DIFFERENCES IN THE ESTIMATION OF LUNG CANCER RISK BETWEEN NIOSH-IREP AND NIH-IREP

A. Iulian Apostoaei and John R. Trabalka

SENES Oak Ridge, Inc.
Center for Risk Analysis
102 Donner Dr.
Oak Ridge, TN 37830

September 20, 2004

Introduction

In May 2003, the National Cancer Institute updated the lung model in their version of IREP (i.e., NIH-IREP), based on the recently published re-analysis of lung cancer incidence in A-bomb survivors (Pierce et al. 2003). To date, NIOSH-IREP has not been updated to reflect the recent study by Pierce et al. (2003). Significant differences are observed between the probability of lung cancer causation estimated with NIH and NIOSH versions of IREP. This paper summarizes these differences and identifies their sources.

Approaches for Modeling the Risk of Lung Cancer in NIH and NIOSH Versions of IREP

The approach for estimating the risk of lung cancer in NIH-IREP is described by Land et al. (2003) and reproduced in Appendix A of this document. The handling of lung cancer in NIOSH-IREP is described in the May 17, 2002, Draft Report of the NCI-CDC Working Group to Revise the 1985 NIH Radioepidemiological Tables (Land et al., 2002), as mentioned in the NIOSH-IREP Technical Documentation Final Report (NIOSH 2002, p. 35). A description of the NIOSH-IREP approach for lung cancer is given in Appendix B of this document.

The major changes incorporated into NIH-IREP that are not currently reflected in NIOSH-IREP are discussed below and they are summarized in Table 1.

- The risk model in NIH-IREP is based on the analysis of lung cancer incidence and smoking history among the A-bomb survivors by Pierce et al. (2003). This analysis includes more follow-up years of the Japanese A-bomb survivors (1950-1994) as compared to the NIOSH-IREP lung model, which is based on a follow-up period from 1950 to 1990.

- The most important feature of the NIH lung model[1], based on the results reported by Pierce et al. (2003), is dependency on age at exposure and attained age of the *ERR/Sv* (see Appendix A). No age-dependency is included in NIOSH-IREP lung model[2] (see Appendix B).

- The likelihood profile distribution for the main model parameter α was derived so that the model could be applied to estimate the statistical uncertainty distribution of the *ERR/Sv* for lung cancer. The approach to uncertainty analysis was employed in the interests of improving the computational speed of IREP in both the NIOSH and NIH versions, and it is applied in both NIOSH and NIH version of IREP for cancers other than lung. In this approach, the uncertainty evaluation was based on the assumption that the estimated value of model parameter α was independent of β, γ, and δ. The details of the approach (designated Approach 2) are described for NIOSH-IREP on page 27 of Land et al. (2002) and for NIH-IREP on page 26 of the report by Land et al. (2003).

  In particular, for NIH-IREP, α is the *ERR/Sv* for age at exposure 30 and attained age 50, for a never smoker. In NIOSH-IREP, α is the ERR/Sv for any age at exposure or attained age and is an average over all smoking categories.

- In NIH-IREP, one profile for α is provided and sex differences are specified using parameter β, while in NIOSH-IREP, α is pre-calculated for each sex. The likelihood profile for parameter α used in computation of statistical uncertainty for the ERR/Sv for lung cancer in never smokers in NIH-IREP is reproduced in Appendix A (Table A.1 and Fig. A.1). The

[1] $ERR=\alpha Dexp[\beta s+\gamma f(e)+\delta g(a)]$, where $\alpha,\beta,\gamma,\delta$ are parameters, D is radiation dose, and s, $f(e)$, and $g(a)$ describe dependency on sex (s), age at exposure (e) and attained age (a). (see Appendix A).
[2] $ERR=\alpha(s)D$, where α is a sex-specific parameter, and D is radiation dose. There is no dependency on age at exposure (e) and attained age (a) ($\gamma = \delta = 0$). (see Appendix B).

tabulated profile for α is the midway between the values for the two sexes. By contrast, in NIOSH-IREP, separate profiles for α are provided for males and females (see Appendix B, Table B1 and Fig. B.1).

- The interaction of smoking and exposure to low-level radiation in the 1985 NIH report was based on an additive model that makes use of smoking-related adjustment factors. These factors are based on relative risks for lung cancer by smoking category given by Rogot and Murray (1980) and the distribution of the U.S. population by smoking status in 1964–1965. However, the factors used in both the NIH and NIOSH versions of IREP were updated using 1993 information on smoking status distribution provided in a 1993 CDC report (CDC 1995). The revised factors (W_S*) for additive interaction based on the updated distribution for US smoking status are given in Appendix A for NIH-IREP (Table A.3) and in Appendix B for NIOSH-IREP (Table B.2). The same factors are used in both NIH and NIOSH versions of IREP, but they are applied differently to scale the risk for different smoking categories. Thus, in NIOSH-IREP the factors are applied accounting for the fact that parameter α is an average for all smoking categories, while in NIH-IREP the factors are applied accounting for the fact that parameter α is for never smokers.

- A similar mathematical approach is being used in both NIOSH and NIH versions of IREP to implement the interaction between smoking and radiation exposure. The approach (reportedly guided by BEIR VI findings for radon-related lung cancer risk; see page 41 in Land et al. 2003) consists of multiplying the calculated ERR/Sv by the term: $[x + (1 - x)W_S^*]$, where W_S^* is the updated smoking adjustment factor described in the previous bullet and x is assumed to follow a triangular distribution (0, 1, 1.1). This uncertainty distribution for x allows the *ERR/Sv* for lung cancer to range from that obtained with an additive interaction ($x = 0$) to that obtained with a multiplicative interaction ($x = 1$), with a probability of about 0.10 for a super-multiplicative interaction ($x > 1$). This adjustment factor is heavily weighted towards the multiplicative interaction model.

In NIH-IREP, an additional weight is assigned to the additive model based on the more recent analysis of Pierce et al. (2003), which indicates that the radiation-smoking interaction among the A-bomb survivors is more nearly additive than that estimated for uranium miners. This additional weight to the additive interaction model is applied for exposure to all radiations types other than alpha radiation. That is, in current version of NIH-IREP, for exposure to all radiations types other than alpha radiation, the uncertainty model for the radiation-smoking interaction places a 50% probability on the purely additive model ($x \equiv 0$) and 50% on the assumed triangular distribution described in the preceding paragraph (which is weighted towards the multiplicative model). For exposure to alpha emitters, only the triangular distribution (which is weighted toward the multiplicative model) is used. This is consistent with the finding that radiation-smoking interaction is more nearly additive for the A-bomb survivors, but more nearly multiplicative for uranium miners (who where exposed mainly to alpha particles). In NIOSH-IREP, which was released before the results of Pierce et al. (2003) were implemented in NIH-IREP, additional weight to the additive model is not considered for exposure to low LET radiation types.

Numerical Comparisons Between Probability of Causation for Lung Cancer Estimated by NIH and NIOSH versions of IREP

Differences between the 99th percentiles of the probability of causation (PC) for different smoking categories and different radiation types produced using NIH-IREP and NIOSH-IREP are compared in Tables 2, 3 and 4. Table 2 shows that, for exposure at age 20 and diagnosis at age 40, NIH-IREP is almost always more claimant-friendly. Table 3 however, shows that, for exposure at age 40 and diagnosis at age 60, NIOSH-IREP is more claimant-friendly for never smokers and light smokers (< 10 cigs/day) for both acute and chronic exposures, while for moderate to heavy smokers, the two codes produce fairly similar values of PCs (at the upper 99th percentile). Table 4 provides PC estimates for a male exposed at age 20 and diagnosed at age 40. In this case NIOSH-IREP is more claimant friendly only for never smokers. For any other smoking status, NIH-IREP produces larger PCs than NIOSH-IREP for the same exposure conditions.

The effect of age at exposure and attained age for both males and females is investigated in more depth in Figures 1-8, for selected smoking categories. Comparison of the upper 99th percentile of the estimated PCs, NIOSH-IREP seems to be more claimant-friendly for never smokers. However, NIH-IREP produces larger upper 99th percentiles of PC for smokers for the majority of exposure conditions investigated, other than females who were exposed at older ages. The reason why NIH-IREP is more claimant friendly to smokers than to non-smokers is due to the larger uncertainty associated with the estimate of ERR at 1 Sv for all smoking categories.

