

Comments on "Proposed Approach for Estimation of Bin-specific Cancer Potency Factors for Inhalation Exposure to Asbestos"

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With more than 20 years having passed since the last EPA risk assessment for asbestos, it is about time to take a new look at the data and conduct a risk assessment that is based on the current state of knowledge of asbestos-induced disease, particularly the current state of knowledge regarding the dependence of risk on fiber type and fiber dimensions. It seems to me that the EPA has two choices here. One choice might be to acknowledge that risk assessments need to be easily understood and transparent, but that the science is complex and difficult to understand. Thus the EPA could choose to make a number of simplifying assumptions and arrive at estimates of risk that it believes to be protective of public health while acknowledging that these numbers do not represent outputs from the best possible analyses. The second choice, which the EPA appears to be making here, is to conduct the best possible analyses of the available data. If this is indeed the choice EPA has made, then it falls short, particularly in its choice of models for analyses.

There are three fundamental issues the EPA has to address here.

1. The choice of the appropriate bin-specific models for asbestos-induced lung cancer and mesothelioma (I will not discuss asbestosis here).
2. The appropriate methods to address exposure measurement error.
3. The appropriate methods for fitting the models to data and estimating the parameters.

The second and third issues are easily dealt with. So long as the exposure measurement error is Berksonian, which is a reasonable assumption, monte carlo methods can be used to integrate over the measurement error distribution even for complicated models for asbestos-induced cancer. See, for example Heidenreich et al. (2004) for an application to radon-induced lung cancer among miners. For parameter estimation, what EPA calls a Bayesian framework is nothing more than maximum likelihood estimation because of the assumption of flat priors. Markov chain monte carlo methods are simply convenient computational tools for maximum likelihood estimation and, more generally, for exploration of the likelihood surface.

The first issue, that of choice of bin-specific models, is much more problematic. Here the EPA has a real opportunity to explore models other than the ones used in 1986 and in the recent Aeolus report. The EPA also has the opportunity to investigate the interaction between asbestos and cigarette smoking in lung cancer. The situation here is more complex than the EPA acknowledges. I direct the EPA's attention to a recent paper by Wraith & Mengerson (2007).

The model for mesothelioma is the one originally developed by Professor Julian Peto and based loosely on ideas of multistage carcinogenesis. This model shows quite clearly that the hazard function for mesothelioma depends on intensity of exposure, duration of exposure and time since exposure stopped. While the hazard function is linear in intensity, it is a cubic function of duration of exposure and time since exposure stopped. Therefore, the hazard function for mesothelioma is not a well defined function of cumulative exposure, a fact that is not clear in the current EPA document. The EPA now has the opportunity to investigate whether other models, such as the two-stage clonal

expansion model, can describe the mesothelioma data. Particularly in view of the fact that clonal expansion is one of the postulated modes of action for asbestos, this model would appear to be particularly appropriate. One consequence of asbestos acting as a promoter is that the bin-specific hazard functions may not be simple multiples of each other as assumed by EPA..

The proposed model for lung cancer presents the greatest problems in my opinion. This is a linear excess relative risk model with the multiplicative fudge factor α thrown in. In this model the risk depends strictly on cumulative exposure: intensity, duration and time since exposure stopped are not independently considered. We have considerable evidence that such a model flies in the face of biology. First, we know that it does not hold for many other lung carcinogens, including cigarette smoking. In fact, we know that the risk of lung cancer among ex-smokers depends in a complicated way on intensity of smoking, duration of smoking and time since smoking stopped. We know that the hazard function for asbestos-induced mesothelioma also depends on all three factors, as noted above. It is incumbent upon the EPA to develop better models for lung cancer, based on individual level exposure information. If such models can be developed for mesothelioma, as attested to by the Peto model, there is no reason that they cannot also be developed for lung cancer. Finally, as I have already pointed out above, a thorough investigation of the interaction of asbestos and smoking in lung cancer should also be undertaken.

I look forward to making these comments in person at the SAB meeting on July 21 and 22.

References

Heidenreich WF, Luebeck EG, Moolgavkar SH. Effects of exposure uncertainties in the TSCE model and application to the Colorado miners data. *Radiat Res* 2004; 161:72–81.

Wraith D, Mengersen K. Assessing the combined effect of asbestos exposure and smoking on lung cancer: A Bayesian approach. *Statist Med* 26:1150-1169, 2007.