UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON D.C. 20460

OFFICE OF THE ADMINISTRATOR
SCIENCE ADVISORY BOARD

November 14, 2008

EPA-SAB-09-004

The Honorable Stephen L. Johnson
Administrator
U.S. Environmental Protection Agency
1200 Pennsylvania Avenue, N.W.
Washington DC. 20460

Subject: SAB Consultation on EPA's *Proposed Approach for Estimation of Bin-Specific Cancer Potency Factors for Inhalation Exposure to Asbestos*

Dear Administrator Johnson:

The Environmental Protection Agency's (EPA) current method for quantifying cancer risk from inhalation exposure to asbestos utilizes exposure measurements based on phase contrast microscopy. The 1986 method used published epidemiologic studies of miners and manufacturing workers to select empirical risk models to derive cancer potency factors for lung cancer and mesothelioma. To address the potential limitations of EPA's 1986 method, EPA's Office of Solid Waste and Emergency Response (OSWER) has proposed an interim approach to account for the potential differences of cancer potency between mineral groups and fiber size distributions. The proposed method adopts a "multi-bin" mathematical model to estimate cancer risk according to mineral groups (amphibole or chrysotile) and measurements of particle dimensions (length and width) based on transmission electron microscopy (TEM). OSWER asked the Science Advisory Board (SAB) to conduct a consultation on the proposed method. OSWER sought SAB advice regarding the soundness of the scientific basis of the proposed method; the choice of the mathematical models, statistical methods, epidemiologic and exposure data used; and, what alternative approaches or methods should be considered.

In response to OSWER's request, the SAB Asbestos Committee (Enclosure 1) held a public meeting on July 21-22, 2008 in Washington D.C. to consider the issue and to provide consultative advice on the proposed method. An SAB consultation is a mechanism for individual technical experts to provide comments for the Agency's consideration early in the development of a technical product. Comments from individual committee members (and subgroups) in response to EPA's charge questions (Enclosure 2) are included in Enclosure 3. While group consensus was not sought for a consultation, the Committee would like to underscore major conclusions that emerged from this consultation as described below.

The general view of the Committee was there is sufficient evidence to support the need for the Agency's effort in developing risk assessment method(s) to account for potential differences in risk on the basis of mineral type and size characteristics of asbestos. As detailed in individual and subgroup comments, there were divergent views regarding whether an effort of this type is warranted at this time. The Committee, however, generally agreed that the scientific basis as laid out in the technical document in support of the proposed method is weak and inadequate. A primary concern is the lack of available data to estimate the TEM specific levels of exposure for the epidemiological studies utilized in this analysis. The Committee also found that the document was woefully inadequate with respect to the representation of available information on epidemiology, toxicology, mechanism of action and susceptibility.

The Committee urged the Agency to support additional targeted research, exposure data collection and fiber analysis, and validation of alternative risk assessment models. In particular, there is a critical need for analyses of more epidemiologic studies using TEM based fiber size specific estimates of exposures as was conducted in the recently published South Carolina textile cohort study. The ongoing research effort focusing on amphibole asbestos exposure in Libby, Montana would yield valuable data and insights to further this scientific effort.

The Committee would like to thank the EPA presenters for their expertise, perspectives and insights that assisted the Committee's understanding of the proposed method. Thank you for the opportunity to provide early advice on this important topic. The SAB looks forward to receiving your response and having further interactions as the Agency moves forward in this endeavor.

Sincerely,

/Signed/

Dr. Agnes Kane, Chair
SAB Asbestos Committee

cc: Dr. Deborah Swackhamer, Chair
EPA Science Advisory Board

Enclosures

ENCLOSURE 1

U.S. Environmental Protection Agency
Science Advisory Board
Asbestos Committee

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Dr. Agnes Kane, Professor and Chair, Department of Pathology and Laboratory Medicine, Brown University, Providence, RI

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Dr. Gary Marsh, Professor, Department of Biostatistics, Graduate School of Public Health, University of Pittsburgh, Pittsburgh, PA

Dr. Gunter Oberdörster, Professor of Toxicology, Department of Environmental Medicine, School of Medicine and Dentistry, University of Rochester, Rochester, NY

Dr. Luis Ortiz, Associate Professor of Medicine, Department of Environmental Health, Director Division of Environmental Medicine, University of Pittsburgh, Pittsburgh, PA

Dr. Julian Peto, Professor, Department of Epidemiology and Population Health , London School of Hygiene and Tropical Medicine, London, , UK

Dr. Christopher Portier, Associate Director, National Institutes of Environmental Health Sciences (NIEHS), Director, Office of Risk Assessment Research, NIEHS, Principle Investigator, Environmental Systems Biology, NIEHS, Research Triangle Park, NC

Dr. Carol Rice, Professor of Environmental Health and Director of the Environmental and Occupational Hygiene Academic Training Program, Department of Environmental Health, Kettering Laboratory, University of Cincinnati, Cincinnati , OH

Dr. Randal Southard, Professor of Soils, University of California, Davis, CA

Dr. Leslie Stayner, Director, Epidemiology & Biostatistics, Epidemiology & Biostatistics, School of Public Health, University of Illinois, Chicago, IL, USA

Dr. David Veblen, Professor of Earth and Planetary Sciences, Department of Earth and Planetary Sciences, Olin Hall, Johns Hopkins University, Baltimore, MD

Dr. James Webber, Research Scientist, Wadsworth Center, New York State Department of Health, Albany, NY, USA

SCIENCE ADVISORY BOARD STAFF

Ms. Vivian Turner, Designated Federal Officer, 1200 Pennsylvania Avenue, NW 1400F, Washington, DC

* Dr. Gelman was unable to attend the July 21-22, 2008 public meeting.

ENCLOSURE 2

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. Do 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?

NOTICE

This report has been written as part of the activities of the EPA Science Advisory Board, a public advisory group providing extramural scientific information and advice to the Administrator and other officials of the Environmental Protection Agency. The SAB is structured to provide balanced, expert assessment of scientific matters related to the problems facing the Agency. This report has not been reviewed for approval by the Agency and, hence, the contents of this report do not necessarily represent the views and policies of the Environmental Protection Agency, nor of other agencies in the Executive Branch of the Federal government, nor does mention of trade names or commercial products constitute a recommendation for use. Reports of the EPA Science Advisory Board are posted on the EPA website at http://www.epa.gov/sab.

ENCLOSURE 3

Comments from Subgroups and Individual Members

Subgroup responses to Charge Question 2

Please comment on the adequacy of Sections 2–5 which serve as the scientific bases for the proposed dose-response assessment approach.

Drs. Veblen, Southard, Gutherie

Section 2 provides background information on asbestos mineralogy, particle size variability, and measurement methods. These sections should (at a minimum) provide the basis for (1) justification of the proposed approach and (2) application of the approach (including potential limitations). Pertaining to justification, the primary points for the proposed binning on mineral type are that:

- *Asbestiform amphiboles and chrysotile have different properties that may result in different biological responses.* The current document does not provide sufficient information on this account.

  Information is needed on properties that may relate to biopersistence, which has been shown to differ between the two groups of minerals. This includes a discussion of solubility and dissolution rates (e.g., Hume and Rimstidt, 1992, Am. Mineral., 77:1125-1128 and references therein for chrysotile; Nagy, 1995, Rev. in Mineral., 31:173-234 for chrysotile; Brantley and Chen, 1995, Rev. in Mineral., 31:119-172 for amphibole) and cleavage/parting that can alter particle length (e.g., Veblen and Wylie, 1993, Rev. in Mineral., 28:61-137). This discussion must also include aspects such as dissolution behavior (such as leaching of surface; e.g., Jaurand et al., 1977, Env. Res., 14:245-254), which impacts the potential release of iron (believed to be an important factor in some aspects of pathogenesis).
  Information is needed on factors related to surface properties, which have been shown to differ between these materials (e.g., see Veblen and Wylie, 1993). Fubini (1997, Env. Health Persp., 105:1013-1020) is a good link between surface properties and biological response.
- *Asbestiform amphiboles and chrysotile can be differentiated.* Section 2.3 addresses this in part. A helpful addition would be to discuss critically the ability of each technique to differentiate amphibole from serpentine (chrysotile).

- *Binning occupational exposures into the two groups is meaningful.* At least two short additions are needed to allow the evaluation of this: background exposures and nature of mineral deposits. Klein (1993, Rev. in Mineral., 28:7-59) provides a discussion on factors related to background exposures, which provides context for assessing studies where the occupational exposures reported for a given asbestos type were zero.. The nature of mineral deposits is important in assessing the likelihood of multiple exposures (e.g., some chrysotile deposits contain small amounts of tremolite asbestos, whereas others do not).

Pertaining to potential application of the approach, it is important to note potential differences between the exposures used in the assessment and those to which this might be applied. This includes the nature of the mineral compositions explored and the nature of commercial exposures to amphiboles compared to exposures to materials from the environment.

- *The human data proposed for use relate to a specific set of materials (specifically to chrysotile and a subset of asbestiform amphiboles).* Yet, in the amphibole category, there are mineral species that are not represented in the proposed epidemiological studies. For example, winchite

and richterite are two examples of amphiboles that can have asbestiform habits and that are implicated in asbestos-related disease at Libby, MT (see Wylie and Verkouteren, 2000, Am. Mineral., 85:1540-1542). Another example is fibrous (not necessarily asbestiform) fluoro-edenite, which is an amphibole that has been implicated in studies of environmental exposures in Bianavilla, Italy (Gianfagna et al., 2003, Min. Mag., 67:1221-1229). These amphiboles differ chemically (and hence in their properties) from those in the proposed epidemiological studies. Can/should the results of the proposed approach be applied to these other types of environmental exposures to amphiboles?

- *The human data proposed for use relate to materials that are mined and processed.* In contrast, environmental exposures are often to materials that have been exposed to the environment, which could include factors such as weathering and concurrent exposure to other materials. In some cases, the environmental conditions may lessen the impact; in others they may augment the impact. IARC recognizes a distinction in risk between exposures to silica in occupational settings versus silica exposure under other conditions (in part due to differences in the surface reactivity). For example, Horwell et al. (2003, Env. Res., 93:202-215) show that generation potential of free radicals diminishes for volcanic ash following environmental aging. Although the proposed approach is not assessing any relationships related to occupational versus environmental exposures, the results may find application beyond the narrow conditions represented in the epidemiological studies. Hence, a discussion of the differences between the processed/commercial exposures and environmental exposures would aid in assessing potential applicability (and/or limitations) of the proposed method.

There are some minor modifications that are also necessary in order to provide a more accurate base:

- Section 2.1-Intro Like it or not, many standard mineralogy texts do not equate "fibrous" and "asbestiform." To qualify as fibrous, a mineral can merely look fibrous and still be hard, brittle, and not separable into thin, flexible fragments. It would be better here simply to define the term asbestiform.

- Section 2.1-Serpentine Modify the sentence on elemental substitutions to note that the most common substitutions involve small amounts of aluminum and ferrous iron; the additional elements noted are minor in comparison to these subsitutions. Veblen and Wylie (1993) is a good reference to serpentine composition.

  The word "lattice" in the first paragraph of this section should be replaced by "structure," so that it reads "in the crystal structure." A lattice is a mathematical construct used to describe crystal structure but is not the structure itself.

  The crystal structure(s) for chrysotile should be described briefly. A description is given for amphibole, so why not chrysotile?
  Section 2.1-Amphibole The first sentence of this section is poor. I suggest replacing it with "Amphiboles possess double chains of silicate tetrahedra that are interconnected by bands of 6- to 8-coordinated cations."

  The elements listed for the B site should be modified to include Mg and Fe, which are the dominant B-site elements for the amosite minerals (for example). Veblen and Wylie (1993) is a

good reference to amphibole? composition. (I would add at least Mn, since this section is discussing amphiboles in general, not just those that can adopt asbestiform habit.—DRV)

Section 2.1-Amphibole The list of amphibole species should read "grunerite" not "gruenerite". Also "riebeckite" not "rebeckite."
Though perhaps a matter of taste, some might find it useful to include chemical formulat for these five amphiboles. (An end-member formula *is* given in the section on serpentine.)

Last word in section 2.1: The proper mineral name is fluor-edenite, not fluro-edenite.

- Section 2.1 Provide a reference to a more comprehensive discussion of properties, such as the recent publication by IOM on Asbestos: Selected Cancers.
- Section 2.3-TEM Change "irradiate" to "illuminate" in the first sentence
- Section 2.3-TEM Change "provides the x-ray diffraction pattern" to "provides the electron diffraction pattern."
- Section 2.3-TEM It is stated that "most TEM instruments" have an accessory that allows the formation of SAED patterns. In fact, an electron diffraction pattern forms in the back focal plane of the objective lens whether one likes it or not. It's true that an aperture is required to make this DP correspond to a specific specimen area, but I know of no TEMs that have ever been manufactured without at least one SA aperture. Biologists may not use it, but they get it anyway, whether they like it or not!

Drs. Oberdörster, Ortiz, Everitt

Sections 3-5 are designed as a backbone to illustrate the needs of the OSWER report. These sections should facilitate analysis of the OSWER document by the members of SAB and the broader public. A potential consequences of endorsing such document is that the general public may equate this support with that of an official change in EPA policy toward asbestos carcinogenic potency. It may be advisable that such document be supplemented to cover the following items.

1. There must be ample discussion in the introduction of these sections stating that this is an interim approach to assess the question of how physical difference in the composition of asbestos fibers modify its cancer inducing capacity. A clear description of the historical and current EPA's needs that motivate the OSWER report should be stated. Specifically, the document should make reference to the current EPA priorities in the clean up efforts of superfund sites such as Libby, Montana and other sites around the US (as discussed during the SAB meeting in Washington, D.C.).

2. A more detailed discussion of the importance of the physical aspects of the asbestos fibers (length as well as width) and whether or not these properties bear directly in the carcinogenic (lung or mesothelioma) capacity of the asbestos fibers is necessary.

3. The report should also clearly state that currently there is a definitive paucity of scientific information, both in animals (Stanton and Wrench , 1972) as well as humans (Stayner LT *et al*., 2007) regarding the use of TEM to characterize fiber size specific asbestos exposure. In the case of Libby there are samples that could be subjected to TEM analysis to properly address this deficiency. Therefore, this aspect could be incorporated in the report as a scientific and investigational priority to the agency.

4. Similarly, there appears to be room for improvement regarding the description of a body of published work describing the factors that modify the environmental host interaction and determine individual susceptibility to asbestos-induced cancer. Specifically, there is little description of epidemiological data addressing the relationship (additive versus multiplicative) between smoking and asbestos exposure on its carcinogenic effects.

5. Finally, the approach to the biology of the carcinogenic mechanisms of asbestos is timid, lacking in molecular depth and not providing a biologic foundation to back the epidemiologic approach map (that could be experimentally adopted to support the imminent fitting of the human epidemiological data) to indicate how the proposed differences in the physical properties of the asbestos fibers determine their carcinogenic potency.

The toxicology section is wholly inadequate as described as it doesn't address the important role of biopersistence in fiber-induced carcinogenesis. It fails to address the synthetic vitreous fiber database which points strongly to the role of fiber biopersistence as being an important factor in fiber potency and cancer risk. The fiber biopersistence issue for chrysotile and amphiboles has been reviewed (most recently by Bernstein and Hoskins, 2006) and should be discussed in this light.

There is also need to review the refractory ceramic fiber studies to discuss the fiber lengths that were associated with rodent fiber-induced disease as this will emphasize the relatively short nature of the 10mm proposed bin and the inadequacy of the existing exposure database in the epidemiology studies.

Another major gap is the lack of discussion of the role of mixed dust exposures on the pathogenicity of any given fiber exposure. I think the study of Davis and colleagues (1991) should be specifically referenced with respect to this.

The charge question gives the impression that the cancer risk assessment approach described in the document is based on a Dose-Response assessment model. Although that would indeed be the most desirable approach, it was never attempted anywhere in the document, but rather the analysis is based on Exposure-Response. There is a significant difference between these 2 approaches, an exposure concentration is not a dose, and only the dose is obviously most directly correlated with the response. Figure 1 depicts the interrelationship between Exposure, Dose and Response and some of the important factors involved. A more detailed description is provided in an earlier review (Oberdörster, 2003, attached). Deposition, nasal filtering capacity, breathing parameters, fiber length and diameter, and clearance behavior are among the important factors that determine dose; in particular the deposition and clearance characteristics of inhaled fibers have been well described by C.P. Yu's group (Dai and Yu, 1998; Yu *et al.,* 1990; 1991; 1998) and most recently by Balashazy *et al.* (2005). The document suffers from not discussing these important very basic issues.

It would also be helpful to mention and briefly describe the classical risk assessment paradigm (NRC, 1983) for further clarification. An attempt to adapt this paradigm together with risk management consideration, specifically for asbestos, is shown in Figure 2.

The document text (p.3) emphasizes that OSWER focuses only on epidemiological exposure-response data, and no attempts are made to integrate results from other sources, including animal data, mode of action, *etc*. However, the numerous animal toxicological studies that have been performed over several decades on different types of asbestos can give important information about differences in biokinetics and biopersistence (retention halftimes, see attached Table 1) of different asbestos types as well as providing information about dose-response relationships and the importance of fiber dimensions for translocation to pleural sites, and translocation pathways. These include several long-term inhalation studies in rats and hamsters with refractory ceramic fibers including asbestos as a positive control by Hesterberg and colleagues (1993; 1994; 1995; 1997; 1998; 1999) that describe retention kinetics, effects, and tissue distribution.

In addition, the classic studies by Stanton *et al*. (1977; 1981), Pott *et al*. (1974, 1976), Wagner *et al*. (1974, 1984) and Davis *et al.* (1986, 1988, 1991, 1999) related to different types of asbestos, including amosite, chrysotile, tremolite should be described as valuable background information on fiber dimension and associated tumorigenic effects and the importance of durability and biopersistence. A

caveat of these earlier studies relates to the very high exposure concentrations and doses used, which even with more benign particles would have resulted in lung overload conditions, including significant inflammation. Also, the impact of co-exposure of asbestos plus a granular dust, whether a benign particle type (TiO_2) or a cytotoxic one (quartz), on cancer induction (increase of both lung cancer and mesothelioma) and altered retention and biokinetics in rat studies as reported by Davis *et al*. (1991), should be included because they highlight the impact of a mixed dust exposure in exposed human workers (see studies by Finkelstein, 1983; Rey *et al*., 1994). This is an important concept to be mentioned and considered in the document especially with regard to asbestos present in superfund sites potentially resulting in combined exposures.

More recent data point to the enormous differences in the biopersistence between chrysotile and amphiboles: Chrysotile from Canada, California and Brazil was cleared from the lungs in rat studies very rapidly, including fibers longer than 20 µm (Bernstein *et al*., 2005a; 2008; 2004; 2005b). Retention halftimes for chrysotile fibers >20 µm ranged from less than 1 day to about 11 days, indicating their low biopersistence. The authors report also less or no pathological responses in rats after subchronic and chronic inhalation exposure to chrysotile, and suggest that low level exposure to chrysotile may not be hazardous and the risk much lower than assumed (Bernstein and Hoskins, 2006). An earlier study in rats on deposition, clearance and translocation of inhaled chrysotile fibers reported a fast fiber length dependent pulmonary clearance, with retention halftimes (T½) from below 10 days to 30 days for fibers up to 8 µm long, and about 100 days for fibers >16 µm in length (Coin *et al.,* 1992). Because retention was measured only for 29 days post-exposure, estimates of the short T½ have a greater level of certainty – and are consistent with significant chrysotile dissolution – than the 100 day T½, which, however, is also consistent with significant dissolution. Although these studies do not exculpate chrysotile from being labeled as a known human carcinogen, they point to a lower carcinogenic potency than amphiboles because of the much lower biopersistence of chrysotile. This should be considered in the risk assessment process.

One suggestion is to compile data of the tox studies in a table form, if available with inclusion of doses retained in the lung. Animal to human extrapolation models for fiber deposition, retention and clearance could be mentioned, as developed by C.P. Yu.

Section 5 focuses mainly on the oxidative stress hypothesis of asbestos-induced tumorigenesis, which is certainly a major mechanism in high dose studies (all animal data) where significant and

persistent inflammation is induced. While a number of mechanistic studies are cited, a more structured approach through listing and brief discussion of 5 major mechanistic hypotheses as proposed by Kane (1996) would be desirable. (Fiber generated radicals damage DNA; fibers interfere with mitosis; fibers stimulate proliferation of target cells; fibers provoke chronic inflammation with release of ROS and cytokines; fibers act as co-carcinogens or carriers of chemical carcinogens).

Either here or in the Toxicology section, the importance of fiber biokinetics should be discussed, which is different between induction of lung cancer and mesothelioma. Once inhaled fibers have deposited in the different regions of the lung (see earlier comment on fiber size dependent deposition in tracheobronchial *vs*. alveolar region), they need to translocate to pleural sites to induce effects (plaques, fibrosis, mesothelioma). The accepted dogma is that fibers >15/20 μm are the most carcinogenic ones. While this may be true for lung cancer (alveolar macrophages cannot fully phagocytose long fibers so they are not cleared), the longer fibers are also least likely to translocate to the pleura. If lymphatic translocation pathways are involved as suggested by Jones, (1987), lymphatic clearance is limited by length and diameter, and this is different for pre-nodal and post-nodal lymph (~9-16 μm long; 0.5 μm thick; Oberdörster *et al*., 1988); thus, long fibers are excluded from this pathway. Indeed, animal studies and human tissue analyses show that by far mostly short fibers (<5-8 μm) were found in pleural tissue, and few, if any, fibers longer than 10-15 μm (Gelzleichter *et al*., 1996; 1999; Boutin *et al*., 1996; Churg and Vedal, 1994; McDonald *et al*., 2001; Sebastien *et al*., 1980; Dodson *et al*., 1990; Suzuki and Yuen, 2001, 2002, 2005). Studies reporting fiber dimensions found in autopsy samples of exposed workers are summarized in Dodson et al., 2003. These authors also suggested to consider other factors than length for identifying a hazardous fiber, such as surface properties (charge, area, activity), chemical composition (Fe, other transition models, biopersistence), physiological factors. Summary findings from all of these studies showed that chrysotile is less prevalent or even absent in human mesothelial tissues; and these studies indicate also that even short fibers have a carcinogenic potential for inducing mesothelioma and contributing to lung cancer.

Other studies raise additional issues: Timbrell (1982) found fiber surfaced area to best correlate with lung pathology (asbestosis) in exposed workers from different mines, introducing the aspect of the most appropriate dose-metric, which may not necessarily be fiber number. Dogan *et al*. (2006) suggested the influence of genetic disposition as susceptibility factor for mesothelioma. He analyzed the familial history of erionite-induced mesothelioma in several Turkish villages where high of erionite levels exist in whitewash slurry used as wall cover on their houses.

Conclusions from the toxicology, fiber tissue burden and mode of action data summarized in the foregoing paragraphs are that (*i*) fiber types of asbestos have different potencies (hazard level) with respect to tumor induction (*e.g.,* low biopersistence for chrysotile); (*ii*) the risks for lung tumors and mesothelioma are different (*e.g*., translocation of long fibers to pleura); and (*iii*) short asbestos fibers should not be considered as harmless (are most prevalent in tumor tissue; inflammation as initiating condition in tox studies). With respect to different types of asbestos, even among amphiboles differences in potencies seem to exist, *e.g*., tremolite, erionite as more hazardous types. Exposure-Dose relationships ought to be clarified in the document. Issues of confounders, mixed exposures and susceptibility should be discussed. Regarding bin selection for the risk model calculations, tumor type, asbestos types, and fiber length categories (<5 μm; 5-20 μm; ≤15 or 20 μm)seem quite appropriate.

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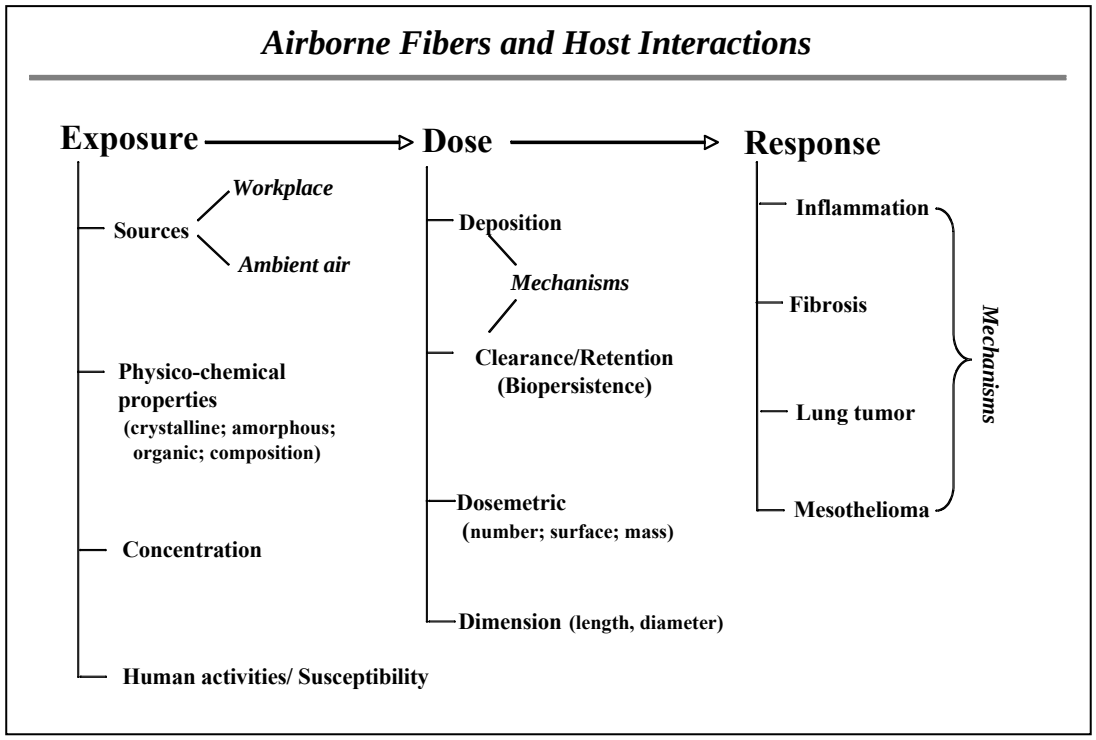
Figure 1:



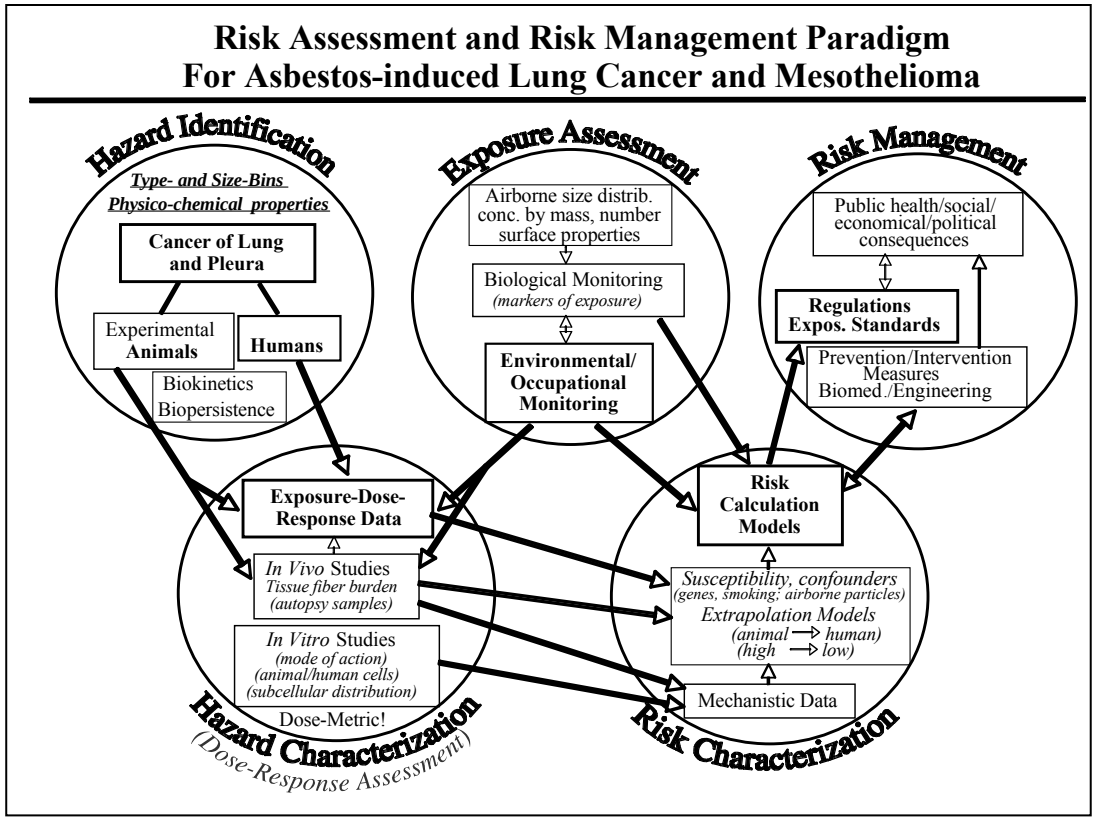


Figure 2

Subgroup responses to Charge Questions 3 & 4 ***(Drs. Lippmann and Stayner)***

3a) Do you agree that the lung cancer and mesothelioma risk models that are proposed are a scientifically valid basis for this fitting effort?