Figure 9 compares the PCs for males and females, for different smoking categories. A single acute exposure of 75 cSv was assumed to have taken place at age 20, with cancer diagnosed at age 60. Both NIOSH-IREP and NIH-IREP indicate that females are more sensitive than males, but the differences between the upper 99th percentiles of PC for the two genders is always larger in NIOSH-IREP. For males and females, NIOSH-IREP produces higher PCs than NIH-IREP only for never smokers.

The magnitude of uncertainties in the estimated PCs is larger in NIOSH-IREP than in NIH-IREP for never smokers only. For all other smoking categories, NIH-IREP produces larger uncertainty ranges than NIOSH-IREP. The increased magnitude of the uncertainty for all smoking categories in NIH-IREP comes from the uncertain smoking adjustment factors that are applied to the parameter α specified for never-smoker (Table 1). The additional 50% weight to the additive model in NIH-IREP has the tendency to reduce the risk estimates and thus the PCs. This tendency is observed in the lower and central estimates (i.e. 50th percentile) of the PCs estimated with NIH-IREP, for all smoking categories (Figure 1-8). However, the upper bound of the risk estimates in NIH-IREP is still given by the multiplicative model, for which a substantial weight is still assigned [50% weight is assigned to the triangular distribution (0, 1, 1.1)]

Conclusions

The differences between the lung cancer models in the NIH and NIOSH versions of IREP appear to be quite significant. NIOSH-IREP is more claimant-friendly for never smokers and for females who were exposed at older ages. NIH-IREP is more claimant-friendly for male smokers, and for females smokers exposed at younger ages.

Our recommendation to NIOSH is to update the lung model in NIOSH-IREP because the new lung model represents the most advanced state of knowledge about radiation-induced lung cancer. As opposed to the NIOSH-IREP lung model, which is based on the analysis of the 1950-1990 data from the Japanese A-bomb survivors, the newer NIH lung model includes more follow-up years of the Japanese cohort (1950-1994; Pierce et al., 2003). Also, in perhaps more than half of the possible exposure situations the NIH lung model is more claimant-friendly.

Since there are categories of people for whom the NIH-IREP lung model is less friendly, NIOSH could consider programming NIOSH-IREP to choose between the new NIH-IREP lung model and the current NIOSH-IREP lung model, and report whatever PC is larger for a given exposure situation (i.e., to "grandfather" the current NIOSH-IREP lung model).

Other experts Who Can Evaluate the Lung Models in NIH and NIOSH Versions of IREP

Individuals who might be consulted to provide a formal evaluation of the significance of the differences include: Ethel Gilbert, Charles Land, Jay Lubin, and Kiyohiko Mabuchi of NCI; Donald Pierce of RERF; Jerome S. Puskin and David J. Pawel of EPA-ORIA, Radiation Protection Division, John Boice, International Epidemiology Institute; David Brenner of Columbia University; Roy Shore, NYU; Faith Davis, U. of Illinois; Jonathan Samet, Johns Hopkins U; David Richardson, U. of South Carolina.

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Land, C. E., Gilbert, E. S., Smith, J. M., Hoffman, F. O., Apostoaei, I., Thomas, B., and Kocher, D. C. 2003. *Report of the NCI-CDC Working Group to Revise the 1985 NIH Radioepidemiological Tables.* NIH Publication No. 03-5387. U.S. Department of Health and Human Services, National Institutes of Health, National Cancer Institute, Bethesda, MD.

Pierce, D. A., Sharp, G. B., and Mabuchi, K. 2003. Joint effects of radiation and smoking on lung cancer risk among atomic bomb survivors. *Radiat. Res.* **159**, 511–520.

Rogot, E., and Murray, J. L. 1980. Smoking and causes of death among U.S. veterans: 16 years of observation. *Public Health Rep.* **95**:213–222.

Table 1. Summary of differences in estimation of lung cancer risk between the NIOSH and NIH versions of IREP

Areas	NIOSH-IREP	NIH-IREP
Risk model	• No age dependency (parameters γ and $\delta \equiv 0$ under all conditions)	• Age dependency ($\gamma \neq \delta \neq 0$ under all conditions) • Values of parameters based on analysis by Pierce et al. (2003), including adjustment for smoking
Parameter uncertainty	• Sex-specific likelihood profiles for parameter α (given as an average over all smoking categories)	• Sex-adjusted likelihood profiles for parameter α (given for never smokers)
Radiation-smoking interaction	• $[x + (1 - x)W_S^*]$, where x is always described as a triangular distribution (0, 1, 1.1). Multiplicative model has a heavier weight than the additive model.	• $[x + (1 - x)W_S^*]$, 50% weight to case where x follows a triangular distribution (0, 1, 1.1), and 50% weight to case where $x \equiv 0$ (additive model).

Table 2. Comparison of 99th percentiles of assigned shares (probability of causation) for lung cancer calculated by the NIH and NIOSH versions of IREP for single doses of 50 cSv to a male age 20 at exposure and age 40 at diagnosis

	Acute exposure		Chronic exposure					
	Photons >250 kev		Photons >250 kev		Alpha		Electrons <15 kev	
Smoking status	NIH	NIOSH	NIH	NIOSH	NIH	NIOSH	NIH	NIOSH
Never smoker	**52.94**	**53.75**	**53.66**	**50.97**	**74.99**	**70.73**	**78.22**	**76.81**
Current smoker								
< 10 cigs/day	**48.31**	**29.53**	**45.81**	**29.98**	**71.85**	**52.69**	**71.62**	**55.83**
10-19 cigs/day	**47.91**	**25.62**	**44.78**	**25.35**	**70.76**	**47.34**	**70.88**	**50.85**
20–39 cigs/day	**47.78**	**25.00**	**44.45**	**24.57**	**70.58**	**45.61**	**70.74**	**49.96**
40+ cigs/day	**47.72**	**24.92**	**44.32**	**24.15**	**70.50**	**45.54**	**70.70**	**49.77**

Table 3. Comparison of 99th percentiles of assigned shares (probability of causation) for lung cancer calculated by the NIH and NIOSH versions of IREP for single doses of 50 cSv to a male age 40 at exposure and age 60 at diagnosis

	Acute exposure		Chronic exposure					
	Photons >250 kev		Photons >250 kev		Alpha		Electrons <15 kev	
Smoking status	NIH	NIOSH	NIH	NIOSH	NIH	NIOSH	NIH	NIOSH
Never smoker	**28.79**	**53.75**	**30.94**	**50.97**	**54.03**	**70.73**	**57.95**	**76.81**
Current smoker								
< 10 cigs/day	**26.51**	**29.53**	**24.56**	**29.98**	**49.63**	**52.69**	**49.02**	**55.83**
10-19 cigs/day	**25.94**	**25.62**	**23.57**	**25.35**	**48.97**	**47.34**	**48.85**	**50.85**
20–39 cigs/day	**25.88**	**25.00**	**23.47**	**24.57**	**48.86**	**45.61**	**48.35**	**49.96**
40+ cigs/day	**25.85**	**24.92**	**23.35**	**24.15**	**48.82**	**45.54**	**47.78**	**49.77**

Table 4. Comparison of 99th percentiles of assigned shares (probability of causation) for lung cancer calculated by the NIH and NIOSH versions of IREP for single doses of 50 cSv to a male age 20 at exposure and age 60 at diagnosis

	Acute exposure		Chronic exposure					
	Photons >250 kev		Photons >250 kev		Alpha		Electrons <15 kev	
Smoking status	NIH	NIOSH	NIH	NIOSH	NIH	NIOSH	NIH	NIOSH
Never smoker	**44.34**	**53.75**	**44.60**	**50.97**	**67.76**	**70.73**	**71.31**	**76.81**
Current smoker								
< 10 cigs/day	**39.66**	**29.53**	**37.21**	**29.98**	**64.21**	**52.69**	**64.07**	**55.83**
10-19 cigs/day	**39.22**	**25.62**	**35.96**	**25.35**	**63.08**	**47.34**	**63.35**	**50.85**
20–39 cigs/day	**39.17**	**25.00**	**35.80**	**24.57**	**62.87**	**45.61**	**63.12**	**49.96**
40+ cigs/day	**39.13**	**24.92**	**35.78**	**24.15**	**62.79**	**45.54**	**63.02**	**49.77**

