedure (Land et al. 2001). Effects of age at exposure and attained age were modeled for all solid tumors as a group. The risk coefficients from these adjustments were then applied to the site-specific models, unless there was a statistically-significant difference between the age-at-exposure terms for the site-specific and general model. These general coefficients 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. This approach was recommended by an international expert committee (Pierce and Preston 1993; UNSCEAR 2000, p. 208). Thus, for most cancers (except as noted below) 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 is, we believe, more appropriate for modeling risks among those exposed as adults.

It may be questioned why exposures as young as age 15 were modeled for IREP. This is a result of the Poisson regression modeling 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, we believe, for EEOICPA, that 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, and basal cell carcinoma, and for all other solid cancers. 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 cancers; however, the data were not modeled in this way for NCI-IREP, and the data were not available to NIOSH researchers. 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.

The NCI-IREP modeling approach 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*).

The second point argued by Dr. Richardson is that there may be increased dose-related risks for some cancers at higher ages at exposure (among adults), which should be incorporated into NIOSH-IREP. This observation has been made in analyses of certain DOE populations (Wing 2000, Richardson et al. 2001), but not in other populations of nuclear workers in which it has been evaluated, nor in analyses of the atomic bomb survivors and those exposed to high doses of x-rays during medical treatments (Cardis et al. *1995a, b; Gilbert 2000*). While this is an area of intense current research, it is very difficult to conclusively elucidate effects of age-at-exposure among complex exposure patterns typified by nuclear workers. Incorporating other temporal factors, such as time since exposure, birth cohort, and temporal aspects of exposure assessment accuracy, could produce risk models that fit as well as those focusing on age at exposure in these cohorts (Gilbert 2000, Wing 2000). While it is plausible that an increased effect of age-at-exposure exists, it must be incorporated into the context and examination of alternative modeling possibilities. Currently, it is not feasible to defensibly do so. We believe this is a high-priority area of research with important implications for future versions of NIOSH-IREP.

In summary, we believe that greater attention should be given to variation in sensitivity to radiation for various adult ages at exposure, by cancer groupings, in future revisions of NIOSH-IREP. No changes regarding age-at-exposure modeling have been made in the current revision of NIOSH-IREP.

(7) The distribution used in NIOSH-IREP for the "dose and dose-rate effectiveness factor" (DDREF)

Comments: There were several comments on the approach used to adjust for low dose-rate exposures in NIOSH-IREP. D. Stram remarked that the approach is not adequately justified, and that it reflects the judgment of a small group, which could be highly criticized. D. Richardson commented that the DDREF was too high, on average, and that it does not reflect the latest research from the low-dose ranges of the Japanese A-bomb survivors. D. Hoel argued against the assumption of linearity at low dose for all solid tumors, suggesting that analyses based on cancer mortality among the A-bomb cohort are subject to bias. R. Hornung questioned why no adjustment was made for a possible inverse dose-rate effect for radon and lung cancers at exposures above 50 working level months.

Response: We concur with D. Richardson that the A-bomb survivor study (which is the epidemiological data source deemed most relevant for adjustment by 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 supra-linear) 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 (e.g., by D. Hoel).

Despite the evidence from the A-bomb survivor study supporting the use of a DDREF of one, there is much evidence from animal studies supporting a DDREF of greater than one, for a variety of endpoints, including cancer (summarized on pp. 60-66 of NCRP 1997), from low-LET exposures. Most expert committees, including the NCRP, the ICRP, and UNSCEAR, advocate the use of an expected value for the DDREF of about 2 (NCRP 1997, p 66; ICRP 1991; UNSCEAR 2000, p 358); however, these recommendations preceded the new analysis of cancer incidence in low-dose ranges of the Japanese A-bomb study (Pierce and Preston 2000).

Therefore, the NCI has shifted the DDREF distribution for all solid cancers in its proposed version of 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.

In response to the comment about the need to incorporate a possible inverse dose-rate effect for radon and lung cancer above 50 WLM, such a separate adjustment is unnecessary. The model for radon exposures developed by NCI researchers incorporates a power-law function in the dose-response relationship that accounts for a possible inverse dose rate effect (Charles Land, personal communication).

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 variability 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. Modification of risk by dose and dose rate for both solid and hematopoietic cancers is another area of active research that will be re-evaluated in future revisions of NIOSH-IREP.

