PROPOSED APPROACH FOR ESTIMATION OF BIN-SPECIFIC CANCER POTENCY FACTORS FOR INHALATION EXPOSURE TO ASBESTOS

CHARGE QUESTIONS TO THE EPA SCIENCE ADVISORY BOARD

OVERVIEW

At present, EPA uses an approach developed in 1986 for quantifying cancer risk from asbestos exposure based on phase contrast microscopy as the measure of asbestos exposure. The 1986 method used existing epidemiological data from cohorts of workers exposed to asbestos in a variety of mining and manufacturing settings to select quantitative risk models and estimate potency factors for lung cancer and mesothelioma. EPA's Office of Solid Waste and Emergency Response (OSWER) is proposing an interim approach to account for the potential differences of cancer potency between different mineral types and particle size distributions at different human exposure conditions. The document submitted for review describes a "multi-bin" mathematical approach to estimate cancer risk according to mineral groups (amphibole or chysotile) and particle size (length and width) based on transmission electron microscopy. There are a number of issues regarding the statistical methods to be used in the fitting (these are discussed in Section 8), as well as a number of issues regarding the epidemiological and exposure data used (these issues are discussed in Sections 9 and 10). The purpose of the following charge questions is to identify the key issues that OSWER has encountered and to seek input from the SAB on the proposed approaches for addressing these issues, what changes to the proposed approaches may be needed, and what alternatives should be considered.

CHARGE QUESTIONS

The proposed approach is based on the hypothesis that there may be significant difference in potency for lung cancer and/or mesothelioma as a function of asbestos mineral type and particle dimensions.

Charge Question 1:

1. Do you agree that the data are sufficient to indicate that such differences may exist and that an effort of this type is warranted?

SECTIONS 2-7

Sections 2-5 of the document provide a synopsis on the physical and chemical characteristics of asbestos, toxicology, epidemiology, and mode of action. An overview of EPA's 1986 dose-response method is described in section 6, and initial EPA efforts to develop bin-specific cancer potencies are described in section 7

Charge Question 2:

2. Please comment on the adequacy of these sections which serve as the scientific bases for the proposed dose-response assessment approach.

SECTION 8

Section 8 of the document describes the statistical approach that OSWER is proposing for use in fitting risk models to the available data. Detailed charge questions related to the proposed fitting process are provided below.

Section 8.2 – Risk Models

OSWER reviewed work done by others in which the adequacy of the risk models for lung cancer and mesothelioma were assessed. OSWER concluded that the existing risk models (i.e., the same models developed by USEPA 1986) were adequate for use in this effort.

Charge Questions 3a-3c:
3a. Do you agree that the lung cancer and mesothelioma risk models that are proposed are a scientifically valid basis for this fitting effort?
3b. Should additional model forms be investigated? If so, what model forms are recommended for investigation, and what is the basis for concluding that these forms warrant evaluation?
3c. For lung cancer, the current risk model is multiplicative with the risk from smoking and other causes of lung cancer. Should the nature of the interaction between asbestos and smoking be investigated further? If so, how should this be done? Do you think the model would be sensitive to additional quantification of the interaction between smoking and asbestos?

Section 8.3 – Fitting Metric

Fitting of the risk models to the data may occur either at the level of individual studies, or at the level of individual exposure groups. OSWER is proposing that fitting occur at the level of exposure groups.

Charge Questions 4a-4b:
4a. Is fitting at the group level (based on the number of cancer cases observed) preferred to fitting at the study level (based on the study-specific KL or KM values)? What are the advantages and disadvantages of this approach?
4b. If so, is it scientifically justifiable to use a Poisson likelihood model for the observed number of cases in each group? Please comment on any other models that should be considered.

Sections 8.4 – Characterizing Uncertainty In Exposure Data

In most cases, there are multiple sources of uncertainty in the measures of exposure reported in published epidemiological studies. Section 8.4 provides an overview of how OSWER proposes to characterize these uncertainties, and the details of the approach are provided in Appendix C. Application of the proposed methods to each epidemiological study are presented in Appendix A.