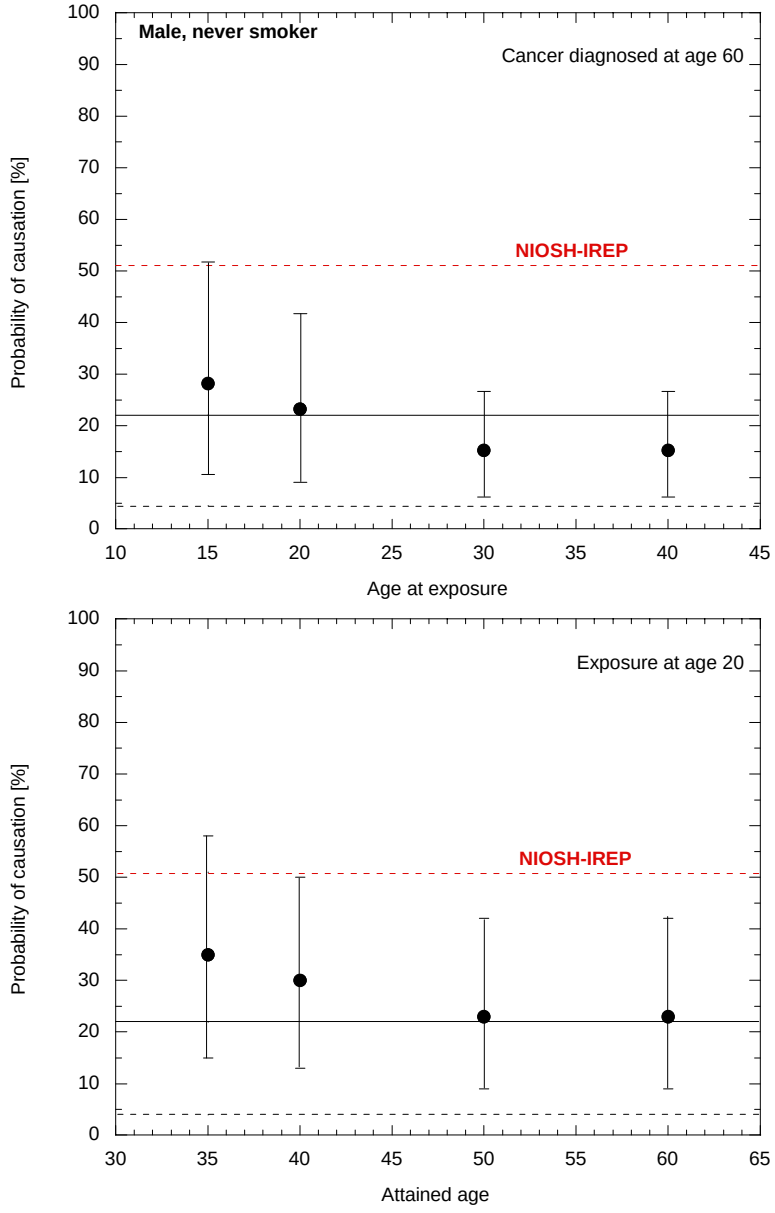

Fig. 1 Probability of lung cancer causation for *never-smoker males* for different ages at exposure and attained ages, from exposure to a constant dose of high-energy photons. The horizontal dashed and solid lines represent the probability of causation (PC) estimated by NIOSH-IREP, while the vertical lines and solid circles represent the PC obtained using NIH-IREP. The upper bounds of all the distributions represent the 99th percentile of each estimated PC. The magnitude of the lung dose is chosen so that upper 99th percentile of the PC estimated using NIOSH-IREP is 50%. The lower bounds represent the 1st percentile of PC. The horizontal solid line and the solid circles represent the 50th percentiles of PC.

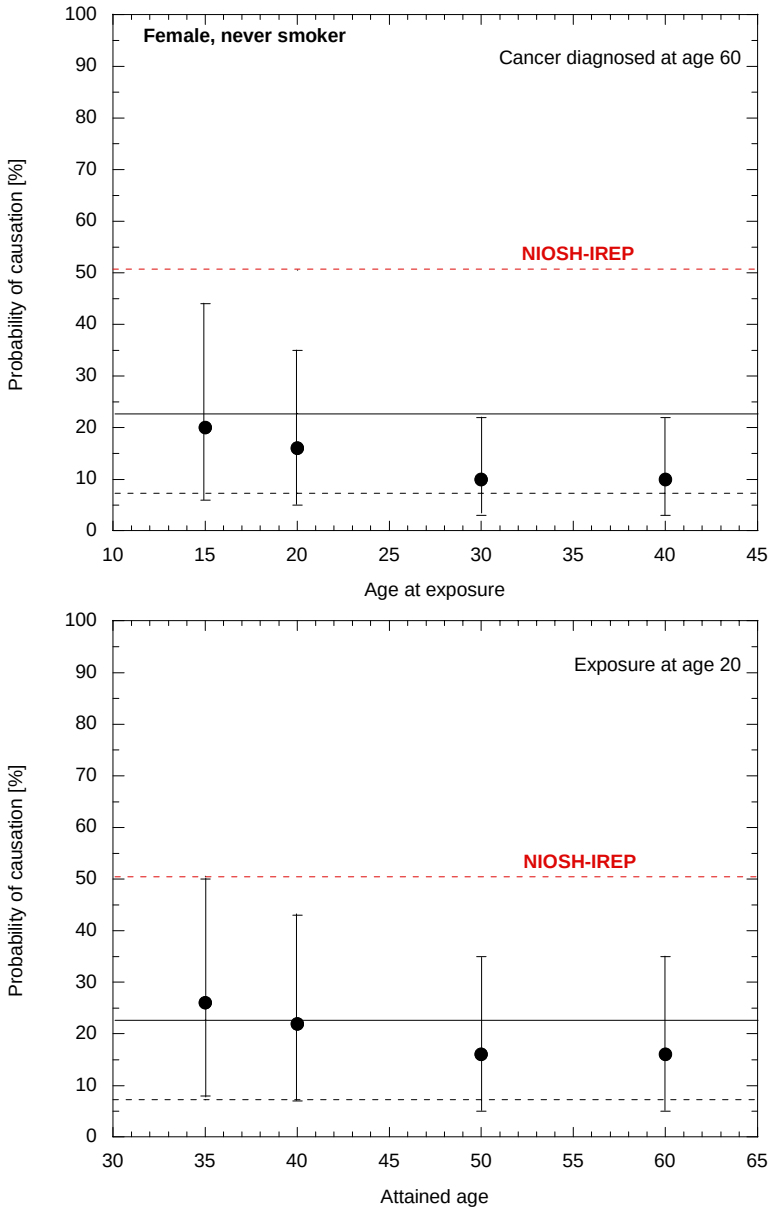

Fig. 2 Probability of lung cancer causation for *never-smoker females* for different ages at exposure and attained ages, from exposure to a constant dose of high-energy photons. The horizontal dashed and solid lines represent the probability of causation (PC) estimated by NIOSH-IREP, while the vertical lines and solid circles represent the PC obtained using NIH-IREP. The upper bounds of all the distributions represent the 99th percentile of each estimated PC. The magnitude of the lung dose is chosen so that upper 99th percentile of the PC estimated using NIOSH-IREP is 50%. The lower bounds represent the 1st percentile of PC. The horizontal solid line and the solid circles represent the 50th percentiles of PC.

