HOW SHOULD NIOSH ESTIMATE RISK OF LUNG CANCER IN WORKERS COVERED UNDER EEOICPA IN THE FACE OF UNCERTAINTIES IN THE INTERACTION BETWEEN SMOKING AND LOW-LET RADIATION

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BACKGROUND

The NCI-CDC Working Group revised the NIH-IREP lung cancer model in response to a report on analyses of the joint effects of radiation and cigarette smoking on lung cancer risk among the Japanese atomic bomb survivors (Pierce et al. 2003). The IREP model allows for interaction on the relative rate scale between radiation dose and cigarette smoking with an uncertainty distribution for an "adjustment factor" that accommodates interactions ranging between additive, multiplicative, or super-multiplicative (Apostoaei and Trabalka 2004). In the NIH-IREP lung model the distribution for this adjustment factor is more heavily weighted toward an additive interaction between radiation dose and cigarette smoking (as compared with the NIOSH-IREP model) and alternate parameterizations of the risk coefficients, derived as a result of the analysis by Pierce et al. (2003), are employed, such that never-smokers are the reference group (rather than an aggregated population of smokers and non-smokers, as is the case for NIOSH-IREP). Consequently, the same inputs entered into NIH-IREP and NIOSH-IREP produce significantly different probabilities of causation for some exposure profiles. Apostoaei and Trabalka (2004) recently recommended that NIOSH adopt the NIH-IREP model for lung cancer. However, since there are categories of people for whom NIH-IREP is less friendly, Apostoaei and Trabalka (2004) also suggested that NIOSH could consider programming NIOSH-IREP to run both the new NIH-IREP lung model and the current NIOSH-IREP lung model and choose whatever probability of causation is larger for a given individual.

To summarize the results of the Pierce et al. (2003) study that led to the approach used in NIH-IREP: They analyzed the joint effect of smoking and external radiation exposure on lung cancer risks in the LSS cohort and found that they were significantly sub-multiplicative and consistent with an additive model. There was a weak suggestion in the LSS data that light smoking tended to act multiplicatively with radiation while heavy smoking appeared to act additively. Given that 84% of men but only 16% of women were smokers, they found that an additive adjustment for smoking reduced the female:male ERR/Sv ratio to values comparable to female:male ratios normally observed for other solid tumors. With adjustment for smoking, there was evidence of a decline in the ERR/Sv with increasing attained age (comparable to other cancer sites), but no evidence of modification by age at exposure.

This led the BEIR VII committee to conclude that Pierce et al. (2003) demonstrated that inferences about the modifying effects of gender and age at exposure on the ERR can be distorted if analyses do not account for an additive interaction between radiation and smoking, because smoking habits in the LSS cohort depend strongly on these factors. They noted that, in contrast to the results from the LSS cohort, studies of underground miners exposed to radon (NRC 1999) or of Hodgkin's disease patients treated with high doses of radiation (Gilbert et al. 2003) rejected additive interactions and found that multiplicative interactions were compatible with the data. However, they also concluded that these studies may be less relevant for estimating the risks of low doses of low-LET radiations than those of the LSS cohort because (1) underground miners were exposed to alpha-emitting radon progeny and (2) the evidence for a multiplicative relation of radiation and smoking comes primarily from analyses of miners in Colorado and China where lung doses (in Sv) were much higher than in the LSS cohort (NRC 1999). Although miner data were compatible with a multiplicative effect and not an additive one, the estimated interaction was super-multiplicative (i.e., akin to the interaction model used in NIOSH-IREP for all types of radiation and in NIH-IREP for exposures to alpha emitters). Hodgkin's disease patients were given very high doses (mean 25 Gy to the lung) and, in addition, were subject to the immunodeficiency inherent with lymphoma and associated with subsequent chemotherapy that was given to many of the patients (NRC 2005).