If "a scientifically valid basis for this fitting effort" means "a basis that allows correct comparisons of the risks at different sites", then the answer is that we do "not" have sufficient information to know that the proposed models will provide valid answers. In a broader sense, the EPA 1986 models were reasonable starting points for this effort in that Crump and Berman [Aeolus 2003], in their 2003 report for the EPA, tested the EPA 1986 models using raw data from the South Carolina, Quebec and Wittenoom, Australia study cohorts, and concluded that these models provided reasonably good predictions for these studies.

On the other hand, we must recognize that these models were based on the best available science in 1986. Even in 1986, they provided rather marginal fits to the available data in the literature, with individual study K_Ls and K_Ms varying by an order of magnitude or more from the models. With the additional knowledge gained since 1986, these models no longer provide reasonable representations of the available data. At the same time, the formulations of some of the modeled variables remain valid, and can be incorporated into improved models.

3b) Should additional model forms be investigated?

It would also be desirable to test the assumption that cumulative exposure (duration x intensity) is an appropriate metric for the lung cancer model. This should be done if published data exist to allow separate modeling of duration and intensity. It may only be possible to conduct such an analysis by obtaining and combining (pooling) the raw data from these studies, which is one of the research recommendations that has been made.

New models should reflect: 1) the Stayner et al. 2008 analyses of the Charlestown, SC textile worker cohort, including the evidence that long, thin chrysotile fibers are particularly influential in lung cancer causation. This provides a human analog to the already well established results from the 2-year rat inhalation bioassays with chrysotile and amosite of Davis et al. 1986a,b) for the lung cancer model. In the amosite bioassay, studies, short amosite fibers produced no lung cancers, while long amosite fibers produced more lung cancers than UICC amosite. In the chrysotile bioassay, short chrysotile fibers produced a much lower cancer yield than UICC and the even longer chrysotile fibers, but the short chrysotile was not as free of long fibers as was intended. With regard to the human experience,

At this point, it may be prudent to assume that long-thin chrysotile fibers are more biopersistent within the lungs than shorter chrysotile fibers and comparable in biopersistence to amphibole fibers, so the revised lung cancer model can be assumed to apply to long fibers of both fiber types. The results from the Charlestown cohort may represent a worst-case example, but would be a scientifically defensible one.

The model for lung cancer implies that age at asbestos exposure is irrelevant, and this should be tested in the available data. In addition, two-stage clonal expansion (TSCE) or other biologically motivated risk models that have been developed specifically for lung cancer should be considered to address the effects of exposure on changing cancer risks over time. Such analyses can only be conducted if a pooled rather than a metanalysis approach were used.

For the mesothelioma model, where fibers must translocate from the lung to the pleura or peritoneal surfaces, it must be recognized that it really only applies to amphibole fibers insofar as it assumes long-term retention there (over decades) of fibers. While chronic chrysotle fiber exposures have been associated with mesothelioma, it is now well-established that such fibers are much less potent in terms of causing mesothelioma than are amphibole fibers (Berman and Crump 2003, ERG 2003, Hodgson and Darnton 2000, Lippmann 1988) and the revised model must reflect this knowledge.

3c) For lung cancer, the current risk model is multiplicative with the risk from smoking and other cause of lung cancer. Should the nature of the interaction between asbestos and smoking be investigated further?

Yes, this relationship should be further evaluated. The observation that there is a multiplicative effect of smoking and asbestos is largely based on the results from the study of insulation workers [Selikoff et al. 1968, Seidman et al. 1979]. These workers were exposed to relatively thick amosite asbestos fibers, and were mostly heavy smokers at a time when most lung cancer was squamous cell cancer in the large airways. It is known that heavy smokers have increased particle deposition in the tracheobronchial tree (Lippmann and Albert (1969), and abnormal particle clearance from these airways (Albert et al. (1969). Since then, cigarettes have changed (lower tar content), most lung cancers are now adenocarcinomas, and most asbestos exposures are to thinner fibers that deposit primarily in smaller lung airways. Also, we now know that there is a tremendous variation in the evidence regarding whether this relationship is multiplicative or additive [see Steenland and Thun 1986 and Vainio and Boffetta 1994]. A recent analyses of this issue suggests that in fact the relationship may be somewhere between additive and multiplicative [Wraith and Mengersen 2008].

If so, how should this be done?

A more thorough investigation of chrysotile asbestos exposed workers (smokers and non-smokers) cancer experience may be productive. The sub-multiplicative effect may be due largely to the inclusion of ex-smokers among the non-smoking group in many studies. Studies with prospective data in which lifelong non-smokers were identified at recruitment are rare, and ex-smokers are increasingly common. Careful evaluation of the quality of smoking histories in different cohorts is an important aspect of further research that is needed. A submultiplicative effect will reduce the predicted risk in smokers. However, it will greatly increase it among non-smokers, so in an extrapolation from old cohorts with a lot of smokers to today's population will increase the overall predicted risk. The predicted overall risk would not be affected by model or measurement misclassification in a population with the same smoking habits.

Do you think the model would be sensitive to additional quantification of the interaction between smoking and asbestos?

The dependence of risk on other parameters (fiber type, size, age, duration, etc.) in the model is unlikely to be strongly affected by assumptions about smoking.

4a) Is fitting at the group level (based on the number of cancer cases observed *[In answering, we will assume this refers to subgroups based on differing levels of exposure])* preferred to fitting at the study level (based on the study-specific KL or KM values)?

The committee was divided on this question. Some believed that it was preferable in those cases where the subgroups are sufficiently large for statistically valid inference. It provides the opportunity to compare and contrast differing results that might reveal causal characteristics (length, width, fiber type) associated with the differing fiber characteristics at a specific workplace operation within each study, that was reported from analyses of some studies (South Caroina, Quebec and Wittenoom). Subgroup analyses would be particularly valuable in any in-depth review of the completed epidemiology studies based on experience at Libby, MT.
Other panelists believed that an approach fitting at the individual level was preferable because it more fully utilized the data available in the studies. This was particularly true for studies where there is extensive exposure-response information available for modeling such as the South Carolina, Quebec and Wittenoon studies that were analyzed in the Aeolus report for EPA in 2003.

What are the advantages and disadvantages of this approach?

If grouping can be done on the exposure-specific results, then there are advantages to an initial fitting on a group level, while preserving the opportunity to combine the results for the study group as a whole.

4b) If so, is it scientifically justifiable to use a Poisson likelihood model for the observed number of cases in each group?

Yes, it is scientifically justifiable and appropriate to use a Poisson likelihood model for the analysis of grouped data. If the individual study group results are modeled, one would probably assume a normal or more likely a log normal distribution applies. In any case, it will be important to test the adequacy of the distributional assumption made. While the assumption of Poisson variation may be correct, it should be evaluated by testing for over-dispersion. If there is over-dispersion, an appropriate change should be made to allow for extra-Poisson variation. In any case, the number of cases will almost always be small, and a Poisson likelihood model would most likely be appropriate.

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Subgroup Responses to Charge Questions 9 and 10 ***(Drs. Portier, Cox, Gelman)***

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?

The use of Bayes Factors for initial comparisons of different binning strategies seems appropriate, but additional evaluation methods may be useful. The key question is: When is one binning strategy unambiguously better than another? Goodness-of-fit tests may not provide clear answers to this question. Some other techniques that may help are as follows.

(a) You could use conditional independence tests. If binning method A is "more informative than" method B, in the sense that model predictions are conditionally independent of the information provided by B, given the information provided by A (but not conversely), then method A is preferable to Method B.

(b) There is also an opportunity to use simulation-based validation. The Agency could use the hypothesized relative risk model to generate simulated data for multiple sites, with people having different distributions of individual exposure histories. Each of the different proposed binning strategies could be applied to the simulated data. The Agency could then compare the results, and use them to identify which binning strategies work best (based on criteria such as number of errors or ordinal correlations between the rank-ordering of the sites using binning and the rank-ordering based on the detailed simulated data.)

Finaly, the Agency could do posterior predictive checks, i.e., simulating replicated datasets from the model and seeing if they look like actual data. To do this, it would be first necessary to create some useful graphical displays of the data that are being used to fit the model.

9b. If different measures of goodness of fit do not yield results that agree, which method should be preferred, and why?

This particular question cannot be answered in the abstract since the answer would depend entirely upon what was seen and why the methods differed. Beyond that, the Agency could use conditional independence tests and relative performance in comparing simulated sites to provide a different approach from standard goodness-of-fit that may help to resolve ambiguous cases. Baysian Model Averaging (BMA) may also prove useful in combining results from multiple plausible models.

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?

Simulation-based validation discussed under 9a is also applicable here.

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?

You are placing too much focus on the nature of this statistic and not asking yourself what it really means. If this value is substantially different than 1, it means you should return to your data set and examine *why* this one data set is so different. Find what that difference is and THEN decide whether it warrants exclusion from the overall analysis. Does it change your inclusion/exclusion criteria? Do you need to reevaluate all of the cohorts? The Agency should also focus on ways to explain the differences that are related to the model structure such as model specification errors, omitted explanatory variables, and omitted confounders.

9e. Is an examination performed of the residuals from the meta-analysis a rigorous and scientifically valid assessment of homogeneity?

These types of analyses are not necessarily scientifically (or statistically) valid unless certain assumptions hold, but they are a reasonable starting point. It would also be useful to also display raw data and replications of the raw data.

It would also be useful to do these same evaluations after making predictions for new data sets such as that emerging from Libby, Montana. The Agency could also attempt to apply the model to develop fiber distributions; these could then be evaluated to see if they are reasonable.

10a. Is this "what if" approach for evaluating sensitivity scientifically valid and useful?

Sensitivity analyses are indeed a valid and useful technique for understanding the importance of assumptions on the primary predictions from the modeling exercise. However, many times we approach these types of exercise without any idea of what we plan to do with the results. The Agency needs to give some thought to what will be done with the results of the sensitivity analysis.

The Agency has a fairly comprehensive approach to the sensitivity issue. The only additional analysis we would suggest is that they consider varying the actual form of the model being applied to these data. Some careful thought should go into this decision for alternative models prior to doing it, since alternate models may demand alternate prior structures and the Agency would basically be conducting multiple complete analyses of these data. The purpose of our suggestion is for the Agency to get a solid "feel" for the impact of alternatives, not necessarily to do multiple full analyses of these data.

Finally, rather than varying one input distribution at a time, try varying the joint distribution of inputs. For example, one might attempt to solve the optimization problem of choosing joint inputs to the model (within their allowed or plausible joint distribution) to maximize the prediction error from the model (using simulated data if necessary.) If the maximized prediction error is small, then this would build confidence in model predictions.

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? Model cross-validation provides another technique with a somewhat similar goal (See Maldonado G, Greenland, (1996) Impact of model-form selection on the accuracy of rate estimation. *Epidemiology* 7(1): 46-54).

Individual Responses to Charge Questions

Dr. Tony Cox
Responses to Charge Questions 1, 5-10, 15

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?*

This is really more than one question.

To the question "*Do you agree that the data are sufficient to indicate that such differences[in potencies of different fiber types] may exist?*", my answer is: Yes.

To the question "*Do you agree that the data are sufficient to indicate that an effort of this type [i.e., refined risk modeling with exposure variables that take into account differences in fiber characteristics] is warranted"*, my answer is: Yes, provided that relevant data on fiber characteristics and risks are used. However, it may be very desirable to develop additional data to support such refined risk modeling.

To the question "*Do you agree that the data are sufficient to warrant the proposed binning strategies as valid approaches to risk estimation?*, my answer would be: Not at present. More data, analysis, and validation are needed.

A decision analysis perspective may be useful in considering what to do next. It seems very plausible that different types of fibers (and different types of asbestos) have very different potencies. Failing to consider these differences could lead to a misallocation of cleanup resources and priorities. The key decision analysis questions now are:

1. Can EPA allocate resources and set priorities for Superfund cleanups *better* by using the proposed binning strategies than by not using them?
2. Would other strategies (e.g., treating fiber characteristics as continuous variables and estimating the joint distribution of characteristics using nonparametric smoothing or other methods) work better than binning (and better than ignoring information about fiber characteristics)?

The most useful question is *not* (or at least should not be) "Does the proposed approach yield correct answers with high confidence using available data?", but rather: "Does the proposed approach support more effective risk management and resource allocation decisions in deciding which Superfund sites should receive highest priority for cleanup?" The answer to the first (irrelevant) question may be no, while the answer to the second may be yes. Simply ignoring differences between exposures with very different compositions of asbestos fiber types, posing very different health risks, is almost certainly *not* the most effective way to improve EPA's ability to make good risk management decisions based on available information.

Many public comments stressed that refined risk analysis is less important than banning activities that create asbestos risks for workers (or others). In light of these comments, it may be worth emphasizing the obvious: EPA has asked us about *how to use data to set Superfund priorities most effectively,* not about whether asbestos hazards should exist to begin with.

5a. Have all of the important sources of uncertainty in cumulative exposure matrices been identified?

(a) No. Other sources include: model form uncertainty, uncertainty about smoking (and other covariates) that may modify the effects of asbestos exposure, omitted explanatory variables, errors and biases induced by bin boundaries and discretization, and use of cumulative exposure (which is probably not a sufficient statistic for predicting risk.)
(b) The relevance of uncertainties about cumulative exposure matrices depends very much on uncertainties about the true exposure-response relation. Thus, uncertainties about dose-response (e.g., possible response thresholds or nonlinearities) should interact with uncertainties about cumulative exposure (e.g., is it above or below a threshold value). (See e.g., Pierce JS, McKinley MA, Paustenbach DJ, Finley BL. An evaluation of reported no-effect chrysotile asbestos exposures for lung cancer and mesothelioma. *Crit Rev Toxicol*. 2008;38(3):191-214.) Ideally, uncertainties in cumulative exposure would be assessed in the context of knowledge and uncertainties in the exposure-response relation.
(c) There is some uncertainty about whether cumulative exposure provides a sufficient statistic for predicting risk. For example, suppose that some effects that contribute to induction of lung cancer or mesothelioma (such as apoptosis or production of specific cytokines in the lung) are disproportionately triggered by certain concentrations of asbestos (see e.g., Nishimura Y, Nishiike-Wada T, Wada Y, Miura Y, Otsuki T, Iguchi H., Long-lasting production of TGF-beta1 by alveolar macrophages exposed to low doses of asbestos without apoptosis. *Int J Immunopathol Pharmacol*. 2007 Oct-Dec;20(4):661-71.) Then *cumulative exposure metrics may not contain enough information needed to accurately predict risks.* In other words, different detailed exposure histories that correspond to identical cumulative exposures might have significantly different effects on risk.
(d) Using discrete bins may introduce biases and uncertainties in estimated exposure-response relations (see e.g., Streiner DL. Breaking up is hard to do: the heartbreak of dichotomizing continuous data. *Can J Psychiatry* 2002; 47(3): 262-6.)
(e) Smoking (and perhaps other exposures) may change the effective cumulative exposure metric for asbestos, e.g., by changing the distribution, retention, and effects of fibers in the lung (Vainio H, Husgafvel-Pursiainen K, Anttila S, Karjalainen A, Hackman P, Partanen T. Interaction between smoking and asbestos in human lung adenocarcinoma: role of K-ras mutations. Environ Health Perspect. 1993 Oct;101 Suppl 3:189-92. Albin M, Pooley FD, Strömberg U, Attewell R, Mitha R, Johansson L, Welinder H. Retention patterns of asbestos fibres in lung tissue among asbestos cement workers. Occup Environ Med. 1994 Mar; 51(3):205-11.). Thus, uncertainty about effective cumulative exposure should incorporate the effects of uncertainty about smoking and other modulators of asbestos exposure effects.
(f) Variability (interindividual heterogeneity) and uncertainty in cumulative exposure metrics should be modeled separately.

5b. Is it appropriate to characterize uncertainty from each source as an independent random variable, using professional judgment? If not, then what instead?

No. I doubt that uncertainties about these different sources are statistically independent. (For example, group average exposure durations and group average exposures for unbounded bins might be correlated. Extrapolations from dust measurements to PCM-based measurements and extrapolations from values based on PCM to values based on bin-specific concentrations might be correlated with each other and with use of bin midpoints to represent average exposures.)

Whether professional judgment is valid or useful in this context is an empirical question. It can perhaps be addressed by independently calibrating different experts and then eliciting joint uncertainty distributions from them independently, using several different methods (e.g., different factorings of the joint distribution into products of marginal and conditional distributions). If the different sources are not considered mutually statistically independent, then copulas or conditional distributions might be used instead of modeling the uncertainties for different sources as independent random variables. Also, elicitation techniques can be used that do not assume specific parametric forms for the uncertainty distributions.

Is there an advantage to quantifying the uncertainty for each source separately, instead of quantifying uncertainty directly about exposure? If so, can that advantage be captured in the form of known or assumed algebraic constraints on the possible uncertainty distributions for exposure? This might be easier and give tighter bounds than quantifying uncertainty separately for each of a bunch of factors and then combining them. (Here is a simple analogy. Suppose that $Y = aX$ and $Z = bY$. Each of a and b may be very uncertain. In that case, quantifying uncertainty directly about the reduced parameter $a*b$, e.g., by regressing observed Z values against observed X values, may be easier and more informative than quantifying uncertainty about each of a and b separately and then combining.)

5c and 5d It seems to me that any selection of specific parametric forms for univariate uncertainty distributions in somewhat *ad hoc*. Also, expert estimates of different quantities (sources of error) are not necessarily independent (since an expert who guesses too high on one item may tend to guess high on others, for example.) Having experts quantify uncertainty distributions directly for the output (exposure metric) and then for the inputs (perhaps represented as a network of variables from which the output can be calculated) may give more chances to validate the internal consistency of judgments (and to resolve any inconsistencies) than simply quantifying univariate distributions for the individual sources of error and then combining them. (In general, there is no unique way to combine marginal distributions to get a joint distribution when independence cannot be assumed. Copulas and Bayesian network representations of dependencies among estimated values of variables may help to better structure and validate the uncertainty analysis.)

6a-c. Measurement error modeling. I don't think this proposed approach is sufficiently well explained, as there are several different computational Bayesian methods for missing data that use MCMC and related methods. I would be interested in seeing a more detailed comparison and evaluation of different mainstream approaches (e.g., bias-correction algorithms, SIMEX, EM algorithm, Data Augmentation algorithm for errors-in-explanatory-variables) and a more detailed rationale for (and explanation of) the proposed approach.

References

Berry SM, Carroll RJ, Ruppert D. Bayesian smoothing and regression splines for measurement error problems. *Journal of the American Statistical Association* 2002 March; 97(457):160-169 http://citeseer.ist.psu.edu/309111.html

Carroll RJ, Ruppert D, Stefanski LA, Crainiceanu C. *Measurement Error in Nonlinear Models: A Modern Perspective, Second Edition* Chapman & Hall. New York. 2006 http://www.stat.tamu.edu/~carroll/eiv.SecondEdition/index.php

7. *Priors.* Yes, alternative priors should be used (e.g., uniform over different ranges, exponential, log-normal, etc.) to reveal the sensitivity of conclusions to the assumed priors. The chosen priors may be reasonable, but they are surely not the only possible reasonable ones. (A multiple-priors or robust analysis may also be useful; see http://www.princeton.edu/~noahw/palgrave2.pdf.)

8. *Binning strategies.* Yes, multiple binning strategies should be evaluated. In addition, a binning-optimization approach might be used (with simulated data, if necessary) to discover what binning strategies minimize k-fold cross-validation errors. Rather than selecting a single strategy, more robust results might be achieved by using a Bayesian Model Averaging (BMA) approach that combines predictions from the several best binning strategies.

9. *a and b. Goodness-of-fit and competing binning strategies.* Consider using *conditional independence tests* (is one binning approach more informative than another?), *model cross-validation* and *BMA* (or bagging) to combine results of multiple binning models, rather than just using goodness-of-fit criteria and selecting one binning strategy. (When model uncertainty is considered, as it ought to be, it often turns out that *selecting* any single model or strategy increases the risk of erroneous conclusions compared to that from *combining* results from several plausible models.)

9c. Validate the modeling approach and results using *simulation-validation* (i.e., simulate a data set on fiber characteristics and risks for several sites, apply the selected binning strategy or strategies to the simulated data, then evaluate and compare the performance of the selected strategies in setting cleanup priorities among the simulated sites. Note that the correct answers are known for simulated data, since all details on fiber characteristics and risks are known.)

9d. If alpha is unexpectedly far from 1, consider model misspecification as a possible explanation. (It may be more sensible to blame the model – and improve it – rather than blaming the data.)

10. *What-if approach.* (a) Rather than varying one input distribution at a time, try varying the joint distribution of inputs. For example, one might attempt to solve the optimization problem of choosing joint inputs to the model (within their allowed or plausible joint distribution) to maximize the prediction error from the model (using simulated data if necessary.) If the maximized prediction error is small, then this would build confidence in model predictions. (b) Model cross-validation provides another technique with a somewhat similar goal.

15a. How to estimate the uncertainty in lifetime cancer risk predictions from uncertain bin-specific potency factors?

15b. How to incorporate exposure uncertainties at Superfund sites? One simple framework for answering both questions is: Use Monte Carlo uncertainty analysis, i.e., sample from the joint distribution of uncertain model-input quantities (including bin-specific potency factors and exposure uncertainties), then push the sampled values through the rest of the model (using a tool such as *Analytica*) to obtain a corresponding distribution for predicted cancer risks.

Model uncertainty is a more difficult (and probably more important) issue. The basic model of lung cancer used here is a relative risk model, not a biologically-based model that predicts effects of exposures on age-specific hazard functions by quantifying effects on underlying mechanistic (e.g., cell transition and proliferation) rate parameters. To make defensible predictions of effects on lifetime risks (and uncertainties about those effects), it might be very desirable to use a more biologically-based model of lifetime cancer risks. (The current report's claim that model specification errors are unlikely to be significant does not seem to me to be very self-evident. Considering other model forms that more directly reflect relevant lung cancer and mesothelioma biology might be valuable.) Without considering how risks *change* over time, given exposure histories, there may be no sound basis for deciding which sites to clean first. The goal of cleaning sites is to reduce health risks, so the relation between reduced exposure and reduced age-specific health risks is crucial for informing EPA's decisions. The relative risk model is not necessarily the best approach for quantifying this risk. TSCE and other models might give better results, and should be considered as well.

Dr. Murray Finkelstein

Charge Question 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.*

I believe that animal and human data suggest that there are potency differences related to asbestos mineral type and dimension. I also believe that an effort by the EPA to study these potency differences would be worthwhile.

I do not believe that an effort of the type outlined in the Proposed Approach is warranted because it is based solely on human epidemiologic data. With the exception of the recently published update of the South Carolina textile plant, none of the human studies provide the data required to analyse the proposed model. In essence, all of the input data would consist of "guesses" and the output from the model would not be credible.

Charge Question 2: *Comment on adequacy of these sections which serve as the scientific basis for the proposed dose-response approach.*

Section 4:

This section is an overview of human studies and covers non-cancer and malignant effects. The section is brief and superficial, but covers outcomes of asbestos exposure in humans.

The material is generally adequate. I will suggest a few editorial changes:

Asbestosis -- Paragraph 2.

The authors write that difficulty breathing is often accompanied by "coughing and rales".
Coughing is a symptom, rales are a sound audible through a stethoscope. Rales are often an early sign of asbestosis. I would suggest deleting mention of rales (which few non-physicians will understand).

Pleural abnormalities

"Pleural effusions are areas".... no.
Pleural effusions are the fluid which collects in the pleural spaces.

Lung Cancer

"The risk of developing lung cancer from asbestos exposure is substantially higher in smokers than non-smokers" ... no.

While it is certainly true that smokers exposed to asbestos have a higher overall risk of lung cancer than do non-smokers, under the multiplicative model, the asbestos-attributable risk of lung cancer is unrelated to smoking status.

Charge Question 11

11a. *Are the study specific selection rules proposed above (Section 9.1) scientifically valid for the intended uses? Should any additional selection rules be added?*

OSWER must decide whether to exclude internally-controlled studies. The OSWER author has misinterpreted ALL internally controlled studies, confusing Odds Ratios and Relative Risks with SMRs. There is no confidence interval for the Reference Category and no value of **α** for any of these studies.

Criterion 3 is unclear in that "atmospheric composition" is not defined. If atmospheric composition means the mix of asbestos fibre types, then this is reasonably assessed. If atmospheric composition means, in addition, the distribution of fibre sizes (length and diameter) then most study cohorts don't provide enough information to enforce this criterion. In practice, OSWER proposes to "average over" the varying processes that create the varying fibre-size distributions.