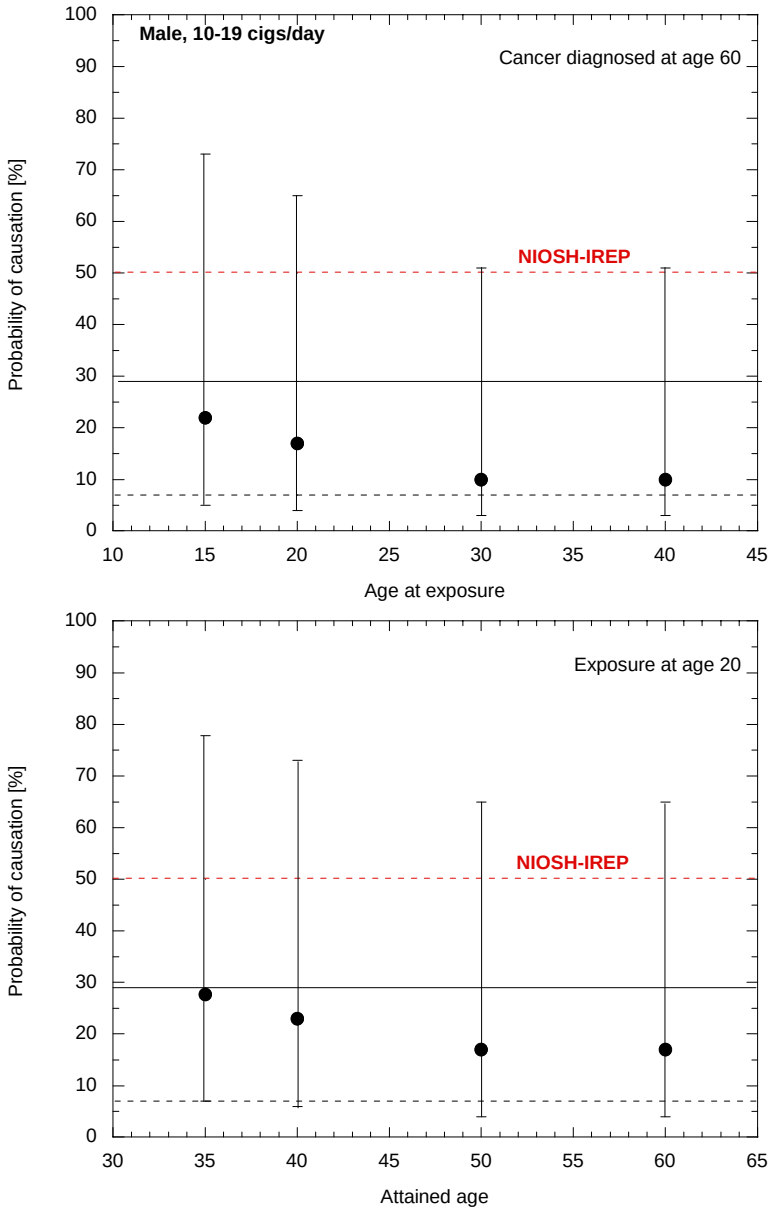

Fig. 3 Probability of lung cancer causation for *males smoking between 10 and 19 cigs/day* for different ages at exposure and attained ages, from exposure to a constant dose of high-energy photons. The horizontal dashed and solid lines represent the probability of causation (PC) estimated by NIOSH-IREP, while the vertical lines and solid circles represent the PC obtained using NIH-IREP. The upper bounds of all the distributions represent the 99th percentile of each estimated PC. The magnitude of the lung dose is chosen so that upper 99th percentile of the PC estimated using NIOSH-IREP is 50%. The lower bounds represent the 1st percentile of PC. The horizontal solid line and the solid circles represent the 50th percentiles of PC.

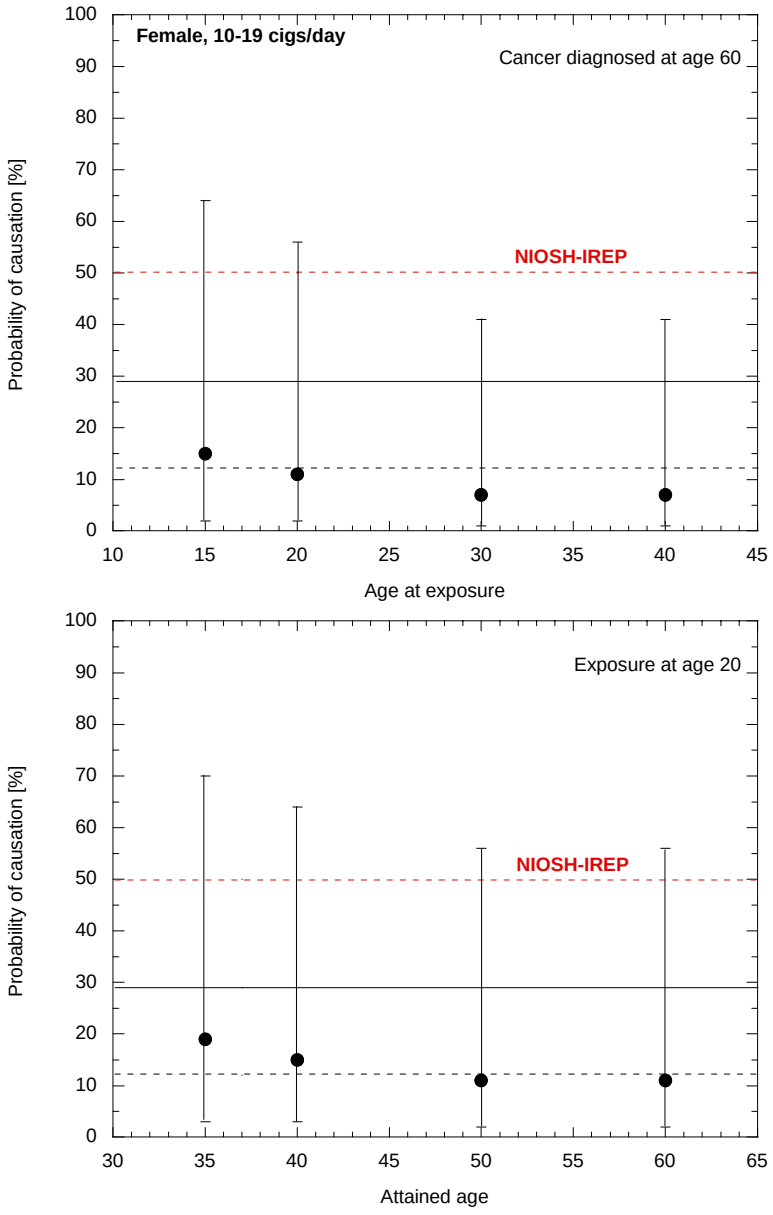

Fig. 4 Probability of lung cancer causation for *females smoking between 10 and 19 cigs/day* for different ages at exposure and attained ages, from exposure to a constant dose of high-energy photons. The horizontal dashed and solid lines represent the probability of causation (PC) estimated by NIOSH-IREP, while the vertical lines and solid circles represent the PC obtained using NIH-IREP. The upper bounds of all the distributions represent the 99th percentile of each estimated PC. The magnitude of the lung dose is chosen so that upper 99th percentile of the PC estimated using NIOSH-IREP is 50%. The lower bounds represent the 1st percentile of PC. The horizontal solid line and the solid circles represent the 50th percentiles of PC.

