Report on the Peer Consultation Workshop to Discuss a Proposed Protocol to Assess Asbestos-Related Risk

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NOTE

This report was prepared by Eastern Research Group, Inc. (ERG), an EPA contractor, as a general record of discussion for the peer consultation workshop on a proposed protocol to assess asbestos-related risk. This report captures the main points of scheduled presentations, highlights discussions among the panelists, and documents the public comments provided at the meeting. This report does not contain a verbatim transcript of all issues discussed, and it does not embellish, interpret, or enlarge upon matters that were incomplete or unclear. EPA will use the information presented during the peer consultation workshop to determine whether the proposed risk assessment methodology can be used to support decisions at asbestos-contaminated sites. Except as specifically noted, no statements in this report represent analyses by or positions of EPA or ERG.

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LIST OF ABBREVIATIONS

ATSDR	Agency for Toxic Substances and Disease Registry
EPA	U.S. Environmental Protection Agency
ERG	Eastern Research Group, Inc.
IARC	International Agency for Research on Cancer
IRIS	Integrated Risk Information System
NIOSH	National Institute for Occupational Safety and Health
PCM	phase contrast microscopy
SEM	scanning electron microscopy
SVF	synthetic vitreous fibers
TEM	transmission electron microscopy
μm	micrometers

EXECUTIVE SUMMARY

Eleven expert panelists participated in a peer consultation workshop to review a proposed protocol to assess asbestos-related risks. The protocol is documented in the report, "Technical Support Document for a Protocol to Assess Asbestos-Related Risk, Parts I and II" (Berman and Crump 1999, 2001). At the end of the 2½-day workshop, which was open to the public, the expert panelists drafted the following summary of their findings:

The peer consultation panel strongly endorsed the conceptual approach of developing an updated cancer risk assessment methodology that takes into account fiber type and fiber dimension. The opportunity is at hand to use substantial new information from epidemiology, experimental toxicology, and exposure characterization on what continues to be an extremely important societal issue—assessing the health risks associated with environmental and occupational exposures to asbestos. The panel recommended that EPA proceed in an expeditious manner to consider the panelists' conclusions and recommendations with a goal of having an updated asbestos risk assessment methodology. It is important that EPA devote sufficient resources so that this important task can be accomplished in a timely and scientifically sound manner. The panel urges that additional analyses underpinning the document, preparation of documentation, and further review be carried out in an open and transparent manner.

Prior to the workshop, the participants received draft copies of the "Methodology for Conducting Risk Assessments at Asbestos Superfund Sites Part 1: Protocol" and "Part 2: Technical Background Document." The panelists generally found that these documents did not provide a complete and transparent description of how the data were analyzed to support the conclusions presented. The incomplete documentation of methodology precluded the replication of the findings, in advance of the meeting, by several panelists. The methodology used was clarified by the comprehensive presentations that Drs. Berman and Crump made at the workshop. However, future drafts of these documents must

clearly describe the methodologies and include sufficient data, perhaps in appendices, such that the findings can be replicated.

The panelists made the following conclusions and recommendations:

- **Measurement methods.** Continuing advances have been made in the application of exposure measurement technology for asbestos fibers during the past two decades. These advances include the use of transmission electron microscopy (TEM) and allied techniques (e.g., energy dispersive x-ray detection, or EDS) as an alternative to phase contrast microscopy (PCM), thereby allowing the bivariate (i.e., length and width) characterization of fibers and fiber type. The proposed risk assessment methodology incorporates these advances in the development of an exposure index. The panel was in agreement that this aspect of the new risk assessment methodology represents a substantial advance over the existing methodology.

- **Integration of exposure and risk assessment models.** A key aspect of the proposed risk assessment methodology is a linking of specific exposure characterization methodology with exposure-response coefficients. It has been emphasized that any change in the exposure characterization metrics must be accompanied by changes in the exposure-response coefficients of the risk assessment models. This was emphasized in the report and the panelists endorsed this view.

- **Access to additional raw data sets.** The panelists strongly recommended that EPA make every attempt to acquire and analyze raw data sets from key human epidemiological studies. Where possible, it would also be desirable to obtain bivariate (i.e., length and diameter) fiber exposure information for these re-analyses. Several panelists believed that review of additional data sets offers substantial opportunity for improving the proposed risk assessment methodology. In the event that raw data cannot be obtained due to confidentiality reasons or other restrictions, the panelists suggested that the authors consider asking those who have access to the data to conduct the necessary statistical analyses and communicate their results directly to EPA for further consideration.

- **Fiber diameter.** The proposed risk assessment methodology uses a diameter cut-off of 0.5 micrometers (μm) for considering fibers. The report states that fibers 0.7 μm in diameter can reach the respiratory zone of the lung. A few panel members indicated that the fiber diameter cut-off could be as high as 1.5 μm during oral breathing. The 0.4 μm cut-off came from rat data, but larger diameters would be expected to be respirable in humans. There was general agreement that the diameter cut-off should be between 0.5 and 1.5 μm. This issue is deserving of further analysis.

Fiber length. The Berman and Crump analyses made a significant contribution by obtaining and analyzing membrane filters from the animal inhalation studies in Edinburgh and conducting quality-assured bivariate length and distribution analyses by TEM—thereby greatly reducing the uncertainty of the exposure side of the exposure-response relationship for chronic fiber exposure in rats. Unfortunately, correspondingly detailed information on bivariate size distribution is not available for humans. This leads to the need to use the animal data, although one must always recognize the uncertainties associated with interspecies extrapolations such as anatomic characteristics and respirability between species. Future analyses may benefit from using other available laboratory animal data sets and human data sets.

The fiber length distributions for the human cohort exposures are much more uncertain. For the Wittenoom, Quebec, and South Carolina cohorts, there are limited fiber length distribution data based on TEM analysis from historic membrane filter samples, but only fiber categories longer than 5 μm and longer than 10 μm were counted. For all other cohorts, the measurements were limited to PCM fiber counts for all fibers greater than 5 μm in length in some, and particle counts (10x objective) on midget impinger samples in others. Both methods do not measure thin fibers, do not discriminate between asbestos and other mineral particles, and provide no information on the concentrations of fibers longer than 10, 20, or 40 μm, or inter-laboratory variations in optical resolution and counting rules. As one approach to addressing the varying uncertainty in assessing exposure in the different studies, Berman and Crump used the available information to make adjustments to the uncertainty ranges in the exposure-response coefficients. The workshop panel welcomed this initiative but suggested alternative approaches (see "Methods," below).

Some panelists felt that an Exposure Assessment Workshop, with participants having a broad range of expertise, could evaluate the uncertainties in historic occupational data sets' exposure measurements. They felt such a workshop could result in a more confident assessment of exposure-response relationships for populations exposed to a variety of amphiboles, chrysotile, and mixtures. With incorporation of other available knowledge on fiber type, process, smoking (if available), and the relative number of excess lung cancer and mesothelioma, it may well be possible to gain a much clearer understanding of the roles of these variables as causal factors for these asbestos-associated cancers. In addition, the workshop would prove valuable in further discussion of mineralogical, geological, and industrial hygiene issues with regard to application of the model to risk assessment in environmental sites of concern.