From an epidemiologic perspective, I would propose the addition of the following new rules:

New rules: 1) Source of outcome (mortality) data must be the same for study subjects and the reference population (not satisfied in Lacquet study)

2) Must stratify or account for latency. Since lung cancer or mesothelioma excesses are not usually seen before 15-20 years from start of exposure, inclusion of early PYR will dilute apparent risk.

11b. *Is it appropriate to assume that all workers in a cohort are exposed to the same 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?*

It is not appropriate to assume that all workers in a cohort are exposed to the same atmosphere with a constant composition. OSWER acknowledges that the fibre size distribution is process dependent, and this has been re-demonstrated in the recent work of Stayner and colleagues.

Averaging over work processes, as OSWER proposes to do, will mask the very risk differences that OSWER is wanting to determine. The best strategy, as implemented by Stayner and colleagues, is to undertake TEM-based exposure-response analyses. Failing this, I think that the best strategy is ignore the fibre size question and to compute sector-dependent risks, eg, mining, textile, friction materials etc.

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?*

No, I agree that these will be difficult to establish, and that the OSWER approach is acceptable.

11d. *For lung cancer, OSWER's approach requires that there be at least 2 exposure groups per study in order to impose some constraint on the value of the study specific value of alpha. However, OSWER is proposing to use data from 3 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 alpha for the combined cohort can be derived from the data of Enterline et al. 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?*

I am not sure that there is a reliable estimate for $\boldsymbol{\alpha}$ for the combined cohort.

The Enterline cohort is composed of retirees from a large company with many work locations. There is no rationale to believe that a single value of alpha is appropriate for all subcohorts.

Also, the deaths are coded to ICD 7.

OSWER has failed to subtract the mesothelioma deaths to get the number of lung cancer cases.

Using linear regression, I calculate a different value for the intercept (116), same as Enterline's.

From Poisson regression log(Obs/Exp) = 0.523 at CumExp = 0. ==> intercept is 1.68. Neither of these is the same as the alpha displayed on Figure A3-4.

I suspect that the data from chrysotile only and asbestos-cement pipe subcohorts is captured in the Hughes and Weill study.

As for values of **α** in other studies:

1. Berry and Newhouse (A1). This is based upon case-control data. There is no value of alpha.

2. Albin at al (A12): The OSWER author treats this study as a standard SMR-type study, which it is not. There was a defined industrial reference population of 1233 men, not a national reference population. Relative risk was computed by age and calendar period adjusted Poisson regression modeling. The data presented in Figure A12-1 are thus not meaningful and the value of **α** is not compatible.

3. Libby vermiculite. The OSWER author treats this study as a standard SMR-type study, which it is not. Comparisons were internal to the cohort, not external to a national reference population.

Relative risk was computed by adjusted Poisson regression modeling. The data presented in Figure A12-1 are thus not meaningful. There is no measure of "expected deaths" for the referents. There is no 95% confidence limit for the Reference Category and no value of **α**.

4. Witennoom crocidolite miners. OSWER fails to recognize that this is a case-control study. Figure A14-1 is thus not meaningful. There is no confidence interval around the Odds Ratio for the reference category. The concept of observed and expected is not well defined. The 90% confidence Intervals are probably inaccurate and there is no value of **α.**

5. China Asbestos Products Factory. The OSWER author treats this study as a standard SMR-type study, which it is not. Comparisons were internal to the cohort, not external to a national reference population. Relative risk was computed by Cox proportional hazards regression modeling. The data presented in Figure A17-1 are thus not meaningful. There is no measure of "expected deaths" for the referents. There is no 95% confidence limit for the Reference Category and no value of **α**.

In summary: Many of the values OSWER derives for **α** are invalid.

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?*

I think that there is a more serious problem. I don't think that the individual data sets are internally homogeneous. There are different process-dependent fibre size distributions, and OSWER proposes to smear over them by combining the size distributions from the various processes.

There is also no reason to believe that the inter-study dose estimates are consistent.

Charge Questions 12:
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?*

New report on South Carolina textile factory by Stayner et al in OEM (doi:10.1136/oem.2007.035584) needs to be considered.

Finkelstein has also published a mesothelioma dose-response study:
Finkelstein M. Analysis of the exposure-response relationship for mesothelioma among asbestos-cement factory workers. Ann NY Acad Sci 1991;643:85-89.

Finkelstein M. The exposure-response relationship for mesothelioma among asbestos-cement factory workers. Toxicology and Industrial Health 1990;6:623-627.

Italian Balangero Mesothelioma

(Mirabelli D, Calisti R, Barone Adesi F, Fornero E, Merletti F, Magnani C.
Excess of Mesotheliomas after Exposure to Chrysotile in Balangero, Italy.
Occup Environ Med. 2008 Jun 4.)

12b. *Are there any studies that are currently proposed for inclusion in the analysis that you believe should be excluded? If so, why?*

The Belgian (Lacquet) study should be omitted because the mortality data for the cases (family doctor or social workers) are derived from a different source than the reference data (death certificates).

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?*

See study specific comments below.

A1. British Friction Products Factory (Berry and Newhouse 1983)

Text of Draft Report

Fraction Amphibole: OSWER proposes a screening level value of 0.5% for the average fraction amphibole in the workplace. However, exposure was likely to be binary (Yes/No). OSWER proposal thus introduces misclassification.

Estimating Cumulative Exposure: OSWER states that occupational histories were extracted from employee personnel files and used to estimate levels of cumulative exposure for each individual. This is not correct. Cumulative exposures were estimated only for subjects in the case-control study.

Smoking Data: OSWER states that the workers demonstrated a reduction in smoking compared to the national population. This is not correct. Berry and Newhouse speculated in their discussion that a reduction in smoking might account for lower SMR, but would not influence case-control study.

Lung Cancer Results: Berry and Newhouse fit a linear model to the case-control data. There was no significant dose-response relationship.

It must be realized that the dose-response results for this study are based upon case-control and not cohort data. The Expected deaths in Figure A1-1 are meaningless in the context of a case-control study. There is no explanation how the author derived his Confidence Limits in the Table. They are meaningless. There is no confidence interval about the baseline in a case-control study.

Uncertainty in Particle Size data: It is likely that the particle size distribution depends upon the job and the expenditure of mechanical energy to disrupt the asbestos fibres. Combining data from mixing, forming, and finishing, averages out all distinctions and is noninformative.

Discussion: This study provides some estimates of risk in a primarily chrysotile environment. There is little useful information about fibre size distribution. OSWER has misinterpreted this case-control study.

A2. South Carolina Textile Plant (Hein et al, 2007)
Text of Draft Report
PCM - f/cc Conversion factors

Dement and McDonald disagree on conversion factors (by about a factor of 2). These are not reconciled.

Uncertainty in Particle Size Data

Data sets for different operations combined. Recent analysis by Dement et al (OEM, 2007) demonstrate differences between operational areas. Combining different operations smears out size distribution differences.

Discussion

This is one of the important studies in asbestos epidemiology. Risk, in relation to fibre dimension data, is available in updated analyses from Stayner and colleagues.

New report in OEM (doi:10.1136/oem.2007.035584) needs to be considered.

A3: Retirees from US Asbestos Products Factory
Draft Report Text

Conversion from mppcf to f-yr: Use default factor of 3 for all processes and all jobs

Lung Cancer Results:

Henderson and Enterline coded to ICD 7:
ICD 162 and 163 include mesothelioma (table 3, 1987)
ICD 7 coding table:

162 Malignant neoplasm of bronchus and trachea, and of lung specified as primary

162.0 Trachea
162.1 Bronchus and lung
162.2 Pleura
162.8 Multiple sites
163 Malignant neoplasm of lung, unspecified as to whether primary or secondary

OSWER has failed to subtract the mesothelioma deaths to get the number of lung cancer cases.

Using linear regression, I calculate a different value for the intercept (116), same as Enterline's.

From Poisson regression log(Obs/Exp) = 0.523 at CumExp = 0. ==> intercept is 1.68. Neither of these is the same as the alpha displayed on Figure A3-4.

Uncertainty in Particle Size data: Lumping all jobs, and factories, together is suspect.

A4. Ontario Asbestos cement

There is a mesothelioma exposure-response study:

Finkelstein M. The exposure-response relationship for mesothelioma among asbestos-cement factory workers. Toxicology and Industrial Health 1990;6:623-627. , and

Finkelstein M. Analysis of the exposure-response relationship for mesothelioma among asbestos-cement factory workers. Ann NY Acad Sci 1991;643:85-89.

A5: New Orleans Cement Products Manufacturing Plants
Uncertainty in Particle Size Distributions

Chrysotile: Averaging over jobs and processes
Amphibole: Combined mining/milling and insulation data sets

Discussion:

Major difficulty is with particle size distributions. All jobs and processes assigned similar distributions. Smearing over distributions averages out all distinctions and is noninformative.

A6: Quebec Mines and Mills
Conversion Factor:

Gibbs (1994): "there were definite patterns with Membrane Filter/Midget Impinger ratios increasing from the predominantly dust-generating operations such as drilling and crushing to fibre-releasing operations such as fibre screening and bagging."

==> substantial uncertainty in conversion factor

Cumulative Exposure:

OSWER states that the "study reports CE rather than CE10. This is not correct. The study reports CE to age 55. This introduces comparability issues with studies reporting CE or CE10.

SMRs are calculated from age 55 onwards.

Uncertainty in Particle Size Distributions

Chrysotile: Averaged over mining and bagging. Uncertainty stated to be low, but differences are smeared out.

Amphibole: Data from talc mining and milling applied to chrysotile mining and milling. Needs to be demonstrated that this is reasonable.

Discussion:

Major difficulty is with particle size distributions. All jobs and processes assigned similar. Smearing over distributions averages out all distinctions and is noninformative. Needs to be demonstrated that using tremolite size distribution from talc mining is relevant for Quebec chrysotile mining.

A7: Pennsylvania Textile Factory
ICD Coding of Malignant Neoplasms

Death certificates obtained and coded by nosologist. The nosologist coded to ICD 7:

162 Malignant neoplasm of bronchus and trachea, and of lung specified as primary

162.0 Trachea
162.1 Bronchus and lung
162.2 Pleura
162.8 Multiple sites
163 Malignant neoplasm of lung, unspecified as to whether primary or secondary
164 Malignant neoplasm of mediastinum

McDonald et al classified lung cancer as ICD 162-164

In ICD 7, mesothelioma and lung cancer both coded to ICD 162. The authors state that there were 10 pleural tumours.

Lung Cancer Results:

The author of the OSWER report ignores the fact that Table 5 in the McDonald report (FigureA7-1) combined lung cancer + mesothelioma + ICD 160 + ICD 161

Mesothelioma:

Because of the combination of endpoints, many of these meso deaths were included with the lung cancer analysis above.

The computations to produce a meso risk estimate are tenuous.

Bias Correction Factor CE vs CE10

McDonald et al present table 5 in relation to dust exposure accumulated to 10 years before death. They do not state how they dealt with subjects who were still alive.

Uncertainty in Particle Size Data

Again OSWER averages over departments and jobs, smearing out any differences.

Discussion

OWSER has failed to recognize that mesothelioma deaths have been combined with lung cancer and other respiratory sites in Table 5. The numbers of observed lung cancer deaths are thus in error.

A8: Connecticut Friction Products
Cumulative Exposure Estimates

Estimates made for Departments rather than jobs

Mesothelioma Data
No cases observed
OWSER make approximations and assumptions about PYR and cumulative exposure.

Uncertainty in Particle Size Data

Again OSWER averages over departments and jobs, smearing out any differences.

A9: British Textile Factory
Uncertainty in Particle Size Data

Again OSWER averages over departments and jobs, smearing out any differences.

A10: Italian Chrysotile Mine

Fraction Amphibole: OSWER guesses that amphibole was present despite the authors report that none was present and that a fibrous silicate, balangeroite, was present.

Lung Cancer Results: It is not clear from the published reports whether or not PYR were assigned to dust categories sequentially as work time accumulated, or whether all PYR were attributed to final category. Failure to assign PYR sequentially would flatten dose-response curve.

Mesothelioma Results: OSWER estimates duration and exposure data. The Piolatto data are superceded by those of Mirabelli et al 2008.

(Mirabelli D, Calisti R, Barone Adesi F, Fornero E, Merletti F, Magnani C.
Excess of Mesotheliomas after Exposure to Chrysotile in Balangero, Italy.
Occup Environ Med. 2008 Jun 4.)

Uncertainty in Cumulative Exposure for Meso: Not certain whether authors moved PYR through exposure categories or assigned all PYR to final one achieved

Uncertainty in Fraction Amphibole: There is no tremolite, but another fibrous silicate in the ore. This was said to be 0.2 - 0.5% of the mass of chrysotile.

Applying size data for tremolite is inappropriate.

Uncertainty in Particle Size Data

Again OSWER averages over departments and jobs, smearing out any differences.

A12: Swedish Cement Plant

Relative Risk: The OSWER author treats this study as a standard SMR-type study, which it is not. There was a defined industrial reference population of 1233 men, not a national reference population. Relative risk was computed by age and calendar period adjusted Poisson regression modeling. The data presented in Figure A12-1 is thus not meaningful. There is no measure of "expected deaths" for the referents, and where the author derives a RR of 1.8 for the referents is a mystery. He has apparently misinterpreted Table 2. Allocation of Observed deaths based upon person-years is not necessarily valid as the relative risk is a regression-adjusted estimate.

Uncertainty in Particle Size Data

Again OSWER averages over departments and jobs, smearing out any differences.

The assignment of particle size data for the amphiboles is highly speculative.

A13: Libby Montana Vermiculite Mine

Pg A13-4. OSWER states that exposure is expressed in terms of f/cc lagged by 10 yrs. This is not true. There is no lag.

Relative Risk: The OSWER author treats this study as a standard SMR-type study, which it is not. Comparisons were internal to the cohort, not external to a national reference population. Relative risk was computed by adjusted Poisson regression modeling. The data presented in Figure A12-1 is thus not meaningful. There is no measure of "expected deaths" for the referents. There is no 95% confidence limit for the Reference Category and no value of $\boldsymbol{\alpha}$.

A14: Wittenoom Australia Crocidolite Miners

OSWER fails to recognize that this is a case-control study. Figure A14-1 is thus not meaningful. There is no confidence interval around the Odds Ratio for the reference category. The concept of observed and expected is not well defined. The 90% confidence Intervals are probably inaccurate.

OWSER estimates cumulative exposure by multiplying concentration by estimate of average duration. This is bound to introduce misclassification.

Uncertainty in Particle Size Data

Again OSWER averages over departments and jobs, smearing out any differences. The statement that the uncertainty in f_{size} is low is not very credible.

A15: Belgian Asbestos Cement Factory

Issues:

Cause of death not based on official records, but from family doctor or social workers who visited relatives. This is unreliable.

Exposure concentration: Fibre counts available 1970-76. Exposures estimated 1928-77 using a logistic function. Would expect levels to be better modeled by step-function with changes occurring with ventilation, layout, or work practice changes.

Recommendation: This study should be omitted because the mortality data for the cases (family doctor or social workers) are derived from a different source than the reference data (death certificates).

A16: Austrian Cement Factory

Lung Cancer SMRs. Figure 16-1 uses smoking-adjusted SMRs. This is one of the few studies where this desirable adjustment is possible, but the use of smoking adjusted SMRs is not consistent with the SMRs abstracted from the other studies in the database.

Uncertainty in Particle Size Data

Again OSWER averages over departments and jobs, smearing out any differences. The statement that the uncertainty in f_{size} is low is not very credible.

A17: China Asbestos Products Factory

Relative Risk: The OSWER author treats this study as a standard SMR-type study, which it is not. Comparisons were internal to the cohort, not external to a national reference population. Relative risk was computed by Cox proportional hazards regression modeling. The data presented in Figure A17-1 are thus not meaningful. There is no measure of "expected deaths" for the referents. There is no 95% confidence limit for the Reference Category and no value of **α**.

Dr. Andrew Gelman

Below are my responses to the charge questions. Before answering these, let me emphasize that I am not an asbestos expert and, although I have looked at the EPA report ("Proposed approach…"), I have not looked at the original research that is cited in the report. Also, as you can see, I've focused my comments in the areas where I am more expert.

1. Yes, I agree that the data indicate that differences in effects of different sorts of asbestos may exist and that an effort of this type is warranted.

2. The scientific basis for the approach seems reasonable to me. There are certainly challenges here in combining data from studies that have different sorts of measurements. In general, I'd recommend including more categories rather than fewer. I can't comment on the biomedical models of health effects.

3a. The mixture model approach makes sense to me. I cannot really comment one way or the other on the specific risk models that are being used (the models of risk given exposure and how this is affected by the time of exposure).

3b. I don't have any particular suggestions of other model forms to be investigated; however, if other reasonable models are proposed, I agree that they should be looked into.

3c. Interactions of smoking and other cancer risks can be large. For example, I know that the added cancer risk from radon exposure is much higher among smokers than nonsmokers. If the data are available, it would make sense to fit separate models for smokers and nonsmokers. Otherwise it might make sense to use a model in which the added risk from asbestos is higher (by some multiple) for smokers than for nonsmokers.

4a. The recommendation in Section 8.3 appears to be to fit separate rates for each group in each study. This makes sense to me. As noted in Section 8.3, this allows more direct modeling of the data. Perhaps this approach has a disadvantage if it is not easy to replicate the methods that were used in preparing the derived statistics for each study.

4b. The Poisson likelihood might be reasonable; however, in practice we almost always use overdispersed models. If the Poisson model is indeed used, it is important to check for overdispersion in

the differences between data and fitted models. In some settings, there is a group-level variance parameter which catches the extra-Poisson variation and eliminates the need for an overdispersed model. That may be happening here (through the alpha_s and Q_sg parameters in the model in Section 8.6.1) but I am not completely sure.

5a. Section 8.4 discusses many potential sources of uncertainty. I do not know of other sources that should be accounted for, but, again, I am not an expert here.

5b. Characterizing the uncertainties as independent probability densities can't be correct, but perhaps it is a reasonable thing to do in practice. The use of "professional judgment" is problematic because such judgments are generally found to be overconfident (that is, often not containing the true values); however it's not clear what the alternative is. It could be useful to propagate each source of uncertainty to see how it contributes to the uncertainty in the final recommendations.

5c. The general approach for characterizing uncertainty used in Appendix C seems reasonable, but, again, with all the details, I could imagine that something important could have been left out.

5d. The assumption that errors combine in a multiplicative fashion could be reasonable. I am not sure how this assumption could be tested given the available data.

6a. I'm not sure why "measurement error models" are labeled as "weighted regression models." My impression is that measurement error models are simultaneous equation models (e.g., a regression model for y given x, along with a measurement model for x.observed given x, where in both cases, x is the true predictor and x.observed is the predictor measured with error). I don't see where "weighted regression comes in."

6b. I don't think weighted likelihood analyses are helpful here. For one thing, there's no direct way to get standard errors from weighted likelihood analysis; for another, the weights should, to be correct, include model error as well as measurement error, so that the appropriate weights depend on estimated parameters such as group-level variances.

6c. I think the Bayesian approach is most appropriate.

7. I don't fully understand the prior distributions in Section 8.6.2. It says that the alphas are likely to fall between 0.5 and 2, but then it puts a Uniform[0.1, 10] prior distribution on each. I have two suggestions:

(a) Check the inferences for the parameters after fitting the model. If the estimates are far from the originally suggested range of (0.5, 2), then see what's going on. Is it just a matter of there being a large posterior uncertainty? If so, perhaps more prior information would be useful. Or are the alphas estimated with precision to be far from their prior range (e.g., an estimate such as 4.0 with posterior sd of 0.5)? If the latter, you have to think harder about what is going on here. I have a similar comment for the priors on the KL_b and KM_b parameters.

(b) Consider a hierarchical model for these parameters. If you have many alpha_s parameters, you can give them a prior dist with parameters estimated from the data. That could make more sense than giving them independent noninformative distributions.

8. The bins seem to be chosen in a somewhat ad hoc, data-based manner. This is fine, but I'd suggest including more bins rather than fewer. I don't see the advantage in reducing the number of bins. I mean, I can see why you wouldn't want hundreds of bins, but I'd think that 5 or 10 bins wouldn't be a problem.

9. Again, I wouldn't focus so much on the binning strategy. I'd choose a reasonably large number of bins that could include whatever variation might be expected, then fit the model from there. I could see going back to the binning question at the end, when you get to policy questions, but I think it makes more sense to estimate for many bins and then do some smoothing at the end, rather than trying to combine bins in the main analysis.

Beyond this, I'd recommend posterior predictive checks, i.e., simulating replicated datasets from the model and seeing if they look like actual data. To do this, it would be first necessary to create some useful graphical displays of the data that are being used to fit the model. Analysis of residuals is fine, but it would be useful to also display raw data and replications of the raw data.

10. The idea of sensitivity analysis is fine although in practice I don't know that much is learned from these things. Still, I think it has to be done.

11. I don't really have any comments on the rules for selecting studies in the meta-analysis. I defer to others who are more familiar with the biomedical literature.

12. I defer to others on whether there are other relevant studies of lung cancer or mesothelioma that should be considered.

13. The extrapolation from dust to asbestos might be questionable but I don't know that it can be avoided. You could see what happens if these studies are excluded entirely, but if that leaves inferences that are too vague, maybe you have to go with the assumption.

14. I can't judge the validity of the assumptions underlying the exposure interpolations, but it seems reasonable to use the published data if that is the closest thing available.

15. Given the methods that are being used, the uncertainty about lifetime cancer risks can be summarized using simulations. However, I would also recommend estimating life-years lost, not just lifetime cancer risks. That way, costs can be expressed as dollars per life-year, which is a slightly different measure than dollars per life. Also could be broken down as estimated lives and life-years lost among smokers and among non-smokers.

Mr. John Harris

General response

The microscopic techniques used by EPA for risk evaluations have both benefits and limitations. The chief advantage to microscopy is to supply important size data information used for binning purposes. There are some modifications to these methods that critical information for risk assessment researchers.

PCM has historically been criticized for not providing any information of the fiber types counted. For mineral identification of asbestos in bulk materials, polarized light microscopy (PLM) has been the standard. However, for smaller fibers, PLM is limited since the analysis is done at 100x as compared to 400x by PCM. Recently, there are new innovations that allow modified PCM microscopes to utilize the mineral identification techniques of PLM on a PCM microscope. This can be a useful tool for investigators that have historical PCM slides that could be recounted to determine chrysotile:amphibole ratios at the PCM level. For studies with limited funding, this might be a good alternative approach to standard PCM alone.

TEM is the best approach for studies needing definitive analysis as described in the documentation provided for this advisory board. Typically for risk assessments, the ISO method (ISO 10312) is preferred as it offers the most analytical intensive method to define and count all fibrous particles regardless of size. The counting rules can be modified to allow analysts to include all fibers that would be normally counted by PCM, or PCM equivalent sized fibers.

One drawback to TEM is the reduced amount of area analyzed. Most asbestos fiber size distributions typically have very few long, thin fibers compared to a very high number of shorter fiber sizes. The reduced analytical area covered by TEM limits the detection of longer, thinner fibers under these conditions. Therefore, a stratified analysis approach makes better sense for TEM studies for historical or current risk assessments. The stratified analysis would use both lower magnification to search only for longer fiber sizes and higher magnification to analysis for all fiber sizes. The analyzed area at low magnification would be relatively large while the analyzed area for high magnification would be standardized to an established sensitivity required.

TEM studies provide a wealth of information of each mineral type present. TEM identification of amphiboles requires more rigorous mineralogical identification using the International Mineralogical Association (IMA) protocol proposed by Leake (1997). TEM chemical systems must be calibrated to better standards, such as microprobe standards, in order to more accurately identify differences in mineral types, especially with amphibole minerals.

In addition to having the correct chemical identification of the mineral type, accurate diffraction data is needed to differentiate minerals with similar chemical compositions to the mineral types of interest. Use of internal aperture standards is not sufficient. Measuring diffraction spacings over several rows or diffraction points are needed to accurately measure crystallographic dimensions to differentiate different mineral classes. This requires more astute attention to details for TEM analysts than routine samples containing commercial grade asbestos.

Some of the ISO counting rules may affect fiber dimensions and bias fiber dimensions for binning. For example, fibers with one end sufficiently embedded in a particle are given an estimated fiber length based primarily on the size of the particle and not the fiber itself. Fibers intersecting with TEM grid bars are recorded as twice their visible length. Complex structures with more than 9 individual fibers are noted as "+" instead of allowing an analyst to measure and count all structures. For complex structures with more than 5 substructures, the additional structures after the first 5 are recorded as "residual" and are estimated based on an average length and width.

Using a TEM combined with SEM capabilities (STEM) solves most of these fiber dimension problems. This enhanced capability allows an analyst to determine whether a fiber is actually embedded in the particle or lying free on the surface or under a particle. By looking at the surface features, we often see round particles composed of asbestos fibers tightly bound that are not countable by any method. The ability to analyze a complex fiber arrangement completely by diffraction, chemistry and surface features provide an accurate description of that structure for binning and identification purposes. Using SEM only for an evaluation of Superfund sites is problematic since only surface features and chemistry are available. Without the higher resolution of TEM, higher penetration of electrons through the sample at higher energies and diffraction capabilities, some particles may be identified definitively by SEM.

I hope this helps guide EPA in its efforts to accurately assess the environmental exposure at Superfund sites.

Charge question 14a:
Are the point estimates and uncertainty distributions for the fraction amphibole term proposed for each study scientifically valid?

Defer to statisticians, risk assessors.

Charge question 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?

No comment

If not, what alternative approach could be followed , or what additional data would be helpful?

No comment

Charge question 14c:
Are there any additional bi-variate TEM data sets available that would be useful in this analysis?

Some additional variables could include properties such as surface area and mineralogy.

Charge question 14d:
Are the point estimates and uncertainty distributions for the fraction amphibole term scientifically valid?

No comment

Charge question 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?

Eliminate impinger data and PCM data as surrogate data for TEM. Use only TEM data sets only.

How sensitive would the model output be to these changes?

Charge question 14f:
Would the model benefit by establishing a common lower cut-point in diameter to normalize the lower detection limit across studies?

Charge question 14g
Do the studies included in the model have surrogate data of sufficient quality and similarity to expected exposure conditions to support the model?

No comment

If not, what alternative approach could be followed?

Charge question 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?

No comment

Charge question 14i:
Are the extrapolation techniques used on the raw TEM data sets to meet bin definitions (e.g., 0.4 µm diameter) transparent, objectively presented and scientifically valid?

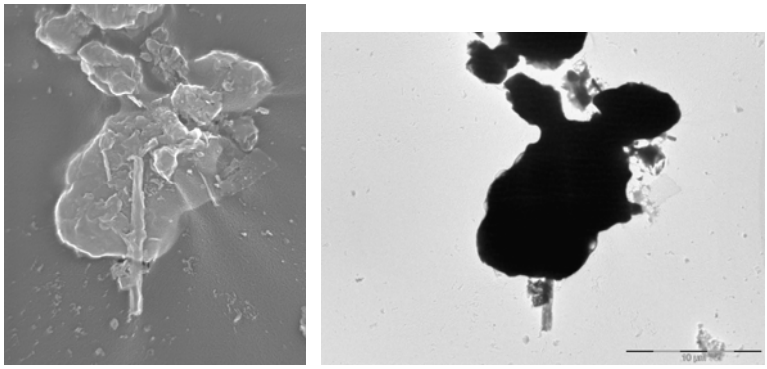
No comment

Are there alternative techniques that you would recommend?