The additive adjustment for smoking in the LSS cohort made by Pierce et al. (2003) reduces the female:male sex ratio in the ERR/Sv to 1.6, which is comparable to the sex ratio in the ERR/Sv for other solid cancers (1.7). For the EAR/Sv for lung cancer estimated by the BEIR VII committee without information on smoking, the female:male sex ratio is 1.5 (NRC 2005; see additional discussion below). In addition, for many solid cancers those who were at a young age at radiation exposure have greater values of ERR/Sv than those who were older when exposed, but for lung cancer this effect is reversed if an adjustment for smoking is not made. Although it was possible to understand these atypical patterns without explicit adjustment for smoking (i.e., because it was well-known that far more males than females were smokers), the results from the analysis by Pierce et al. (2003) indicated that lung cancer radiation risks, adjusted using an additive radiation-smoking interaction, could have sex and age-time patterns similar to those seen for solid cancers that are *not* strongly related to smoking.

The BEIR VII committee did not use smoking-adjusted risk coefficients from the LSS in its analyses (NRC 2005). Rather, they applied adjustments for both age at exposure and attained age to risk coefficients for lung cancer that were developed from their analysis of all solid cancers (excluding thyroid and non-melanoma skin cancers). The resulting female:male sex ratio in the ERR/Sv was 4.4, while that for the EAR/Sv was 1.5, as noted above. They dealt with the issue of smoking and the differences in the sex ratios by applying a weight of 0.7 to the EAR-based estimate and 0.3 to the ERR-based estimate (NRC 2005), citing the evidence from the study by Pierce et al. (2003) in support of their decision. If background incidence rates for males and females are equal, this approach effectively reduces the overall female:male sex ratio in such a combined risk estimate to 2.3, a value that is closer to the value of 1.6 obtained by Pierce et al. (2003) when the ERR/Sv alone was adjusted for smoking.

In essence, the results from the approach used by the BEIR VII committee is comparable to what would result if a *sub-additive* smoking interaction had been employed as an adjustment to the ERR/Sv alone. The net effect of this "correction" for additivity on effects of smoking is thus more comparable to the net effects of the combined approaches for risk transport and smoking interaction used in NIH-IREP than in NIOSH-IREP.

To obtain a formal review of the NIOSH-IREP and NIH-IREP lung models, NIOSH approached a number of experts in the field epidemiology and radiation risk assessment and received evaluations from: David Brenner, Faith Davis, David Richardson, and Jonathan Samet. The reviewers were asked to respond to three basic questions:

- In your expert scientific judgment, should NIOSH adopt the NIH-IREP lung cancer risk model for exposures other than radon for use in NIOSH-IREP?
- If so, should the model be adopted intact, or should NIOSH modify it in some way to better fit the characteristics and radiation exposures of nuclear weapons workers covered under EEOICPA?
- Alternatively, should NIOSH-IREP be programmed to run both lung cancer models and to output only the higher probability of causation?

It should be noted that the reviewers did not have access to the final BEIR VII report, because it was not made available until late June 2005. However, Jonathan Samet reportedly reviewed the report prior to its release.

SUMMARY OF EXPERT OPINIONS

None of the reviewers recommended that NIOSH use the current NIOSH-IREP lung model exclusively. One reviewer (Faith Davis) recommended that NIOSH-IREP model be dropped and NIH-IREP lung model be adopted intact because she favored the alternative parameterization of risk coefficients and heavier weighting of an additive interaction between smoking and external radiation (derived from the analysis by Pierce et al. 2003) that was used in NIH-IREP. Contrary to the views expressed by Davis, there seems to be an agreement among Brenner, Samet, and Richardson that the interaction between smoking and radiation suggested by the analysis by Pierce et al. (2003, despite its attributes, may not fully characterize the uncertainty in this interaction. A variety of reasons are given, including potential lack of comparability of smoking patterns and effects of smoking on lung cancer in Japanese males compared to the U.S. population, potential time dependencies in smoking-radiation interactions, birth cohort effects, limited numbers of individuals exposed at older ages, and lateness of follow-up initiation,

commencing about 19 y after exposure, in the Japanese A-bomb survivors. Two of these reviewers (David Richardson and Jonathan Samet) suggested running both NIOSH- and NIH-IREP lung models. The last reviewer (David Brenner) suggested using the NIH-IREP model, but with an interaction between radiation and smoking equally weighted between the additive and multiplicative interactions, and proposed that three radiation-smoking interaction models be included in IREP outputs. The specific opinions of these experts in support of their conclusions are discussed in the next sections.

