February 10, 2005

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Centers for Disease Control and Prevention (CDC)
NIOSH/Office of Compensation Analysis and Support (OCAS)
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Dear Mr. Henshaw;

Enclosed please find the review of the NIOSH-IREP lung cancer risk model that you requested in November, 2004.

Please note that my comments are based on professional judgment accumulated as a cancer epidemiologist over the last twenty years. In compiling these comments I have reviewed all materials provided by you in the NIOSH request and online plus additional relevant materials. I am not a statistician so have not commented on the appropriateness of the underlying theoretical aspects of the statistical models. Rather, I reviewed this material with respect to the application and interpretation of the proposed models and their face validity in the context of what we know about lung cancer risks in human populations.

My invoice for this work is also attached.

I hope you will find these comments useful.

Sincerely,

Faith Davis, PhD
Professor

Response to NIOSH 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?

I believe that adopting the NIH-IREP lung cancer risk model as posed would provide NIOSH with the best currently available probability of causation estimates. Comments follow with respect to each of the major changes incorporated in the NIH-IREP model that are not currently reflected in the NIOSH-IREP model (Apostoaei, 2004).

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) demonstrates the difficulty of separating out the effects of attained age and age at exposure, yet clearly demonstrates 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 be well reasoned by Pierce at al 2003. The fact that ERR/Sv estimates from this model in nonsmokers closely approximate those expected based on other radiogenic tumor 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.

Sex differences are incorporated in both models. The handling of the pre-calculated coefficient in the NIOSH model versus the separate parameters in the NIH model is a statistical consideration. 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.

Both the NIOSH-IREP and NIH-IREP models incorporate a smoking/radiation interaction and use the same distribution of weights for smokers from a 1993 CDC report. The use of never smokers as the reference category for these weights, in the NIH model, seems a more accurate reflection of smoking risks than the averaging procedure used in the NIOSH schema. In the NIH-IREP model for all other types of radiation a term was added to reflect the new additive effects observed by Pierce et al 2003. As such, the differences across the two models in the probability of causation estimates by smoking category and exposure subtypes appear appropriate.

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?

The NIH-IREP model is a substantial improvement over the NIOSH-IREP with respect to how it handles the independent effects of age and the smoking/radiation interaction effects and the resulting probability of causation estimates appear more scientifically defensible than the current NIOSH-IREP model. As such, I think the NIH-IREP model should be adopted intact.

While it may seem counterintuitive to implement a model that is more claimant-friendly for smokers, given smoking is the predominant risk factor for lung cancer, this appears to be primarily the case only for those exposed to radiation at early ages who probably should be given the benefit of the doubt. The fact that NIH-IREP model is more claimant friendly to smokers, in some cases, reflects the influence that joint effects have on confidence bounds. The NIOSH-IREP model has an interaction term which scaled the risk as an average for all smoking categories which seems inappropriate given what we know about smoking and radiation risks at this time. The NIH-IREP model has substantially better estimates for the non-smokers and the wide confidence bounds for the smokers reflects our current state of knowledge.

The public health policy implication of a switch to the NIH-IREP model should be considered. Is it possible that this new model, which will be in the public domain, will encourage some workers to smoke? While it may seem unlikely, I would not want to encourage workers to initiate or continue smoking thinking that they are more likely to get compensated in the event of a lung cancer diagnosis. Perhaps worker education would be a way to approach this.

Alternatively, should NIOSH-IREP be programmed to run both lung cancer models and to output only the higher probability of causation?

The comparisons of estimates are reassuring as the differences are what one would expect given the changes in the models. The fact that the estimates from the NIH model vary around those from the previous NIOSH model for the never and former smokers is quite appropriate given the absence of age in the NIOSH model. The fact that these estimates are lower at older ages appropriately reflect the change in our understanding of the strength of the joint effects for radiation and smoking on lung cancer risk. The fact that these estimates are consistently lower in the NIH-IREP than the NIOSH-IREP model for smokers (both males and females) reflects the important new estimates provided by Pearce et al 2003. The narrower confidence intervals among non- and ever smokers seem appropriate given the human data in these subgroups and the impact of smoking is either not present or limited. The wider confidence intervals seen in the younger age at exposure and smoking groups are to be expected given that the effects of smoking overwhelm the radiation effects and can be justified based on the rather strong evidence for interactive effects. While the actual estimates seem to differ in males and females when one considers the upper bound of the confidence intervals there may be little practical difference in the two models with respect to gender. It is clear that the two models will result in different decisions under some circumstances. However, as the NIH-IREP model reflects the best available estimates relevant to this exposure population, I recommend 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. 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. Estimates from this model are well reasoned both biologically and statistically and should replace the prior model.

References

Apostoaei AI, Trabalka JR. Differences in the estimation of lung cancer risk between NIOSH-IREP and NIH-IREP. SENES Oak Ridge, Inc., 2004 (unpublished report commissioned by NIOSH, 27 pages, PDF file)
Armitage and Doll

Armitage P, Doll R. The age distribution of cancer and a multi-stage theory of carcinogenesis**.** Br J Cancer. 2004 Dec 13;91(12):1983-9.

Land CE, et.al. Draft Report of the NCI-CDC Working Group to Revise the 1985 NIH Radioepidemiological Tables, May 17, 2002, excerpts. (Note: This is an unpublished early draft of the report published in 2003 [see “Online References”] that formed the basis for the lung cancer model used in NIOSH-IREP; relevant pages are excerpted here. 51 total pages, PDF file)

Land CE, Pierce DA. Likelihood profile for parameter alpha used in computation of statistical uncertainty for ERR/Sv in NIH-IREP lung cancer model; re: Table IV.D.3, page 50, Report of the NCI-CDC Working Group to Revise the 1985 NIH Radioepidemiological Tables (Personal communication from Dr. Charles Land, 2004, titled by NIOSH for this reference. 5 pages, MS Word file)

Pierce DA, Sharp GB, Mabuchi K. Joint effects of radiation and smoking on lung cancer risk among atomic bomb survivors. Radiation Research 159: 511-520, 2003 (10 pages, PDF file)