The Berman and Crump index assigns zero risk to fibers less than 5 μm in length. Fibers between 5 and 10 μm are assigned a risk that is one three-hundredth of the risk assigned to fibers longer than 10 μm. Panelists agreed that there is a considerably greater risk for lung cancer for fibers longer than 10 μm. However, the panel was uncertain as to an exact cut size for length and the magnitude of the relative potency. The panelists also agreed that the available

data suggest that the risk for fibers less than 5 μm in length is very low and could be zero. This specific issue was addressed by an expert panel convened by the Agency for Toxic Substances and Disease Registry (ATSDR) in October 2002. Some panelists suggested that, for mesothelioma, greater weight should perhaps be assigned to fibers in the 5 to 10 μm length range and to thinner fibers.

Fiber type. For *mesothelioma*, the panelists supported the use of different relative carcinogenic potencies for different fiber types. The panelists unanimously agreed that the available epidemiology studies provide compelling evidence that the carcinogenic potency of amphibole fibers is two orders of magnitude greater than that for chrysotile fibers. There was some discussion about the precise ratio expressed due to questions about the availability of exposure data in existing studies (e.g., Wittenoom). There was recognition that time since first exposure is an important factor in determining risk for mesothelioma and some discussion is needed on the importance of duration and intensity of exposure.

For *lung cancer*, the panelists had differing opinions on the inferences that can be made on the relative potency of chrysotile and amphibole fibers. Some panelists supported the finding that amphibole fibers are 5 times or more potent for lung cancer than are chrysotile fibers. Other panelists did not think the statistical analyses in the draft methodology document supports this relative potency and wondered if additional review of the epidemiological data might identify factors other than fiber type (e.g., industry considered) that provide further insights on the matter. These other factors can then be considered when the risk assessment is applied.

 # Cleavage fragments. The panel knew of little data to directly address the question as to whether cleavage fragments of equal durability and dimension as fibers would have similar or dissimilar potency for lung cancer. The general view is that data indicate that durability and dimension are critical to pulmonary pathogenesis. Therefore, it is prudent at this time to assume equivalent potency for cancer in the absence of other information to the contrary. Consideration of conducting a rat inhalation study using tremolite cleavage fragments was recommended to address this issue. For mesothelioma, it was viewed that thin fibers greater than 5 μm in length are more important. Cleavage fragments that do not meet these criteria would not contribute to risk of mesothelioma.

Other amphiboles. The panel agreed with the report's conclusion that the potency of currently regulated and unregulated amphibole fibers should be considered equal based on the reasoning that similar durability and dimension would be expected to result in similar pathogenicity.

 # Methods. The panelists extensively discussed the approach to conducting the meta-analysis of the large number of epidemiological studies. A number of the panelists urged that consideration be given to using more traditional approaches that would include development and application of specific criteria for inclusion of studies into the exposure-response analysis, examination of

heterogeneity and sources of the heterogeneity, and the use of sensitivity analysis to identify influential studies.

The panelists also urged, in the study-specific analysis, exploration of alternative exposure-response models other than the lung cancer and mesothelioma risk models EPA has been using since 1986. This would possibly include non-linear response models (e.g., log-linear models), examination of separate effects for concentration and duration, time since first exposure, time since cessation of exposure, possibly dropping the "α factor," and different methods for measurement error. The adequacy of different models should be examined using goodness of fit statistics across all studies. The possibility of internal analyses should be re-examined (i.e., it may be possible to obtain partial data, such as age-specific person years data, from authors). Exploration of non-linearity should also include shape of the curve in the low exposure area.

The panelists also urged alternative approaches to meta-analyses. In particular, panelists recommended meta-regression using original (untransformed) exposure-response coefficients, in which predictor variables include the estimated percentage of amphiboles, percentage of fiber greater than 10 μm, and categorical grouping of studies according to quality. Original exposure-response coefficient variances should be used in conjunction with random effects models in which residual inter-study variation is estimated. Analyses restricted to long latency and a predictor variable for industry type should be considered. A priori distribution for inter-study residual variance might also be considered. Meta-regression will allow simple inspection of likelihoods to consider the importance of different predictor variables. Sensitivity analyses should be conducted in which the inclusion or exclusion of specific studies or groups of studies is evaluated.

Cigarette smoking. Most panelists felt strongly that future analyses need to pay more attention to the effects of smoking on the lung cancer exposure-response model and extrapolations to risk. However, the current data sets have variable and limited information available on smoking. The panelists noted that smoking is the primary cause for lung cancer, but the lung cancer dose-response relationship for smoking is complex due to the effects of smoking duration, intensity, and cessation.

The impact of smoking has effects on both the estimation and the application of the model for projecting risk of lung cancer due to asbestos exposure. This may be an especially critical issue for low-exposure extrapolation. With respect to estimation, accepting the form of the proposed model, the effect of smoking may require different K_L values for smokers and non-smokers. The panelists recognized that there is limited epidemiologic data to address this issue, but recommend that it be investigated. With respect to applying the model to make risk projections for any future cohort, the background rate of lung cancer employed in the model needs to be carefully determined to capture the smoking behavior of the cohort.

Localized tremolite exposures. During the course of public comments, the panel received input from several individuals who expressed concerns about environmental exposures to tremolite asbestos from localized geologic formations in California. The individuals suggested that inadequate attention had been given to characterization of the exposures to residents of these communities. While the panel was not in a position or charged with the evaluation of this issue, the panel did feel that this was a potentially serious matter deserving of attention by the appropriate public health authorities. Evaluation of these kinds of situations would benefit from the use of the improved risk assessment methodology being considered.

The remainder of this report summarizes the discussions and observations that led to these findings, reviews the panelists' comments on many topics not listed in this executive summary, and documents the observer comments provided at the workshop.

1. INTRODUCTION

This report summarizes a peer consultation by 11 expert panelists of a proposed protocol to assess asbestos-related risks. Contractors to the U.S. Environmental Protection Agency (EPA) developed the proposed protocol, which is documented in a report titled: "Technical Support Document for a Protocol to Assess Asbestos-Related Risk" (Berman and Crump 2001). The purpose of the peer consultation workshop was to provide EPA feedback on the scientific merit of the proposed protocol. The peer consultation workshop took place in a meeting open to the public on February 25–27, 2003, in San Francisco, California.

This report summarizes the technical discussions among the expert panelists and documents comments provided by observers. These discussions largely focused on three topic areas: interpretations of the epidemiology and toxicology literature, the proposed exposure index, and general questions about key assumptions and inferences in the protocol. The remainder of this introductory section presents background information on the protocol (Section 1.1), describes the scope of the peer consultation workshop (Section 1.2), and reviews the organization of this report (Section 1.3).