(8) Risk coefficients used in NIOSH-IREP for bone cancer

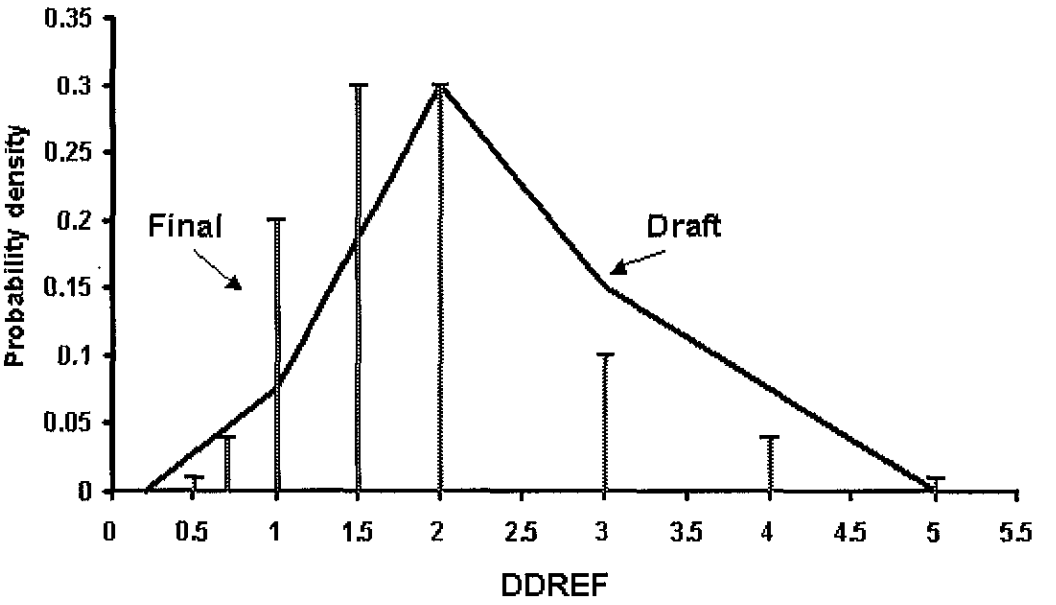
Comments: The NCI and one of the subject matter expert reviewers (D. Hoel) argued that the bone cancer incidence and mortality data are too sparse to support the development of a unique bone cancer model from the Japanese A-bomb survivor study. Both the NCI and D. Hoel recommend the use of the "miscellaneous cancer" risk coefficients for bone cancer claims under EEOICPA.

Response: The risk coefficients used in the draft NIOSH-IREP, taken from the mortality data from Pierce and colleagues (Pierce et al. 1996), were used in a recent risk assessment of plutonium at the Rocky Flats facility (Grogan et al. 2000). However, in that risk assessment, these estimates were supplemented with risk coefficients from animal and human studies of internal exposures, which were not considered consistent with the approach used to develop risk coefficients for use in NCI-IREP (which also form the basis of NIOSH-IREP).