Charge Questions 5a-5d:
5a. Have all of the important sources of uncertainty in cumulative exposure matrices been identified? If not, what other sources should be accounted for?
5b. Is it appropriate to characterize the uncertainty from each source in terms of an independent probability density estimated using professional judgment? If not, what alternative approach is suggested?
5c. Are the general strategies for selecting distributional forms and parameter values described in Appendix C (and applied in Appendix A) appropriate for characterizing uncertainty in exposure metrices? If not, what alternative strategies are recommended?
5d. Based on the assumption that each of the sources of error is independent, OSWER is proposing an approach where the errors combine in a multiplicative fashion. Please comment on the scientific validity of this approach and provide detailed suggestions for other approaches OSWER should consider.

Section 8.5. Fitting Approach

OSWER considered a wide range of strategies for fitting the epidemiological data to the risk models, including simple minimization of squared errors, weighted regression, maximum likelihood methods, measurement error models, Monte Carlo simulation, and Bayes-MCMC. Based on the recognition that there is substantial error in both the independent variable (observed number of cases in an exposure group) and the independent variable (metric of cumulative

exposure for the group), OSWER is proposing Bayes-MCMC as the most robust statistical approach for fitting the data.

Charge Questions 6a-6b:

6a. Is it appropriate to account for measurement error in the exposure data by using "measurement error" models (weighted regression methods)? If so, how would the weights assigned to each exposure value be assigned?

6b. Is the assignment of a PDF for data quality sufficient or should data quality be factored into a weighted likelihood analysis?

6c. Do you think that the proposed strategy of fitting the risk models to the available epidemiological data using Bayes-MCMC is scientifically justifiable? If not, what alternative strategy do you suggest, and why?

Section 8.6.2 –Specification of Priors

Assuming that Bayes-MCMC is the method that will be used, it is necessary to specify prior uncertainty distributions for each of the fitted parameters, including $\boldsymbol{\alpha_s}$ (the vector of study-specific relative risks of lung cancer at zero exposure), $\mathbf{KL_b}$ (the vector of bin-specific potency factors for lung cancer), and $\mathbf{KM_b}$ (the vector of bin-specific potency factors for mesothelioma).

Charge Question 7:

7. Are the priors proposed in Section 8.6.2 for $\boldsymbol{\alpha_s}$, $\mathbf{KL_b}$, and $\mathbf{KM_b}$ consistent with available knowledge? If not, what alternative priors should be considered, and why?

Section 8.7 – Comparing Results For Different Binning Strategies

OSWER is proposing an approach in which the best binning strategy is determined empirically (by finding the strategy that yields the best fit with the data), rather than specifying a binning strategy *a priori* that is expected to be optimal based on information from other sources. Conceptually, an infinite number of binning strategies might be considered. The choice of the size cutoffs for length and width are judgmental, and are also limited by the availability of particle size distribution data (see Section 10). OSWER is proposing 20 different binning strategies for evaluation. Length bins proposed for use include <5, 5-10, and >10 um. Width bins proposed for use are <0.4 and 0.4 to 1.5 um.

Charge Questions 8a-8d:

8a. Do you agree that multiple binning strategies should be evaluated, or do you believe that a physiological basis exists that can be used to identify a particular set of length and width cutoffs that should be assessed? If so, what would those length and width cutoffs be, and can these bins

be implemented considering the limitations in the available TEM particles size data sets? (see Section 10)
8b. Are there any of these strategies that you feel do not warrant evaluation? If so, why? Are there any additional strategies that you recommend for inclusion? If so, why?
8c. Assuming that fitting is performed using Bayes-MCMC, OSWER is proposing that a comparison of goodness of fit between different binning strategies be based on the Bayes Factor. Dou you agree that this is a statistically valid method for comparing binning strategies? Are there any other comparison methods you would recommend? If so, why?
8d. Is it important to account for differences in the number of fitting parameters (bin-specific potency factors) when comparing 1-bin, 2-bin, and 4-bin strategies to each other? If so, how should that be done?

Section 8.8 – Other Methods For Characterizing Goodness-of-Fit

OSWER is proposing that the initial evaluation of goodness-of-fit of different binning strategies be based on the Bayes Factor, but is also proposing a number of additional evaluations to assess both relative and absolute goodness-of-fit. These are described in Section 8.8.