1.1 Background

EPA's current assessment of asbestos toxicity is based primarily on an asbestos review completed in 1986 (EPA 1986) and has not changed substantially since that time. The 1986 assessment considers six mineral forms of asbestos and all asbestos fiber sizes longer than 5 micrometers (μm) to be of equal carcinogenic potency. However, since 1986, asbestos measurement techniques and the understanding of how asbestos exposure contributes to disease have improved substantially. To incorporate the knowledge gained over the last 17 years into the agency's toxicity assessment for asbestos, EPA contracted with Aeolus, Inc., to develop a proposed methodology for conducting asbestos risk assessments. The proposed methodology distinguishes between fiber sizes and fiber types in estimating

potential health risks related to asbestos exposure. The methodology also proposes a new exposure index for estimating carcinogenic risk.

As a key step in determining the scientific merit of the proposed risk assessment methodology, EPA decided to obtain expert input on the draft report through a peer consultation workshop. The purpose of the workshop was to obtain feedback from subject-matter experts during the development stage of the proposed risk assessment methodology; the workshop was not an official peer review. Eastern Research Group, Inc. (ERG), organized and implemented the peer consultation workshop under a contract to EPA.

1.2 Scope of the Peer Consultation Workshop

The peer consultation involved many activities before the workshop (see Section 1.2.1), at the workshop (see Section 1.2.2), and after the workshop (see Section 1.2.3). The following subsections describe these activities.

1.2.1 Activities Prior to the Peer Consultation Workshop

This section describes the major activities ERG and the expert panelists conducted prior to the peer consultation workshop:

Select expert panelists. ERG selected the expert panelists for the peer consultation workshop. ERG sought to compile a panel of experts with broad experience and expertise in the following disciplines: toxicology, epidemiology, biostatistics, asbestos sampling and analytical methods, EPA's human health risk assessment guidelines, and asbestos-related environmental and occupational health issues. Appendix A lists the expert panelists ERG selected, and Appendix B includes brief biographies that summarize the panelists' areas of expertise.

  Every panelist is either a senior scientist, physician, or researcher with extensive experience in the aforementioned fields, as demonstrated by peer-reviewed publications, awards, and service

to relevant professional societies. To ensure the peer consultation offered a balanced perspective, ERG intentionally selected expert panelists with a broad range of affiliations (e.g., academia, consulting, state and federal agencies). When searching for panelists, ERG asked all candidates to disclose real or perceived conflicts of interest.

Prepare a charge to the expert panelists. ERG worked with EPA to prepare written guidelines (commonly called a "charge") for the peer consultation workshop. The charge includes 12 specific questions, organized into 4 topic areas. Discussions at the workshop largely addressed the technical issues raised in the charge, but the expert panelists were encouraged to discuss other relevant matters that were not specifically addressed in the charge questions. A copy of the charge is included in Appendix B.

Distribute review documents and other relevant information. Several weeks prior to the peer consultation workshop, ERG sent every panelist copies of the charge and the proposed risk assessment methodology (Berman and Crump 2001). These items formed the basis of the technical discussions at the workshop. In addition, ERG distributed several additional publications on related topics (see Table 1, at the end of this section, for list of the publications). The supplemental publications were provided largely in response to panelists' requests for further background information on selected issues. The panelists also circulated publications amongst themselves on specific topics. Finally, one of the meeting chairs noted for the record that, upon arriving in San Francisco, he also received a memo and copies of many abstracts and other information from Cate Jenkins of EPA. The meeting chair offered to share these materials with other panelists during the workshop.

Obtain and compile the panelists' premeeting comments. After receiving the workshop materials, the panelists were asked to prepare their initial responses to the charge questions. Booklets containing the premeeting comments were distributed to the expert panelists before the workshop and were made available to observers at the workshop. These initial comments are included in this report, without modification, as Appendix B. It should be noted that the premeeting comments are preliminary in nature. Some panelists' technical findings may have changed after the premeeting comments were submitted.

1.2.2 Activities at the Peer Consultation Workshop

The 11 expert panelists and approximately 75 observers attended the peer consultation workshop, which was held at the Westin St. Francis Hotel in San Francisco, California, on February 25–27, 2003. The workshop was open to the public, and the workshop dates and times were announced in the

Federal Register. Appendix C lists the observers who confirmed their attendance at the workshop registration desk. The workshop schedule generally followed the agenda, presented here as Appendix D.

The workshop began with introductory remarks from Ms. Jan Connery (ERG), the facilitator of the peer consultation. Ms. Connery welcomed the expert panelists and observers, stated the purpose of the workshop, identified the document being reviewed, and explained the procedure for observers to make comments. Mr. Richard Troast (EPA) then provided background information on the review document and EPA's ongoing efforts to assess asbestos toxicity (see Section 1.1). Mr. Troast identified the main differences between EPA's existing asbestos risk assessment methodology (EPA 1986) and the proposed methodology (Berman and Crump 2001). Mr. Troast noted that the expert panelists' feedback will ultimately help EPA complete its update of asbestos health risks for the Integrated Risk Information System (IRIS); he clarified that the final IRIS update will be subject to peer review or Science Advisory Board review before being implemented. Following these opening remarks, Dr. Wayne Berman and Dr. Kenny Crump—the authors of the proposed methodology—presented detailed information on the review document; Section 2 of this report summarizes their presentations.

After the background presentation, Dr. Roger McClellan and Dr. Leslie Stayner chaired the technical discussions that followed. For the remainder of the meeting, the panelists engaged in free-flowing discussions when answering the charge questions and addressing additional topics not specified in the charge. Observers were given the opportunity to provide verbal comments three different times during the workshop; these observer comments are documented in Appendix E. Representatives from EPA and the document authors provided clarifications on the proposed methodology periodically throughout the 2½-day workshop.

1.2.3 Activities Following the Peer Consultation Workshop

The primary activity following the peer consultation workshop was preparing this summary report. A technical writer from ERG who attended the meeting prepared a draft of this report, which ERG distributed to the 11 expert panelists and asked them to verify that the draft accurately reflects the tone and substance of the panelists' discussions at the workshop. After incorporating the panelists' suggested revisions to the draft report, ERG submitted the final report (i.e., this report) to EPA.

1.3 Report Organization

The structure of this report follows the order of the technical discussions during the meeting. Section 2 summarizes Dr. Berman and Crump's background presentations. Sections 3 through 6 are records of the panelists' discussions on the four main topic areas: interpretations of the epidemiology and toxicology literature (Section 3), the proposed exposure index (Section 4), general questions (Section 5), and conclusions and recommendations (Section 6). Finally, Section 7 provides references for all documents cited in the text.

The appendices to this report include background information on the peer consultation workshop. This information includes items that were on display at the workshop and items generated since the workshop (e.g., a final list of attendees). The appendices contain the following information:

- List of the expert panelists (Appendix A).
- The panelists' premeeting comments, the charge to the reviewers, and brief bios of the expert panelists (Appendix B).
- List of registered observers of the peer consultation workshop (Appendix C).
- Agenda for the peer consultation workshop (Appendix D).
- Observer comments provided at the peer consultation workshop (Appendix E).
- Observer post-meeting comments (Appendix F).