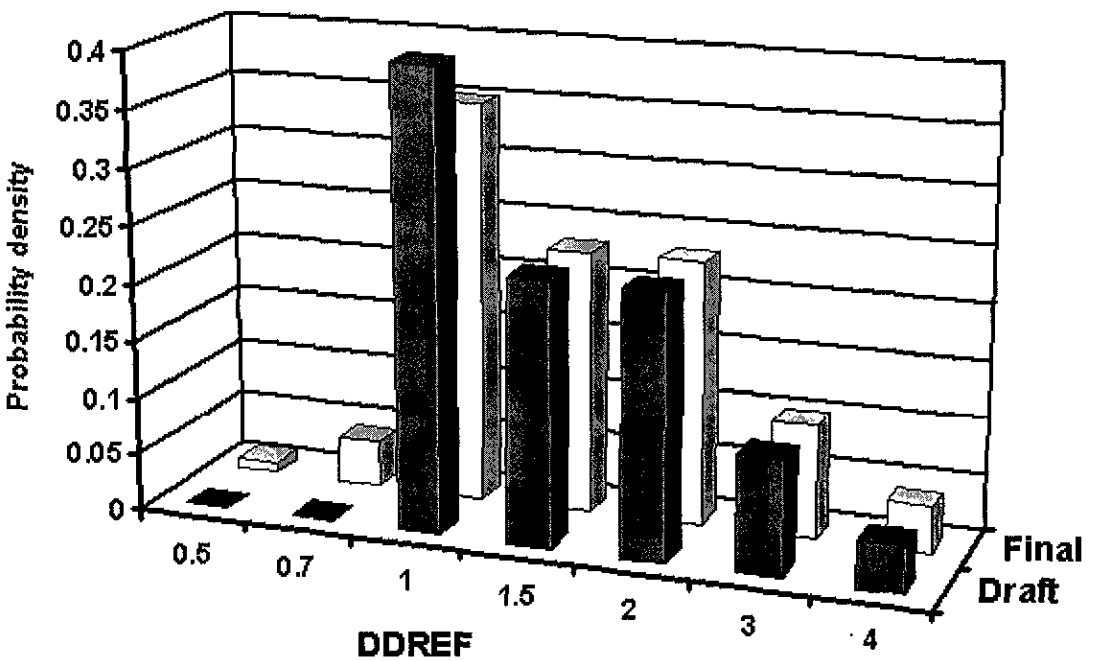
The primary argument against the use of the miscellaneous cancer risk coefficients for bone cancer claims is that the model includes many disparate types of cancers, including those of bone, connective tissue, eye, male breast cancer, non-thyroid endocrine glands, and ill-defined sites. The alternative, 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. Therefore, we concur with the NCI and subject matter expert reviewer 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, which is the same set of risk coefficients used in 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.

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)



(9) Models for chronic lymphocytic leukemia in NIOSH-IREP

Comments: One of the subject matter expert reviewers (*D. Richardson*) criticized the lack of a risk model for chronic lymphocytic leukemia (CLL) in NIOSH-IREP, stating that the assumption that CLL is non-radiogenic for purposes of compensation under EEOICPA is inconsistent with the approach used for other cancers. He argued that the upper bound on the confidence interval of risk coefficients for CLL in the international nuclear workers' study is higher than that for acute lymphocytic leukemia (ALL).

Response: The latest version of the NCI-IREP program does not include a recommended model for CLL. CLL is specifically excluded from the type-specific leukemias, as well as from the general leukemia model. The NIOSH-IREP technical documentation summarizes the evidence regarding an association between CLL and ionizing radiation exposure in many studies. No reviewed studies demonstrated such an association. We concur that there is need for a much more formalized evaluation of the radiogenicity of CLL than was possible in the initial development of NIOSH-IREP. It would have been preferable to use uncertain estimates of CLL risk from the same source as for other marginally (or non-) radiogenic cancers. The approach used for other rare cancers (to use risk coefficients for clusters of "similar" cancers) is not suitable for CLL, however. The only similar cancers for CLL model estimation are other leukemias, and it has been well-established in studies among radiation-exposed Western populations that risk coefficients for CLL, if non-zero at all, are much lower than those for other leukemias. It would not therefore be appropriate to use risk coefficients from other leukemia models for CLL.

Dr. Richardson has pointed to evidence from the combined international nuclear workers studies that the upper bound on the confidence interval of risk coefficients for CLL is higher than for ALL. This argument does not seem compelling. No association was found between CLL and radiation exposure in that cohort, despite the occurrence of 27 deaths from CLL (Cardis et al 1995a, p. 57). There were only eleven cases of ALL mortality in that cohort (Cardis et al. 1995a, p. 60), and just four of these had radiation exposures above 1 cSv (rem). Combined with the weight of evidence from other epidemiological studies, and from the treatment of CLL by various expert committees, this argument does not, at this time, justify the use of risk coefficients derived from ALL, or any other leukemia model, in the Japanese A-bomb survivor cohort for CLL.

In summary, no modification was made to the approach used in NIOSH-IREP for CLL, which is considered non-radiogenic for purposes of DOE workers' compensation. As stated in the technical documentation, however, and in the rule on probability of causation under EEOICPA (42 CFR 81), this determination is subject to modification as advances in knowledge warrant.

(10) Interaction of radiation with other carcinogenic exposures

Comments: Several subject matter experts commented about the assumptions in NIOSH-IREP regarding radiation interactions with other carcinogens. R. Shore stated that "most hormonal factors do not interact (with radiation)." D. Richardson suggested the inclusion of an uncertainty factor to account for workplace chemical interactions with radiation. R. Hornung questioned the lack of adjustment for tobacco use in cancers other than lung.