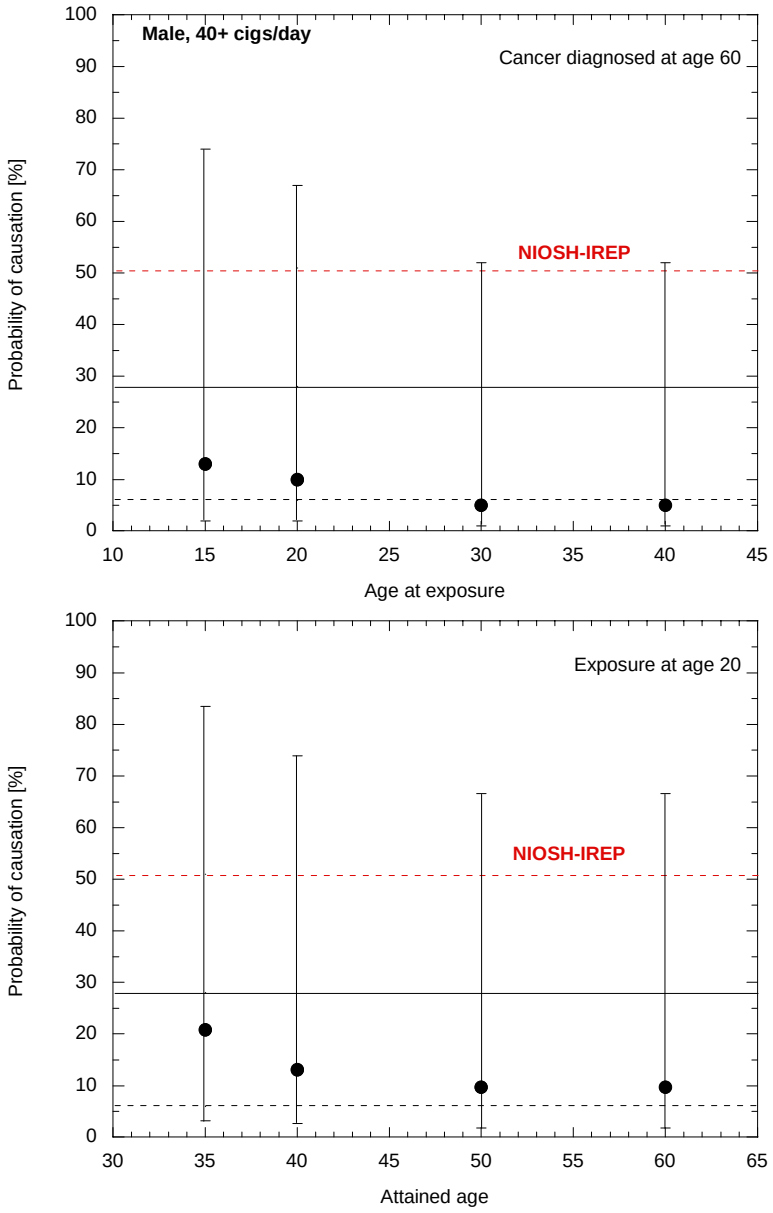

Fig. 5 Probability of lung cancer causation for *males smoking more than 40 cigs/day* for different ages at exposure and attained ages, from exposure to a constant dose of high-energy photons. The horizontal dashed and solid lines represent the probability of causation (PC) estimated by NIOSH-IREP, while the vertical lines and solid circles represent the PC obtained using NIH-IREP. The upper bounds of all the distributions represent the 99th percentile of each estimated PC. The magnitude of the lung dose is chosen so that upper 99th percentile of the PC estimated using NIOSH-IREP is 50%. The lower bounds represent the 1st percentile of PC. The horizontal solid line and the solid circles represent the 50th percentiles of PC.

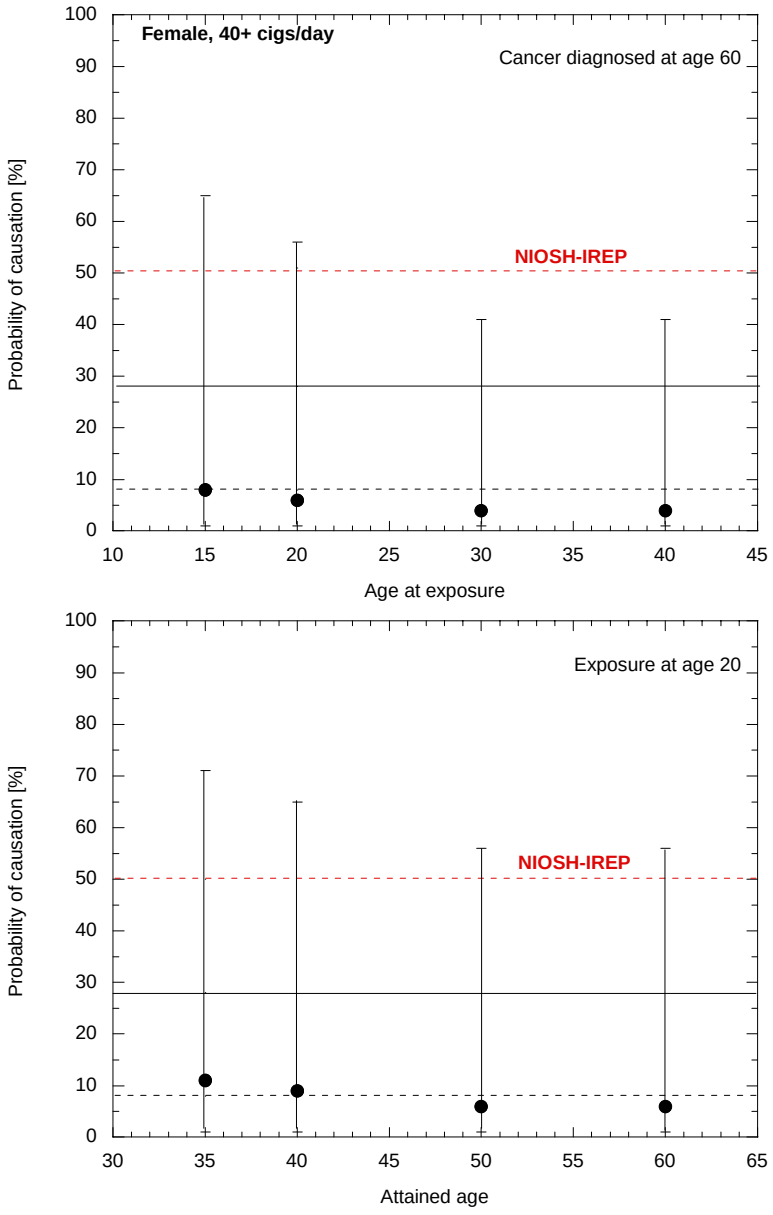

Fig. 6 Probability of lung cancer causation for *females smoking more than 40 cigs/day* for different ages at exposure and attained ages, from exposure to a constant dose of high-energy photons. The horizontal dashed and solid lines represent the probability of causation (PC) estimated by NIOSH-IREP, while the vertical lines and solid circles represent the PC obtained using NIH-IREP. The upper bounds of all the distributions represent the 99th percentile of each estimated PC. The magnitude of the lung dose is chosen so that upper 99th percentile of the PC estimated using NIOSH-IREP is 50%. The lower bounds represent the 1st percentile of PC. The horizontal solid line and the solid circles represent the 50th percentiles of PC.

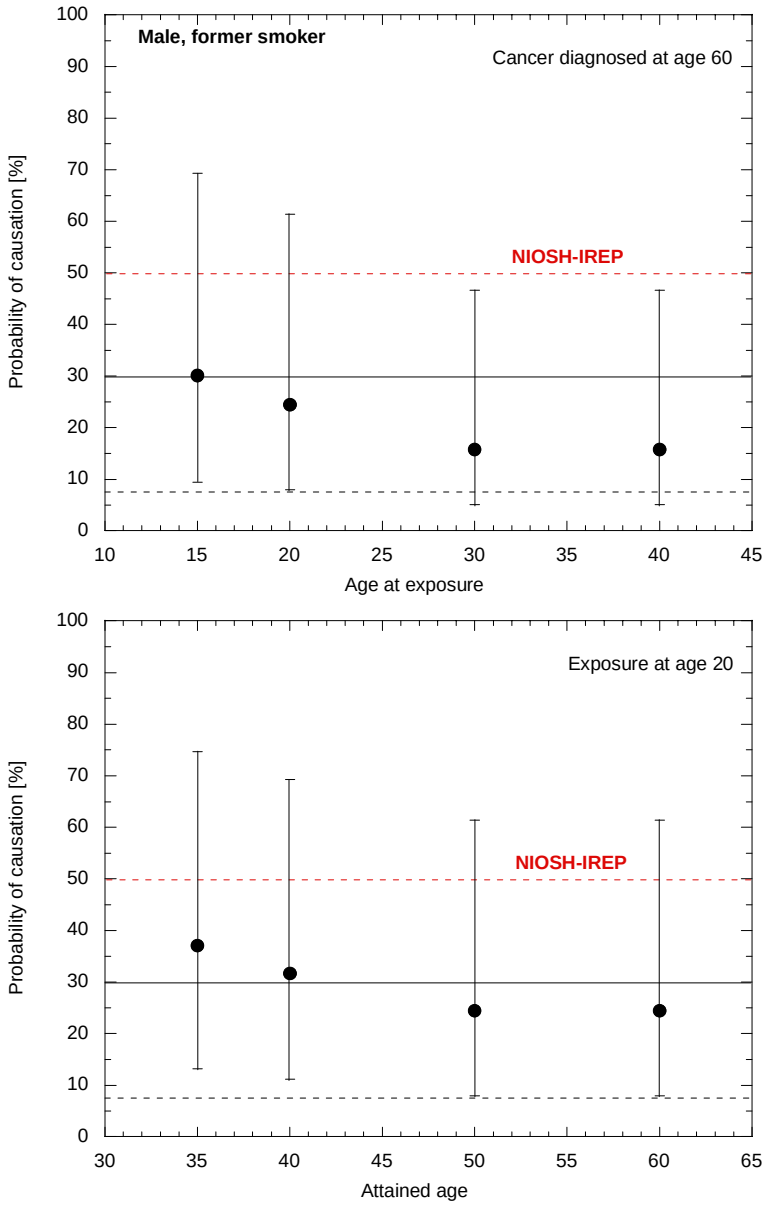

Fig. 7 Probability of lung cancer causation for *former smoker males* for different ages at exposure and attained ages, from exposure to a constant dose of high-energy photons. The horizontal dashed and solid lines represent the probability of causation (PC) estimated by NIOSH-IREP, while the vertical lines and solid circles represent the PC obtained using NIH-IREP. The upper bounds of all the distributions represent the 99th percentile of each estimated PC. The magnitude of the lung dose is chosen so that upper 99th percentile of the PC estimated using NIOSH-IREP is 50%. The lower bounds represent the 1st percentile of PC. The horizontal solid line and the solid circles represent the 50th percentiles of PC.