Table 1
References ERG Provided to the Expert Panelists

Berman, DW and Crump K. 1999. Methodology for Conducting Risk Assessments at Asbestos Superfund Sites; Part 1: Protocol. Final Draft. Prepared for U.S. Environmental Protection Agency. February 15, 1999.
Berman, DW and Crump K. 2001. Technical Support Document for a Protocol to Assess Asbestos-Related Risk. Final Draft. Prepared for U.S. Department of Transportation and U.S. Environmental Protection Agency. September 4, 2001.
Berman, DW, Crump, K., Chatfield, E., Davis, J. and A. Jones. 1995. The Sizes, Shapes, and Mineralogy of Asbestos Structures that Induce Lung Tumors or Mesothelioma in AF/HAN Rats Following Inhalation. Risk Analysis. 15:2,181-195.
Berman, DW. 1995. Errata. Risk Analysis. 15:4, 541.
Committee on Nonoccupational Health Risks of Asbestiform Fibers. Breslow, L., Chairman. 1984. Asbestiform Fibers Nonoccupational Health Risks. Washington, DC: National Academy Press.
EPA 1986. Airborne Asbestos Health Assessment Update. U.S. Environmental Protection Agency. EPA 600/8-84-003F. 1986.
NIOSH Interdivisional Fiber Subcommittee Report. Prepared by the NIOSH Interdivisional Fiber Subcommittee. 1999.

2. BACKGROUND ON THE PROPOSED PROTOCOL TO ASSESS ASBESTOS-RELATED RISK

This section summarizes presentations given by the principal authors of the proposed risk assessment methodology. These presentations were given because several panelists asked ERG, prior to the peer consultation workshop, if the authors would provide detailed background information on how the methodology was developed. This section reviews the major presentation topics, but does not present the panelists' comments on the proposed protocol. Sections 3 through 6 document the expert panelists' technical feedback on the protocol.

Motivation for developing the proposed protocol. Dr. Berman identified several reasons for developing the updated protocol for assessing asbestos-related risks. These reasons include EPA's existing asbestos models being inconsistent with inferences from the scientific literature, the need for having uniformly-applied sampling and analytical procedures to measure asbestos characteristics most predictive of risk, and the belief that EPA's current asbestos risk assessment methodology may not be adequately protective in some circumstances. To improve upon the current methodology, the authors intended to develop a risk assessment model that adequately predicts cancer risk in all studied environments and can therefore be applied with much greater confidence to environments that have not been studied. Dr. Berman outlined the general approach taken to develop the proposed protocol, as summarized in the following bulleted items.

Dr. Berman provided background information on and definitions for asbestos, other fibrous structures, asbestos morphology, and cleavage fragments. He also described the capabilities and limitations of the analytical techniques that have been used to characterize asbestos exposures, such as midget impingers, phase contrast microscopy (PCM), scanning electron microscopy (SEM), and transmission electron microscopy (TEM). Dr. Berman explained how differences in these analytical techniques must be critically evaluated when comparing results reported in all epidemiological and other types of studies that examine asbestos exposure. Dr. Berman also stressed that it is not just differences in analytical techniques, but choice of specific methods for each analytical technique that affects results. Further information on these topics is included in Chapter 4 of the proposed protocol (Berman and Crump 2001).

Re-analysis of human epidemiological data. Dr. Crump described how the authors evaluated the human epidemiological data. He displayed a list of the studies that were considered, noting that he had access to raw, individual-level data for three occupational cohorts: chrysotile textile workers in South Carolina, United States; crocidolite miners in

Wittenoom, Australia; and chrysotile miners and millers in Quebec, Canada. All data sets with exposure data were considered in the analysis, and criteria were not established for selecting studies. Dr. Crump then presented findings for asbestos-related risks for lung cancer and mesothelioma.

For lung cancer, Dr. Crump first reviewed EPA's existing lung cancer model for asbestos exposure (see equation 6.1 in the proposed protocol), which relates the relative risk of lung cancer mortality linearly to cumulative asbestos exposure, with a 10-year lag time. Dr. Crump noted that the model predicts that relative risk for developing lung cancer remains constant after asbestos exposure ceases—an assumption he showed was reasonably consistent with findings from epidemiological studies. Dr. Crump also discussed how the model assesses interactions between exposures to cigarette smoke and to asbestos—an issue the panelists revisited several times later in the workshop (e.g., see Section 3.1.1 and the executive summary). Dr. Crump presented a series of tables and figures demonstrating the adequacy of multiple lung cancer models: first using EPA's existing lung cancer model, next using a modified version of the model that accounts for differences in the background rates of lung cancer, and finally using the proposed lung cancer model, which considers an exposure index that assigns greater carcinogenic potency to amphibole fibers and to longer fibers.

Similarly, Dr. Crump reviewed the performance of EPA's mesothelioma model for asbestos exposures (see equation 6.11 in the proposed protocol), which predicts that mesothelioma risks vary linearly with the average asbestos exposure and increase quadratically with time from onset of exposure. Dr. Crump presented several tables and graphs indicating how well EPA's existing model and the proposed protocol fit the human epidemiological data. He made several conclusions about the existing risk model, including that mesothelioma risk coefficients varied considerably across the cohorts and the risk coefficients were generally higher for cohorts exposed primarily to amphibole fibers, compared to those exposed primarily to chrysotile fibers. Dr. Crump also noted that the data did not support consideration of a sub-linear or threshold dose-response relationship. This latter point generated considerable discussion later in the workshop (e.g., see Section 4.3).

Dr. Crump then described the meta-analysis the authors conducted to evaluate the relative potency of amphibole and chrysotile fibers. First, he explained how the authors weighted the different studies in the meta-analysis, based on uncertainty factors assigned to the individual studies. Dr. Crump identified the four uncertainty factors and described generally how each factor was assigned. Sources of uncertainty included representativeness of air sampling data, the availability of conversion factors to express exposures in terms of PCM concentrations, and whether data on exposure duration were available. Dr. Crump then highlighted the main conclusions from the meta-analysis. For lung cancer, the meta-analysis suggested that amphibole fibers are approximately five times more potent than are chrysotile fibers, but the difference in potency was not statistically significant (i.e., the authors could not reject the hypothesis that

chrysotile fibers and amphibole fibers are equally potent). For mesothelioma, the meta-analysis suggested that chrysotile fibers are 0.002 times as potent as amphibole fibers, and the difference in potency was statistically significant.

Inferences drawn from the broader literature. Dr. Berman described how the authors incorporated inferences from the broader scientific literature into the proposed protocol. He reviewed key findings on how various mechanisms are biologically related to how asbestos causes disease. These mechanisms included respiration, deposition, degradation, clearance, translocation, and tissue-specific biological responses. Chapter 7 of the review document provides detailed information on the relevance of these mechanisms, with emphasis on the influence of fiber type and fiber dimension.