Response: The current (default) assumption in NIOSH-IREP is that radiation interacts in a multiplicative way with chemical exposures and cigarette smoking. That is, the proportional increase in cancer risk from radiation exposure is assumed to be the same for individuals with different levels of exposure to chemical carcinogens. The one exception is for cigarette smoking and trachea, bronchus or lung cancer. In this case, the distribution of the interaction term between smoking and ionizing radiation exposure is centered on a sub-multiplicative interaction, with small probability of the interaction being super-multiplicative or additive. No adjustment exists for other tobacco-related cancers because of a lack of information about the form of interaction between these cancers and radiation exposure. In the absence of such information, the interaction is assumed to be multiplicative, and no adjustment to the risk models is needed.

Because EEOICPA does not allow consideration of compensation claims for chemical exposure, the use of an adjustment for DOE workplace-related chemical exposures could have the effect of reducing a claimant's chance of compensation for a cancer that may have been caused by joint exposure to radiation and chemicals. The default assumption, of a multiplicative interaction, is likely to be favorable to the claimant, since exposures that have the same mode of action are likely to interact in a sub-multiplicative manner (Land et al. 2001, p. 39).

In addition, it is not scientifically supportable nor practically feasible to adjust NIOSH-IREP risk models for the multitude of occupational and community exposures that may modify risk from radiation exposures. The risks associated with most chemical exposures, and the appropriate form of their interaction with radiation, have not been adequately quantified. Moreover, it would be very difficult to obtain data on the individual claimant's exposure to chemicals or radiation in the community. Access to data on past occupational exposures to chemicals is also infeasible at this time.

The adjustment for smoking history in NIOSH-IREP has been adopted from the approach developed by NCI. The NCI's review of relevant literature, and a scientific consensus panel opinion (UNSCEAR 2000, pp. 201-203), concluded that the best-supported models to evaluate the form of interaction between smoking and radiation are based on meta-analyses of radon-exposed workers. Combined analyses of these studies suggests that the most appropriate form of interaction is sub-multiplicative, but greater than additive (Lubin and Steindorf 1995). This information was used to develop an uncertainty distribution for the form of interaction between smoking and radiation in the lung cancer risk models that is centered on a sub-multiplicative model (i.e., assuming that the excess *relative* risk per unit of radiation dose is lower for individuals who smoke more), but includes the possibility of either a multiplicative model (i.e., that excess relative risk per unit of radiation dose is the same for various levels of smoking) or a super-multiplicative model (i.e., that excess relative risk per unit dose is higher for individuals who smoke more). As with all assumptions, this uncertainty distribution is subject to modification in future revisions of NIOSH-IREP, pending the availability of new scientific information.

(11) Dose rate assumptions for badge readings.

Comment: One subject matter expert (R. Shore) commented that it is unrealistic to assume that worker doses are acute, since there is much data that suggests that most doses are protracted. He noted that this is inconsistently handled for neutron and gamma exposures.

Response: 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 2001, 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.

By this definition, work-related medical x-ray exposures are clearly acute. Neutron and gamma exposures in the workplace are indeterminate as to the dose rate. For neutron and gamma exposures, as specified in NIOSH-IREP, the doses will be entered at the level of the badge reading. 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 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.

(12) Consideration of carcinoma *in situ* in NIOSH-IREP

Comment: One subject matter expert (D. Hoel) asked for clarification of the decision to consider carcinomas *in situ* (CIS), for purposes of estimating probability of causation.

Response: With the improvement in cancer screening technology, many cancers of epithelial origin are now being detected before they have spread to the basement membrane of the affected tissue. As discussed in the NIOSH-IREP documentation, diagnosis and treatment for many of these neoplasms is the same as for cancer in later stages. It is uncertain what proportion of these would proceed to invasive malignant neoplasms without intervention. Because many of the conventional treatments for these neoplasms are the same as for cancer in later stages, it is impossible to determine this at the level of the individual claimant. A policy consistent with others 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. The same risk model is employed for a CIS as for the corresponding malignant neoplasm. No distinction is made among the sites at which the CIS might develop with regard to this policy.