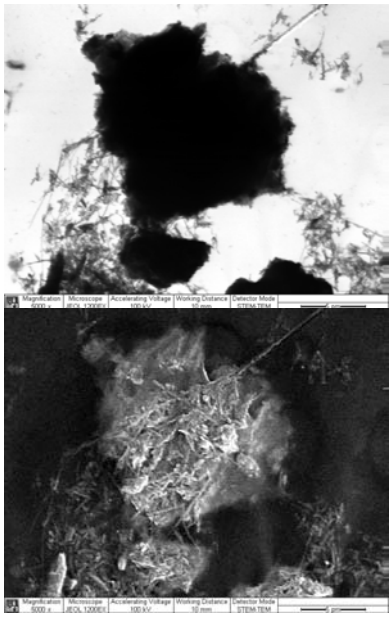
I would recommend that EPA either consider modifying ISO TEM methodology to better fit a more accurate identification of particle types and sizes common to Superfund sites or develop TEM methodologies of their own. Described below are some observations of our experiences with difficulties encountered at some of these sites.

a. Current use of the ISO counting rules for PCM equivalency using TEM procedures can create biases. These biases include:
    i. ISO 10312 method does not include nonasbestos fibers in its counts. They are noted as comments. Investigators should be aware of this bias when comparing ISO data with PCM data.
    ii. Matrices (fibers embedded in particulates) need surface imaging capabilities (i.e., STEM) to accurately determine the true fiber length as well as whether the fiber is truly embedded or simply landed on the surface (see image below). For fibers lying underneath particles, the TEM grid can be turned over and the fiber visualized on the bottom surface of the replica. There may be possible methods to determine fiber length within a matrix if needed. Under ISO counting rules,

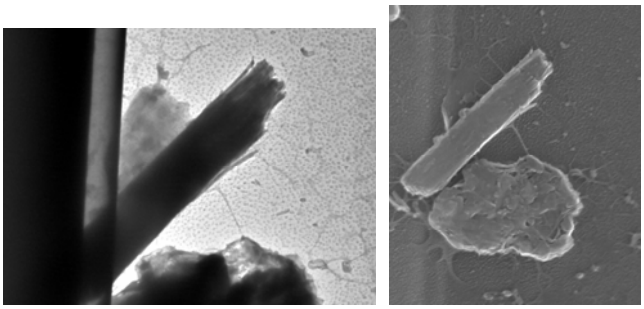
this structure length would be measured by the analyst at more twice the true length since more than 30% of the virtual length of the protruding fiber is obscured. By increasing a fiber length, the aspect ratio of the fiber is also increased and incorrectly reported.



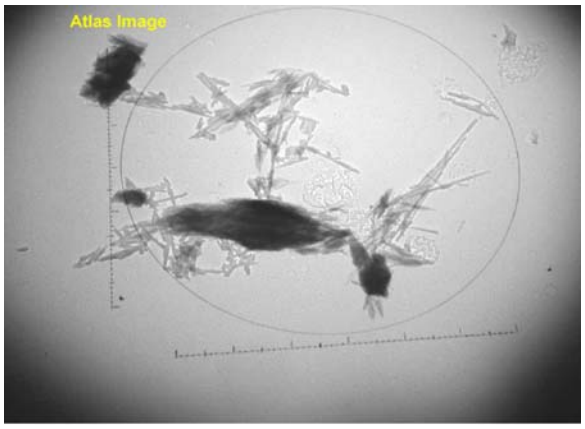
iii. For investigations of activity-based sampling involving risk assessments, our laboratories looks for noncountable particles with compacted fibrous asbestos that would not be included in either PCM counts nor ISO counting rules. These types of unique asbestos-laden particles need to be included in counts until future investigations determine the health effects of these types of particles. Shown below is an example of one of these particles from a naturally-occurring asbestos site in Swift Creek, Washington:



iv. Structures touching grid bars are given a measurement of twice its visible length. Most often, this creates a longer structure than actually exists.



v. There are limitations in recording data for complex structures that may bias reported numbers of fibers detected by PCM but not recorded effectively in ISO method studies. Substructure (or "total structure") counts larger than 10 are given a "+" and are no indication of the actual fiber loading. When more than 5 total structures are part of a primary structure, a designation of "residual" is applied and total structure counts are estimated. All total structures should be included. For example, the chrysotile structure below from the Atlas mine in California shows a complex structure that would be defined primarily using a "+" designation instead of detailed numerical values.



vi. All structures should be digitally imaged for future investigators as binning categories and other morphological characteristics are modified.

2. TEM EDS chemical analysis of amphiboles need to be standardized based on mineralogical methods such as the International Mineralogical Association method by Leake from 1997 There is no standardization among asbestos labs providing analysis which can create biases between PCM and TEM results.

The determination of asbestiform or nonasbestiform varieties of minerals should not be done during the analysis by the analyst. Instead, it must be done post-analysis by epidemiologists. Since the definition of cleavage fragments has been and will continue to be a moving target, all potential structures that fit 3:1 aspect ratio with minimum fiber lengths should be included in counts for future binning to determine suitability for current and future studies.

Dr. Karl Kelsey

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?

The committee chose to rephrase this question. I believe this to be a wise choice, as the question, as posed is confusing. I would agree that the epidemiologic data are consistent with the hypothesis that asbestos mineral type and particle dimensions have different potency for mesothelioma. This is based upon the multiple, consistent epidemiologic observations demonstrating differences in the occurrence of MPM in workers whose exposure was known to be to different types of asbestos.
However, I do not agree that the data are sufficient to indicate that differences in potency by mineral type or dimension exist in the case of lung cancer. The data are not consistent for lung cancer, with the South Carolina workers particularly standing out as a group primarily exposed to crysotile with very dramatic lung cancer risks.

In sum, the data are coherent for the suggestion that fiber type and dimension are important for MPM I am (and I believe the committee was) also supportive of an effort to represent this scientific consensus in the risk assessment process. The approach that is proposed, however, is flawed. The flaws are potentially fatal ones. Chief among the flaws is the attempt to use the occupational exposure data. These data are sparse and truly not amenable, in the vast majority of cases, to the multiple binning approach being proposed. Even the two bin approach is problematic, based upon the nature of the exposure data.

Finally, and importantly, the document presented for review by the committee was profoundly inadequate with respect to its representation of the animal and mechanistic data. Indeed, for example, there are data that suggest that there may be heritable susceptibility to the action of asbestos in generating MPM (see multiple publications from Carbone,.including: Dogan AU, Baris YI, Dogan M, Emri S, Steele I, Elmishad AG, Carbone M; Genetic predisposition to fiber carcinogenesis causes a mesothelioma epidemic in Turkey. Cancer Res. 2006 May 15;66(10):5063-8 and Roushdy-Hammady I, Siegel J, Emri S, Testa JR, Carbone M. Genetic-susceptibility factor and malignant mesothelioma in the Cappadocian region of Turkey. Lancet. 2001 Feb 10;357(9254):444-5). That is, there may be a susceptible subgroup of the population and, if that is the case, assuming that this subgroup responds to asbestos in the same fashion as the population as a whole is not conservative.
The work by the EPA, while laudable in its intent, is flawed in its execution. I am supportive of going forward with investigation of the impact of fiber type and dimension on mesothelioma risk, but any modeling exercise must be clearly labeled as what it is – the document reviewed has only the very loosest of biologic ties, does not consider susceptibility, includes uncertainty in exposure assessment that cannot conceivably be scientifically estimated and, in essence, seeks only to fit epidemiologic data to a better underlying mathematical construct. This effort is well intended and is an earnest and important research enterprise but it is not supportable as an endeavor that will contribute to better estimation of disease risk; that is, it is not an effort that is in the interest of overall public health at this time.

2) Please comment on the adequacy of the overview of EPA's OSWER Draft Report.

The sections of the report that serve as the scientific basis for the proposed dose-response modeling are very poor. As noted in my response to charge question 1, I would advocate that this document

acknowledge its tenuous relationship to biologic mechanism and not include the mechanistic sections. They are manifestly inadequate as written.
Simple examples: nowhere in this document is there any reference to the now large body of data that suggests that there may be a portion of the population that is susceptible to the toxic effects of asbestos (Carbone, M – multiple references above). The data describing the toxicology and "mode of action" of asbestos ignores completely the fact that both lung cancer and mesothelioma are known to harbor significant epigenetic gene alterations that contribute to the genesis of these diseases (Suzuki M, Toyooka S, Shivapurkar N, Shigematsu H, Miyajima K, Takahashi T, Stastny V, Zern AL, Fujisawa T, Pass HI, Carbone M, Gazdar AF.Aberrant methylation profile of human malignant mesotheliomas and its relationship to SV40 infection. Oncogene. 2005 Feb 10;24(7):1302-8.; Christensen BC, Godleski JJ, Marsit CJ, Houseman EA, Lopez-Fagundo CY, Longacker JL, Bueno R, Sugarbaker DJ, Nelson HH, Kelsey KT.Asbestos exposure predicts cell cycle control gene promoter methylation in pleural mesothelioma.Carcinogenesis. 2008 Feb 28.;Destro A, Ceresoli GL, Baryshnikova E, Garassino I, Zucali PA, De Vincenzo F, Bianchi P, Morenghi E, Testori A, Alloisio M, Santoro A, Roncalli M.Gene methylation in pleural mesothelioma: correlations with clinico-pathological features and patient's follow-up.Lung Cancer. 2008 Mar;59(3):369-76.;Tsou JA, Galler JS, Wali A, Ye W, Siegmund KD, Groshen S, Laird PW, Turla S, Koss MN, Pass HI, Laird-Offringa IA.DNA methylation profile of 28 potential marker loci in malignant mesothelioma.Lung Cancer. 2007 Nov;58(2):220-30.
Pu RT, Sheng ZM, Michael CW, Rhode MG, Clark DP, O'Leary TJ.Methylation profiling of mesothelioma using real-time methylation-specific PCR: a pilot study.
Diagn Cytopathol. 2007 Aug;35(8):498-502.)

There are also omissions of major animal works germane to the question of how fiber size and type impact mesothelioma and lung cancer risk.

3a) Do you agree that the lung cancer and mesothelioma risk models that are proposed are a scientifically valid basis for this fitting effort?

This is a complex question. The models are an attempt to parse crude data in a parsimonious fashion consistent with a set of assumptions. Uncertainty in exposure makes testing for validity impossible. Fitting the data are possible, but this does not necessarily imply the models are valid.

3b) Should additional model forms be investigated?

Yes; Dr. Peto had several suggestions that might be profitably pursued.

3c) For lung cancer, the current risk model is multiplicative with the risk from smoking and other cause of lung cancer. Should the nature of the interaction between asbestos and smoking be investigated further?

Given that there is no consensus on the mode of action of asbestos in generating the multiplicative interaction with tobacco, additional investigation is most certainly needed. The epidemiology strongly suggests that the interaction is multiplicative, but awaits data that might allow for a more complete description of the biology and the nature of this association.

If so, how should this be done?

The research community might be asked to investigate the nature of this interaction in grant funded research with and RFA that precisely articulated the questions of interest.

Do you think the model would be sensitive to additional quantification of the interaction between smoking and asbestos?

Yes. Any synergy will skew models and be very sensitive to this interaction in a modeled dose-response.

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)?

Fitting should be done in a fashion that is least prone to propagate error and misclassification.

What are the advantages and disadvantages of this approach?

As above**.**

4b) If so, is it scientifically justifiable to use a Poisson likelihood model for the observed number of cases in each group?

Poisson models seem appropriate for sparse data.

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?

I believe that multiple binning strategies are an attractive intellectual advance in risk assessment. However, there is really only one study that has compared anywhere near the number of exposure assessment techniques that would be needed to accurately assess the effects of using a multiple binning strategy. On the face of it, I believe that this is not possible. It will amplify uncertainty in unknown ways and is simply not good science.

If so, what would these length and width cutoffs be, and can these bins be implemented considering the limitations in the available TEM particle size data sets?

The human data primarily address below and above 10 um only. The data cannot address width adequately, as prior methods were unable to assess small width fibers. Hence, this cannot be done with any scientific validity.

8b) Are there any of these strategies that you feel do not warrant evaluation?

Yes**.**

If so, why?

The binning approach is not feasible as it propagates uncertainty, is based upon selective and incomplete data, has not been subjected to sensitivity analysis, and does not consider susceptibility.

8c) Assuming that fitting is performed using Bayes-MCMC, OSWER is proposing that a comparison of goodness of fit between different strategies be based on the Bayes Factor.

Do you agree that this is a statistically valid method for comparing binning strategies?

NA

Are there any other comparison methods you would recommend?

No.

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?

NA.

If so, how should that be done?

Dr. Paul Lioy

Section 8.4 – Characterizing Uncertainty in Exposure Data
5a. Have all of the important sources of uncertainty in cumulative exposure matrices been identified? If not, what other sources should be accounted for?

Based upon the observations of Dr. Peto, no. However, the most pressing issues relate to the need of a defined research program, especially for bullets 7-9. Experimental data is required to provide values other than default factors for long term applications of the Bin approach to Asbestos at Superfund sites and other fibers. For Asbestos alone, at superfund sites, the ratio of dust to fibers will be variable and not all associated with the asbestos fibers. Thus the need for data on actual fiber counts in the selected Bins, or any other Bins.

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?

Yes, this is fine for the initial application, but not necessarily reality. For the most important issues you will need better designed studies, and appropriate data collected to minimize uncertainties. You will be hard pressed to make totally justifiable assumptions, thus the need to do research at this time.

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 matrices? If not, what alternative strategies are recommended?

Yes, comprehensive.

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.

For uniform processes the error can be assumed to be independent, but it is not necessarily true for asbestos at superfund sites, which is a mixed waste from disparate origins.
Sum of absolute values of errors is more conservative, as well as the root mean square of the uncertainties.

Section 8.5. Fitting Approach

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?

Yes, weighing is reasonable but should be conditional based upon those variables having the highest impact on the estimates of exposure.

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

No comment.

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?

Yes. An excellent application for a modeling procedure that will improve results and evolve understanding *over time based upon new data*. Based upon the discussions at the meeting, new data is essential since dust to PCM ratios from industrial and occupational studies are not directly applicable.

Section 8.62 – Specification of Priors

7. 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?

The Bayes approach requires appropriate probability density functions. Given the level of understanding a uniform distribution with wide boundaries is a reasonable start for sensitivity analysis. These need to

be augmented with more appropriate data on asbestos at superfund sites to achieve a normal or log normal PDF. The Agency should take advantage of all the work being funded at Libby to begin to validate the Bin approach. This is an opportunity that should not be lost!

Section 10.2 – Extrapolation from Dust to PCM-Based Measures

13a. Is it scientifically justifiable to employ a default dust-to-PCM conversion factor when there are not site-specific data available?

After careful consideration of the extensive discussions made by fellow committee members at the meeting, No, it is not justified to use a default. The basic premise of transferability of dust in an industrial setting to superfund application has too much uncertainty. This problem needs to be eliminated by better data and determining the strength and utility of TEM measurements in the overall "bin" approach.

The agency needs to use the South Carolina data as a first level attempt at understanding of the utility of the Bin approach. However, it must look for opportunities, like Libby, to establish a comprehensive framework for the future validation of the Bin approach.

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?

Yes.

Section 10.3 – Extrapolation from PCM to Bin-Specific Measures

14a. Are the point estimates and uncertainty distributions for the fraction amphibole term proposed for each study scientifically valid?

No, uncertainties in the measurement and estimation techniques. Again the Libby research and the South Carolina data must be fully exploited in validation of the Bin approach.

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?

I have no answer, except what are the biases that are introduced, and how does one reasonably select the error PDF without data? The analyses will be highly uncertain, and could lead to poor conclusions. You need to obtain the TEM data to reduce uncertainties. Sort of an obvious answer.

14c. Are there any additional bi-variate TEM data sets available that would be useful in this analysis?

No answer, I am not knowledgeable on this point.

14d. Are the point estimates and uncertainty distributions for the fraction amphibole term scientifically valid?

See answer to 14a.

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?

No. However, this is related to 14b**.**

14f. Would the model benefit by establishing a common lower cut-point in diameter to normalize the lower detection limit across studies?

Yes, but it should be based upon inter-comparison studies of blind samples among the TEM analysts.

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?

No, need to obtain data that can be of value in validation studies

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?

Yes, because of the ability to complete sensitivity analyses.

14i. Are the extrapolation techniques used on the raw TEM data sets to meet the bin definitions (e.g. 0.4 µm diameter) transparent, objectively presented and scientifically valid? Are there alternative techniques that you would recommend?

Yes.

Section 11 – Utilizing Potency Factors to Compute Life Time Risk

15a. What method is best for estimating the uncertainty in lifetime cancer risk prediction?

A validation study must be completed to get a much better handle on uncertainties, and the overall utility of the bin method.

15b. Assuming that estimates of exposure at Superfund sites will also have uncertainty, how should the overall uncertainty in risk predictions be characterized?

Ambiguous question. For all risks or just asbestos risk? Site specific applications and data are usually the best way to minimize uncertainties.

Note, as discussed at the meeting:
The agency needs to do a better job of explaining the purpose of the proposed appraoch, initially superfund sites, and any intention of applying it to other asbestos issues, and fibers. As written, the committee was not given a full understanding of the over all conceptual framework

General Comment:
I agree with Dr. Lippmann on the need to have the Bin approach generalized for all fibers. In the US, Asbestos is primarily a Superfund and removal issue, however, other fibers are in use and being produced. *Note the aftermath of the WTC did not have any reasonable standards for clean up of many vitreous fibers etc. , and we still do not in 2008.* I cannot re-emphasize this point more.

Dr. Mort Lippmann
Overview Remarks
While the document being reviewed is narrowly focused on OSWER needs, any endorsement will lead to a document that has much wider implications to risk assessments for airborne fibers within and beyond EPA. Thus, it is important that the document be based on a broader review of the effects of fibers on human diseases, and of the properties of fibers that affect these diseases. In order to provide this perspective, the document should:

- Discuss fiber properties (lengths, widths, and biopersistance), and whether they differ as they influence mesothelioma, and lung cancer in humans and rats (Rodelsperger 2004).

- Discuss lessons learned from long-term animal inhalation studies to asbestos, other mineral fibers (Wagner et al. 1990), and synthetic vitreous fibers (SVFs) (Miller et al., 1999,), as well as those learned from human experience.

- Discuss biopersistence data from animal inhalation studies involving synthetic vitreous fibers (SVFs) with varying *in vitro* solubilities and *in vivo* solubilities in the lung as they inform differential cancer risks of chrysotile and amphibole asbestos fibers (Eastes and Hadley 1995, 1996), and commercial chrysotle asbestos (Davis et al. 1985) and chrysotile asbestos that is contaminated with tremolite asbestos (Pooley and Wagner 1988).

- Discuss relevance of fiber dimensions and biopersitence to risks from exposure to multi-walled carbon nanotubes. The Poland et al. (2008) paper demonstrates that nanotube bundles with >24% of lengths >15 *u*m were as or more toxic in short term assays as the long asbestos fibers shown by Davis et al. (1985) to be more carcinogenic than UICC amosite, while amosite with virtually no fibers <5 *u*m in length produced no tumors..

The risks of exposure to chrysotile fibers should be considered separately from those of amphibole fibers. Both are important, but they are not the same, even when fiber length and width are considered. It is important to consider both, because:

- Amphibole fibers in Libby, MT are of immediate concern, and can best be addressed by considering analogous human risks associated with other amphibole exposures. Also, a focus on exposures to fibers from the Libby mines and the human experience from those exposures is warranted because there are membrane filters that can be analyzed by modern measurement methods that can provide the most comprehensive data set on the lengths, widths, and compositions of amphibole fibers associated with a significant number of cancer cases that were well diagnosed.

- Exposures to chrysotile asbestos remain the most common exposures to carcinogenic fibers in the US, and EPA's guidance is needed on the risks associated with building maintenance and demolition.

- Much of the chrysotile asbestos in-place in buildings came from the Thetford mines in Quebec or other mining regions where a significant fraction of the raw fibrous material was tremolite asbestos, an amphibole form of asbestos that is much more biopersistent than chrysotile. The risks are therefore greater than those from amphibole-free chrysotle.

The concept of binning by fiber composition (e.g., amphiboles vs. chrysotile) and by fiber dimensions (e.g., length and/or width intervals) is sound and desirable in terms of the use of descriptors of measurable exposure variables that are much more closely related to the health risks associated with fiber inhalation. While the draft that we reviewed did not provide a sufficient amount of data on fiber size to justify any specific size-related bins, the SAB Panel's discussions pointed the way to data resources that would enable the authors to do so in the next draft document, and we urge that they do so. They must seize the opportunity to do so, because this area of the overall challenge is the one most amenable to significant progress. The literature on the influence fiber size and composition on toxicity and cancer is very extensive, albeit primarily in rodent models. However, in this case, interspecies extrapolation has much less uncertainty than in most cases because the physiological and anatomical differences affecting fiber deposition in, and clearance from, the airways are well known (Lippmann 1988, 1994, Case et al. 2000, Berman et al. 1995, Brody et al. 1981). Fortuitously, the recent publication by Stayner et al. (2007) on the associations of long chrysotile fibers with lung cancer in chrysotile textile workers in Charlestown, SC provides important new support for the importance of long fibers in carcinogenesis that was first demonstrated by Stanton and Wrench (1972) in rat instillation studies, and later by Davis and colleagues (1978, 1985, 1986, 1987) in a long series of 2-year inhalation studies in rats. By contrast, the uncertainties inherent in the risk models are much greater, with K_Ls and K_Ms varying among the historic studies by an order of magnitude or more, and with little prospect that retrospective re-analyses can refine them further.

Finally, it is important that EPA gets the exposure-related risk issues right this time and there would be no excuse if it doesn't, because:

- Our ability to routinely sample and identify airborne fiber distributions by length, width, and chemical and crystallographic composition is much more mature than in 1986.

- Our understanding of the influence of fiber length, width, and biopersistence on fiber toxicity is much more mature than in 1986.

- There would be continued reliance on outmoded risk models and grossly inappropriate air monitoring methods, which would therefore continue to cause unnecessary public concerns about de-minimus risks, unwarranted litigation, and asbestos risks that increase from unwarranted removals of in-place asbestos.

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Dr. Gary Marsh

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

I would agree that the available experimental and human epidemiology data support the hypothesis that the mineral type and size characteristics of asbestos are associated with markedly different risks for malignant mesothelioma. While support for this hypothesis as it relates to the risk for lung cancer is much less consistent, some recent work, such as the meta-analysis of Hodgson and Darnton (2000), provides some compelling support for the hypothesis that lung cancer risks are related to asbestos fiber type. Much of the evidence against this hypothesis for lung cancer stems from the epidemiology study of the Charleston, South Carolina asbestos textile workers, and the meaning and significance of these anomalous results remain a subject of scientific debate.

While the available epidemiology data provide support for this type of effort, it is apparent that we do not have adequate environmental data within the epidemiology studies to enable scientifically sound model fitting by fiber size bins. In particular, aside from the recent work of Stayner et al. (2007), we do not have TEM-equivalent data for any of the existing epidemiology studies and the proposed PCM to TEM conversion methods have been deemed by the SAB as too unreliable for practical purposes. This effort should be re-visited as more TEM or TEM-equivalent data become available that are directly related to human health outcomes.

Model fitting by asbestos fiber type (i.e., 2 bins) using the proposed methods appears to be feasible based on the available epidemiological data. An alternative approach to this latter effort might be an update of the meta-analysis performed by Hodgson and Darnton (2000).

2) Please comment on the adequacy of Section 4 (Overview of Human Studies) which serves as part of the scientific bases for the proposed dose-response assessment approach.

As the authors admit, this section is relatively brief, providing a general overview of the published studies that have reported adverse effects from human exposure to asbestos. The reader is referred to several government agency reports (IARC, 1977), WHO (2000) and ATSDR (2001; 2004) for more detailed reviews (it should be noted that many other excellent reviews are available in the peer-reviewed literature). This brief summary succeeds in providing some basic background information on the main non-cancer and cancer health outcomes as well as a brief overview of the role of fiber type with focus on relatively more recent studies. The section on mesothelioma is particularly brief, especially regarding studies of worker populations occupationally exposed to asbestos.

While the brevity of Section 4 may be appropriate for the larger goals of the overall document, an unnecessary and disconcerting disconnect exists between the literature for lung cancer and mesothelioma summarized in Section 4 and the literature actually used in the modeling protocol, which is described in general in Section 9 and in considerable detail in Appendix A. That is, many of the "primary" and "other" literature cited in Appendix A and used in the modeling of these two health outcomes were not cited in the general epidemiology overview in Section 4.

Because the epidemiological literature of human health effects from asbestos exposure is vast and can defy attempts to summarize adequately, a logical and consistent approach is needed when selecting a representative set of articles for background purposes. One simple alternative approach to the choice of lung cancer and mesothelioma studies in Section 4 might be to include, as a minimum subset, all the studies cited in Appendix A, as well as a representative selection of studies that did not meet the criteria for inclusion in Section 9, but are nonetheless relevant. For example, as described in two recent review articles (Goodman et al., 2004; Laden et al., 2004), a substantial number of epidemiological studies have consistently demonstrated the absence of risk from lung cancer and mesothelioma among vehicle mechanics exposed to low levels of chrysotile. The meta-analysis of Hodgson and Darnton (2000) should also be discussed in detail in this document as it bears directly on the objectives of this risk assessment.

Other areas that should be further developed in this section include: (1) the influence of fiber properties (composition, length, wide, durability) on the risks of human lung cancer and mesothelioma; (2) an overview of the animal toxicology data, especially the long-term inhalation studies, pertaining to asbestos, other mineral fibers and synthetic vitreous fibers, and their implications regarding human health risks; and (3) background information on the relevant asbestos exposures and perceived human health risks related to Superfund sites (including an in-depth review of the background and completed epidemiology studies at the Libby, Montana site) as this is the purported impetus behind this entire risk assessment exercise.

3a Do you agree that the lung cancer and mesothelioma risk models that are proposed are a scientifically valid basis for this model fitting?

This is a complex question, whose meaning was discussed extensively at the SAB meeting. My response to what I believe this question is asking was essentially included in my response to question (1) above. To reiterate, while the available epidemiology data provide support for this type of effort, it is apparent that we do not have adequate environmental data within the epidemiology studies to enable scientifically sound model fitting by fiber size bins. In particular, aside from the recent work of Stayner et al. (2007), we do not have TEM-equivalent data for any of the existing epidemiology studies and the proposed PCM to TEM conversion methods have been deemed by the SAB as too unreliable for practical purposes. This effort should be re-visited as more TEM or TEM-equivalent data become available that are directly related to human health outcomes.

Model fitting by asbestos fiber type (i.e., 2 bins) using the proposed methods appears to be feasible based on the available epidemiological data. An alternative approach to this latter effort might be an update of the meta-analysis performed by Hodgson and Darnton (2000).