Faith Davis

The case for use of NIH-IREP as the only model for estimating lung cancer risk in nuclear weapons workers covered under EEOICPA was made by reviewer Faith Davis. Her rationale was the following:

- The NIH-IREP model provides estimates of lung cancer risk based on four additional years of follow-up from the RERF cohort and, as such, estimates more closely approximate current risks and are an improvement over those currently used in the NIOSH-IREP model.
- The inclusion of age is an important feature of the revised NIH-IREP model and would be a very important modification to the NIOSH-IREP model. The process of carcinogenesis has fundamental age dependencies that have been repeatedly shown in both animal and human data (Armitage and Doll 2004). Pierce et al (2003) demonstrated the difficulty of separating out the effects of attained age and age at exposure, yet clearly demonstrated the potential importance of both.
- The confidence intervals around the probability of uncertainty estimates from the NIH-IREP reflect multiple important factors, including: updated risk estimates from a subset of the RERF cohort, a change in the number and form of parameters in the risk model, and a change in the uncertainty estimation approach. Each change appears to have been well reasoned by Pierce at al. (2003). The fact that estimates of the ERR/Sv from this model in nonsmokers closely approximate those expected for other radiogenic tumors results lends credence to this new lung cancer model. The declining ERR/Sv across smoking levels and the large confidence limits among smokers reflects the interactive effects of radiation and smoking and the dominant

effect of smoking on lung cancer risk. As such, the narrower confidence intervals among non-smokers and wider confidence intervals among smokers in the NIH-IREP model versus the NIOSH-IREP model are scientifically sound and reflect a substantive improvement.

- The confidence bounds for males and females among never smokers are, for the most part, narrower in the NIH-IREP model compared to the NIOSH-IREP model across both age constructs. This suggests that the adjustment by sex, in combination with the introduction of the age parameters in the NIH-IREP model, is providing more robust estimates which may better reflect the underlying biological processes for these tumors.
- The use of never smokers as the reference category in the NIH model, seems a more accurate reflection of smoking risks than the averaging procedure used in the NIOSH schema.
- As the NIH-IREP model reflected the best available estimates relevant to this exposure population, she recommended implementing this model and discontinuing the use of the NIOSH-IREP model: To use both models for the indefinite future would set a difficult precedent for that point in the future when better estimates than these become available.
- She concluded that at this time the NIH-IREP model provides better estimates than the NIOSH-IREP model from several perspectives – they are based on more recent risk estimates, a newer interaction distribution with respect to radiation and smoking is incorporated and better reflected across smoking categories; and most importantly, estimates are specific to age. She also concluded that estimates from this model are well reasoned both biologically and statistically and should replace the prior model.

Jonathan Samet

While agreeing with the conclusions of Pierce et al. (2003) with respect to rising risks for lung cancer associated with an increased level of smoking in Japan since World War II, Samet pointed out that the temporal profile of smoking in the LSS cohort (an unknown) and its age-birth cohort dependence complicate interpretation of models with

time-dependent factors (such as those used by Pierce et al. 2003). Other important points included the following:

- Extension of the follow-up period by four years would represent only a modest increment to the LSS database in terms of follow-up time and numbers of lung cancers that should not have a significant effect on risk estimates.
- Information on smoking in the LSS cohort was limited and only limited attention was given to effects of measurement error in assessment of smoking patterns and to the possibility of age and birth-cohort dependent measurement error.
- Inadequate model specification could potentially bias assessment of the smoking-effect modification toward additivity.
- There was evidence of different smoking patterns and lower lung cancer risks at any level of smoking among Japanese males compared to the U.S. population.[1]

David Richardson

Richardson concluded that the epidemiological literature provides a very limited scientific basis for characterizing the joint effects of cigarette smoke and external exposure to ionizing radiation on lung cancer risk. He also raised the most detailed objections to exclusive use of the NIH-IREP model. His major points follow:

- NIOSH is concerned with appropriately characterizing the interaction on a relative rate scale between two time-varying continuous exposure variables (i.e., occupational radiation doses and cigarette smoking rates). In contrast to the statistical evaluation of product terms for two fixed binary exposure variables, an evaluation of the interaction between smoking history and occupational radiation exposure history may be relatively complex. Statistical evidence of a smoking-radiation dose interaction may depend upon model assumptions about the etiologically-relevant periods of exposure for each agent, assumptions about the importance of the temporal ordering of exposures, and assumptions about the shapes of the exposure-response patterns for single versus joint exposures. Misspecification of such assumptions may lead to incorrect conclusions about the nature of the interaction between exposures.