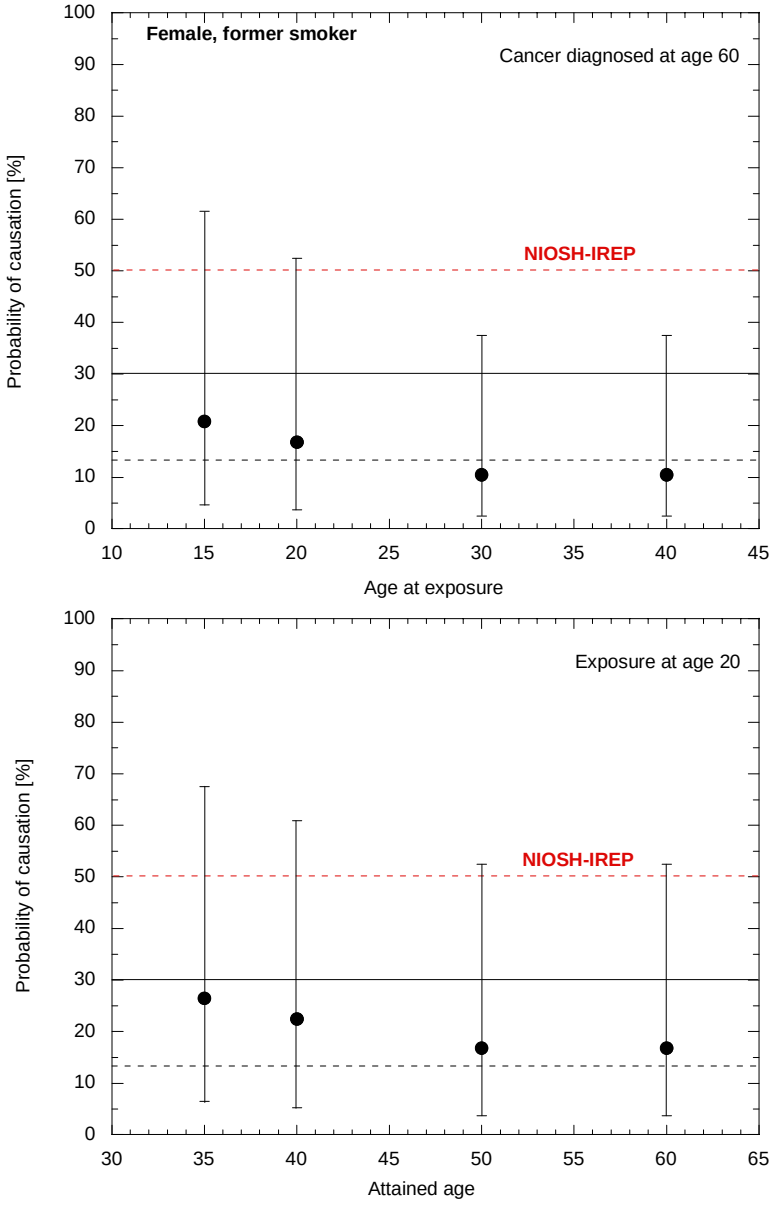

Fig. 8 Probability of lung cancer causation for *former smoker females* for different ages at exposure and attained ages, from exposure to a constant dose of high-energy photons. The horizontal dashed and solid lines represent the probability of causation (PC) estimated by NIOSH-IREP, while the vertical lines and solid circles represent the PC obtained using NIH-IREP. The upper bounds of all the distributions represent the 99th percentile of each estimated PC. The magnitude of the lung dose is chosen so that upper 99th percentile of the PC estimated using NIOSH-IREP is 50%. The lower bounds represent the 1st percentile of PC. The horizontal solid line and the solid circles represent the 50th percentiles of PC.

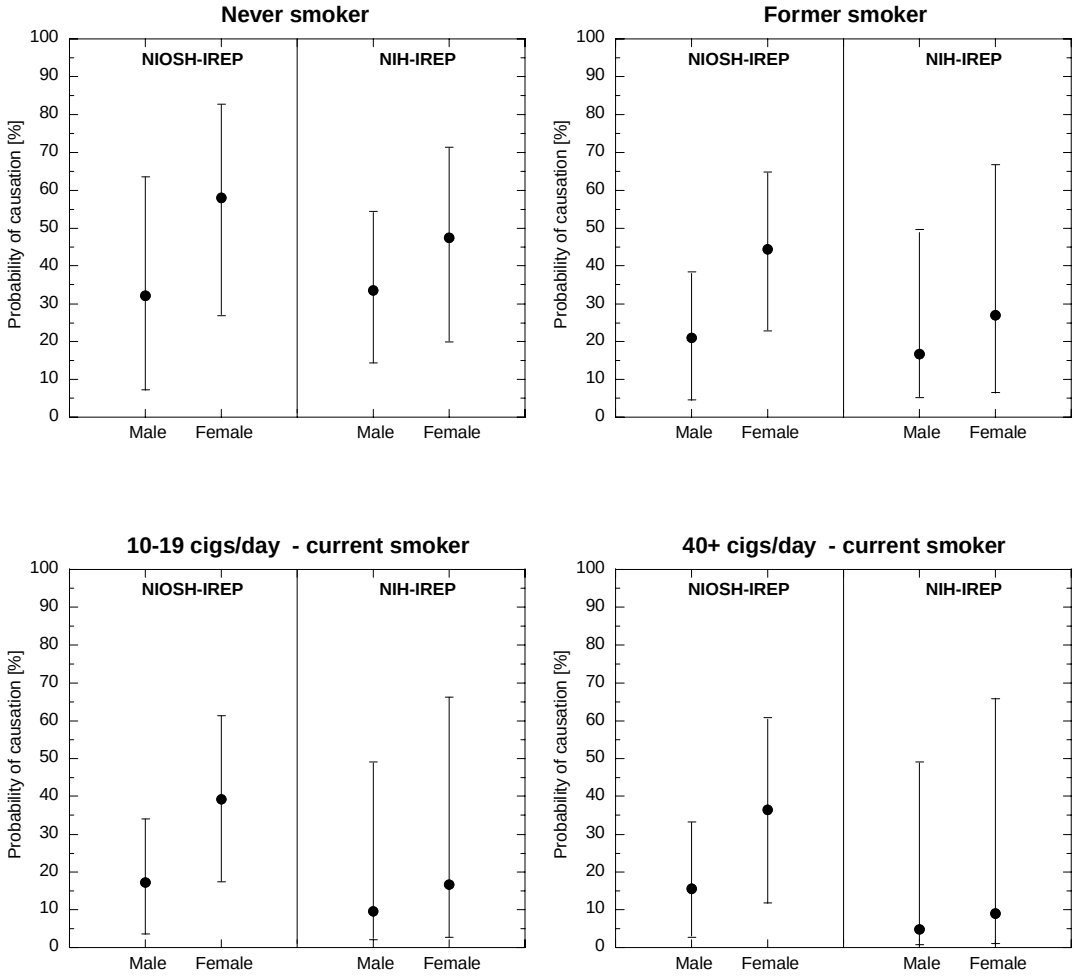

Fig. 9 Probability of lung cancer causation for the two genders, for different smoking categories, from exposure to an acute dose of 75 cSv of high-energy photons. It was assumed that exposure took place at age 20 and the lung cancer was diagnosed at age 60. The upper bounds of all the distributions represent the 99th percentile of each estimated probability of causation (PC). The lower bounds represent the 1st percentile of PC. The circles represent the 50th percentiles of PC.