Derivation of the exposure index. Dr. Berman explained how the authors derived the exposure index, which is largely based on an earlier re-analysis (Berman et al. 1995) of six animal inhalation studies conducted by a single laboratory. That re-analysis found that lung tumor incidence is adequately predicted using an exposure index that assigns no carcinogenic potency to fibers shorter than 5 μm, relatively low carcinogenic potency to fibers with lengths between 5 and 40 μm and diameters less than 0.4 μm, and the greatest carcinogenic potency to fibers longer than 40 μm and thinner than 0.4 μm. However, these findings could not be applied directly to the human epidemiological data, because the epidemiological studies do not include exposure measurements that quantify the relative amounts of asbestos fibers shorter and longer than 40 μm.

Dr. Berman noted that the proposed protocol includes an *ad hoc* assumption that the fiber size weighting factors optimized from the laboratory animal studies can be applied to humans, but with a length cut-off of 10 μm in the exposure index, rather than a cut-off of 40 μm. Dr. Berman emphasized that this assumption was made to model the critical characteristics of asbestos in a manner that reasonably captures cancer risks observed across multiple epidemiological studies. He acknowledged that asbestos potency is likely a continuous function of fiber length, but the exposure measurements from the available animal and epidemiological studies do not support incorporating such a continuous function in the exposure-response model. The panelists commented on the proposed exposure index when discussing topic area 3 (see Section 4).

Dr. Berman also noted that the authors selected a conservative set of dose-response coefficients (see Table 6-30 of the review document), rather than using the optimized ones from the animal studies (see Table 6-29). However, the conservative and optimized dose-response coefficients were reasonably consistent: none of the conservative coefficients differed by more than a factor of 4 from the corresponding optimized ones.

Conclusions regarding proposed protocol. Dr. Berman indicated that the proposed protocol is substantially more consistent with inferences documented in the scientific literature (i.e., that

long, thin structures contribute most to risk) than EPA's existing risk assessment methodology. Further, the proposed protocol provides a better fit to cancer risks observed in the human epidemiological studies than does EPA's existing model, and the proposed protocol appears to underestimate risks of lung cancer and mesothelioma less frequently and to a lesser degree than the existing approach. Finally, by recommending use of a standardized analytical method that links directly to the exposure index, the proposed protocol will help ensure that future risk assessments are conducted in a consistent fashion and their results can be readily compared from one study to the next.

3. COMMENTS ON TOPIC AREA 1: INTERPRETATIONS OF THE EPIDEMIOLOGY AND TOXICOLOGY LITERATURE

This section summarizes the panelists' discussions on the interpretations of the epidemiology and toxicology literature. The meeting co-chairs—Dr. McClellan and Dr. Stayner—facilitated the discussions on this topic area, which focused first on lung cancer (see Section 3.1) and then on mesothelioma (see Section 3.2). This section presents a record of discussion of the topics mentioned during the workshop. Several panelists referred to their premeeting comments (see Appendix B) for additional suggestions for how the review of epidemiology and toxicology literature can be improved.

3.1 Lung Cancer

The panelists discussed at length whether the epidemiology and toxicology literature support the proposed protocol's finding for how lung cancer potency varies with fiber type and fiber length. This section summarizes these discussions, first on fiber type (Sections 3.1.1 and 3.1.2) and then on fiber length (Sections 3.1.3 and 3.1.4). General issues regarding the lung cancer evaluation are presented in Section 3.1.5.

3.1.1 Lung Cancer and Fiber Type: Inferences from the Epidemiology Literature

According to the proposed risk assessment methodology, amphibole fibers have a 5-fold greater lung cancer potency than do chrysotile fibers. The panelists had differing opinions on whether this finding is consistent with the epidemiology literature. On the one hand, some panelists indicated that the epidemiology literature is consistent with amphibole fibers being more potent for lung cancer, though the magnitude of this increase may not be known precisely. One panelist noted, for example, that multiple analyses (e.g., Hodgson and Darnton 2000, Berman and Crump 2001, and the statistical analyses a panelist presented during this discussion) all point to a consistent increased lung cancer potency for amphibole fibers compared to chrysotile fibers, albeit a small increase. On the other hand, other

panelists did not believe the epidemiology literature supports this conclusion, for reasons stated below. Finally, other panelists were not convinced that the epidemiology literature supports the higher lung cancer potency for amphibole fibers, but they believed the difference in potency seems likely based on evidence from the animal toxicology studies (see Section 3.1.3) and lung burden studies. A summary of the panelists' discussion on this topic follows:

Comments on specific publications. Several panelists cited specific studies to support their positions on the relative lung cancer potency of chrysotile and amphibole fibers, but the panelists often had differing opinions on the inferences that should be drawn. The panelists mentioned the following specific studies:

- Some panelists noted that a recent re-analysis of 17 cohorts (Hodgson and Darnton 2000) indicates that the lung cancer potency for amphibole fibers is 10 to 50 times greater than that for chrysotile fibers. One panelist did not agree with this finding, due to the crude approach the article uses to characterize relative potency. Specifically, this panelist noted that carcinogenic potency was calculated by dividing the overall relative risk for a given cohort by the average exposure for the entire cohort, even for cohorts where the data support more sophisticated exposure-response modeling. He was particularly concerned about the authors' decision to omit the cohort of South Carolina textile workers from the meta-analysis. This decision was apparently based on the South Carolina cohort being an outlier, due to its much higher lung cancer potency when compared to other studies. The panelist noted, however, that the lung cancer risk for the South Carolina cohort is not unusually high when compared to other cohorts of textile workers. The panelist was concerned that omitting this study might have biased the article's finding regarding relative lung cancer potency. No other panelists discussed the review article.

- One panelist cited a study of Quebec chrysotile miners and millers (Liddell et al. 1997, 1998) that reports that increased lung cancer risk was limited to the mining region with the highest level of tremolite asbestos, after correction for smoking and exposure. The article was distributed to the panelists on the first day of the workshop, but no panelists commented further on the study.

- One panelist noted that his review of multiple textile cohorts (Stayner, Dankovic, and Lemen 1996) found relatively small differences in lung cancer potency, even though some of the cohorts were exposed to asbestos mixtures containing different proportions of amphibole fibers.

- One panelist indicated that further evidence on how fiber types relates to lung cancer potency can be gleaned from epidemiological studies that were not included in the meta-analysis due to inadequate exposure data for exposure-response modeling. Examples include a study of non-occupationally exposed women from two chrysotile asbestos mining regions (Camus et al. 1998) and a study of railroad workers employed by shops that processed different proportions of amphibole fibers (Ohlson et al. 1984). Both studies, she noted, provide evidence that amphibole fibers exhibit greater lung cancer potency. This panelist added that studies of auto mechanics have provided no convincing evidence of increased lung cancer due to chrysotile exposure, though she acknowledged that the absence of an effect might reflect the short fiber length in the friction brake products. One panelist cautioned about inferring too much from these studies regarding fiber type because they were not controlled for other factors, such as fiber length and level of exposure.

- One panelist added that a recent study of a cohort of Chinese asbestos plant workers (Yano et al. 2001) should be considered in future updates to the proposed protocol; the workers in the cohort had increased risks for lung cancer and were reportedly exposed to "amphibole-free" chrysotile asbestos. However, another panelist cited a publication (Tossavainen et al. 2001) that indicates that asbestos from many Chinese chrysotile mines actually does contain varying amounts of amphibole fibers.