[1] The last part of this conclusion is not fully supported by the reference materials supplied by Samet and seems to be refuted by data in Table 3 of Pierce et al. (2003).

- The situation considered by Pierce et al. (2003) is somewhat simpler than that of direct concern to NIOSH since in the case of the study of atomic bomb survivors radiation dose is considered as a fixed variable. Subjects were treated as continuous smokers (at a fixed rate based upon the response to at least one survey about cigarette smoking) or never smokers. They do not consider age at start of smoking or its relation to age at time of bombing; they do not consider age at termination of smoking or its relation to age at onset of cancer; and, they do not consider the duration of smoking or cumulative pack-years. Their cited reasons for this simplification included the analytical difficulties of utilizing information on each person's smoking history and the limitations of the available smoking history data.
- A fundamental question, however, is whether the investigators' simplified approach to treating the temporal aspects of joint exposures have led to spurious conclusions about the true nature of the joint effects of these agents.[2] Mechanistic models and experimental evidence for some carcinogen pairs suggest that the temporal patterns of exposures and subsequent disease risk are fundamental considerations when trying to appropriately characterize the joint effects of the exposures. In the case of cigarette smoking, prior epidemiological research has established that the temporal aspects of smoking history are important considerations when evaluating smoking effects on lung cancer risk (Brown and Chu 1987; Doll, Peto et al. 2004). It is reasonable to postulate that the temporal aspects of smoking history may be as important or more important to analyses of the joint effects of smoking and radiation dose on lung cancer risk.
- The study question investigated by Pierce et al. requires relatively complete and valid information on individual survivor's smoking histories. The survey data used in this analysis, in contrast, provides snapshots in time of smoking histories for those who responded to mail questionnaires or clinic visits. Such information is highly incomplete (missing entirely for about 45% of survivors); for those with some information on smoking history, information analyzed on smoking rate pertains to the average smoking rate reported at one or more survey dates. No information in these

[2] This concern was echoed by Jonathan Samet, as noted earlier.

analyses characterizes the potential variation in smoking rates over decades of life prior to the atomic bombing or, in fact, prior to first survey in the 1960s.

- As in any epidemiological analysis based on self-reported information it is reasonable to question the reliability of this information. The authors state that about 2400 (i.e, roughly 5%) of those who responded to at least one mail or clinical survey provided incomplete or inconsistent information and had to be excluded from analyses. It is likely that other survivors provided information that was inaccurate but not logically inconsistent and therefore was included in these analyses.
- Crucially, the analyses reported by Pierce et al. are constrained to provide information on the nature of the smoking-radiation dose interaction only for the period that begins approximately two decades after radiation exposure. If the joint effects of radiation and smoking exposures on lung cancer risk were relatively largest in these early years after radiation exposure, and diminished with protracted time since exposure, then the analysis by Pierce would mischaracterize their joint effects due to the limitation of only examining later periods of follow-up.
- The requirement that persons be alive and cancer-free at the time of the smoking surveys also has implications for evaluations of variation in ERR/Sv with age-at-exposure. As illustrated in Figure 3 of the paper by Pierce et al.(2003) a relatively small number of A-bomb survivors who were aged 50 or older at time of bombing were eligible for inclusion in this analysis; and a substantial proportion of these survivors would be classified in the lowest (i.e. referent) radiation dose category.
- Neither the findings of Pierce et al. (2003) nor the other findings in the epidemiological literature provide compelling support for the conclusion that the radiation-smoking interaction is likely additive on the relative rate scale, as described by the current NIH-IREP model.[3]
- Unfortunately, neither is there is there compelling evidence to support the NIOSH-IREP model. Rather, the nature of this interaction remains poorly characterized and the epidemiological literature provides an extremely limited scientific basis for this aspect of compensation decisions. A decision about how to model this interaction

[3] The smoking-radiation interaction in NIH-IREP is not purely additive, but accommodates interactions ranging between additive, multiplicative, or super-multiplicative. Thus, the last part of this statement made by Richardson is incorrect (see later commentary in Discussion section).

therefore becomes primarily a policy decision about how to make a compensation determination in the face of scientific uncertainty.