Appendix A – Treatment of lung cancer in NIH version of IREP

The risk model for lung cancer in NIH-IREP is described by the following equation (Land et al. 2003; page 23; equation IV.D.1):

$$ERR = D \times \alpha \times exp[\beta\, s + \gamma \times f(e) + \delta \times g(a)] = D \times ERR/Sv$$

where

- D = radiation equivalent dose (Sv) delivered to the organ responsible for induction of cancer.
- $\alpha, \beta, \gamma, \delta$ = parameters of the model associated with each modifier.
- s = sex modifier ($s = sexvar$ = - 0.5 males and + 0.5 for females).
- $f(e)$ = $min[max(-15,e-30),0]$ where e is the age at exposure.
- $g(a)$ = $min(ln(a/50),0)$ where a is the attained age.

In particular, α is the *ERR/Sv* for age at exposure 30 and attained age 50, for a never smoker. The profile for α is given in the Table A.1 and Fig. A.1.

The joint distribution of β, γ, and δ is a multivariate normal with the specified means and covariance matrix (this distribution corresponds closely to the profiles for these parameters). Alpha is assumed to be uncorrelated with β, γ, and δ (Table A.2). This approach is similar to the treatment of most of the other cancer sites, except for the sex parameter, β. Alpha applies to both males and females, and gender differences are introduced by the sex modifier s. Thus, there is a unisex profile for parameter α for lung cancer, not separate ones for each sex.

In the logarithmic scale, the *ERR/Sv* (for person of a given gender, given at exposure age e and given attained age a) is assumed to be normally distributed with the mean and variance of logarithms defined by the equations below.

$$ERR/Sv(e,a) = ERR/Sv(e=30,a=50) \times F(s,e,a) = \alpha \times F(s,e,a)$$

The modifying factor $F(s,e,a)$ is assumed to be independent α and is described by a lognormal distribution with a mean of logarithms and a variance of logarithms given by:

$$\text{mean} = \beta \times s + \gamma \times f(e) + \delta \times g(a), \text{ and}$$

$$\text{variance} = \text{var}(\beta) + \text{var}(\gamma) \times f(e)^2 + \text{var}(\delta) \times g(a)^2 +$$
$$2 \times \text{cov}(\beta,\gamma) \times f(e) + 2 \times \text{cov}(\beta,\delta) \times g(a) + 2 \times \text{cov}(\gamma,\delta) \times f(e) \times g(a)$$

For a given attained age, the *ERR/Sv* for these cancer types decreases exponentially between ages at exposure of 15 and 30 and is constant outside this interval. Similarly, for a given age at exposure, the *ERR/Sv* decreases linearly with attained age, up to attained age 50, after which it remains constant.

By using the mean values and the covariance matrix (Table A.2) and the definition for functions *f(e)* and *g(a)*, the means of logarithms and the variance of the logarithms are given by the following equations:

$$\text{mean} = 0.843 \times s + (-0.05255) \times \min(\max(-15, e-30), 0) + (-1.626) \times \min(\ln(a/50), 0) \text{ and}$$

$$\text{variance} = 0.0625\, s^2 + 0.00033 \times [\min(\max(-15, e-30), 0)]^2 +$$
$$0.56203 \times [\min(\ln(a/50), 0)]^2 +$$
$$2 \times (-0.000347) \times s \times \min(\max(-15, e-30), 0) +$$
$$2 \times 0.00836 \times s \times \min(\ln(a/50), 0) +$$
$$2 \times (-0.00708) \times \min(\max(-15, e-30), 0) \times \min(\ln(a/50), 0)$$

To estimate risk and probability of causation for different smoking categories, the ERR for never smokers is multiplied by the term: $[x + (1 - x)W_S^*]$, where W_S^* is the smoking adjustment factor (Table A.3). The uncertainty distribution for x allows the *ERR/Sv* for lung cancer to range from that obtained with an additive interaction ($x = 0$) to that obtained with a multiplicative interaction ($x = 1$). A 50% probability is given to the purely additive model (where $x \equiv 0$) and 50% to a triangular distribution with a minimum value of 0, a mode of 1.0 and a maximum value of 1.1. This triangular distribution has more weight towards the multiplicative model, with a probability of about 0.10 for a super-multiplicative interaction ($x > 1$).

Table A.1 The profile for $\alpha = ERR/Sv(e{=}30,a{=}50)$ used in NIH-IREP for an exposure age > 30 and an attained age > 50. This distribution applies to both males and females. Sex differences are introduced by the parameter *s* in the risk model.

Percentile	α [a]
99.75	1.8218
99.50	1.7243
98.75	1.5899
97.50	1.4825
95.00	1.3681
87.50	1.2002
84.15	1.1519
50.00	0.8603
15.85	0.6127
12.50	0.5792
5.00	0.4750
2.50	0.4133
1.25	0.3610
0.50	0.3024
0.25	0.2642

[a] Table IV.D.3, page 50 of Land et al. (2003)

Table A.2 Mean values and covariance matrix for the parameters of the NIH-IREP risk model for lung

Parameter		Covariance matrix variable			
Name	Mean	variable	*s*	*f(e)*	*g(e)*
β	0.4215	*s*	0.0625		
γ	-0.05255	*f(e)*	-0.000347	0.00033	
δ	-1.626	*g(a)*	0.00837	-0.00708	0.56203

Table A.3 The smoking adjustment factor *W** used in NIH-IREP [a,b].

Smoking category	Male [a]	Female [a]
Never smoked	1.0000	1.0000
Former smoker	0.2511	0.2513
Current smoker (? cig/day)	0.0886	0.0897
<10 cig/day (currently)	0.2574	0.2564
10-19 cig/day (currently)	0.1034	0.1051
20-39 cig/day (currently)	0.0591	0.0590
>40 cig/day (currently)	0.0422	0.0410

[a] Source: Table IV.I.1, page 69 of Land et al. (2003).
[b] These adjustment factors are the same with the ones used in NIOSH-IREP (Table B.2) but, they are centered on never smokers