- Several panelists noted that the proposed protocol's meta-analysis found a 5-fold difference in lung cancer potency between amphibole and chrysotile fibers. However, other panelists indicated that the reported difference was not statistically significant. Some panelists had additional reservations about the authors' meta-analysis, as summarized in the following bulleted items.

Comments on the meta-analysis approach. Several panelists commented on alternate approaches the authors could have used to conduct their meta-analysis of the epidemiology studies. One panelist noted that the lung cancer potencies reported by the various studies exhibit considerable heterogeneity. In such cases, meta-regression is conventionally used to identify which factors account for the variability in the results (i.e., in the lung cancer potencies). This panelist suggested that the meta-analysis should have considered other factors in addition to fiber type and dimension; such other factors could include industry, follow-up time for the cohort, and estimated percentage of amphibole fibers in the exposures, to the extent that data on these other factors are available.

To demonstrate how more detailed investigation might reveal further insights, one panelist presented his own initial statistical analysis of the epidemiological studies. This analysis used a fixed effects model and a random effects model, both inverse weighted by the variance of the studies. His analysis examined how industry and fiber type contribute to the heterogeneity

observed among the cohorts and found that the industry of the cohort appears to be a stronger predictor than fiber type. The panelist explained that the purpose of displaying his statistical analysis was to highlight how other approaches to conducting meta-analysis can offer different insights on the epidemiological data. This panelist recommended that the authors conduct similar meta-regression analyses to investigate the importance of various variables on the lung cancer potency.

This panelist also demonstrated how a sensitivity analysis might yield additional information on influential studies. Using a fixed effects model, the panelist first showed how lung cancer potency factors (K_L) vary with exposure to chrysotile fibers, amphibole fibers, and mixed fiber types. When all epidemiological studies were considered in his analysis, the amphibole fibers were found to be three times more potent than the chrysotile fibers. When the cohort of chrysotile miners and millers from Quebec was omitted from this analysis, however, the amphibole fibers were found to be nearly two times *less* potent than the chrysotile fibers. Conversely, when the cohort of textile workers from South Carolina was omitted, the amphibole fibers were found to be more than ten times more potent than the chrysotile fibers. Given that the conclusions drawn about the relative potency of chrysotile and amphibole fibers appear to be highly sensitive to whether single studies are omitted from the analysis, this panelist was more skeptical about whether the increased potency of amphibole fibers is a robust finding. He recommended that the authors, when completing the proposed protocol, conduct similar sensitivity analyses to help reveal the factors or studies that appear to contribute most to lung cancer.

Another panelist agreed with this feedback, and provided further comments on the meta-analysis, noting that these analyses typically start with establishing criteria for study inclusion. After selecting studies to evaluate, she said, various statistical analyses can be used to test hypotheses and to understand the concordance and disparity among the individual studies. The panelist thought such an approach is needed to help understand the variability in potency factors observed across the multiple studies and to identify for further analysis the studies found to be most descriptive of exposure-response. To clarify the authors' approach, Dr. Berman indicated that the meta-analysis considered any published epidemiological study with sufficient quantitative exposure data that allowed for a reasonable estimate of the exposure-response relationship; uncertainty factors were than assigned to give greatest weight to the most robust studies. In response, additional panelists concurred with the original comment that meta-analyses conventionally begin with establishing explicit study inclusion criteria. These panelists clarified that they are not advocating removing a majority of studies currently considered in the proposed protocol, but rather being more judicious in selecting the studies to evaluate.

One panelist offered additional comments on the meta-analysis. He supported, for instance, the use of sensitivity analyses, and encouraged the authors to conduct additional analyses to identify influential studies, factors that contribute to risk, and the impact of different weighting factors. The panelist also noted that more sophisticated statistical methodologies (e.g., Bayesian

modeling, Markov Monte Carlo) can be used to generate distributions of outputs, rather than discrete values, which might offer greater understanding of the inferences that can be drawn from the epidemiological studies.

Disparate findings from the South Carolina and Quebec cohorts. Multiple panelists noted that the issue of the relative lung cancer potency of chrysotile and amphibole fibers depends largely on how one interprets the disparate findings from the cohort of textile workers in South Carolina and the cohort of chrysotile miners and millers in Quebec. Two of these panelists indicated that the relative potency issue likely will not be resolved until the underlying reasons for the differences between these two studies are better understood. The other panelist viewed the difference in potency observed across industries (i.e., mining versus textile) as a more important matter than the difference between the two specific cohorts. When discussing these studies, two panelists indicated that the increased lung cancer risk for the South Carolina cohort might be attributed to exposure to amphibole fibers, which are known to be found in trace levels in commercial chrysotile.

Relevance of fiber durability. One panelist noted that the issue of fiber durability often enters the debate on the relative lung cancer potency of chrysotile and amphibole fibers. Though he agreed that the animal toxicology data indicate that amphibole fibers are more persistent than chrysotile fibers, the panelist noted that trends among the human epidemiological data—particularly the fact that lung cancer risk does not appear to decrease with time since last exposure, even for chrysotile—suggest that the lower durability of the chrysotile fibers might not be important.

Influence of smoking. The panelists had differing opinions on how the proposed protocol should address cigarette smoking. In terms of inferences drawn from the epidemiological literature, two panelists noted that very limited data are available on smoking, making quantitative analysis of its interactions with asbestos exposures difficult. Specifically, only one study includes detailed information on smoking, but that study found no difference in lung cancer potency between smokers and non-smokers. During this discussion, Dr. Berman explained that the proposed protocol assumes a multiplicative interaction between smoking and asbestos exposure, consistent with EPA's 1986 model. Dr. Berman noted that a multiplicative factor in the model, α, represents the background risk in the studied cohort relative to the risk in the comparison population, and both groups include smokers; he added that the influence of smoking is addressed implicitly in the model because it is a relative risk model in which the effect of asbestos is multiplied to the background risk that is present. A panelist clarified, however, that neither the potency factors nor α were derived based on observations of smoking prevalence in the epidemiological studies.

One panelist emphasized that the confounding effects of smoking greatly complicates the analysis of lung cancer potency. He noted that the relative lung cancer risk from asbestos exposure is

considerably lower than that for cigarette smoking. As a result, the panelist wondered how the meta-analysis can truly discern the relative potency of the asbestos fiber types from studies that present no information on cigarette smoking. This panelist provided an example to illustrate his concern: if a given cohort has between 5 and 10% more smokers than the typical population, this increased prevalence of smoking alone could totally confound relative risks attributed to asbestos. The panelist indicated that all future analyses of epidemiological data will suffer from similar limitations, so long as detailed information on smoking is not available.

General comments. During this discussion, some panelists offered several general comments that apply to the entire proposed protocol. These comments included concerns about the transparency of the analyses, questions about data tables being inconsistent with text in the body of the report, and some panelists' inability to reproduce certain findings from the available data. These general comments are reflected in the executive summary of this report.