David Brenner

David Brenner pointed out that the interaction between smoking and high radiotherapy doses was reasonably well described by a multiplicative model. He also noted that radon studies either found a multiplicative interaction or an interaction that was intermediate, but closer to multiplicative. He also reported that a study of the Mayak workers suggested that the balance between different interaction models depends on the smoking level; higher smoking levels make the interaction more multiplicative, while lower levels make it more additive. In the Mayak workers, this pattern was thus essentially opposite to that for the members of the LSS cohort studied by Pierce et al. (2003) (as discussed earlier).

Brenner's final conclusion appears to capture the views of all three reviewers with dissenting opinions, namely that the overall weight of evidence suggests the interaction between smoking and external radiation is intermediate between additive and multiplicative, and we really cannot say more than that. Although Brenner does not recommend running both models to deal with these uncertainties (as do Samet and Richardson), he did suggest running NIH-IREP with three independent parameterizations of the interaction between smoking and radiation.

Brenner deemed it unreasonable to use the NIH-IREP model which weights the balance much more towards an additive interaction.[4] He suggests, as an alternative, a model in which all values of y between zero and 1 are equally likely. He also concluded that it would be reasonable to include, within 95% confidence limits, a model which is 50% additive ($y = 0$) and the rest of the probability distributed equally between $y = 0$ and $y = 1$,[5] as well as a model which is 50% multiplicative ($y = 1$) and the rest of the probability distributed equally between $y = 0$ and $y = 1$. He also suggested removing the

[4] Both he and Richardson apparently misunderstood the net effect of the smoking-external radiation interaction in NIH-IREP, which alters the balance from mainly multiplicative to weakly additive, as discussed in our previous evaluation of the review by David Brenner (see Apostoaei and Trabalka 2005).]

[5] Brenner incorrectly calls this approach "the NIH-IREP model". As we pointed out in our previous evaluation of his review (Apostoaei and Trabalka 2005) Brenner confused the risk transport model in NIH-IREP with that used for the radiation-smoking interaction.

"tails" below 0 and above 1 in this distribution, but did not provide a rationale for this choice.[6] He also suggested that risk estimates from *all three models* be included in IREP outputs, with appropriate annotations for each. See Apostoaei and Trabalka (2005) for additional commentary on Brenner's review.[7]

DISCUSSION

It seems likely that the effects of smoking are more complicated than those of radiation, perhaps contributing to carcinogenesis by causing both mutations and by facilitating the progression toward malignancy of cells with mutations caused by other factors, such as radiation. This might explain the weak suggestion in the LSS data that light smoking tends to act multiplicatively with radiation while medium and heavy smoking appear to act additively. It might also explain why studies of radon exposure have largely indicated effects intermediate between additive and multiplicative (Pierce et al. 2003), but often weighted more towards multiplicative effects.

Pierce et al. (2003) found that the best fit to the most recent LSS data is obtained if the radiation-smoking interaction is considered additive for all smoking categories. The analysis by Pierce et al. (2003) indicates that accounting for an *additive* radiation-smoking interaction allows the lung model to show gender and age dependencies similar to the dependencies observed for other solid cancers. In other words, ignoring radiation-smoking interaction, or assuming a multiplicative interaction would result in age and gender dependencies which appear to have much less biological plausibility. Thus, the additive radiation-smoking interaction used by Pierce et al. (2003) provides not only a better statistical fit to LSS data, but also seems to eliminate questionable gender and age dependencies observed in the LSS lung data.

[6] There are no "tails" below 0 in the smoking-radiation interaction adjustment in either NIH- or NIOSH-IREP. His reference is to the specification for the risk transport model (see footnote 5).]

[7] It is conceivable that Brenner's recommendations were influenced by misinterpretation of the interaction model in NIH-IREP. He might not have reached the same conclusions had he fully understood the nature of the current algorithms for the smoking-radiation interaction, which entails use of a hybrid model with intermediate additive and multiplicative components.