Section 9 – Epidemiological Data Proposed for Use

Section 9.1 – Criteria for Study Selection

11a) Are the study specific selection rules proposed scientifically valid for the intended use?

The first and second proposed study selection rules (published in refereed journal and must provide data that can be expressed in terms of the quantitative risk models for lung cancer and/or mesothelioma) are straightforward, logical and scientifically valid. The wording of the second rule might be revised as "The study must provide data that can be *used directly or to provide accurate (reliable and valid) estimates* that can be expressed in terms of the quantitative ….", as this conforms better to the actual procedures that are proposed.

The third rule (the study cohort must consist of individuals who were exposed to approximately the same atmospheric composition of asbestos) is problematic as it is ill defined and does not seem to have been applied consistently to all candidate studies to include/exclude subjects. Moreover, confusion arises between the rule used to exclude studies due to exposure mixes and the detailed procedure described in Section 10.3 to estimate the "fraction amphibole data" (as well as the detailed procedure used to characterize the uncertainty in the fraction amphibole described in Appendix C). For example, contrast the first statement on page 74 under "cohorts with mixed exposure",

". . . OSWER recommends that studies in which health statistics were combined across two or more sub-cohorts exposed to substantially different workplace atmospheres should be excluded."

and the statement on page 72, Section 9.1.3:

"Hence, studies in which the cohort is known to be composed of individuals who are exposed to differing types of atmospheres are excluded from the data fitting process."

with the procedure on page 79 under "chrysotile plus amphibole":

"In some studies, the description of the workplace and its operations makes clear that both chrysotile and amphibole were used in the workplace. Ideally, data from TEM studies of air samples collected from the workplace would serve as a basis for estimation of the relative amounts of chrysotile and amphibole in the exposure atmosphere. However, in the absence of such data, information on the relative amounts of the different types of asbestos purchased or processed can be used as a rough surrogate for the relative amounts in the atmosphere."

The authors need to clarify the distinction between excluding studies based on mixed atmospheres, and including studies with mixed atmospheres and estimating the fraction amphibole. The clarification of this distinction should include a detailed explanation of the reasons why each of the excluded candidate studies was excluded.

Should any additional selection rules be applied?

Another selection rule that might be considered by OSWER is that the studies meet some specified level of data quality. As noted on page 69, this was recommended by some peer consultation panel members who reviewed the approach of Aeolus (1999, 2001), but was rejected by OSWER as an impracticable requirement. As noted on page 70, OSWER believes that the assignment of PDFs around each data input item should account for any differing levels of data quality between groups and studies

11b) Is it appropriate to assume that all workers in a cohort are exposed to 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 the appropriate assumption, what alternative strategy would be available?

See the response to 11a

11c) Should a set of minimum 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?

One approach to this would be to require that included studies meet the minimum "Good Epidemiology Practices or GEPs" described by Cook (1991). GEPs, which are now commonly applied in occupational epidemiology projects, were modeled after their "Good Laboratory Practices or GLPs" counterparts in the toxicology area, and provide standardized guidance regarding protocol development, reporting, quality assurance of data maintenance and documentation of analytic procedures.

11d) For lung cancer, OSWER's approach requires that there be at least two exposure groups per study in order to impose some constraint on the value of the study specific value of α. However, OSWER is proposing to use data from three cohorts of described by Enterline and Henderson (1979) event 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 excluded?

I believe this approach is appropriate and scientifically defensible although it may not be the best approach. The error associated with this estimation should be adequately handled adequately by the weakly informed prior for α described in Section 8.6.2. (i.e., each α_s is UNIFORM (0.1, 10)).

Another approach to estimating a study-specific α_s or global α would be to adjust the general population rate for lung cancer by the likely positive confounding by smoking that would occur in a blue collar working population. This could be done on a study-specific basis using the lung cancer rates of the local population or more globally by using national lung cancer rates. Estimates of the positive confounding by smoking could be obtained from available government reports or published epidemiology studies and incorporated into the adjustment using Monte Carlo-based sensitivity analysis (e.g., see Steenland and Greenland, 2004).

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?

First, some of the better detailed discussions of basic meta-analysis methods and related tests of homogeneity can be found in Bailey, 1987; Berlin et al., 1989; Deeks et al., 2001; DerSimonian and Laird, 1986; Fleiss, 1993; Higgins et al., 2003 and Petitti, 2001. However, it remains unclear exactly how these methods would apply or need to be modified for incorporation within the proposed risk assessment methods.

With the above qualification in mind, briefly, a basic meta-analysis should include a formal test of homogeneity of the risk estimates comprising a given meta-RR. Statistical heterogeneity of the RRs is assessed by the I^2 index, which describes the percentage of total variance across a given set of studies that is greater than that expected by chance. The I^2 index is calculated from the heterogeneity chi-square (Q) and degrees of freedom (df) statistics from a meta-analysis ($I^2 = 100\% \times (Q-df)/Q$), and is compared to the chi-squared distribution with n-1 degrees of freedom, where n is the number of studies. Many software packages are available to perform meta-analyses, including Stata10 (Stata Corp., 2007).

If you recommend statistical testing, please provide guidance on the reliability of a decision based solely on the test statistic.

With the above qualification in mind, because heterogeneity tests for meta-analysis of studies are generally conservative (i.e., they have low power) and to avoid type II errors, it is often recommended that a significance level of 0.10 instead of the more traditional 0.05. Also, some authors use these qualitative terms to characterize values for I^2: low (0-24%), moderate (25-49%), high (50-74%) and very high (>75%) (Fayerweather, 2007).

If testing produces evidence of heterogeneity between some studies, what steps can be recommended?

With the above qualification in mind, when the null hypothesis of homogeneity is not rejected, then a fixed effects model is preferred. If there is significant heterogeneity, a random effects model is preferred. The fixed effects model assumes that any differences between study results are due solely to chance, while in the random effects model the observed effect is assumed to vary around some average with sampling error.

Random effect models should not be used to "explain away" heterogeneity. In the presence of significant heterogeneity, efforts should be made to explore the reasons for the heterogeneity and/or to reduce the level of heterogeneity. These efforts might include stratification by other study factors to identify homogeneous subgroups or meta-regression, in which the characteristics of the studies or the subjects of the studies are used as explanatory variables in a multivariate regression with the effect size (or some measure of the deviation from the summary measure of effect) as the dependent variable.

Section 9.2 and 9.3 – Studies Proposed for Use and Studies Excluded

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?

The above recommendation that the model fitting be limited to fiber type bins notwithstanding, it seems that the Stayner et al. (2007) paper that used TEM data to reevaluate risks in the South Carolina cohort should be considered for inclusion in any model fitting effort that attempts to address fiber size. Otherwise, I am not currently aware of other studies that should be included in the model fitting effort.

Per my response to question 11a, it would be helpful to see a detailed discussion of the reasons why each of the excluded candidate studies were excluded from the model fitting exercise. In other words, it would be useful to see the entire list of candidate studies considered by OSWER for inclusion.

12b) Are there any studies that are currently proposed for inclusion in the analysis that you believe should be excluded? If so, why?

As noted during the SAB meeting, a number of the proposed studies for evaluating lung cancer risks utilized internal comparisons and thus do not provide an estimate of alpha. All the studies currently included do appear to have satisfied the first two selection criteria, and as noted above, uncertainties exist in the current document regarding the selection of studies based on mixed atmospheres.

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?

As noted above, while the available experimental animal and human epidemiology data provide underlying support for this type of effort (i.e., support regarding differential risks for mesothelioma and possibly lung cancer by fiber type and size), it is apparent that we do not have adequate environmental data within the available epidemiology studies to enable scientifically sound model fitting by fiber size bins. In particular, aside from the recent work of Stayner et al. (2007), we do not have TEM-equivalent data for any of the existing epidemiology studies and the proposed PCM to TEM conversion methods have been deemed by the SAB as too unreliable for practical purposes. This effort should be re-visited as more TEM or TEM-equivalent data become available that are directly related to human health outcomes.

One questionable area related to the availability of epidemiology data is how the model fitting process for lung cancer will explicitly account for available (or unavailable) data on tobacco smoking histories. Appendix A of the draft document describes the disposition of smoking history data for each of the included studies. These data range from none to detailed data at the individual subject level. Without any provision for the available data and considering the effect modification evidence for smoking and asbestos, the model fitting will be combining higher risks from asbestos among smokers with lower risks among non-smokers. It is also not clear why smoking data were not considered as a source of uncertainty in Appendix C?

Also, given the uncertainties surrounding the inclusion or exclusion of studies involving worker exposures to mixed atmospheres (see response to question 11a), it is not entirely clear how the modeling of the potency factors will explicitly account for mixed atmospheres when they occur.

Dr. Luis Ortiz

Question 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?

The data available supports the notion that differences in asbestos type and particle dimension confer significant differences in carcinogenic (as it pertains to lung cancer and mesothelioma) potency and therefore, the proposed new approach appear to be warranted to more definitively resolve the issue. However, this new proposed approach levels on the harmonization of pre-existent data (mostly epidemiological reports from well characterized cohorts of asbestos exposed subjects) to adopt a multi bin mathematical approach to estimate cancer risk according to mineral groups and measurements of particle size based on transmission electron microscopy. Therefore, it appears that a number of simplifying assumptions that were necessary during the harmonization process deserve further analysis (even prospective validation) and as such the new approach should be considered interim.

Question 2) Please comment on the adequacy of Sections 2-5 of the overview of EPA's OSWER Draft Report.

Sections 2-5 are designed as a backbone to illustrate the needs of the OSWER report. These sections should facilitate analysis of the OSWER document by the members of SAB and the broader public. A potential consequences of endorsing such document is that the general public may equate this support with that of and official change in EPA policy toward asbestos carcinogenic potency then it may be advisable that such document be supplemented to cover a number of item as discussed below.
There must be ample discussion in the introduction of these sections stating that this is an interim approach to assess the question of how physical difference in the composition of asbestos fibers modify its cancer inducing capacity. A clear description of the historical and current EPA's needs that motivate the OSWER report should be stated. Specifically, the document should make reference to the current EPA priorities in the clean up efforts of superfund sites such as Libby, Montana and other sites around the US (as discussed during the SAB meeting in Washington, D.C.).

Section 2 is adequate in length for the purpose of the OSWER report as it describes both the fundamental aspects of the differences in asbestos fibers and clarifies basic aspects of the methodology used to study the question at hand. However, a more detailed discussion of the importance of the physical aspects of the asbestos fibers (length as well as width) and whether or not these properties bear directly in the carcinogenic (lung or mesothelioma) capacity of the asbestos fibers is necessary.
Although Section 3 provides a summary of pertinent data linking the experimental exposure of animals to asbestos with the subsequent development of cancer this section does not provide description of the in-depth biology necessary to support the larger questions addressing the fitting of the published human data as it pertains to the evaluation of whether differences in asbestos type and fiber dimension confer significant differences in their ability to induce tumors (which is the question at hand).
This section of the OSWER report should also clearly describe that currently there is a definitive paucity of scientific information, both in animals (Stanton and Wrench J. Natl. Cancer Inst. 48:797-821,1972) as well as humans (Stayner LT et al. Occup Environ Med. 2007 Dec 20; [Epub ahead of print]) regarding

the use of TEM to characterize fiber size specific asbestos exposure. In the case of Libby there are samples that could be subjected to TEM analysis to properly address this deficiency. Therefore, this aspect could be incorporated in the report as a scientific and investigational priority to the agency Similarly, there appears to be room for improvement regarding the description of a body of published work describing the factors that modify the environmental host interaction and determine individual susceptibility to asbestos-induced cancer. Surprisingly, there is little mention of experimental animal data addressing the relationship between smoking and its effects on the asbestos induced malignancy (which is charged in question 3).

Sections 4-5 constitute a summary of studies describing the effects of asbestos in human beings and provide an overview of the potential biological mechanism of the asbestos mode of action. Although these sections are intended as an introductory summary to the reader of the OSWER draft report these sections are superficial in relation to the importance of the work proposed by the OSWER and although they summarize some of the key published data linking asbestos to both lung cancer and mesothelioma they do not address in detail the issue of whether variability of fiber type confer differences in potency towards carcinogenesis. The summary of the data linking asbestos to mesothelioma is particularly brief and would benefit from adding additional references (some of which are subsequently included in Appendixes). As was the case of the animal data, there are almost no descriptions of the potential interactions of asbestos with smoking and certainly, no consideration to the relevance of individual susceptibility as it pertains to the pathogenesis of lung cancer and mesothelioma.
Finally, the approach to the biology of the carcinogenic mechanisms of asbestos is timid, lacking in molecular depth and not providing a biologic foundation to back the epidemiologic approach map (that could be experimentally adopted to support the imminent fitting of the human epidemiological data) to indicate how the proposed differences in the physical properties of the asbestos fibers determine their carcinogenic potency. Therefore, although the number of references could be adequate for a report of this magnitude, a more clear articulation of these references could be structured to reflect the historical perspective that motivated the adoption of the fitting methodology proposed in the current report.

Question 3: Do you agree that the lung cancer and mesothelioma risk models that are proposed are a scientifically valid basis for this fitting effort? Should additional model forms be investigated?

In general the approach is sound and so the modeling is scientifically valid. However, the development of a progressive approach to determine the importance that asbestos fiber type and size confer to specific risk estimates requires the availability of data sets derived with the use of transmission electron microscopy (TEM) to appropriately describe the asbestos fiber size and length distribution to which subjects are exposed. Currently, it appears that the only published data available is that of Stayner et al (Occup Environ Med. 2007 Dec 20) characterizing the South Carolina textile cohort. Therefore, further validation may be pertinent at this point and it appears that the superfund at Libby could offer a great opportunity to validate the measurements of the amphibole particles by using TEM as appropriate filters are available.

As presented in the OSWER document, these data are not available and therefore the working data sets had been extrapolated from pre-existent cohorts (17 in total). These calculations assume a number of simplifying assumptions that introduce bias. While the current OSWER report acknowledge most of these bias and adopted stringent protocols to limit and correct them questions remain regarding the ability of this fiber size specific TEM matrixes to account for within industry variation. Thus, as

demonstrated in Dement et al 2007, application of TEM to a well described (previously characterized by use of PCM-based fiber count) cohort of subjects from the Charleston, SC, textile plant identified differences in asbestos fiber size among the different operations in this plant. Thus, the TEM-generated matrix did not accurately predict inter occupational and industry specific variations of these measurements.

TEM data sets appear to more adequately provide evidence that suits their use in assessing the risk of asbestos-induced lung cancer. However, this does not appear to be the case with mesothelioma and fewer TEM derived matrixes are available due to the prevailing limitations in inferring the equivalent calculations.

Similarly, there appear to be inconsistencies in judging the rational for excluding the value of data sets from specific cohorts to conduct risk assessment. A clear example of this, identified by the correspondence shared by the members of the asbestos SAB, is the exclusion of the studies by Selikoff and Seidman on insulator workers.

As stated in the OSWER report the current notion regarding the interaction between asbestos and lung cancer is that this relationship is multiplicative. However, given the ongoing changes in the biology of the lung cancer (increased number of subjects with lung cancer had not been smokers), the decrease in the population exposed to smoking, then it appears that it is imperative that the nature of this interrelation be revisited at this point. The proposed model appears adequate to do so and it appears premature to look for alternative methods as no other strategy (ies) has been validated to assess the asbestos conferred risk of lung cancer or mesothelioma models that are likely to be superior to the current one.

Question 4: 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)?

The rational to support binning by fiber composition (amphiboles vs. chrysotile) and by fiber dimensions (length or width intervals) is sound as the information available support the concept that these variables may directly influence the biological effects of asbestos fibers inhaled into the lung or deposited in the pleura. Otherwise, it was the general consensus at the SAB meeting that the OSWER report did not provide a sufficient data to support binning based on fiber size. However, as stated above, the SAB consider that the current efforts at Libby offer a unique opportunity to prospectively study this important question.

Question 8: 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 these length and width cutoffs be, and can these bins be implemented considering the limitations in the available TEM particle size data sets?

As discussed above the rational for this approach appears to be reasonable. However, the fundamental issue that limits this approach is the lack of current available data to support the methodological approach. As discussed in the SAB meeting currently, there is only one well-characterized cohort of asbestos exposed subjects in which fiber characteristics have been analyzed by TEM (Stayner LT et al.

Occup Environ Med. 2007 Dec 20) as such this limitation (paucity of validated data) decreases enthusiasm for the approach.

I would also like to defer in this questions to the comments consigned at the SAB by Dr. M. Lippmann in which he stressed the fact that while descriptions of bins according to length make sense for lung cancer (Lippmann, M. 1994. Occup. Environ. Med, 51:793-8) they may not be suitable for studying the causation of mesothelioma as fiber diameter determine the ability of asbestos fiber to traffic via lymphatic channels to deposit into the pleura.

Questions 11 and 12: Are the study-specific selection rules proposed above scientifically valid for the intended uses? Should any additional selection rules be added? Is it appropriate to assume that all workers in a cohort are exposed to the same atmosphere with a constant composition (mixture of asbestos types and sizes is constant) unless the authors report information to the contrary?

The reality is that there is a paucity of data to support such an enterprise and only one recently published article has comprehensible TEM characterized asbestos fiber properties and correlated them to relevant epidemiological data (Stayner LT et al. Occup Environ Med. 2007 Dec 20). Therefore, every effort should be made to consider available information (transparent and scientifically valid data that could undergo stringent and un-bias scrutiny) and incorporate this data if there is a valid scientific reason. As mentioned above, recent information indicate that even data set obtained by using fiber size specific TEM matrixes do not account for within industry variation (Dement et al 2007). Thus, this appears to be an area ripe for research application to pertinent cohorts such as the Libby mining sites.

Questions 13 and 14: Is it scientifically justifiable to employ a default dust-to-PCM conversion factor when there are no site-specific data available? 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?

The answer to this question is not because previous experience has shown that impinger data cannot reliable used to generate PCM comparisons. Therefore, it appears that this limitation will also limit the use of such data to estimate TEM fiber size distributions. Similarly, as discussed during the SAB meeting, there are limitations to the ability of PCM estimates to produce consistent fiber size distributions as measured by TEM.

Asbestos Charge Questions Section 3 (Toxicology) & Section 5 (mode of action) and
Please comment on the adequacy of these sections (3-5), which serve as the scientific bases for the proposed dose-response assessment approach.

Sections 3-5 are designed as a backbone to illustrate the needs of the OSWER report. These sections should facilitate analysis of the OSWER document by the members of SAB and the broader public. A potential consequences of endorsing such document is that the general public may equate this support with that of and official change in EPA policy toward asbestos carcinogenic potency then it may be advisable that such document be supplemented to cover the following items.

1. There must be ample discussion in the introduction of these sections stating that this is an interim approach to assess the question of how physical difference in the composition of asbestos fibers modify

its cancer inducing capacity. A clear description of the historical and current EPA's needs that motivate the OSWER report should be stated. Specifically, the document should make reference to the current EPA priorities in the clean up efforts of superfund sites such as Libby, Montana and other sites around the US (as discussed during the SAB meeting in Washington, D.C.).

2. A more detailed discussion of the importance of the physical aspects of the asbestos fibers (length as well as width) and whether or not these properties bear directly in the carcinogenic (lung or mesothelioma) capacity of the asbestos fibers is necessary.

3. The report should also clearly state that currently there is a definitive paucity of scientific information, both in animals (Stanton and Wrench J. Natl. Cancer Inst. 48:797-821,1972) as well as humans (Stayner LT et al. Occup Environ Med. 2007 Dec 20; [Epub ahead of print]) regarding the use of TEM to characterize fiber size specific asbestos exposure. In the case of Libby there are samples that could be subjected to TEM analysis to properly address this deficiency. Therefore, this aspect could be incorporated in the report as a scientific and investigational priority to the agency.
4. Similarly, there appears to be room for improvement regarding the description of a body of published work describing the factors that modify the environmental host interaction and determine individual susceptibility to asbestos-induced cancer. Specifically, there is little description of experimental animal data addressing the relationship (additive versus multiplicative) between smoking and asbestos exposure on its carcinogenic effects.

5. Finally, the approach to the biology of the carcinogenic mechanisms of asbestos is timid, lacking in molecular depth and not providing a biologic foundation to back the epidemiologic approach map (that could be experimentally adopted to support the imminent fitting of the human epidemiological data) to indicate how the proposed differences in the physical properties of the asbestos fibers determine their carcinogenic potency.

Dr. Julian Peto

Leslie Stayner recognises that his response raises various crucial points in relation to fibre type and other issues on which the Panel do not agree. I have therefore addressed his remarks directly in my response (see below) rather than writing a separate commentary. Our response to the EPA should identify crucial areas of disagreement. Whether amosite causes a greater lung cancer risk than chrysotile is one such issue, although in the absence of adequate exposure data in fibre/ml longer than 5 microns in any of the epidemiological studies, let alone in subdivisions of length, this is not a well-defined question.

This approach would clarify the points of disagreement and give the public an idea of who holds which opinions, and why they hold them. My only plea is that we agree to distinguish clearly between scientific evidence and consideration of the social or legal effects of the EPA's position. Both are proper issues for discussion, but they must not be confused.

Two fundamental weaknesses in the proposed analysis were discussed by the Panel but are perhaps not generally appreciated. The first is the assumption that the lung cancer risk is proportional to duration of exposure. The draft EPA report states that this was established in the 1986 EPA report, but it would be useful for the evidence on this to be reexamined systematically, particularly in cohorts exposed to chrysotile. Amphibole exposures of less than 5 years duration have caused substantial lung cancer risks,

but this does not seem to be true of chrysotile, perhaps because it disappears from the lung much more rapidly.

The second and more important weakness is the virtual absence of any reliable measurements of the historical exposure levels that caused substantial cancer risks in any of the cohorts. Fibre counts, let alone counts in each range of fibre size, were non-existent before the 1960s, different methods of measuring particles gave very different readings, and parallel measurements of particles and fibres gave different ratios in different workplaces, and even in different areas within the same industry using the same instruments. Last but not least, the most heavily exposed workers were not monitored at all. Richard Doll and I discussed these problems at length in our UK report (Doll R and Peto J: Asbestos: Effects on health of exposure to asbestos. Health and Safety Commission. Her Majesty's Stationery Office, London 1985). There were no systematic historical data on most amphibole workers, and the following extracts from our report illustrate the weakness of the best of the chrysotile studies.

S Carolina chrysotile textile factory: 'The exposure data obtained in this factory are less extensive than appears at first sight. A total of 5576 samples were taken before 1975, but only 376 midget impinger samples were taken before 1960, including 112 by a life insurance company and 81 by the US public health service or state board of health between 1930 and 1945. It is difficult to know how representative these were, and many activities, including fibre mixing with pitch forks in an area where there was no dust suppression, were unmonitored.'

Quebec chrysotile mines and mills: 'The Quebec [exposure] data, which are the most extensive, began to be collected in 1949…….There were no routine measurements in the open pits, and few in the underground mines, and the exposure estimates assigned to the substantial proportion of the cohort who worked in these areas may be particularly unreliable. The conversion of high particle counts to fibre counts is also difficult, as only 34 (5%) of the parallel samples [taken in the1970s]… exceeded 3 mppcf, while the estimated average exposure levels of men with 20 or more years service ranged from 4.2 mppcf for "low" exposure to 46.8 mppcf for "very high" exposure….As in our own study [the Rochdale textile factory] the lack of contemporary particle and fibre counts during the period when the exposures that caused the highest observed excess risks occurred, together with the poor correlation subsequently observed between particle and regulated fibre counts, make it impossible to quantify the dose-specific effect at low fibre counts with much confidence.'

The basic data on which the proposed analyses depend are thus so unreliable even for chrysotile that we concluded: 'We hesitate to suggest that the [exposure data] are insufficiently reliable to justify making any quantitative extrapolation from past experience to the effects of current exposures. Nevertheless, this may in fact be the case, and we may have to be satisfied with qualitative conclusions based on knowledge of the direction in which progress has been made and epidemiological observations of the effects of qualitatively different types of exposure.' In relation to the amphiboles we concluded: 'The use of crocidolite and amosite (and, we assume, other types of amphibole asbestos) is, in practice, more hazardous than the use of chrysotile, possibly because of the longer residence time of amphibole fibres in the lungs, but possibly also for other reasons ….No worthwhile data are, however, available to enable quantitative comparisons to be made between the effects on humans of the different fibre types. It can be concluded only that the use of amphiboles should be avoided whenever possible and that extra precautions need to be taken when exposure to them occurs. It is possible, though we believe unlikely, that the hazardous effects of chrysotile are mainly due to contamination with small amounts of

tremolite.' I am not at all sure that the limitations in the exposure data that we drew attention to in 1985 have been overcome, but they should certainly be discussed more critically in a new EPA report than they were in the last one.

I would like two further documents that are mentioned in my response to be attached to the Committee's final report:
(1) My 1985 comments on the first draft of the 1986 EPA report (attached at the end of this document) directly addresses the main points of disagreement.

(2) My 1981 report to the EPA on asbestos in schools (also attached at the end of this document) used the same models for lung cancer and mesothelioma as the 1986 report and the current draft, and is also directly relevant. It was never made public, and by 1985 it could not be traced in the EPA's archives. Incidentally, I would like the fact that I developed these models to be acknowledged.

Response by Julian Peto to Leslie Stayner's comments on the EPA draft report: Proposed Approach for Estimation of Bin Specific Cancer Potency Factors for Inhalation Exposure to Asbestos

I agree with Leslie Stayner's comments on fibre dimension but I disagree with his statement that there is little or no difference in lung cancer risk between chrysotile and the amphiboles. He offers no evidence apart from a reference to the factory in S Carolina to explain why he disagrees with the majority of independent scientists and the pooled data on this issue. The idea that even a few years of exposure to chrysotile at levels averaging 1 fibre/ml or less could cause a substantial risk of either mesothelioma or lung cancer flies in the face of all evidence. Amosite exposure can increase the lung cancer risk substantially after brief exposure (Seidman et al 1979), but substantial chrysotile exposure has not been shown to do so. As we mentioned in our 1985 report to the UK Health and Safety Commission (Doll and Peto 1985), the studies that Richard Doll and I conducted in a Rochdale textile factory using mainly chrysotile gave a dose-specific estimate for lung cancer of the same order as the S Carolina study (Peto et al 1985). The SMR for lung cancer was about two in workers exposed for between 10 and 20 years at levels that probably averaged between 5 and 10 fibres/ml, but in men who worked for 1-5 years the SMR was not detectably increased (7 lung cancer deaths observed, 9.9 expected). Note that these analyses were restricted to men employed after 1932, when conditions had greatly improved. There were 13 lung cancer deaths compared with only 1.6 expected and 2 mesotheliomas in men with more than 10 years of very heavy chrysotile exposure in this factory before 1932 (Peto et al 1985). There was a large excess of respiratory cancer in the S Carolina factory, but the excess in men exposed for 1-5 years (McDonald et al 1983: 10 observed, 6.1 expected) was not statistically significant. In Quebec chrysotile miners the lung cancer SMR was 2.4 in workers who were heavily exposed for more than 20 years in the 1930s and 1940s and 1.5 for 5-20 years of exposure (23 lung cancer deaths) but was not detectably increased for less than 5 years (27 deaths) (McDonald et al 1980). Such data convinced most independent scientists many years ago that amphiboles are more dangerous than chrysotile for lung cancer as well as for mesothelioma, and the 1986 EPA report was wrong in its fixed view that there is little difference in hazard. My formal comments to the EPA on that report (attached letter to Dennis Kotchmar dated 13th Aug 1985) are directly relevant to the questions that we are now readdressing 23 years later. The report that EPA commissioned me to write on asbestos in schools in 1981 is also attached. In it I applied the lung cancer and mesothelioma dose and time models that I had published in 1979, and these have been used in most subsequent Government reports in the US and Western Europe,

including the 1986 EPA report and the current draft. Assuming that dose-response is linear, that the mixture of fibre types in schools would be similar to that of US insulators' exposure, and that insulators were on average exposed at 30 fibre/ml, I showed that the lifetime cancer risk at an average of 0.002 fibre/ml in schools would be of the order of 1 in 100,000. This report was not published, and a copy could not be found in the EPA's archives when I mentioned this in 1985 while reviewing the draft 1986 report.