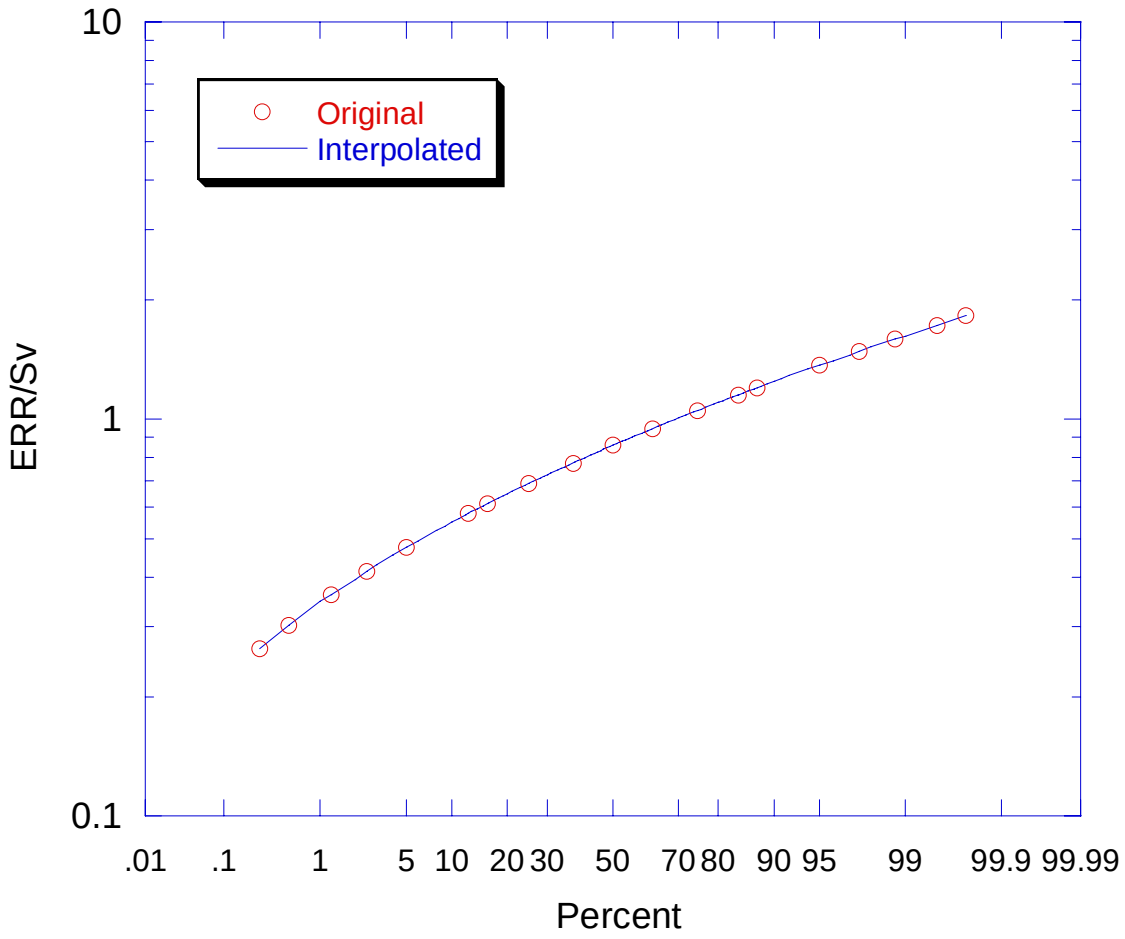

Fig. A.1 Profile for α, the ERR/Sv for exposure age 30 and attained age 50 used in NIH-IREP (Table IV.D.3, page 50 of Land et al., 2003)

Appendix B – Treatment of lung cancer in NIOSH version of IREP

The risk model for lung cancer in NIOSH-IREP is described by the following equation (page 25 in Land et al., 2002):

$$ERR = D \times \alpha(s) \times exp[\gamma \times f(e) + \delta \times g(a)] = D \times ERR/Sv$$

where

- D radiation equivalent dose (Sv) delivered to the organ responsible for induction of cancer.
- $\alpha, \beta, \gamma, \delta$ = parameters of the model associated with each modifier.
- s = sex modifier.
- $f(e)$ = $min[max(-15,e-30),0]$ where e is the age at exposure.
- $g(a)$ = $min(ln(a/50),0)$ where a is the attained age.

In particular, α is the *ERR/Sv* for any age at exposure and any attained age 50, for a population of both smokers and non-smokers smoker. The profile for α was obtained for males and females separately (Table B.1 and Fig. B.1). No age effects are included in the NIOSH version of IREP (i.e., $\gamma = \delta = 0$).

To estimate risk and probability of causation for different smoking categories, including never smokers, the population-averaged ERR is multiplied by the term: $[x + (1 - x)W_S^*]$, where W_S^* is the smoking adjustment factor (Table B.2). The uncertainty distribution for x allows the *ERR/Sv* for lung cancer to range from that obtained with an additive interaction ($x = 0$) to that obtained with a multiplicative interaction ($x = 1$). The parameter x is described by triangular distribution with a minimum value of 0, a mode of 1.0 and a maximum value of 1.1. This triangular distribution has more weight towards the multiplicative model, with a probability of about 0.10 for a super-multiplicative interaction ($x > 1$).

Table B.1 The profile for $\alpha = ERR/Sv$ for males and females in NIOSH-IREP. This distribution applies to all ages at exposure and all attained ages.

Percentile	Male	Female
99.75	1.114	3.449
99.50	1.053	3.307
98.75	0.968	3.109
97.50	0.8987	2.948
95.00	0.8237	2.775
87.50	0.7112	2.516
84.15	0.6783	2.441
50.00	0.474	1.973
15.85	0.2953	1.563
12.50	0.2681	1.504
5.00	0.1885	1.323
2.50	0.1408	1.214
1.25	0.09998	1.119
0.50	0.05369	1.012
0.25	0.02386	0.9406

[a] Table IV.D.3 on page 83 in Land et al. (2002)

Table B.2 The smoking adjustment factor W^* used in NIOSH-IREP [a,b].

Smoking category	Male	Female
Total	1.00	1.00
Never smoked	4.74	3.9
Former smoker	1.19	0.98
Current smoker (? cig/day)	0.42	0.35
<10 cig/day (currently)	1.22	1.00
10-19 cig/day (currently)	0.49	0.41
20-39 cig/day (currently)	0.28	0.23
>40 cig/day (currently)	0.2	0.16

[a] Source: Table IV.I.1, page 97 of Land et al., 2002.
[b] The adjustment factors in NIH-IREP (Table A.3) are the same with the ones in this table, but NIH-IREP factors are centered on never smokers. That is, the values in Table A.3 ore obtained by dividing the W^* values in this table by 4.74 for males and 3.9 for females.

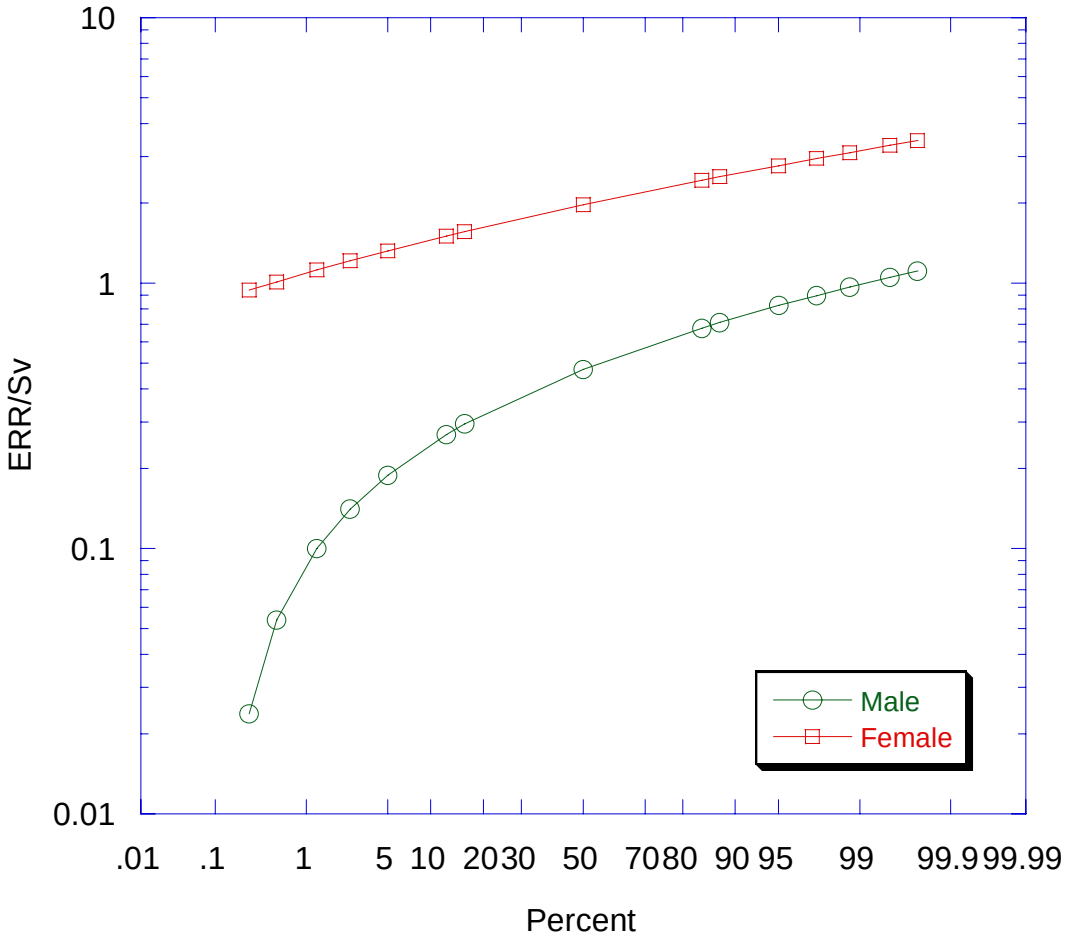

Fig. B.1 Profile for α, the ERR/Sv for males and females used in NIOSH-IREP for all ages at exposure and all attained ages. (Table IV.D.3 on page 83 in Land et al., 2002)