Richardson, Samet, and Brenner pointed out that the analysis by Pierce et al. (2003) has several weak points which should be taken into account in a model based on this analysis. Subjects of the study by Pierce et al. (2003) were treated as either as continuous smokers or never smokers, and age at the start of smoking was ignored. Also, the smoking survey of the cohort did not start until 1964, meaning that an important number of early cancers were not included in the study and the age structure of the cohort exposed to radiation does not match the age structure of the cohort of included in the smoking survey. Brenner also pointed out that, when other lung cancer studies are taken into consideration (i.e., radon studies, Mayak workers, high-dose treatment studies) in addition to the analysis by Pierce et al. (2003), one could conclude that the radiation-smoking interaction can be anywhere between additive and multiplicative. The conclusion of these three experts is that the assumption of an additive radiation-smoking interaction is questionable, to say the least.

Thus, the overall weight of evidence suggests the interaction between smoking and external radiation is intermediate between additive and multiplicative, and the uncertainty in the radiation-smoking interaction could be better represented in the lung cancer models in either version of IREP.

The experts selected by NIOSH to review the lung model and the interaction between radiation and smoking provided the following opinions: Davis concluded that NIH-IREP currently provides the best characterization of lung cancer risks, two other reviewers (Samet and Richardson) suggest running both models and using the result that is most claimant friendly, and one reviewer (Brenner) suggests running NIH-IREP with alternate distributions to represent the interaction between smoking and external radiation, with as many as three different outputs.

Given the evidence presented above, Brenner's primary recommendation (a model for the interaction in which all values of y between zero and 1 are equally likely) merits strong consideration. The net result is a balance between the weighting of additive and multiplicative interactions (50%−50%) that is almost midway between that of NIH-IREP (65% additive and 35% multiplicative) and of NIOSH-IREP (26% additive and 74% multiplicative). It also captures all of the central and extreme values from the

alternate specifications he gave without the complexity introduced by running completely separate models.

We programmed this alternative model in a research version of NIH-IREP by using a uniform distribution between the additive and multiplicative interactions (y = uniform between 0 and 1). We investigated how the 99th percentile of PC obtained using Brenner model would change compared to the 99th percentile of PC estimated using the original NIH-IREP lung model (Table 1). Since the upper bound of PC is given by the multiplicative interaction while the lower bound of PC is given by the additive interaction, the 99th percentile does not change significantly when the weight of the radiation-smoking interaction is shifted from 65% additive−35% multiplicative (NIH-IREP code) to 50% additive−50% multiplicative (as proposed by Brenner). That is, this shift in weights causes a decreases the central value of PC, but the 99th percentile is virtually unchanged.[8]

While performing these tests, we also discovered that there is a difference in the transport between populations *as implemented* in NIH-IREP computer code, and the transport between populations *as described* by Land et al. (2003). In the NIH-IREP computer code the transport between populations is modeled using the trapezoidal distribution shown in Figure IV.G.1 of Land et al. (2003) that assigns a uniform weight between an additive and a multiplicative risk. However, Land et al. (2003) indicate that a 50% weight was given to the additive transport model, and 50% to the trapezoidal distribution described above, based on the analysis by Pierce et al. (2003). That is, Land et al. (2003) recommends a 50% weight be given to the additive model both in the transport between populations and in the radiation-smoking interaction. As seen in Table 1, the 50% weight assigned to the additive model in the model for transport between populations has only a minimal impact. This is the result of fact that the upper bound of assigned share is driven by the multiplicative model, and is relatively unaffected by the weight assigned to the additive model (which is responsible for the lower bound of the assigned share.)

[8] The small fluctuations shown in Table 1 are of the same magnitude with those obtained by changing random seed number.

An obvious concern, however, is that the *risk coefficients* for never smokers in the NIH-IREP model were derived from an analysis of the LSS data largely on the basis of an assumed additivity in the joint interaction of smoking and external radiation, as indicated by Pierce et al. (2003). According to Table 1 in Pierce et al. (2003), lower risk coefficients should be expected if an epidemiologic analysis is performed assuming a multiplicative interaction model. However, risk coefficients based on a multiplicative model (or on a model using an intermediate radiation-smoking interaction as recommended by Brenner) are not available. We don't know at this time by how much the risk coefficients would be reduced, if new analyses were to be performed using alternate specifications of the radiation-smoking interaction. However, using a multiplicative interaction model instead of the additive model would result in somewhat lower risk coefficients, but would also introduce an average bias toward higher risks through changes in the radiation-smoking model and in transport between populations model. Thus, these two effects will compensate each other to some degree.