Leslie concludes by stating that any research by the EPA on differences in risk between asbestos fibres that is published before a ban on the few remaining uses of chrysotile has been introduced is an insult to those now dying of mesothelioma. They and their generation will in fact be completely unaffected by any change in current exposure, and we cannot base our scientific conclusions on this dubious prediction of their reaction. Some estimate of the number of future deaths that this ban might prevent or cause in the US would be more relevant. That requires either more research or a consensus statement by panel members on the plausible range of health effects of different policies on asbestos management based on existing models and evidence. My personal view is that a ban is now irrelevant, and the important issue is whether the risk from the amosite and crocidolite that remains in some ships and waste sites and in many buildings can and should be abated.

Our report should be open about these scientific and political differences of opinion. We should include an appendix comprising Leslie's statement, this one from me, and comments from other Panel members on fibre type differences in hazard so that the public can judge the spectrum and credibility of expert opinion for themselves. We cannot write a report that conceals these disagreements, and they need to be clarified. The reservations about the weak epidemiological evidence on fibre size that we all expressed at the Panel's public meeting on July 21-22 are already being misrepresented as doubts about differences between chrysotile and amphiboles.

Dr. Christopher Portier

General Comments: Two key elements are not readily addressed in this proposal. First, what is the scientific support for the underlying model. Because the entire analysis is based upon the assumed model and models within this class, there should be some discussion of the scientific basis for this model. This is confounded by the second issue, and that is the loss of data, especially for mesothelioma, that results from the need to divide the exposure into the two separate forms. I view the epidemiological data as falling into three separate datasets; everything appropriate for 1 bin analysis (group A), everything appropriate for a 2 bin analysis (Group B) and everything appropriate for a 4 bin analysis (Group C). I assume that group C is a subset of Group B which is a subset of group A. I would suggest you do three analyses for the 1 bin case (Groups A, B and C), two analyses for the 2 bin case (groups B and C) and a single analysis for the 4 bin case (group C). Comparing A to B to C for the 1 bin case tells me what is the impact of study selection in this situation. Same for the 2 bin case. These types of comparison will tell about the impact of study selection on the posterior distribution for the potencies. If there is a substantial difference in central tendency or variance in the posteriors, the Agency should consider not using the binning approach or develop a method that allows for all of the data to be used in the analysis or in the validation of the analysis.

Charge Question 1: I have insufficient detailed knowledge of all of the studies being evaluated, especially on the clarity of the exposure, to provide any definitive opinion on this question.

Charge Question 2: My answer to this question is no. I feel the authors could have spent a bit more space on the toxicological data because the clarity of the differences in response for fiber size and type could be better supported through a careful examination of these data.

Charge Question 3: There was considerable discussion of potential differences in absorption, distribution and elimination of fibers as a function of size, chemistry and fiber type. As a long-term goal, the Agency might wish to pursue the development of models for ADME as a tool for potentially addressing differences in risk due to the different types of particles.

On the question of whether the models that are proposed are a scientifically valid basis for the fitting effort, I believe it is. Given that all they have to work with is population-based epidemiological data, the exercise is nothing more than a curve-fitting exercise to explore trends in the data. As such, these models are as good any one might wish to use and better than some due to the long history of these models in asbestos-related epidemiological studies. This is not to say the model is correct; there is no doubt that this multiplicative model is a simplification of a much more complicated biological process. The authors may wish to try other models to explore the implications of model choice on the eventual predicted risks. Seeing no differences from a broad spectrum of models gives more confidence in the results. Seeing large differences may lead to a discussion of potential assumptions that support one model in favor of another or to additional data/experimentation that could lead to one specific answer.

Charge Question 4: The assumption of Poisson variation may be correct, but should be evaluated by testing for over-dispersion. If there is over-dispersion, an appropriate change should be made to allow for extra-Poisson variation.

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?

As far as I can tell, yes. However, I am no expert on this.

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?

Of course this assumption is wrong. The real question one has to ask is if this is appropriate in this case or whether there is sufficient correlation between uncertainties that by treating these as independent one is inflating the overall uncertainty. A sensitivity analysis of the distributions chosen for each factor will tell you something about the relative importance of that factor. It would be wise to search for a data set

that might tell you something about correlations between the most important factors and try using these observed correlations to look at the sensitivity to correlation.

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?

The approach seems appropriate. I am concerned that several distributions are based upon expert judgment and ranges that seem to have no direct reference associated with them. These types of judgments tend to be fairly optimistic and I suggest the sensitivity analysis look at this carefully.

In trying to find priors, my first choice would be to identify data that informs the prior directly, start with an uninformed prior and use a hierarchical Bayesian model and update the prior in each iteration. If this is not possible, use the scant data to develop an informed prior that is not updated. Failure to do this, I would use an uninformed prior, do some sensitivity analysis and, for priors that seem to be important, possibly se expert solicitation to identify a prior.

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.

There is really not much that can be said here about this approach. There does not seem to be a way to test the assumption. Clearly other approaches (e.g. additive) could be used and would likely yield different results. But these would also not appear to be testable with the available data.

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?

I am not certain why "weighted regression" enters into this? It is appropriate to use a measurement error model to account for measurement error in exposure data from an epidemiological study.

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

Not sure what is being asked here since you have chosen the Bayesian approach. For the Bayesian approach, the approach for including data quality should be fine.

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?

The authors are very critical of the ML method but do not apply the same scrutiny to the Bayesian methods. You basically can't get something from nothing. The Bayesian approach is giving you a different answer and is based on a range of assumptions that may be very wrong but generally are not testable. The rosie picture painted for the Bayesian approach should be more critically reviewed in this document. That said, the Bayesian approach is appropriate.

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?

As far as this document goes, these priors seem appropriate. However, it seems to me that there might be enough data to use an informed prior or even to set up a second hierarchy where the parameters for the priors are informed by data. This would use more of the available data in a direct fashion.

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?

The proposed approaches seem appropriate.

9b. If different measures of goodness of fit do not yield results that agree, which method should be preferred, and why?

That would depend entirely upon what was seen and why they differed. Question cannot be answered in

the abstract.

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?

No comment.

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?

You are placing too much focus on the nature of this statistic and not asking yourself what it really means. If this value is substantially different than 1, it means you should return to your data set and examine why this one data set is so different. Find what that difference is and THEN decide whether it warrants exclusion from the overall analysis. Does it change your inclusion/exclusion criteria? Do you need to reevaluate all of the cohorts?

9e. Is an examination performed of the residuals from the meta-analysis a rigorous and scientifically valid assessment of homogeneity?

It is not rigorous, but it is useful.

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?

Sensitivity analyses are indeed a valid and useful technigue for understanding the importance of assumptions on the primary predictions from the modeling exercise. However, many times we approach these types of exercise without any idea of what we plan to do with the results. The Agency needs to give some thought to what will be done with the results of the sensitivity analysis.

The Agency has a fairly comprehensive approach to the sensitivity issue. The only additional analysis we would suggest is that they consider varying the actual form of the model being applied to these data. Some careful thought should go into this decision for alternative models prior to doing it, since alternate models may demand alternate prior structures and the Agency would basically be conducting multiple complete analyses of these data. The purpose of our suggestion is for the Agency to get a solid "feel" for the impact of alternatives, not do multiple full analyses of these data.

Dr. Carol Rice

Charge Question 2, section 4 (epidemiology)
Please comment on the adequacy of these sections which serve as the scientific bases for the proposed dose-response assessment approach. [NOTE: is dose-response evaluated, or exposure-response?]

Non-cancer effects: section 4.1
It is not clear whether this section has been updated since the last version was presented to EPA. One useful update is Rohs et al (2008). A PubMed search shows other citations which may be considered for radiographic changes. Non-cancer mortality is also described in many of the cohort studies, including an update of the Libby workers provided by Sullivan (2007).

Cancer effects: Section 4.2

The selection of the cohorts should be carefully evaluated in relation to the usefulness of the exposure estimates in a "grouped analysis". While the methods in an individual study may provide useful internal comparisons, the amount of estimation needed may lead to serious misclassification when studies are combined, as is proposed. A careful review by industrial hygienists familiar with the sampling methods used over time (especially impinger, MCE filter) and analyses of collected samples (particle counting, fiber counting, fiber identification and sizing) is needed. Work provided to us by Stayner (see Dement et al and references) provides a benchmark of procedures against which other exposure metrics can be compared.

The Agency might consider seeking original data from studies other than the Charleston cohort, to determine if the original metrics might be validated with additional data or other metrics might be created. For example, exposures experienced by the Enterline cohort might be described by data collected and stored by the corporation. A careful review by hygienists of original exposure data might reveal other alternatives: comparison temporally in time, if not side-by-side measurements; examination of differences between particle count by operation to replace a linear regression across all operations. Should expert assessment be undertaken, the work of Dr. Gurumurthy Ramachandran would be very important to consider (Ramachandran et al 2003; Hewett et al 2006).

Dr. Peto referred to a report describing further the Canadian exposure metric formulation; I have asked him to forward that to me. An informative review of data available for many of the asbestos cohorts is found in Gibbs (1994).

Role of fiber type: Section 4.3

From an industrial hygiene point of view, comparison of the exposure estimates is a challenge from study to study. The proposal to use few conversion factors (including industry-wide factors for various metrics) can be expected to introduce substantial error. It is likely that this will be non-differential leading to an inability to find any real difference, but possible that an extreme example might result that could lead to an erroneous conclusion (Wacholder, Dosemeci, Lubin,1991; Wacholder, 1995).

The need for application of multiple conversion factors is illustrated in the recent Dement study, where 10 factors were used to convert from PCM-based estimates to estimates of exposure to fiber length and width as would have been achieved if TEM analysis had been conducted on the original samples. A recent report by Dodic-Fikfak (2007) of determination of conversion factors from mppcf (using a Konimeter, not impinger) and filter samples for a single plant resulted in five different values, depending upon operation.

The summary by Gibbs (1994), illustrates the need for multiple conversion factors. He describes the 4152 midget impinger samples from the mines and mills and 3096 mill dust samples used in the Canadian studies. In later studies looking into conversion factors between impinger and filter samples for the Canadian work locations, he noted that overall, the relation was only about 13% better than random assignment; however, much of the variability was explained if job-site and mine-site was considered. A review of papers cited by Gibbs may also be informative; see especially Ayer, Lynch and Fanny (1965). The discussion in Enterline (1981) provides a perspective in terms of environmental epidemiology.

Charge Questions 5,6,7

I was asked to provide some comment on the "inputs" to the model. See the sections above regarding uncertainty in the exposure data, need for IH review and input into study selection and need for IH input into the conversion factors.

Charge Questions 15 a, b.

15a. What method is best for estimating the uncertainty in lifetime cancer risk predications that are associated with the uncertainty in the bin-specific potency factors?

Defer to Dr. Cox. The Agency might consider using only animal data as a "test of the model", as exposure in many cases is more carefully characterized. This is of course not without uncertainty (e.g, contamination, sizing bins) or experimental issues (e.g., dosing regime, time to sacrifice) or animal selection/differences.

15b. Assuming that estimates of exposure at Superfund sites will also have uncertainty, how should the overall uncertainty in risk predications be characterized?

The level of uncertainty depends on the nature and extent of exposure information, and the context of 'estimates of exposure'.

At a generic Superfund site, there will be qualitative records of what has been placed in the site, core samples, perimeter air samples and perhaps personal measurements of airborne particulate during remediation. These provide little data in general to compare with a risk prediction. Prudent actions to protect workers and public health will include limiting potential, unknown exposure.

At Libby, there are well-characterized bulk and airborne material. These data are better than the input into the risk prediction.

Citations for Charge Question 2

Epidemiology

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Dement JM, Kuempel ED, Zumwalde RD, Smith RJ, Stayner LT, Loomis D. 2007. Development of a Fiber Size-Specific Job-Exposure Matrix for Airborne Asbestos Fibers. OEM. 11/5/2007 (online).

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Dr. Leslie Stayner

Following are my specific comments on the charge questions that I was asked to respond to (1, 2, 3, 4, 11 and 12). As requested, I have also included at the end of my comments several recommendations for future research. I also want to make some general overarching comments, since I am afraid that my main concerns might be lost in the details of my responses to these questions.

First of all, I unfortunately do not believe that there is adequate epidemiologic data to support the development of the bin specific risk assessment models that EPA is seeking to develop at this time. I believe that most if not all of the participants in our meeting agreed on this point. The use of data on fiber size dimensions from one study to estimate fiber size dimensions for another is simply not credible. At this point there is only one epidemiologic study that provides fiber size specific results, which is our reanalysis of the South Carolina cohort [Stayner et al. 2007]. Although this study provides support for the concern that long and thin fibers may be more strongly associated with lung cancer mortality than short and thick fibers, the correlations in the exposures to different fiber sizes make it impossible to determine their relative potency. There is one more study underway by Dr. John Dement at Duke University of North Carolina textile workers that will be using essentially the same methodology as our study to conduct fiber size specific analyses. It is possible that in the future we may combine the data from these 2 studies and be able to obtain more definitive estimates of the relative potency of different fiber sizes. However, this may still not be a sufficient amount of data and both studies are of primarily chrysotile exposed workers and thus will not provide information on amphiboles. This is why I strongly recommend that EPA support efforts to study other populations where it would be possible to characterize the fiber size distributions, and in particular of workers at the Libby facility.

Secondly, I do not believe that a good case can made that the potency of asbestos fibers for lung cancer varies by fiber type. The only analysis that supports this conclusion is the Hodson and Darnton paper. However, in reaching this conclusion they disregarded the findings from South Carolina cohort as an outlier even though most observers would rate this study as having one of the best exposure assessments of any of the studies. The fundamental and yet unresolved issue is that there is a large degree of disagreement in the results from the studies (i.e., heterogeneity), and particularly between the findings from the South Carolina and Quebec cohorts. I believe that the disagreement in the results between the two studies may in part be explained by differences in the fiber size distributions. In fact in our study we did find a higher percentage of long and thin fibers in South Carolina [Stayner et al. 2007] than what had been reported in previous studies of Quebec mines and mills [Gibbs and Hwang 1975, Gibbs and Hwang 1980]. If possible, further analyses of samples from the Quebec mines and mills would be extremely helpful in attempting to resolve this issue. It is also quite possible that the discrepancy in findings between these two studies may be explained by errors in the exposure estimates for the Quebec study, which could have weakened the observed exposure-response relationship. The lack of correlation between mppcf and fiber/cc measurements in the Quebec studies does suggest that there would have been substantial misclassification of exposures from the conversion to fiber counts. In any case, I do not believe at this time that is appropriate for EPA to make an assumption in its modeling that there is a difference in lung cancer potency for different fiber types.

Finally, I want to make a comment and suggestion to EPA regarding the extremely hostile reactions we heard from many of the public commentators at our meeting regarding this proposal. I believe that in moving forward with this proposal while not supporting a ban on asbestos this administration is in a sense adding insult to injury to the workers and communities who have been victims of past exposures to asbestos. The primary effort of the EPA at this time should be to convince this administration and members of our Congress to pass proposed legislation banning the use and production of asbestos products in our country. This ban would not only insure that we will never repeat our tragic mistakes of the past, but will also send a strong signal to other countries in the world who are currently importing and using asbestos in large quantities. Of course, I recognize that a ban will not address the issues of natural occurring asbestos or the remnants of asbestos in hazardous waste and buildings in our country and that a more reliable risk assessment model would be extremely useful for prioritizing the cleanup of these situations. However, until such an asbestos ban is passed it is difficult to see how modifications in the risk assessment models for asbestos will not be viewed with deep suspicion by the victims of asbestos in this country.

Charge Question 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?

This question needs to be divided into two questions. The first part being is there sufficient information to suggest that there are differences in potency of asbestos by fiber type and dimensions. The second part of this question is whether such an effort as described in this proposal is warranted. I will provide my views on each of these questions separately below.

Is there sufficient information to suggest that there are differences in potency of asbestos by fiber type and dimensions?

I agree that there is evidence that asbestos fiber potency varies by mineral type and particle dimensions. However, my confidence in this statement varies by cancer type. There is I believe a general consensus in the scientific community that chrysotile asbestos is less potent than amphiboles for mesothelioma. Support for this was discussed in a review we published in 1997 [Stayner et al. 1997]. This view was strongly supported by the reanalysis of the Davis rat inhalation studies based on TEM data by Berman et al. [1995], by the meta-analyses of the epidemiologic literature that was conducted by Hodson and Darnton [2000], and by Berman and Crump [Aeolus] in their 2003 report developed for the EPA. All of these analyses revealed highly statistically significant evidence that chrysotile is less potent than amphiboles for mesothelioma. It also worth noting that the analysis by Hodson and Darnton also indicated that amosite is less potent than crocidolite for mesothelioma.

The role of fiber size in mesothelioma induction is less clear. As recently reviewed by Dodson [2003], the results from toxicological studies have been conflicting with some studies indicating long fibers, and other studies indicating short fibers may be play a role in mesothelioma induction in animals. Short thin fibers are the predominant type found in pleural tissues in studies of workers by Suzuki [2001].

However, I don't believe that what is found in the either pleural or lung tissues can necessarily be inferred to be the fibers that actually cause the disease (either for mesothelioma or lung cancer).

For lung cancer, I do not believe the available evidence convincingly demonstrates that mineral type is an important determinant of potency. My basis for this conclusion was discussed in the 1997 review article [Stayner et al. 1997]. Nothing that has been published since our review article has changed my views on this subject and if anything I believe there is now further support for this position. The analysis of the Davis rodent inhalation studies using a TEM analysis by Berman et al. [1995] failed to demonstrate evidence of a difference in lung tumor potency by fiber type. In their meta-analysis of the epidemiologic studies that they performed for EPA in 2003 [Aeolus], Berman and Crump also failed to find significant evidence that lung cancer mortality varied by fiber type. Although their analysis did suggest that potency was slightly less than amphiboles (26 to 42% in 3 different models) these differences are likely to be explained by random error given the fact that these differences were not found to be even close to statistically significant (p=0.23 to 0.51 in 3 models). In addition, these differences are so small that they are not important from a public health viewpoint.
A much larger difference in lung cancer potency was reported in the metanalysis reported by Hodson and Darnton [2000]. They suggested that chrysotile asbestos was 10 to 50 times less potent than amphiboles. However, as they suggest the interpretation of their findings is greatly complicated by the large difference in lung cancer potency derived from the studies of South Carolina textile workers, and Quebec miners and millers. There was strong evidence of heterogeneity in the slope for lung cancer in the Hodson and Darnton metanalysis that was largely attributable to the differences between the Quebec and South Carolina studies. Hodson and Darnton chose to in effect ignore the results from the South Carolina study in developing their estimates of lung cancer potency for chrysotile asbestos. They reasoned that "Taking account of the excess risk recorded by cohorts with mixed fibre exposures (generally,1%), the Carolina experience looks untypically high." However, I think it is a very questionable judgment to ignore the findings from the South Carolina study when in fact, as was noted in the Berman and Crump report for EPA in 2003, this was one of the studies with the best information on asbestos exposure levels. Actually I would think a stronger justification could be made for deleting the Quebec study because of the large degree of uncertainty that exists in their exposure estimation procedures related to their conversion from particle count measurements to fiber counts as discussed at our meeting. I have previously demonstrated in an analysis that I presented at the EPA 2003 meeting in San Francisco that if one deletes the Quebec study the result of the meta analysis would indicate that the potency for chrysotile appears to be greater for chrysotile than amphiboles. I would not advocate deleting the Quebec study, but this merely suggests that the results from meta-analyses are not robust and dependent on whether one includes the Quebec or the South Carolina studies. Drawing conclusions on relative potency for lung cancer will not be possible in meta analyses of the epidemiologic data until we have explained the large differences in lung cancer potency between these two studies.

In contrast to fiber mineralogy, I do believe that there is substantial evidence to indicate that lung cancer potency is likely to vary by fiber dimensions. Stanton [1981] was the first to suggest that long and thin fibers might be more potent than thick and short fibers in inducing lung cancer based on pleural implementation studies in rats. Inhalation studies of chrysotile asbestos exposure in rats conducted by Davis et al. [1988] confirmed that long fibers were more potent in inducing lung tumors than short fibers. The reanalysis of the Davis studies using TEM analysis by Berman and Crump [1995] provided strong evidence that long and thin fibers were most strongly related to lung cancer risk. These toxicologic findings are supported by the results from our recently published study of the South Carolina

cohort using TEM based size specific estimates of chrysotile exposure [Dement et al. 2007 and Stayner et al. 2007]. In this study we reported that cumulative exposure to long and thin fibers were most strongly associated with lung cancer mortality. It should be noted, however, that short and thick fibers were also associated with lung cancer mortality and that the interpretation of the study findings were complicated by the strong correlations between the different size specific exposure measures. Although I agree that the potency of asbestos fibers is likely to vary by fiber dimensions, I do not believe that we have adequate data at this time to quantify these differences.

Is the effort as described in this proposal warranted?

Although I am sympathetic to the need for modification to our current risk assessment paradigms for asbestos, I do not believe that the approach outlined in this proposal would yield valid or useful results. The simple reason for my skepticism in this regard is that the data currently available to modify these models is grossly inadequate for this purpose. The primary problem lies with the data available to estimate the TEM specific levels of exposure for the cohort studies included in this analysis. Using TEM data from one study setting to estimate fiber size distributions at another facility and even worse for another industry is simply not reliable. This was clearly the opinion of the members of our panel with expertise on TEM analysis who answered no to question 4 b in our charge (Is it scientifically valid to use surrogate TEM data to estimate bin specific concentrations and exposure values in studies where data are not reported?). The 2003 report prepared for EPA by Berman and Crump [Aeolus] also provides empiric evidence that this approach doe not work since the addition of fiber size to their models resulted in at best a marginally significant improvement in model fit for lung cancer [p=0.04 to 0.1] depending on model], and mesothelioma [p=0.05 to 0.24].

As far as estimating difference in potency by fiber type for lung cancer the EPA approach will face the same problems as encountered in the previous meta-analyses with regard to the large extent of heterogeneity in the study findings and the unexplained differences in potency for lung cancer risk observed in the South Carolina and Quebec studies.

It is important to recognize that although the report includes an extensive effort to estimate the uncertainties underlying the estimation of bin specific and fiber type exposures, that this effort can not correct for these errors and could even conceivably introduce biases into the estimation of the model parameters. There is so much uncertainly about how to estimate the pdfs for their uncertainty analysis that I am concerned that their misspecification of the pdfs could actually introduce error into the estimation process.

Given these concerns, I think it would be irresponsible for EPA to move forward with this risk assessment model until we have more reliable data on which to base such an assessment. I do not accept the argument that if EPA conducts this analysis it would be viewed by the agency and perhaps more importantly by the public as “hypothesis generating exercise”. Coming from a government agency, the results from this assessment will undoubtedly be used by lawyers and policy makers. The testimonies of several lawyers at our meeting demonstrated how even the 2003 Berman and Crump analysis is being currently used in legal cases. Furthermore, it is not even credible that results from the analysis would not be used by EPA since it is stated in the overview of the report (page 1) that OSWER is proposing to use this as “an interim approach to account for the potential differences of cancer potency between different mineral types and particle size distributions.”

Charge Question 2- Sections 6 & 7:

Sections 6 and 7 provide an accurate summary of the risk assessment methods that were used in the EPA 1986 and the Berman and Crump analysis that was conducted for EPA. Berman and Crump have developed manuscripts for three papers based on their work for EPA, which I believe they are submitting for publication in a peer review journal. There may be some slight modifications in these papers that should have been noted in this document.

As a Co-Chair of the 2003 panel that reviewed the EPA proposal in 2003, I do not feel the description of our conclusions is accurately portrayed in this report. This report suggests (page 46) that the "consultation panel generally endorsed the basic idea of a multi-bin approach". Although I think this is true conceptually, several members of the panel had very serious misgivings about our ability to develop such a model based on the data available at that time. This report then lists a number of issues and limitations of the 2003 report, but it seems to attribute these comments to our panel. Our panel made individual comments and I don't believe this is a fair summary of all of our concerns. One over riding concern that I had at the time was that there was insufficient epidemiologic data to support the development of a fiber size specific model. This unfortunately remains my chief concern today. I also expressed a concern that the 2003 model provided fiber type specific slopes for lung cancer risk even though their own analysis did not support their being significant evidence for this.

Charge Questions 3a-c

3a. Do you agree that the lung cancer and mesothelioma risk models that are proposed are a scientifically valid basis for this fitting effort?

I believe the EPA 1986 models are a reasonable starting point for this effort. Crump and Berman [Aeolus 2003] in their 2003 report for the EPA tested the the EPA 1986 models using raw data from the South Carolina, Quebec and Wittenoon study cohorts and found that these models provided reasonably good predictions for these studies.

3b. Should additional model forms be investigated?

While it would be nice to evaluate biologically based models, such as the 2 stage clonal expansion model, as was suggested by Dr. Cox, I do not believe that this is possible given the data that is available to EPA. It would also be desirable to test the assumption that cumulative exposure (duration x intensity) is an appropriate metric for the lung cancer model as was suggested by Dr. Peto. Again I don't think the data exists in the papers to allow separate modeling of duration and intensity.
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 further evaluated?

Yes I believe this relationship should be further evaluated. The observation that there is a multiplicative effect of smoking and asbestos is largely based on the results from the study by Selikoff of insulator workers [Selikoff et al. 1968]. There in fact is a tremendous variation in the evidence regarding whether this relationship is multiplicative or additive [see Steenland and Thun 1986 and Vainio and Boffetta

1994]. A recent analyses of this issue suggests that in fact the relationship may be somewhere between additive and multiplicative [Wraith and Mengersen 2008].

4a. Is fitting at the group level preferred to fitting at the study level?