(13) Other issues

Comments: Several reviewers commented on the need for better documentation of the assumptions and uncertainty analysis used in NIOSH-IREP, and specific suggestions were made for improvement of the technical background document. One reviewer suggested the incorporation of adjustments to the risk transfer function for cancers (in addition to skin), based on race/ethnicity or other factors. One reviewer (D. Richardson) requested more information about how doses would be estimated to organs in practice.

Response: NIOSH will implement the specific suggestions made for improving the technical background document. We concur that better documentation of the models and assumptions is needed within NIOSH-IREP. However, the primary basis of NIOSH-IREP is NCI-IREP, the documentation of which is awaiting finalization at NCI and HHS (and is not yet available to be published). As soon as it is feasible, the final NCI-IREP will be made available along with the NIOSH-IREP documentation. The primary means of communicating the underlying assumptions of the models will be to embed them in the "View Model Details" area of the NIOSH-IREP website.

We concur that differences in background cancer rates should be incorporated into NIOSH-IREP, if feasible, if differences are substantial, and if underlying reasons for these differences are understood. The only cancer that met these criteria at this time was skin cancer, as discussed in the technical documentation for NIOSH-IREP. That is, skin cancer has the most highly-variable incidence rates (by racial/ethnic group), and variation is due to the variability in the presence of melanin in the skin. Since the primary causal factor is known for skin cancer, its expected interaction with ionizing radiation exposure can be modeled within NIOSH-IREP, and can be determined fairly simply on an individual basis for estimating a claimant's probability of causation. As information on etiologic factors underlying racial and ethnic differences in cancer incidence rates improves, it may be possible to include this variability in NIOSH-IREP.

Finally, the dose estimation procedures are detailed more completely in the dose reconstruction regulation, and in the technical documentation for the dose reconstruction process. Citations for these methods have been added to the NIOSH-IREP technical documentation.

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Table 2. Synopsis of subject matter expert comments on the NIOSH-IREP technical documentation

Comment	NCI	Shore	Richardson	Stram	Hoel	Hornung
Use of upper 99% confidence interval estimate of PC	--	Called it "nonsensical"; prefers U.K approach	--	Supports the development of a random effects analysis (see NAS review) to reduce tendency for rarer cancers to be compensated.	Substantial issues (NAS covered)	Will this result in less-radiogenic cancers being more likely to be compensated?
Use of A-bomb data	Prefer	--	Cautioned against it. Says models should adjust for "healthy survivor effect". Should include other bias and random error components, as described in NCRP 126. Error terms for dose should include random component.	--	Substantial issues (NAS covered). There are "quality differences" between incidence and mortality data that support the use of the former	--
A-bomb dosimetry adjustment for error	--	--	Bias adjustments result in decreases to ERR/Sv estimates. Some allowance for distribution <1 is warranted. Existing approach not a valid way of dealing with random measurement error.	--	--	--
Modeling age-at-exposure	Use existing models (mostly adjust for greater effects at earlier ages), using data for those exposed at age ≥15	--	Objects to age-at-exposure modeling based on A-bomb results, particularly to slope based on childhood effects Says it should be categorical, not linear, term. Should add new uncertainty term.	--	--	--
DDREF	Breast and thyroid will be discrete and include shift of 5% to 0.6	--	Believes it is too high, not supported by low-dose A-bomb data (says central value of 2 not supported by data).	Not adequately justified; reflect judgment of small group. This will be especially highly criticized	Questions use of "lineanty at low dose" for all solid tumors (but seems to argue-erroneously- this is due to use of mortality data by Pierce (not true)	Why no inverse dose-rate effect for high radon exposure levels? Workers at Fernald may well have cum exposure above 50 WLM.
RBE	--	--	Report should emphasize the paucity of epidemiological data upon which RBEs are based.	Reflects judgment of small group, rather than expert consensus.	Point out that neutron RBEs increase with decreasing dose.	--

Table 2. Synopsis of subject matter expert comments on the NIOSH-IREP technical documentation