Based on the recommendations of the reviewers and given the studies and data available to date, NIOSH is facing the choice between the following modeling options:

1. Program the NIOSH-IREP computer code to run both NIOSH-IREP and NIH-IREP lung models and report the PC produced by either model, or a PC obtained by combining the output of the two models.

2. Use NIH-IREP lung model as currently coded.

3. Use NIH-IREP lung model, with intermediate weights between the additive and the multiplicative models for transport between populations and radiation-smoking interactions.

Whatever approach is adopted, we should ensure that the documentation of exactly what is done be as clear as possible to the user. The IREP lung model(s), as they stand, lack clear documentation (as was also recognized by David Brenner). A user of IREP, either the NCI or the NIOSH version, could have difficulty understanding how the models are being used to estimate assigned share, let alone discerning the differences between these two versions of IREP.

Table 1. Comparison of 99th percentiles of assigned shares (probability of causation) for a person exposed to a single dose of 50 cSv at age 20 and diagnosed with lung cancer at age 40[a]

MALE	Acute exposure [b]				Chronic exposure [b]			
		NIH-IREP		NIOSH-IREP [f]		NIH-IREP		NIOSH-IREP [f]
Smoking status	Land et al. (2003)[c]	NIH-IREP software[d]	Brenner[e]		Land et al. (2003)[c]	NIH-IREP software[d]	Brenner[e]	
Never smoker	51.62	52.94	52.94	**53.75**	50.62	53.66	53.66	**50.97**
Current smoker								
< 10 cigs/day	47.29	48.31	48.74	**29.53**	42.84	45.81	45.06	**29.98**
10-19 cigs/day	47.03	47.91	48.16	**25.62**	42.41	44.78	44.57	**25.35**
20–39 cigs/day	46.90	47.78	47.99	**25.00**	42.40	44.45	44.10	**24.57**
40+ cigs/day	46.72	47.72	47.92	**24.92**	42.20	44.32	44.06	**24.15**

Table continues on the next page

Table 1 (continued). Comparison of 99th percentiles of assigned shares (probability of causation) for a person exposed to a single dose of 50 cSv at age 20 and diagnosed with lung cancer at age 40[a]

FEMALE	Acute exposure [b]				Chronic exposure [b]			
		NIH-IREP		NIOSH-IREP [f]		NIH-IREP		NIOSH-IREP [f]
Smoking status	Land et al. (2003)[c]	NIH-IREP software[d]	Brenner[e]		Land et al. (2003)[c]	NIH-IREP software[d]	Brenner[e]	
Never smoker	68.24	70.09	70.09	**76.14**	67.23	69.70	69.70	**74.39**
Current smoker								
< 10 cigs/day	61.53	65.49	64.46	**55.18**	58.12	63.18	60.82	**56.12**
10-19 cigs/day	60.51	64.87	63.97	**51.39**	57.82	62.38	59.44	**51.98**
20–39 cigs/day	60.31	64.86	63.87	**50.88**	57.72	62.03	59.15	**50.90**
40+ cigs/day	60.30	64.86	63.83	**50.79**	57.69	61.78	59.08	**49.73**

[a] We performed tests for other ages at exposure and attained ages, and we obtained similar results.

[b] Exposure to photons with energy greater than 250 keV.

[c] Assumes 50% weight on additive model in both the transfer between populations and radiation-smoking interaction.

[d] Assumes 50% weight on additive model radiation-smoking interaction only. The transport between populations is modeled using a uniform weight between the additive and the multiplicative models.

[e] Assumes uniform weight between the additive and the multiplicative model for both transport between populations and radiation-smoking interaction.

[f] Assumes uniform weight between the additive and the multiplicative model for transport between populations, and a triangular distribution weighted towards a multiplicative model for radiation-smoking interaction [y = triangular (0,1,1.1)].

EXPERT OPINIONS

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