Charge Questions 9a-9e:
9a. What method(s) is(are) preferred for characterizing the absolute goodness-of-fit of any selected binning strategy? Should any of these methods be used to supplement the relative comparisons based on the Bayes Factor? If so, how?
9b. If different measures of goodness of fit do not yield results that agree, which method should be preferred, and why?
9c. What methodological options do you recommend for validating the results of the modeling efforts? What are the strengths and limitations of these options compared to others that might be available?
9d. In lung cancer studies, it is expected that the value of α_s should be relatively close to 1.0. If the fitted value of any particular value of α_s is substantially higher or lower than 1.0, should this be taken to reflect that the data set giving rise to the value are somehow flawed or are too uncertain for use, and should be excluded? If so, what criteria would you suggest for recognizing values that warrant concern?
9e. Is an examination performed of the residuals from the meta-analysis a rigorous and scientifically valid assessment of homogeneity?

Section 8.9 – Sensitivity Analysis

OSWER is proposing an approach for evaluating the sensitivity of the results to the various assumptions and choices used in the effort that is based on series of "what if" tests. For example,

this may include excluding all or some of the data from one or more of the studies, and assessing how those exclusions impact the results. Likewise, one or more of the PDFs used to characterize uncertain input data may be changed to evaluate if/how the results are altered.

Charge Questions 10a-10b:
10a. Is this "what if" approach for evaluating sensitivity scientifically valid and useful?
10b. Are there other techniques that you recommend for characterizing the sensitivity of the outcome to the data and methods that are used? If so, what?

SECTION 9. EPIDEMIOLOGICAL DATA PROPOSED FOR USE

Section 9 of the document describes the methods that are proposed for selecting studies for use in the effort, along with a list of studies that are proposed for inclusion. Detailed charge questions related to Section 9 are provided below.

Section 9.1 – Criteria For Study Selection

OSWER has reviewed the published literature and identified studies that include sufficient exposure-response data to allow the study to be included in the model fitting effort for lung cancer and/or mesothelioma. These rules are as follows:

- The study must be published in a refereed journal.
- The study must provide data that can be expressed in terms of the quantitative risk models for lung cancer and/or mesothelioma
- The study cohort must consist of individuals who were exposed to approximately the same atmospheric composition of asbestos.

Some members of the 2003 Peer Consultation panel recommended that a minimum set of data quality requirements be imposed as part of the study selection procedure, while other members favored inclusion of all studies and the use of uncertainty factors to account for differences in data quality. OSWER considered these peer consultation recommendations, and is proposing that no data quality requirement be imposed because a) formulation of the data quality rules would be very difficult, and b) the method for characterizing uncertainty in the data from each study ensures that data from strong studies has more influence on the results that data from weak studies.

Charge Questions 11a-11e:
11a. Are the study-specific selection rules proposed above scientifically valid for the intended uses? Should any additional selection rules be added?

11b. Is it appropriate to assume that all workers in a cohort are exposed to the an atmosphere with a constant composition (i.e., the mixture of asbestos types and sizes is constant) unless the authors report information to the contrary? If this is not an appropriate assumption, what alternative strategy would be available?
11c. Should a set of minimal data quality requirements (other than those above) be established for inclusion of a study in the analysis? If so, what elements of data quality should be considered, and how should those data quality rules be established?
11d. For lung cancer, OSWER's approach requires that there be at least two exposure groups per study in order impose some constraint on the value of the study specific value of α. However, OSWER is proposing to use data from three cohorts described by Henderson and Enterline (1979), even though there is only one dose group for each cohort. This is because a reliable estimate of α for the combined cohort can be derived from the data of Enterline et al. (1987). Is this approach appropriate and scientifically justifiable? If not, can you suggest an alternative strategy for retaining the data from this important study or should this study be excluded?
11e. One key assumption in any meta-analysis is that the data sets included in the analysis are homogeneous. How should the assumption of homogeneity be assessed prior to combining the data from the studies or groups? If you recommend statistical testing, please provide guidance on the reliability of a decision based solely on the test statistic. If testing produces evidence of heterogeneity between some studies, what steps can be recommended?