I do not believe that fitting at the group level should be preferred to fitting at the study level. The primary advantage of fitting at the group level appear to be that it permits a better description of the uncertainties involved. However, this advantage does not outweigh the serious loss of information that results from grouping of the data. For several of the studies (South Carolina, Quebec and Wittenoon), it is possible to obtain the raw data and to directly fit a slope (K_L or K_M) for these studies. Using group categories for these studies results in substantial misclassification of exposures since it is necessary to assign a midpoint or mean for each of the categories. In act Berman and Crump in 2003 were able to obtain the raw data from these studies, and I would urge the EPA to use these individual data in subsequent analyses.

4b. If so, is it scientifically justifiable to use a Poisson likelihood model for the observed number of cases in each group?
Yes it is scientifically justifiable and appropriate to use a Poisson likelihood for the analysis of grouped data. If the individual study results are modeled instead, as I would suggest, one could probably assume a normal or more likely a log normal distribution applies. In any case, it will be important to test the adequacy of the distributional assumption made.

Charge Questions 11 & 12

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

I do not believe these selection rules are appropriate. The first rule that a study has to be published in a peer reviewed journal is in principle okay, but is not okay as it was applied. This rule was used as a basis for rejecting the use of the raw data from South Carolina, Quebec, and Wittenoon which was used in the previous analysis conducted by Berman and Crump for EPA in 2003. Although the findings from these studies have all been published in peer review journals, the report rejected using the data from these studies because the new analysis is not published. I believe this is being too restrictive and results in the loss of some valuable information for the purposes of this risk assessment.

The second criterion requires studies to provide information that can be expressed in terms of the models selected is reasonable in principle, but it also too restrictive as applied. Case-control studies and other studies that could not be used to estimate the alpha were rejected on this basis. However, the alpha is a correction parameter and one that is not necessary in studies where there is not likely to be a difference in the background rates of diseases in the exposed and unexposed groups. For most case-control studies alpha would be expected to be one if the study is properly designed.

The third criterion is unclearly written, but my understanding from the meeting was that this criterion was primarily intended to exclude studies where the percentage of different fiber types or dimensions was not constant over time. This was the basis for the exclusion of the Selikoff study of insulators.

This study was used in the 2003 report by Berman and Crump. It seems it would be preferable to include it, and express this issue is an uncertainty in the analysis.

As a general principle, I believe it is better not to exclude too many studies in a meta-analysis. Rather I think the approach should be to investigate whether weaknesses and strengths of the study designs are explanations of the heterogeneity observed in the analysis.

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?

No, I do not believe it is appropriate to assume the composition (fiber size and type) is a constant in the study if the authors do not state otherwise. Fiber dimensions were not found to be constant over different operations in our study of South Carolina chrysotile textile workers [Dement 2008]. In many study situations the fiber size dimensions would be likely to vary over time. The use of fiber types also would be expected to have varied substantially in many industries over time. The only alternative would be to limit the analysis to studies with well documented information on how the fiber size and type varies over time and by operations in the study facilities. Unfortunately this only available for one study, which is the recent study of South Carolina textile workers [Stayner et al. 2007] or from the toxicologic studies?

Research Recommendations

1. Meta and Pooled Analyses
The Agency should consider conducting or funding a new meta-analysis to further evaluate the evidence that asbestos cancer potency varies by fiber type. This effort is important because there are new studies that were not incorporated in the most recent meta-analyses conducted by Hodson and Darnton or Berman and Crump [2003]. It is critically important that these analyses fully assess heterogeneity and possible explanations for any heterogeneity.

The Agency should also consider the possibility of funding a pooled analysis in which the raw data from the individual epidemiologic studies are combined. Such an effort would be a substantial improvement over a meta-analysis since the analysis would not be restricted to the categories of exposure and other covariates that were reported in the different studies. It would also be possible in this analysis to evaluate the assumption that cumulative exposure (product of duration and intensity of exposure) is an appropriate metric for the development of the lung cancer model. A good model of how this study might be conducted is the IARC pooled analysis for exposure to silica [Steenland et al. 2001]. In fact the IARC is uniquely well positioned to conduct such international collaborative efforts, and I would highly recommend pursuing this possibility with them. I have already had a preliminary discussion with one scientist at IARC (Dr. Kurt Straif) and he was very interested in this possibility particularly since IARC is re-evaluating asbestos next year.

2. Libby Montana
There is a critical need for analyses of more epidemiologic studies using TEM based fiber size specific estimates of exposures as was conducted in the recently published South Carolina textile cohort study

[Stayner et al. 2007]. Based on discussions at our meeting it appears that there are old sampling filters and slides that may be reanalyzed using TEM methods to develop a fiber size specific exposure matrix for the study of workers that was recently updated by Sullivan [2007]. It may also be possible to do fiber size specific analyses with the community but I think this is unlikely given the limited number of cases of respiratory disease that have been reported. It may also be possible to find other asbestos cohorts where a fiber size specific analysis could be conducted.

3. Medical Screening & Treatment

There is to my knowledge hardly any current research on treatment for asbestos related diseases. I believe this is a very important and promising area for future research. Mesothelioma incidence in the U.S. has just begun to peak and thus there are still many workers and community exposed individuals who will develop this disease in the future. There also remains a large burden from lung cancer and asbestosis in our country. Research on secondary prevention of these diseases either through early detection or treatment at an early preclinical stage of the disease has great potential for preventing the further development of asbestos related diseases.

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Dr. James Webber

I have split my comments into two sections. The first section, *A. Charge Questions*, is devoted to answering specific charge questions. The second section, *B. Need for Future Research*, is on the final page and sketches my thoughts on what must be done before the EPA can consider going forward with their OSWER risk-assessment proposal.

A. Charge Questions
Below, I have answered the charge questions on which I serve as primary and secondary lead. In addition, I have responded to other charge questions where I felt I could make meaningful contributions.
Charge Question 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?

No. A careful review of existing data reveals that environmental exposure measurements are currently insufficient and/or inadequate for developing a new risk-assessment model. Conversions of impinger (dust) concentrations and even PCM (fiber) data into (TEM-equivalent) fiber-size distributions cannot be considered reliable because of the orders-of-magnitude uncertainty at each conversion step. At present, only the data of Stayner *et al.* (2007) provide dependable fiber-size distributions that are associated with known lung cancer and mesothelioma outcomes. As more TEM-based environmental exposure data that are directly associated with health outcomes become available, this effort could be re-visited.

References

Leslie T Stayner, Eileen Kuempel, Steve Gilbert, Misty Hein and John Dement. An epidemiologic study of the role of chrysotile asbestos fiber dimensions in determining respiratory disease risk in exposed workers. *Occup. Environ. Med.* published online 20 Dec 2007;

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

Section 6

The conversion factor in Section 6.2 ("k", page 34) for "relative mesothelioma hazard" includes RMH_{all} (page 35). RMH_{all} excludes friction-product data because of their "uncertainty in the KL_{PCM} values", where KL_{PCM} is lung cancer potency. This exclusion is unwarranted in that the physical/biological/chemical mechanisms that cause lung cancer have not been convincingly related to mesothelioma mechanisms.

Section 7

1) The Aeolus model that lumps amosite and crocidolite into one amphibole category must be re-evaluated. The fiber size distributions of the two amphiboles are extremely disparate, as seen in the tables and figures of Appendix B. For example, crocidolite has a lower PCME, ~0.007, versus ~0.3 for amosite. Chrysotile and the minor amphiboles are midway at ~0.04-0.12.

2) Equations 7-1 and 7-4 use the percentage of PCME fibers as denominators of lung cancer potency. This reduces the significance of fibers shorter than 5 µm and/or narrower than 0.25 µm. A review of the raw data in Appendix B reveals that using PCME as a denominator disregards the role of more than 90% of the airborne asbestos fibers. This extreme bias drives the modeled potency of these numerous small fibers to be self-fulfillingly minor. This also creates positive bias for amosite potency when one considers that the PCME for amosite is much greater than for other asbestos types. Apparently a similar approach was used for mesothelioma, where downplaying these small fibers may be an even more egregious oversight. Evidence continues to build that smaller fibers are more likely to reach extrapulmonary sites and be associated with mesothelioma (Dodson *et al., 1990; Dodson, 2006; Suzuki & Yuen, 2001).*

3) Yes, I agree with EPA 2003 decision, as outlined in Section 7.8, to not pursue the Aeolus method.

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Dodson, R.F. *et al.* Asbestos content of lung tissue, lymph nodes and pleural plaques from former shipyard workers, *Am. Rev. Respir. Dis.* 142, 843-847, 1990.
Dodson, R.F. Analysis and relevance of asbestos burden in tissue. In *Asbestos: Risk Assessment, Epidemiology, and Health Effects*, Dodson, R.F and Hammar, S.P. ed., CRC Press, Boca Raton, FL, 2006.
Suzuki, Y., and Yuen, S.R. Asbestos tissue burden study on human malignant mesothelioma, *Ind. Health*, 39, 150-160, 2001.

Charge Question 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?

One possible investigation would be the potential interaction of fiber-width exposure and smoking. Fiber width is the primary determinant of aerodynamic diameter, which causes thicker fibers to be intercepted in the upper portions of the bronchial tree. The compromised mucociliary escalator in smokers probably enhances residence time of these thicker fibers in this upper region. Hence an epidemiologic study using fiber-width bins for asbestos-worker exposure might reveal different lung cancer potencies for specific fiber widths for smokers versus non-smokers.

Charge Question 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)

Multiple binning should be evaluated, ***but only using TEM-analyzed environmental exposure data that is directly associated with health outcomes***. Studies continue to reveal the importance of fiber width in potency. Fiber width is the most critical dimension in determining deposition site in the respiratory system, plays a significant role in determining surface area exposed to tissue, and may be a factor in mobilizing fibers from alveoli to pleural space. Future attempts to model fiber potency should have at least two bins for width. One possible width division could be an aerodynamic diameter of 2.5 μm, which is the cutpoint for EPA fine (~respirable) particles. This would be ~0.5 μm width for amphibole asbestos and ~0.65 μm width for chrysotile.

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

The first criterion, "published in a refereed journal" is too restrictive given the paucity of studies that have been suggested by OSWER for this undertaking. While publication in a peer-reviewed journal is a good indicator of quality, one can't be certain that lack of such publication is an indicator of poor quality. It would be appropriate to let a subset of the Science Advisory Board (SAB) act as reviewers of unpublished candidate studies to determine if they meet certain quality criteria. Probably all members of the SAB have served as reviewers for publications and would certainly wield a fine-toothed comb on any studies that are proposed for inclusion. However, to retain the transparency of this effort, it would

be appropriate to continue exclusion of those studies whose details cannot be disclosed to the public, as suggested in Section 9.3.

Charge Question 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?

Stayner et al.'s (2007) recent study, using TEM results from archived filters from a South Carolina textile plant during the 1960s, provides the only set of data that can currently be used for reliable risk assessment.

References

Leslie T Stayner, Eileen Kuempel, Steve Gilbert, Misty Hein and John Dement. An epidemiologic study of the role of chrysotile asbestos fiber dimensions in determining respiratory disease risk in exposed workers. *Occup. Environ. Med.* published online 20 Dec 2007;

Charge Question 13a: Is it scientifically justifiable to employ a default dust-to-PCM conversion factor when there are no site-specific data available?

No. The OSWER statement in Section 10.2 "However, most values of CF are found to range between 1 and 10 PCM s/cc per mppcf (USEPA 1986)." is misleading when compared to the data presented in Table C-1, where CF ranges from 0.1 to 21.9. Thus the potential for error in using any default value is enormous when on-site impinger/PCM comparisons are not available. Impinger data cannot be reliably used to derive PCM concentrations, let alone TEM fiber-size distribution.

Charge Question 14a: Are the point estimates and uncertainty distributions for the fraction amphibole term proposed for each study scientifically valid?

No. The data from Addison and Davis for 81 samples of chrysotile were produced by XRD, which cannot distinguish asbestiform tremolite from non-asbestiform tremolite. Furthermore, since XRD measurements are made largely on the basis of mass, a single moderate tremolite fiber could weigh as much as a ten, or even a thousand, chrysotile fibers. Given the unknown impact of any tremolite found in these chrysotile samples, no amphibole fraction should be given to chrysotile that was not mixed with amphibole asbestos on-site. But this skirts the issue that ***only TEM-analyzed environmental exposure data that is directly correlated with health outcome should be used for risk assessment***. TEM analysis will unequivocally determine what fraction of airborne asbestos, if any, was amphibole.

Charge Question 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?

No. Comparisons of concurrently collected TEM and PCM concentrations have produced inconsistent conversion factors. Hence, PCM data cannot be used to create TEM-equivalent fiber-size distributions.

Charge Question 14d: Are the point estimates and uncertainty distributions for the fraction amphibole term scientifically valid?
No. Summarizing my comments for 14.a: The tremolite contamination of chrysotile remians completely indeterminate in a fiber-population sense. An amphibole fraction should not be applied to chrysotile. ***Only TEM analysis of exposure environments can reliably determine the extent of exposure to amphiboles.***

Charge Question 14f: Would the model benefit by establishing a common lower cut-point in diameter to normalize the lower detection limit across studies?

No. TEM analysts are capable of detecting even the thinnest asbestos fiber. Given the probable importance of width in potency, raw diameter measurements from TEM should be utilized.

B. Need for Future Research

TEM Analsysis of Retrospective Environmental Exposure

The greatest need for the type of risk assessment outlined in the OSWER proposal is additional environmental exposure data produced by TEM analysis. Only TEM can reliably reconstruct the bivariate fiber-size distributions needed for modeling and unequivocally determine whether or not amphibole asbestos was present along with chrysotile in the environments under study. Archived filters representing occupational environments that produced lung cancer and mesothelioma should be sought and analyzed by TEM, as done by Stayner et al. (2007). Even archived PCM slides from these environments should be sought for TEM analysis. This would, of course, require development of a methodology to transfer asbestos reliably from under the cover slip to a TEM grid.

Animal Studies
I leave it up to SAB panel members who have more expertise in this area to make recommendations. However, I would strongly caution that non-inhalation studies be performed with fiber-size distributions that are appropriate to the targeted cell types. Throwing big fibers onto pleural mesothelial cells does not replicate what happens in people or animals, as evidenced by the works of Dodson (2006) and Suzuki et al. (2001). Elutriation has proven to be an effective means of producing fibers of the desired aerodynamic diameters (Webber et al. 2008).

References

Dodson, R.F. Analysis and relevance of asbestos burden in tissue. In *Asbestos: Risk Assessment, Epidemiology, and Health Effects*, Dodson, R.F and Hammar, S.P. ed., CRC Press, Boca Raton, FL, 2006.

Leslie T Stayner, Eileen Kuempel, Steve Gilbert, Misty Hein and John Dement. An epidemiologic study of the role of chrysotile asbestos fiber dimensions in determining respiratory disease risk in exposed workers. *Occup. Environ. Med.* published online 20 Dec 2007.

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Additional Materials Supplied by Dr. Julian Peto Are Attached

1985 Comments on the first draft of the 1986 EPA Report

1981 Report to the EPA on Asbestos in Schools

ECAO-HA-79-6
INC 35

Institute of Cancer Research: Royal Cancer Hospital

in association with

THE ROYAL MARSDEN HOSPITAL

DIVISION OF EPIDEMIOLOGY
CANCER RESEARCH CAMPAIGN CHAIR OF EPIDEMIOLOGY:
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01-643 8901

13th August 1985

Dr. Dennis J. Kotchmar,
United States Environmental Protection Agency,
Environmental Criteria & Assessment Office,
(MD-52),
Research Triangle Park,
North Carolina 27711, U.S.A.

Dear Dr. ~~Kotchmar~~ Dennis,

I enclose my comments on Dr. Nicholson's asbestos report. As I have just written a similar report with Sir Richard Doll in which we have discussed most of the contentious issues, I have referred to our report (Doll and Peto, 1985) in several places.

I have seen Sir Richard's comments, and agree with all of them, but I have tried to avoid repeating them. I've picked up a few spelling errors, but it might be worth getting someone to proof-read the text again.

Yours sincerely,

Julian Peto

Julian Peto

000584

AIRBORNE ASBESTOS HEALTH ASSESSMENT UPDATE

EPA 600/8-84-003F

General comments

The report is well written, and provides an excellent reference document. My main reservation, and one which is inevitable in relation to any review on asbestos which attempts to draw quantitative inferences on which policy decisions will be based, is that none of the major questions can be answered with much confidence.

Three important conclusions which I would not accept as well established are:

(i) There is little evidence that crocidolite and amosite are much more dangerous than chrysotile. There are no good dose-response data for these amphiboles, but there is strong suggestive evidence that they may be very much more dangerous than chrysotile, and this is now widely believed, particularly outside the U.S. Crocidolite may be particularly dangerous and although little is used in the U.S. it would be irresponsible to encourage its use elsewhere.

(ii) Asbestos causes a substantial risk of gastro-intestinal and other non-respiratory cancers. This is not the main subject of this report, but it has important implications in relation to asbestos in water supplies. Several recent reports have questioned the association (see for example, Doll and Peto, 1985), and the issue remains unsolved.

(iii) Exposure levels in asbestos-containing buildings, particularly schools, are often high enough to cause a serious health hazard. Measurements in Canada and Britain suggest very much lower levels than have been reported in the U.S., and it is not clear whether this reflects a real difference between the materials and the way in which they were applied, or is due to differences in methods of sampling and analysis. Asbestos removal is likely to entail enormous costs and may even increase exposure, and the reasons for the discrepancy between U.S. and other results should be established before widespread removal is undertaken.

Chapter 3

(i) Selection of studies for dose-response estimation. The exposure estimates for most studies are too unreliable to be of much value. This is not important for the practical purpose of estimating the dose-specific lung cancer risk for chrysotile, as the geometric mean of the lung cancer risks presented as the best overall estimate is very close to the estimates obtained in two chrysotile textile factories in which extensive measurements were made (Doll and Peto, 1985). For other exposures, however, and particularly for crocidolite and amosite, this uncertainty should be emphasised. Exposure estimates for studies used to estimate the mesothelioma risk (Table 3-30, p.88) are all of dubious reliability. There were no contemporary measurements in three (Selikoff et al., Seidman et al. and Finkelstein), and in the fourth (Peto) the mesothelioma risk was so high that we subsequently concluded that a large proportion of the mesotheliomas (we arbitrarily assumed 50%, but this could be too low) were

due to the small amount of crocidolite used in the factory (Doll and Peto, 1985).

(ii) Fibre type (see also "General comments" above) pp. 103-113

The data in Table 3-35 show:

1) a consistently low ratio of pleural mesothelioma to lung cancer for pure chrysotile
2) virtually no peritoneal mesotheliomas for pure chrysotile
3) a substantially higher ratio of pleural mesothelioma to excess lung cancer, and a high peritoneal mesothelioma risk, in the "predominantly chrysotile", "predominantly crocidolite" and "mixed exposure" studies.

One obvious explanation of these data is that even quite small amounts of crocidolite or amosite can cause a substantial mesothelioma risk, and that chrysotile alone almost never causes peritoneal mesothelioma. Moreover, brief intense exposure to chrysotile has never been shown to cause either lung cancer or mesothelioma, in contrast to both amosite and crocidolite. These observations are dismissed as being of less importance than the large differences in dose-specific risk between different industries using the same fibre type, but this may be a very dangerous assumption. For example, if the substantially higher mesothelioma risk in the "predominantly chrysotile" studies is due to amphiboles, which constituted only a few per cent of the total asbestos exposure in these studies, the dose-specific risk (at least for mesothelioma) might well be ten times higher for amphiboles than for chrysotile. There are no good exposure data on which to

base dose-specific risk estimates for either amosite or crocidolite, but both seem to be more dangerous than chrysotile when used in the same way.

Table

One aspect of/3-35 that deserves special comment and explanation is the adjustment of the lung cancer excess among Canadian chrysotile miners, from 46.0 to 126.2. This is the largest of the pure chrysotile studies and is often cited as showing that the ratio of mesothelioma risk to excess lung cancer is quite high for pure chrysotile. This adjustment greatly reduces this ratio, and hence adds weight to the argument that chrysotile is very different from the amphiboles.

(iii) Gastro-intestinal and other cancers pp. 94-97. See "General comments" above. In our report (Doll and Peto, 1985) we commented that the excess SMR for other cancers followed much the same pattern as for G.I. cancers, being highest in cohorts that suffered a large excess of lung cancer and mesothelioma. We inferred (a) that there is no reason to single out G.I. cancers for special mention, and (b) that a general increase in all cancers seems biologically implausible, and these increases may therefore all be due largely or even entirely to misdiagnosed lung cancers and mesotheliomas. The discussion of these issues on pp. 94-97 reaches a different conclusion, but it is well documented, and my only specific comments are (a) our alternative interpretation might be mentioned and criticised, and (b) the statement on p.97 that "the excess at other sites is ..... generally less than G.I. cancer" does not seem to be supported by Table 3-33.

Chapter 5

The data on ambient asbestos exposure given in Chapter 5 stand in marked contrast to British data collected by the Department of the Environment and cited in Doll and Peto (1985). The British data suggest that ambient levels in contaminated buildings are rarely much higher than 0.001 fibre/ml, while the U.S. data include many very much higher values assuming a conversion factor of 30 $\mu g/m^3/f/ml$ (p.136). This raises two important questions, both of which should be discussed.

1). The method of counting respirable asbestos fibres by electron microscopy used in the British study is claimed to provide counts that are directly comparable with optical microscope measurements. The major difference between this method and that used in the U.S. may be the dispersion of fibre clumps by ultra-sonification (p. 138). Results in nanograms cannot be converted to counts of respirable fibres of a specified size range reliably (pp. 154-156), and the report should either recommend the British method or discuss its deficiencies.

2). Comparative studies of British and American measurements are now being conducted by the British Department of the Environment and the E.P.A., in an attempt to resolve this issue. Preliminary results of this work should show whether there is a real difference between British and U.S. schools, or whether the measurements taken in Britain or the U.S. (or both) were defective. Can this information be obtained?

Optical fibre counts are extremely unreliable at low concentrations, as most of the fibres counted are not asbestos. The results shown in Table 5-8 may therefore be very much too high, particularly the first four, which are 100 times higher than typical ambient measurements by electron microscopy.

Chapter 6

There is a striking contrast between the ratios of mesothelioma to excess lung cancer shown for pure chrysotile in Table 3-35 and the predicted ratios shown in Table 6-3. For exposures of up to 20 years duration the male ratio in Table 6-3 is about 1:1 for exposure beginning at age 20 and about 1:2 for exposures beginning at age 30, while the overall ratio for pure chrysotile in Table 3-35 is only about 1:10. This is because the four cohorts used to estimate the mesothelioma risk all had quite high mesothelioma rates (Table 3-30, p.88), and all were exposed to some amphibole. It should perhaps be mentioned that the mesothelioma predictions are likely to be substantially too high for chrysotile. Conversely, however, it might also be mentioned that there are no good dose-response data for amosite or crocidolite, and the estimates shown in Tables 6-1 to 6-3 could be substantially too low for both lung cancer and mesothelioma for amphiboles (see comments on Chapter 3).

The data on household contacts (pp. 162-165) are important, but it seems likely that they resulted from quite high concentrations of respirable fibres, and in the absence of fibre counts in these homes the inference that low-dose effects may be grossly underestimate

by extrapolation (last sentence, p.164) should perhaps be deleted. It seems extraordinary that the prevalence of abnormalities in household contacts (35%) was almost as high as in asbestos workers (45%; Table 6-5).

Minor points

p xii, l. 9-10 : It might be better to say: "The risk of mesothelioma is approximately proportional to cumulative exposure, and also increases sharply with increasing time since first exposure."

p xii, last 2 l : "Uncertainties in conversion between optical fiber counts and electron microscope fiber counts" might be preferable. (See comments above on Chapter 5. If these are accepted, many references to mass measurements will have to be altered or qualified.)

p xiii. My address is now: Section of Epidemiology, Institute of Cancer Research, Sutton, Surrey SM2 5PX, England.

p 2, l. 1. Should fibre differences be dismissed? See comments above.

p 2. l.26. "Document" misspelled.

p 2. last l. Replace "mass determinations "by" fiber counts"

p 10 British standard is now 0.5 fibers per ml.

p 46 last line. Replace 'are' by 'may be'. In many studies, errors in dose estimation may well exceed statistical errors in response.

p 47 Equation 3-3d. It might be preferable to replace I_L/I_E by relative risk, and replace f.d by the average cumulative dose of the cohort.

p 48 l. 24. Insert "per" before f-y/ml. The units of k_L are $(f\text{-}y/ml)^{-1}$.

Table 3-10. Peto 1980 could be replaced by the estimate cited by Doll and Peto (1985) of $k_L \times 100 = 0.54$. (Entire post-1932 cohort. The separate estimate for post-1950 workers was 1.5.) Alternatively, as the paper from which this is taken is still in press, a footnote could be added to the table to avoid having to alter the text and fig. 3.7.

pp 54-57. Doll and Peto (1985) could be mentioned in a footnote, as it discusses most of these points in detail, and presents updated mortality results for the Rochdale factory in a larger cohort which includes short-service workers.

pp 63-64. I believe that the average duration of mining exposure of Asbestos and Thetford residents is higher than that of McDonald's cohort, which included many short-service workers who left the area.

pp 81, last sentence. Another possible explanation for the low mesothelioma risk beyond 50 years in U.S. insulators is that early recruits suffered less exposure, perhaps because of different materials or work practices in the early 1920's.

p 98 last para. l. 4 "Eradication" misspelled.

p 105. First sentence. Difference in rel. risk (pre v post 1950 at Rochdale) no longer significant ($0.05 < p < 0.10$). An important point : heavy brief chrysotile exposure has never been shown to cause increased risk, unlike amosite (Seidman et al., 1979) or crocidolite (Jones et al.)

p 111. para. 2 l. 8 (twice) and l.10 "Peritoneal" misspelled.

p 114. l. 14. Peritoneal, not parietal.

p 163. Chi-squares in Table 6-5. The first (7.1) has been calculated with no continuity correction, and the second (114) seems slightly too high.

p 164. last para. "..... and adjusted to a continuous rather than day-time exposure". This seems to imply that Tables 6:1, 6.2 and 6.3 were calculated for daytime exposures, but the rates in these tables are stated on p. 157 to be for continuous exposure, which is presumably 24 hours/day, 7 days/week. This should be clarified both on p. 157 and on p.164. In particular, assuming continuous exposure at 0.01 f/ml must exaggerate the likely risk, as few, if any, individuals are likely to spend their entire lives in such conditions.

p 168 para 2. l. 13. "Tract" misspelled.

AN ALTERNATIVE APPROACH FOR THE RISK ASSESSMENT OF ASBESTOS IN SCHOOLS

Report to the U.S. EPA

Julian Peto

April 6, 1981

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REVIEW OF ASBESTOS IN SCHOOLS EXTENSION

1.0 Description of Risk Assessment Methodology

The only dose/time relationship for a human cancer that has been examined in any detail is that of lung cancer in continuing cigarette smokers and lifelong non-smokers (Doll, 1978). Lung cancer incidence I_N in non-smokers satisfies the relationship:

$$\text{(i)} \quad I_N = k_N.(\text{age})^{4.5}$$

while the excess I_E in continuing smokers (those who have smoked at a constant rate continuously) is approximately:

$$\text{(ii)} \quad I_E = k_E.(\text{duration of smoking})^{4.5}.$$

The constants k_E (smoking effect) and k_N (background independent of smoking) determine the absolute risk. k_E depends on the amount smoked, inhalation and tar level; it is approximately 100 x k_N in smokers of about a pack per day.