3.1.2 Lung Cancer and Fiber Type: Inferences from Animal Toxicology and Mechanistic Studies

The panelists offered varying insights on the inferences that can, or should, be drawn from animal toxicology studies and mechanistic studies regarding the relative lung cancer potency for chrysotile and amphibole fibers.

Citing various publications (e.g., Lippmann 1994), multiple panelists noted that the animal toxicology studies do not support the 5-fold difference in lung cancer potency between chrysotile and amphibole fibers. Two panelists added that the absence of different potencies might result from the animal studies being of too short duration (typically no longer than 2 years) for the greater dissolution of chrysotile fibers to be an important factor. Another panelist added that exposure levels in some animal studies are not relevant to human exposures; as an example, he noted that a recent rat inhalation study (Hesterberg et al. 1998) involved exposure levels at 11,000 fibers per cubic centimeter. These panelists indicated that the animal studies are generally more informative of how lung cancer potency varies with fiber length (see Section 3.1.4), and are less informative on how potency varies with fiber type.

The panelists noted that *in vitro* studies exhibit various findings, depending on the study design and endpoint assessed. One panelist, for instance, indicated that some *in vitro* studies suggest that chrysotile fibers are actually more potent than amphibole fibers. Other panelists added that many *in vitro* studies show crocidolite being considerably more toxic than chrysotile. These panelist cautioned against drawing firm conclusions from the *in vitro* studies, however, given that the study duration is far too short for any impact of dissolution to be observed. Finally, another panelist referred to the International Agency for Research on Cancer (IARC) consensus statement on fiber carcinogenesis for an overview of inferences that can be drawn from mechanistic studies: "Overall, the available evidence in favor of or against any of these mechanisms leading to the development of lung cancer and mesothelioma in either animals or humans is evaluated as weak" (IARC 1996).

Based on the previous comments, the panelists cautioned about attempting to draw inferences from the animal toxicology for several reasons. One panelist indicated that the animal studies have limited utility because lung cancer in humans results from a complex set of exposures, including cigarette smoke, and because rats, when compared to humans, develop different types of tumors at different sites. Another panelist reiterated that the duration of most animal studies precludes one from observing dissolution effects. Given these limitations, two panelists emphasized that conclusions should be based primarily on the epidemiological data, especially considering the volume of human data that are available. Though not disagreeing with this recommendation, one panelist noted that the exposure index—one of the major outcomes of the proposed protocol—is, in fact, based on observations from animal studies.

3.1.3 Lung Cancer and Fiber Dimension: Inferences from the Epidemiology Literature

The panelists made several observations regarding what can be inferred from the epidemiology literature on how lung cancer potency varies with fiber dimension, though they first noted that most published epidemiology studies do not include detailed data on the distribution of fiber dimensions to which cohorts were exposed. Overall, the panelists generally agreed that indirect evidence from the

epidemiological studies supports the proposed protocol's finding that longer fibers have greater carcinogenic potency for lung cancer. They added, however, that the epidemiology literature provides no evidence to support or refute the magnitude of the relative potencies used in the proposed protocol (i.e., fibers longer than 10 μm being 300 times more potent than those with lengths between 5 and 10 μm). The panelists made no comments about fiber diameter when discussing this matter. Specific discussion topics follow:

- ***Observations from the epidemiology literature.*** The panelists identified several studies that provide general insights on the role of fiber size in lung cancer. One panelist, for instance, noted that cohorts of textile workers, which were believed to be exposed to relatively longer asbestos fibers, exhibit higher lung cancer relative risks than do cohorts of miners or cement product workers. Another panelist indicated that studies of taconite miners from Minnesota (Cooper et al. 1988) and gold miners from South Dakota (McDonald et al. 1978) found no increased lung cancer risks among the cohorts, which were known to be exposed primarily to fibers shorter than 5 μm (see Dr. Case's premeeting comments for further information on these studies). This panelist added that the Minnesota Department of Health is currently updating the study on taconite miners and a publication is pending. Another panelist added that epidemiology studies of workers exposed to asbestos from friction brake products show no clear evidence of increased lung cancer. This panelist acknowledged that these epidemiology studies do not include exposure measurements, but other studies of this work environment have indicated that the asbestos fibers in friction brake products are predominantly short chrysotile fibers.

- ***Relevance of fibrous structures shorter than 5 μm.*** Some panelists noted that no epidemiology studies have examined the relative potency specifically of fibrous structures shorter than 5 μm, thus no conclusions could be drawn from the epidemiology studies alone. While not disagreeing with this observation, one panelist reminded panelists that airborne particles and fibers have a broad distribution of fiber lengths, with a clear majority (75–90%) of fibrous structures being shorter than 5 μm. This panelist added that indirect inferences can be drawn from the epidemiology studies listed in the previous bulleted item. Another panelist noted that the fibrous structures shorter than 5 μm behave more like particles rather than fibers, at least in terms of lung deposition and clearance patterns. Finally, two panelists indicated that an ATSDR expert panel recently evaluated the issue of relative potency of fibers shorter than 5 μm; however, the final report from that expert panel meeting was not available until after the peer consultation workshop. The final report has since been released, and a conclusion from that panel was that "there is a strong weight of evidence that asbestos and synthetic vitreous fibers shorter than 5 μm are unlikely to cause cancer in humans" (ERG 2003).

Statistical analyses in the proposed protocol. As indirect evidence that longer fibers have greater carcinogenic potency, one panelist indicated that the exposure-response modeling by Drs. Berman and Crump showed an improved fit to the observed relative risk from epidemiology studies when using an exposure index that assigns greater weight to longer fibers and no risk to fibers shorter than 5 μm. Another panelist concurred, but added that the authors could have attempted to determine the specific weighting (i.e., between longer and shorter fibers) that would optimize the fit to the epidemiological studies.

3.1.4 Lung Cancer and Fiber Dimension: Inferences from Animal Toxicology and Mechanistic Studies

The panelists generally agreed that the animal toxicology studies and mechanistic studies indicate that fiber dimension—especially fiber length—plays an important role, both in terms of dosimetry and pathogenesis. However, panelists had differing opinions on the specific cut-offs that should be used for fiber diameters and lengths in the exposure-response modeling (though panelists generally concurred that fibers shorter than 5 μm should be assigned zero potency).

Fiber length. Multiple panelists noted that the animal toxicology studies provide compelling evidence that lung cancer potency increases with fiber length. Another panelist agreed, but had reservations about assigning no potency to fibrous structures shorter than 5 μm, based on a recent study of refractory ceramic fibers (Bellman et al. 2001) that found that the incidence of inflammation and fibrosis appears to be related to the presence of small fibers in the lung. This panelist indicated that exposure to small fibers likely has some bearing on the oxidative stress state and inflammation in the lung, and he suspected that the exposure-response relationship for long fibers might depend on co-exposures or past exposures to shorter fibers. Based on these observations, the panelist was hesitant to exclude fibrous structures shorter than 5 μm from the proposed risk assessment methodology. On the other hand, another panelist added that animal toxicology studies have shown that fibrosis endpoints are strongly related to fiber length, with exposures to shorter fibers showing less evidence of fibrosis or lung damage. The panelists revisited the significance of fibers shorter than 5 μm when discussing the proposed exposure index (see Section 4).