Comment	NCI	Shore	Richardson	Stram	Hoel	Hornung
Basal cell carcinoma	Separate from SCC. Use age-specific, newly calculated estimates.	Argues against greater PC for non-whites, but says evidence shows greater ERR/Sv for non-whites (which refutes his argument). Says "same *ERR/Gy estimates appropriate* to all populations (agree); therefore, Table 3 not needed (disagree). Says some studies show interactions w/sun exposure are multiplicative.	--	Tacitly agrees with concept of adjusting background rates by racial group.	Agrees with use of Ron 1998 data as source of risk coefficients. Linear dose response is reasonable. Argues for *use of multiplicative risk* estimates across racial groups, based on linea capitis data. Better discussion needed	Questions use of GSD to compute half-width of CI. Are skin doses better-estimated than other sites in *the A-bomb study*?
Squamous cell carcinoma	Separate from BCC. Use newly calculated estimates (not age-adjusted).	Squamous cell carcinoma risk coefficients should be dropped because they are negative.	--		Argues essentially non-radiogenic.	
Malignant melanoma model	"Estimate not inconsistent with...BCC", suggest using BCC model	Says review of literature is selective. Suggests ICRP and Shore 1990. Believes matig mel is not inducible except at high dose. Does not like use of *BCC model.*	--	--	Should evaluate more recent Muirhead study, which found non-significant dose-response, based on 30 *cases. Cardis study* showed non-sig. D-R.	
Bone cancer model	Small number of cases, and DC unreliability for LSS preclude its *modeling. Recommend* using "miscellaneous site" model.	--	--	--	Does not like the existing model. Large body of radium dial painters *suggests a threshold.* Could be very different from LNT. Cardis data shows negative dose response (11 cases). British workers study also *negative. Should use* miscellaneous site model	Questions use of GSD to compute half-width of CI. Should discuss radium dial *painter literature and its* applicability to DOE exposures (e.g., Fernald).
Male breast cancer	--	--	--	--	Should use miscellaneous site model *(not enough evidence* that MBC is hormonally related)	--
CLL	--	--	Method "inconsistent" with other cancer types. Says *IARC CLL CI is higher than* ALL	--	--	--

Table 2. Synopsis of subject matter expert comments on the NIOSH-IREP technical documentation

Comment	NCI	Shore	Richardson	Stram	Hoel	Hornung
Radiation interactions	--	"Most hormonal factors do not interact (with radiation)." *Pointed out other references*	Should re-evaluate lung cancer smoking interactions. *Can't discriminate between* additive and multiplicative in A-bomb study; radon-exposed populations are poor surrogate. Believes human evidence is paramount. Should include an uncertainty factor to account for workplace chem interactions (and other "transfer" issues).	--	Likes smoking category discussion.	Smoking is associated with other cancers (bladder, *larynx, pharynx, pancreas*). Why is smoking singled out in this model?
Dose rate assumptions for badge readings	--	Unrealistic to assume doses are acute. Much data (e.g., daily mon in early years) indicates nearly all doses are protracted. Inconsistently handled for neutrons and gamma exposures. Unsure how DDREF is handled for low doses in NIOSH-IREP.	--	--	--	--
NIOSH-IREP documentation	--	Needs to stand on its own without NCI-IREP	Specific text suggested	Need to include better comparison of NIOSH-IREP results with original 1985 tables, and provide especially clear justification for estimates that have changed.	--	Too little discussion of sources of uncertainty and how they are implemented. Should go through a case example that is targeted to the right audience. Table 5 should reference the source of the risk models. Clarify that RBE for alpha is used for only *non-radon* exposures.
Software implementation	--	--	--	Much better than PC version. Running repeated simulations would be tedious over the web.	--	How is uncertainty implemented in software? How is dose type actually implemented in the software?
User-defined uncertainty	--	--	--	Should use to accommodate uncertainty about differences in baseline rates.	--	--

Table 2. Synopsis of subject matter expert comments on the NIOSH-IREP technical documentation

Comment	NCI	Shore	Richardson	Stram	Hoel	Hornung
Carcinoma in situ	--	--	--	--	Will CIS be handled the same for all sites (incl. prostate?) May need to clarify which sites are problematic.	--
Other issues	--	Typos, and ICD code discrepancies in Table 2	Agrees that fixed US background rates are a limitation.	Should include description of the assumptions used in the term PC (rather than Assigned Share). Should not adjust for differences in radiosensitivity (agrees with NIOSH-IREP). Should adjust other background rates by racial group. Clarify that PC does not predict chance of getting cancer.	--	--