1.1 Mesothelioma

Mesothelioma rates behave in a similar way. The incidence I_E following asbestos exposure (Selikoff and Peto, 1981; unpublished) is:

$$\text{(iii)} \quad I_E = k_E.(\text{time since first asbestos exposure})^{3.5}$$

while I_N, the incidence in the unexposed population (Henderson and Peto, 1981; unpublished) is:

$$\text{(iv)} \quad I_N = k_N.(\text{age})^{3.5}.$$

For mesothelioma among U.S. insulation workers, the ratio $k_E:k_N$ is approximately 10,000. (See fig. 1) The only marked difference between the models for asbestos-induced mesothelioma and smoking-induced lung cancer relates to the effects of stopping exposure. Lung cancer incidence remains approximately constant when smoking stops (Doll, 1978) and its age-distribution is very different for continuing smokers and ex-smokers. This appears not to be true of mesothelioma, however, and equation (iii) fits the incidence pattern in various studies irrespective of fibre type or duration of exposure (Selikoff and Peto, 1981; unpublished).

1.2 The Effect of Exposure Level and Duration of Exposure

A possible explanation of the preceding observations is that asbestos initiates the process of mesothelial carcinogenesis, and that the probability that one day's exposure will give rise to a mesothelioma T years later is roughly proportional to T^3. Adding up the separate effects of each day of exposure then leads to the prediction that

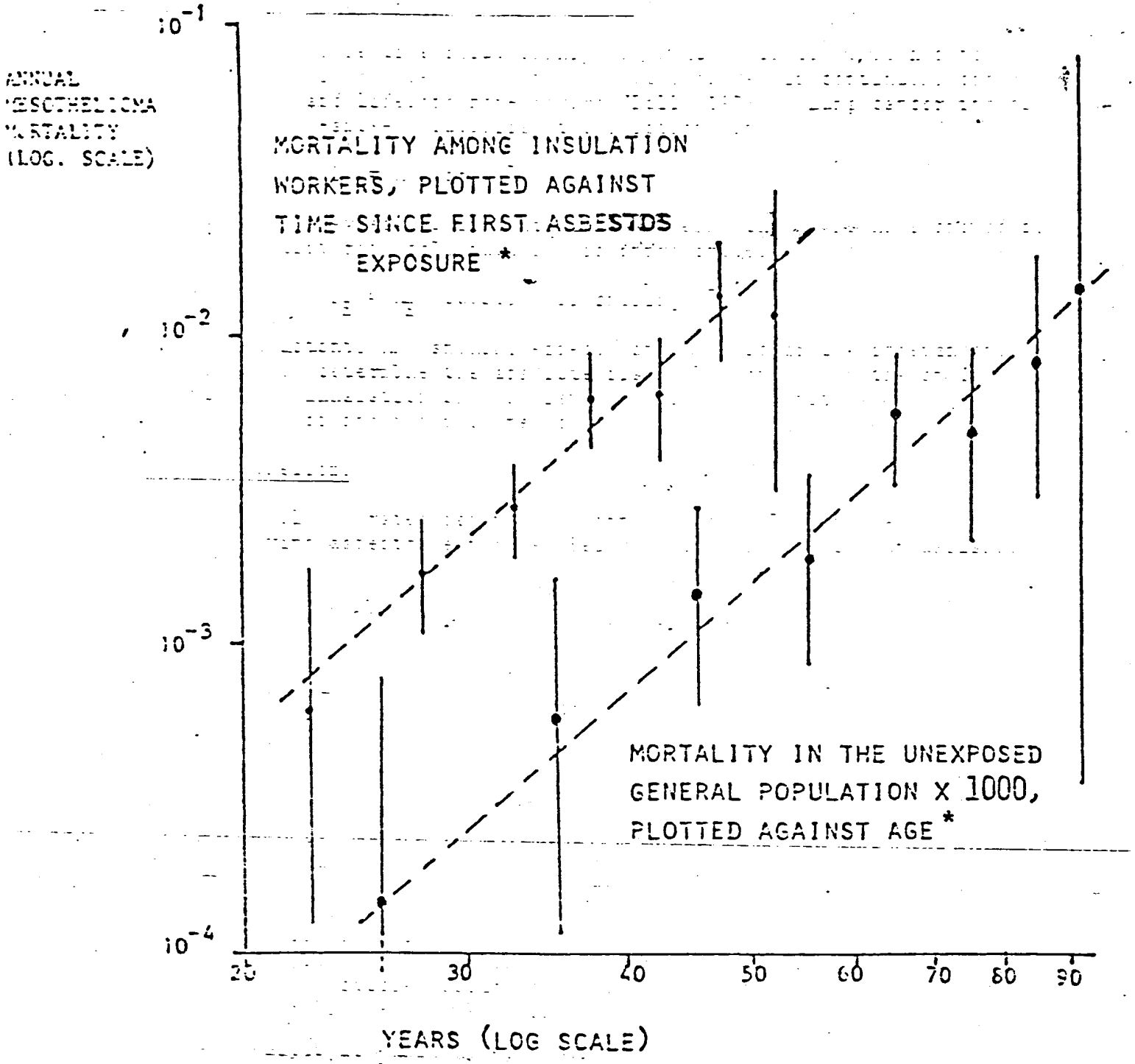


FIGURE 1. Data from Selikoff and Peto, 1981; unpublished and Henderson and Peto, 1981; unpublished

continuous exposure will produce an incidence pattern that rises as (time since first exposure)^4, brief exposure will produce an incidence proportional to (time since first exposure)^3, and intermediate duration produces an intermediate effect. More formally, this model predicts that an exposure of duration T_o years will produce an incidence proportional to $T^4-(T-T_o)^4$ at time T years after first exposure. The corresponding incidence patterns are shown in Table 1. These rather specific predictions cannot be tested directly. The incidence patterns shown in Table 1 increase as (Time)^3 following 1 years' exposure and as (Time)^4 for continuous exposure, but even these extremes are both quite adequately described by the approximation of equation (iii) that incidence rises as (Time)$^{3.5}$ irrespective of duration of exposure.

For the purposes of the present calculation, the predictions in Table 1 carry two other important implications. (1) The predicted risk is approximately proportional to duration of exposure for durations of between 1 and 6 years. Movement of students between schools can therefore be ignored, as the number of mesotheliomas in 2,000,000 people each exposed for 3 years will be roughly the same as that among 1,000,000 exposed for 6 years. (2) The incidence caused by 6 years' exposure 30-40 years after first exposure is roughly 0.5 times that caused by continuous exposure, and the corresponding factor for 10 years' exposure is about 0.7. Observed incidence rates in cohorts of industrial workers who have suffered prolonged exposure and whose exposure levels have been estimated can therefore be used to develop a dose-response relationship which can be adjusted for the effects of shorter exposures at measured levels.

This model, under which each increment of exposure produces an additional independent increment in subsequent cancer risk, predicts that dose-response is linear; in other words, the incidence of mesothelioma, and hence the lifelong risk, will be proportional to the fibre level following a given duration of exposure.

These relationships are summarized by the approximate formula for excess mesothelioma incidence:

$$\text{(iv)}\quad I_E = k\cdot(\text{time since first exposure})^{3.5}\cdot(\text{fibre/ml}),$$

the constant k being proportional to the product of average hours of exposure per day and the duration adjustment factor discussed above (0.5 for 6 years' duration, 0.7 for 10 years, 1.0 for continuous exposure).

It would of course be possible to base predictions on the specific model tabulated in Table 1, which would give much the same results as equation (iv), but I prefer to use it only to estimate the duration adjustment factors. The effect of different durations of exposure cannot be estimated accurately from any existing study, and some speculative assumption has to be made for this purpose. The advantages of using equation (iv) are that if alternative factors are suggested they can be substituted directly; and that it is scientifically less tendentious.

TABLE 1. Incidence rates calculated from the formula $T^4-(T-T_o)^4$, where T is years since first exposure to asbestos, and T_o is duration of exposure. Incidence rates among U.S. insulation workers first exposed 1922-1946 (per 10^5 per annum) are also shown.

	Duration of asbestos exposure (T_o)						Incidence x 10^5 per annum (U.S. Insulators)
		1	6	10	20	Continuous	
Years	12.5	2	6	7	7	7	
since	22.5	11	49	62	69	69	61
first	32.5	35	167	231	294	300	277
expo-	42.5	80	400	578	809	878	647
sure (T)	52.5	151	786	1166	1743	2044	1156

In an earlier analysis (Peto, 1979) a quadratic rather ... dence time model was analysed, and overall incidence was approximated by $(\text{time})^3$ rather than $(\text{time})^{3.5}$, but the estimates presented here provide a better fit to the data now available. The exponent of time cannot be estimated precisely, however. Even the estimate based on 138 mesotheliomas (Selikoff and Peto, 1981; unpublished) has a standard error of ±0.4.

.3 Lung Cancer

The relative risk for lung cancer caused by prolonged exposure to asbestos appears to reach a maximum about 25 to 35 years after first exposure. In one study we have conducted in England, and in North American insulators, (Selikoff et al., 1979), the relative risk subsequently fell, but this decline may be an artifact. In both these studies the relative risk reached a very high level (about 6 in American insulators, (Selikoff et al., 1979), and more than 10 in English asbestos textile workers heavily exposed before 1933). This high mortality, together with deaths due to asbestosis and mesothelioma may have selectively removed the most heavily exposed men, particularly among the heavier cigarette smokers. It is therefore reasonable to suppose that the relative risk would reach a maximum about 20 years after first exposure and subsequently remain at about this level following less prolonged exposure at lower dust levels.

If asbestos is eventually inactivated or eliminated, the effect of brief exposure in childhood could be negligible. On the other hand, there is some evidence that the eventual relative risk following both brief and prolonged exposure increases slightly as age at first exposure falls (Selikoff et al., 1973), and it could be argued that the effect of childhood exposure might be greater than among those first exposed as adults. The assumption that the relative risk will rise for about 20 years and then remain constant following exposures of up to 10 years duration, and that the eventual proportional excess (i.e. relative risk minus 1) will be proportional to both dust level and duration of exposure but independent of age, seems a reasonable compromise between these extremes. Thus for lung cancer the calculation will be based on the formula for excess incidence $I_E(a)$ at age(a):

$$\text{(v)}\quad I_E(a) = c \cdot (\text{fibre/ml}) \cdot (\text{duration of exposure}) \cdot I_U(a),$$

where $I_U(a)$ denotes the lung cancer incidence in an individual of age(a) who has not suffered asbestos exposure. As the effects of smoking and asbestos are approximately multiplicative for lung cancer the risk calculation must be carried out separately for smokers and non-smokers, using appropriate age, sex and smoking-specific lung cancer rates $I_U(a)$.

1.4 Exposure Measurements and Dose Relationships

Methods for measuring fibre counts have altered in recent years, the most significant change being the use of a microscope eyepiece

graticule in fibre counting (Steel, 1979). This procedure increases the fibre count by a factor of 2 or more, and throughout the following discussion fibre counts are assumed to have been measured in this way. Thus, for example, the old estimate of the average exposure of North American insulation workers' exposures, 10 to 15 fibre/ml (Nicholson, 1976), becomes about 30 fibre/ml.

The product (fibre/ml):(duration of exposure) in equation (v) is simply cumulative dose, and the constant c can be estimated from data on industrial cohorts such as the North American insulators. In view of the delay of about 20 years before the maximum relative risk for lung cancer is reached, however, recent exposure will not have had its full effect. It is difficult to justify any very precise adjustment to allow for this "wasted exposure". A reasonable approximation migh be to assume that the relative risk of about 6 (a proportional excess risk of about 5) among North American insulators 30-35 years after first exposure reflects the effects of 20 years' exposure at 30 fibre/ml, or 600 fibre/ml years. The constant c can then be calculated from equation (v):

(vi) c = (relative risk minus 1)/(cumulative dose)
$= 5/600 = 0.0083,$

since $I_E(a)/I_U(a)$ is by definition relative risk minus 1.

Finally, some adjustment must be made for the shorter working week and longer holidays of school pupils and staff compared with industrial workers. A factor of 0.5 will be assumed for both, giving a final estimate for schools for the constant c of 0.0042.

For mesothelioma, the constant k in equation (iv) can also be estimated from the experience of North American insulators. Their incidence of mesothelioma 30-35 years after the start of prolonged exposure at about 30 fibre/ml was 3×10^{-3} per annum (Selikoff and Peto, 1981; unpublished), so

(vii) $k = 3 \times 10^{-3}/(32.5^{3.5} \cdot 30)$
$= 5.1 \times 10^{-10}$

The constant must be adjusted for the shorter working week in schools (a factor of about 0.5, as above), and for duration of exposure (a further factor of 0.5 for 6 years' exposure or 0.7 for 10 years exposure; see above). Thus $k = 5.1 \times 10^{-10} \times 0.5 = 1.3 \times 10^{-10}$ (6 years' exposure), or 1.8×10^{-10} (10 years' exposure.

1.5 Final Dose-response Formulae

Lung cancer 20 or more years after first exposure:

(viii) Excess incidence = normal (age, sex and smoking-specific) incidence x fibre/ml in school x duration x 0.0042.

The excess during the first 20 years will be so much lower than later, due to the lower initial relative risk, and to the steep increase with age of lung cancer incidence in both smokers and non-smokers, that it can be ignored.

Mesothelioma:

(ix) Excess annual incidence = $k \cdot (\text{years since first exp.})^{3.5} \times (\text{fibre/ml in school})$,

where $k = 1.3 \times 10^{-10}$ (6 years' exposure), or
$k = 1.8 \times 10^{-10}$ (10 years' exposure).

1.6 Definition and Calculation of Lifelong Risk

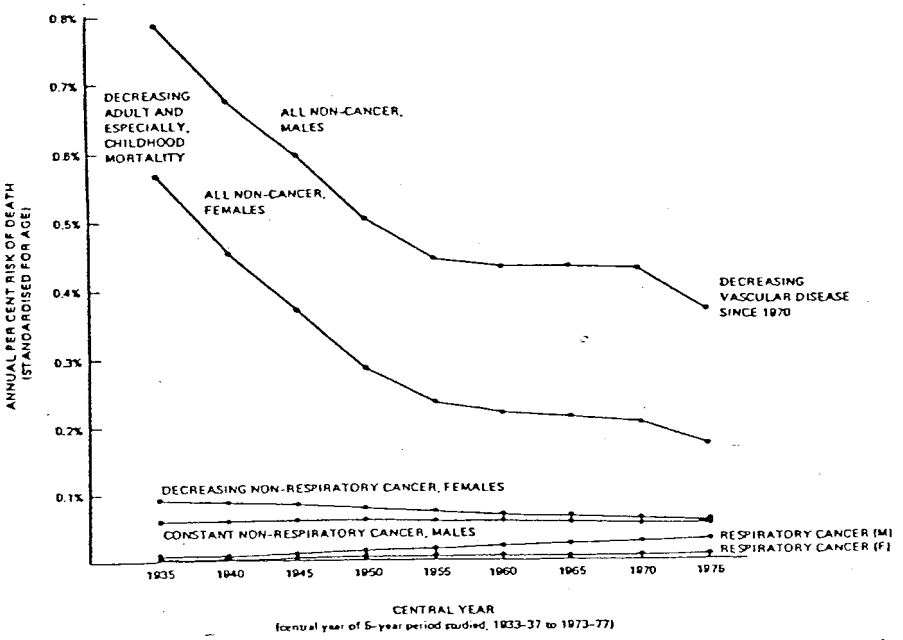
Lifelong risk is defined as the probability that an individual exposed to asbestos will die as a result of his exposure. The calculation of lifelong risk depends only on the age-specific survival rate s(a) of the population at each age(a), and the age-specific excess incidence I(a) caused by asbestos for each disease. (Incidence and mortality are similar for both lung cancer and mesothelioma.) The lifelong risk is then simply the product of $s(a) \cdot I(a)$ over all ages greater that a_o, divided by $s(a_o)$, where a_o is age at first exposure. Deaths occurring after age 80 are ignored in the following calculations. They can of course be added if required, but this would entail extrapolation well beyond any existing observations, particularly for mesothelioma, and would not greatly affect the results. It is assumed throughout that individual risks due to exposures of the sort encountered in schools are too low to appreciably affect life expectancy, even if the number of resulting deaths is substantial.

1.7 Choice of Death Rates for Lung Cancer and for the Calculation of s(a)

It is difficult to predict overall mortality in the future. For the purpose of predicting mesothelioma mortality the life-table based on 1972 U.S. national mortality, combining all races and both sexes, has been used (Table 2). Death rates have already fallen substantially since 1972, however (Fig. 2), and are likely to fall further. This will increase the lifelong risk due to mesothelioma, perhaps substantially, as the probability of surviving to old age, when the mesothelioma risk is highest, will increase. These calculations should be repeated using projections of future national death rates, if any are available.

For the lung cancer projections for smokers and non-smokers the position is still more difficult. Female lung cancer rates in old age are very much lower than male rates but if current smoking trends continue the sexes may well suffer similar rates 50 years hence at all ages. The effects of future changes in tar level and consumption may also be considerable in both sexes. U.S. male lung cancer rates are still rising at all ages above 50 due to the "smoking cohort" effect, whereas in Britain this has now ceased, and British

FIGURE 2 Data from Doll and Peto (1981)



Annual age-standardized death rates, 1933-77, among Americans under 65 years of age.

rates are falling slightly between ages 50 and 65, and markedly below age 50 (Fig. 3), probably due largely to the switch to filter cigarettes in about 1960 in Britain. It is clear from Fig. 3 that U.S. male rates are likely to exceed British rates at all ages within a decade or so. They are already equal or higher below age 55, and at older ages the curves are converging rapidly.

The lung cancer projections for non-smokers given below are based on the U.S. male death rates for lung cancer and all causes from Hammond (1966) (Tables 2 and 3). For smokers, rates for all causes in male current smokers have also been taken from Hammond (1966) (Table 2) but current British male lung cancer rates, inflated by a factor of 50% at each age to allow for the exclusion of non-smokers and ex-smokers, have been used as a basis for projection of future U.S. lung cancer rates among male current smokers in the U.S. (Table 3). For the reasons outlined in the preceding paragraph these would provide a better basis for prediction than Hammond's 1966 rates for current smokers if current smoking habits persist. This constitutes a necessarily arbitrary guess, however. If either tar levels or cigarette consumption fall substantially in the future the resulting predictions will be too high, and the calculation and corresponding predictions must be regarded as illustrative rather than definitive. More recent American Cancer Society data should be used if available.

No predictions of female lung cancer excesses are presented. For the reasons outlined above, it is possible that the risk to women will be similar to that among men, but no firmer statement can be defended.

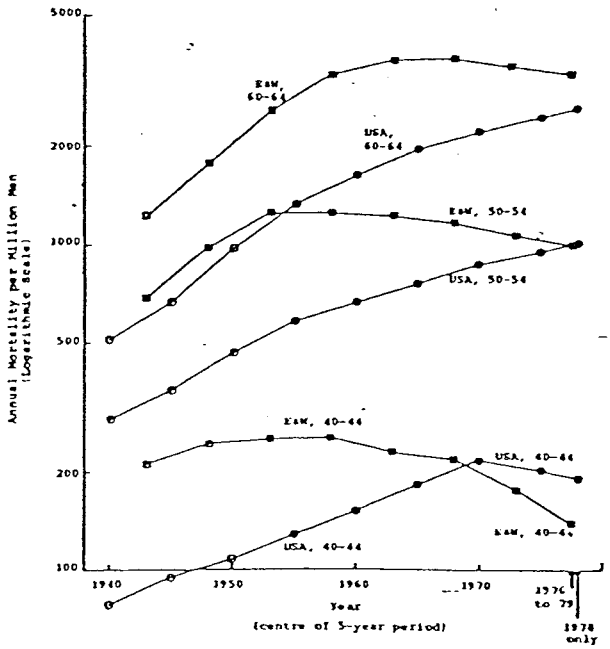
Apart from the difficulties outlined above and the fact that the calculations for mesothelioma are not based on survival rates of the same population as those used for lung cancer, survival rates for male smokers and non-smokers (columns (B) and (C), Table 2) were not available below age 35. (See notes to Table 2). These irritating details are mentioned to emphasize again that the following calculations should be regarded as illustrative of the method, and do not provide results which can be quoted out of context.

2.0 Example Calculations

2.1 Calculation of Mesothelioma Risk

Using column (A) in Table 2 as the survival rate s(a) at age(a) and computing annual excess mesothelioma incidence I(a) from equation (ix), the calculation of risk following exposure at 1 fibre/ml for 6 years starting at age a_o = 12 ($k = 1.3 \times 10^{-10}$) or 10 years from age a_o = 30 ($k = 1.8 \times 10^{-10}$) is shown in Table 4. The number of deaths per 10^5 individuals exposed from age a_o in each 5-year age-range = $5 \times 10^5 \times I(a) \times s(a)/s(a_o)$. The risk caused by any other concentration is calculated by simple proportion. Thus, for example, at 0.002 fibre/ml the lifelong risk would be 0.002 x 329.1 = 0.66 deaths per 10^5 exposed children. Note that most deaths (71% in children, and 85% in adults) would occur after age 60.

FIGURE 3 Data from Doll and Peto (1981)



Comparison of lung cancer trends in the U.S. (USA, *round symbols*) in selected age groups with corresponding trends in England and Wales (E&W, *square symbols*).
Data from tables E1-E4; points for 1940 to 1950 are estimates corrected for under-certification (open symbols); *points for subsequent years are observed rates* (solid symbols).

TABLE 2. Survival rates (A) for males and females, all races (U.S. 1972); (B) for male non-smokers; and (C) for male current smokers of 10-19 cigarettes per day. (B) and (C) are calculated from Hammond (1966) Appendix Tables 2a and 3a. Hammond (1966) did not present death-rates for lower ages, and the survival rates at lower ages have been arbitarily assumed to be the same for (B) and (C) as for (A).

Age (a)	Survival s(a) (A) Total U.S.	Survival s(a) (B) Male NS	Survival s(a) (C) Male S
0	1.000	1.000	1.000
12	.976	.976	.976
22.5	.966	.966	.966
27.5	.959	.959	.959
30	.955	.955	.955
32.5	.951	.951	.951
37.5	.942	.942	.942
42.5	.928	.934	.932
47.5	.907	.923	.917
52.5	.876	.911	.885
57.5	.831	.886	.836
62.5	.760	.849	.765
67.5	.679	.783	.660
72.5	.569	.690	.523
77.5	.432	.560	.387

TABLE 3. Lung cancer death rates per 10^5 per annum (A) for non-smokers (Hammond, 1966) and (B) for male smokers. The smokers' rates (B) were estimated by multiplying national British rates for 1977 by a factor of 1.5.

Age	$I_U(a)$ Non-Smokers (A)	$I_U(a)$ Smokers (B)
32.5	-	2.6
37.5	-	8.1
42.5	2.3	20.1
47.5	5.0	63.8
52.5	4.9	159.9
57.5	10.5	273.3
62.5	13.9	500.1
67.5	14.7	763.7
72.5	16.1	1010.4
77.5	35.8	1197.5

TABLE 4. Calculation of excess mesothelioma risks in successive 5-year age intervals up to age 80 due to exposure at 1 fibre/ml for 6 years from age 12, or 10 years from age 30.

Age (a)	Survival at mid-point of interval s(a)	Children 6 years from age 12 Incidence $I(a) \times 10^5$	Children 6 years from age 12 Deaths in 5-year interval $\times 10^5$	Staff 10 years from age 30 Incidence $I(a) \times 10^5$	Staff 10 years from age 30 Deaths in 5-year interval $\times 10^5$
0	1.000				
$a_o = 12$	$s(a_o)=.976$				
20-24	.966	<0.1	0.2		
25-29	.959	0.2	0.9		
$a_o = 30$	$s(a_o)=.955$				
30-34	.951	0.5	2.5	-	-
35-39	.942	1.1	5.3	<0.1	0.1
40-44	.928	2.0	9.7	0.1	0.6
45-49	.907	3.5	16.1	0.4	1.9
50-54	.876	5.5	24.7	1.0	4.5
55-59	.831	8.3	35.2	2.0	8.5
60-64	.760	11.9	46.3	3.5	14.0
65-69	.679	16.6	57.6	5.8	20.7
70-74	.569	22.4	65.3	9.0	26.8
75-79	.432	29.6	65.4	13.3	30.1
TOTAL DEATHS PER 10^5:			329.1		107.2

2.2 Calculation of Lung Cancer Excess Risk

Using column (C) in Table 2 as the survival rate s(a) at age(a), and column (B) in Table 3 as the lung cancer rate $I_U(a)$ in male smokers, the corresponding risk calculations (see equation (viii)) are shown in Table 5. The excess during the first 20 years after first exposure is assumed to be negligible. The risk is proportional to duration and to fibre level, but age at first exposure has virtually no effect. A concentration of 0.002 fibre/ml for 6 years from age 12, for example, would thus cause $0.002 \times 301.6 = 0.60$ deaths per 10^5 exposed children. As for mesothelioma, the majority of deaths occur after age 60 (80% in children, and 84% in adults).

Repeating these calculations for non-smokers, using column (B) in Table 2 and column (A) in Table 3 gives predicted total excess lung cancer risks per 10^5 at 1 fibre/ml of 9.6 (compared with 301.6 in smokers) for children and 15.0 (compared with 494.4 in smokers) for adult staff. These are an order of magnitude lower than the predicted mesothelioma risks, and for practical purposes can be ignored.

TABLE 5. Calculation of excess lung cancer risks in successive 5-year age intervals up to age 80 following exposure at 1 fibre/ml for 6 years from age 12, or 10 years from age 30. (Male smokers of 10-19 cigarettes/day.)

Age (a)	Survival at mid-point of interval s(a)	Lung cancer death-rate in unexposed smokers x10^5 $I_U(a)$	Children 6 years from age 12	Staff 10 years from age 30
			Deaths per 10^5 in 5-year interval*	
0	1.000	-	-	-
a_o = 12	$s(a_o)$=.976			
20-24	.966	-	-	-
25-29	.959	-	-	-
a_o = 30	$s(a_o)$=.955			
30-34	.951	2.6	0.3	-
35-39	.942	8.1	1.0	-
40-44	.932	20.1	2.4	-
45-49	.917	63.8	7.6	-
50-54	.885	159.9	18.3	31.1
55-59	.836	273.3	29.5	50.2
60-64	.765	500.1	49.4	84.1
65-69	.660	763.7	65.1	110.8
70-74	.523	1010.4	68.2	116.2
75-79	.387	1197.5	59.8	101.9
TOTAL DEATHS PER 10^5:			301.6	494.4

* = $I_U(a) \times 5 \times 0.0042 \times$ duration (6 or 10) $\times \frac{s(a)}{s(a_o)}$

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