Sections 9.2 and 9.3. Studies Proposed for Use and Studies Excluded

Section 9.2 lists each of the lung cancer and/or mesothelioma studies that OSWER has identified as being sufficient for inclusion in the data fitting effort. There are a number of studies where cumulative exposure was not reported in the units needed for modeling. In order to utilize these studies, it was necessary to use the data provided to estimate cumulative exposure in the needed units (e.g., Yano et al. 2001, McDonald et al. 1982, 1983, 1984). Section 9.3 identifies several studies that were considered for use, and the reasons why they are proposed for exclusion.

Charge Questions 12a-12c:
12a. Are you aware of any studies that should be included in the model fitting effort that are currently excluded or omitted? If so, what are these studies, and do they meet the requirements for study inclusion?
12b. Are there any studies that are currently proposed for inclusion in the analysis that you believe should be excluded? If so, why?.
12c. In cases where the epidemiological data are not reported in the form needed for use in the fitting effort, are the methods used to estimate the exposures scientifically sound, and are the methods used for characterizing the uncertainty in the estimates appropriate?

SECTION 10. METHOD PROPOSED FOR ESTIMATING BIN-SPECIFIC EXPOSURES

One of the largest problems with this effort is that none of the published studies included bin-specific exposure estimates. Therefore, the effort is contingent upon methods for estimating bin-specific exposures based on the data provided. Specific charge questions related to this process are provided below.

Section 10.2 – Extrapolation from Dust to PCM-Based Measures

A number of studies reported exposure in terms of dust rather than asbestos. In some cases, data are available to extrapolate from dust to asbestos levels. In other cases, no data are provided. OSWER is proposing to use an "average" extrapolation factor in this case.

Charge Questions 13a-13b:
13a. Is it scientifically justifiable to employ a default dust-to-PCM conversion factor when there are no site-specific data available?
13b. Are the uncertainty distributions specified in Appendix A to characterize the uncertainty in this extrapolation consistent with available information and are they statistically appropriate?

Section 10.3 – Extrapolation from PCM to Bin-Specific Measures

The process of extrapolating from PCM-based measures of exposure to bin-specific measures of exposure requires two types of data: 1) the fraction of the atmosphere that is chrysotile and the fraction that is amphibole, and 2) particle size data for both the chrysotile and the amphibole components. In the absence of reliable study-specific data, OSWER is proposing to use published TEM particle size data from similar workplaces as the basis of the particle size data needed for step 2.

Charge Questions 14a-14i:
14a. Are the point estimates and uncertainty distributions for the fraction amphibole term proposed for each study scientifically valid?
14b. Is it scientifically valid to use surrogate TEM data to estimate bin-specific concentrations and exposure values in studies where these data are not reported? If not, what alternative approach could be followed, or what additional data would be helpful?
14c. Are there any additional bi-variate TEM data sets available that would be useful in this analysis?
14d. Are the point estimates and uncertainty distributions for the fraction amphibole term scientifically valid?

14e. Can you suggest any ways to improve the process used to identify select the best available matching TEM data set(s) to a workplace? How sensitive would the model output be to these changes?
14f. Would the model benefit by establishing a common lower cut-point in diameter to normalize the lower detection limit across studies?
14g. Do the studies included in the model have surrogate data of sufficient quality and similarity to expected exposure conditions to support the model? If not, what alternative approach could be followed?
14h. Are the PDFs described in Appendix C to characterize the uncertainty in the extrapolation of TEM particle size data from one location to another sufficient and helpful in understanding the implications of the method used?
14i. Are the extrapolation techniques used on the raw TEM data sets to meet the bin definitions (e.g., 0.4 um diameter) transparent, objectively presented and scientifically valid? Are there alternative techniques that you would recommend?

SECTION 11 – UTILIZING POTENCY FACTORS TO COMPUTE LIFETIME RISK

Assuming that it is possible to derive a set of bin-specific potency factors, it is expected that these will be used to evaluate lifetime risk of cancer to an individual with a specified exposure history using the same basic life-table approach used by EPA (1986). However, each bin-specific potency factor will be uncertain. Therefore, it is important to specify the uncertainty in the risk predictions that arise from the uncertainty in the potency factors.

Charge Questions 15a-15b:
15a. What method is best for estimating the uncertainty in lifetime cancer risk predictions that are associated with the uncertainty in the bin-specific potency factors?
15b. Assuming that estimates of exposure at Superfund sites will also have uncertainty, how should the overall uncertainty in risk predictions be characterized?