Fiber diameter. The panelists offered several comments on the role of fiber diameter in the proposed protocol. Noting that fibers with diameters up to 1.5 μm are capable of penetrating to sensitive portions of the lung during oral inhalation, one panelist indicated that this range of fiber diameters should not be excluded from future risk assessments. Other panelists shared the

concern of assigning no lung cancer potency to respirable fibers with diameters greater than 0.5 μm, especially considering that respirability patterns in laboratory animals differ from those in humans (i.e., thicker fibers are more likely to deposit in the human lung than they are in the rat lung).

The panelists also discussed a statement in the proposed protocol that "few fibers thicker than 0.7 μm appear to reach the deep lung." First, one panelist indicated that the proposed protocol includes outdated information on fiber deposition patterns; he recommended that the authors obtain more current insights from specific publications (e.g., Lippmann 1994) and from the latest lung dosimetry model developed by the International Commission on Radiological Protection. Second, another panelist questioned the relevance of deposition in the deep lung, because humans tend to develop bronchogenic carcinomas, while rats develop bronchoalveolar carcinomas. Another panelist cautioned against inferring that asbestos fibers must deposit on bronchial airways to cause lung cancer in humans, noting that significant accumulation of asbestos fibers does not occur in the airways where carcinomas develop in humans, due primarily to mucociliary clearance; this panelist suspected that deposition of fibers in the deep lung is likely related to lung cancer formation in humans, though the mechanisms of carcinogenesis are not fully understood.

3.1.5 Other Issues Related to Lung Cancer

The panelists discussed several additional issues related to the proposed protocol's evaluation of lung cancer potency. Most of the discussion focused on the utility of non-linear exposure-response modeling, but other topics were also addressed:

Consideration of non-linear exposure-response models. The panelists had differing opinions on the extent to which the proposed protocol should consider non-linear exposure-response modeling. On the one hand, one panelist strongly recommended that EPA consider exploring the applicability of non-linear exposure-response models, given his concerns with linear low-exposure extrapolation. This panelist acknowledged that the revised linear model in the proposed protocol clearly provides an improved statistical fit to the epidemiological data when compared to EPA's 1986 lung cancer model, but he advocated more detailed exploration of non-linear cancer risk models, particularly to account for observations of cohorts with low exposures. This panelist was particularly concerned about the cancer risks that would be predicted for low exposures: because the slope in any linear lung cancer model will be determined largely by highly-exposed individuals, he questioned whether the slope derived from

high exposures truly applies to lowly-exposed individuals. To demonstrate his concern, this panelist indicated that the epidemiological studies consistently show that cohorts (or subsets of cohorts) with low exposure generally exhibit no increased lung cancer risk (standardized mortality ratios not statistically different from 1.0). To account for the possibility of a threshold or non-linearity in the exposure-response relationship, this panelist recommended that EPA investigate alternate exposure-response models, such as linear-linear models (i.e., models with two linear exposure-response regions having different slopes) or log-linear models.

Other panelists generally supported these comments. One panelist, for instance, noted that EPA's Draft Revised Guidelines for Carcinogen Risk Assessment indicates that exposure-response relationships should first be evaluated over the range of exposure observations, and then various approaches to extrapolate to exposure levels outside (i.e., below) this range should be investigated. Another panelist added that some studies finding no evidence of lung cancer risks among large cohorts with low exposures should factor into the decision of whether the lung cancer model should include thresholds; he cited a study of non-occupationally exposed women from chrysotile mining regions in Canada (Camus et al. 1998) to illustrate his concern. Other panelists noted that the utility of this study is limited, because exposures were not measured for individuals; further, a panelist clarified that approximately 5% of the individuals considered in this study were occupationally exposed. Finally, one panelist indicated that evidence from the epidemiology literature strongly suggests there are asbestos exposure levels below which lung cancer will not occur; this panelist added that he is unaware of any epidemiological study that has found evidence of lung cancer risk at exposure levels below 25 fiber-years. He recommended that the proposed protocol at least acknowledge the lowest exposure level at which lung cancer effects have been demonstrated.

On the other hand, some panelists were not convinced of the utility of conducting detailed analyses at low exposures and investigating possible thresholds. One panelist, for instance, indicated that a meaningful quantitative analysis of potential thresholds will not be possible, so long as the authors do not have access to raw data from additional epidemiological studies. Further, this panelist suspected that the protocol authors would find considerable heterogeneity among exposure-response slopes for low exposures, and he questioned what conclusions could be drawn by focusing exclusively on the low exposure region. Another panelist agreed, adding that the failure to find significantly increased cancer risks among lowly-exposed cohorts very likely results from poor statistical power and other uncertainties, and not necessarily from the presence of an actual exposure threshold for asbestos-related lung cancer. Finally, one panelist indicated that the National Institute for Occupational Safety and Health (NIOSH) previously examined a threshold model for the cohort of South Carolina textile workers, and that analysis revealed that the best fit of the exposure-response data was a threshold of zero (i.e., the best fit indicated that there was no threshold).

Consideration of cigarette smoking. Several times during the workshop, the panelists debated the ability of the proposed risk assessment model to address interactions between cigarette smoking and asbestos exposure. One panelist recommended that the authors review a recent study that examined the role of cigarette smoking on lung cancer among chrysotile miners and millers in Quebec, Canada (Liddell and Armstrong 2002). Although the panelists generally agreed that smoking is an important consideration for developing and applying the model, some panelists were not convinced that the available data are sufficient to develop an exposure-response model that accurately portrays the interactive effects of asbestos exposure and smoking. The panelists further discussed this issue further later in the workshop.

Transparency of the proposed protocol. Several panelists indicated that the review of epidemiological data in the proposed protocol is not presented in a transparent fashion. One panelist, for instance, sought more information on the uncertainty factors used in the meta-analysis, such as what ranges of factors were considered, what criteria were used to assign the factors, and a table of the factors that were eventually applied. This panelist also recommended that the proposed protocol identify the α-values that were determined for each epidemiological study and provide explanations for any cases when these values are unexpectedly large. Another panelist indicated that the proposed protocol should more clearly differentiate conclusions that are based on a meta-analysis of many epidemiological studies from conclusions that are based on a detailed review of just one or two studies.

The need to obtain additional raw data sets. The panelists unanimously agreed that EPA should make every effort to try to obtain additional raw data sets for the epidemiology studies, such that the authors can further test how adequately the proposed risk assessment model predicts risk. The executive summary of this report presents the panelists' specific recommendation on this issue.

3.2 Mesothelioma

The following paragraphs document the panelists' responses to charge questions regarding inferences from the epidemiology and toxicology literature on how mesothelioma potency varies with fiber type (Sections 3.2.1 and 3.2.2) and fiber length (3.2.3 and 3.2.4).

3.2.1 Mesothelioma and Fiber Type: Inferences from the Epidemiology Literature

The expert panelists unanimously agreed that the epidemiology literature provides compelling evidence that amphibole fibers have far greater mesothelioma potency than do chrysotile fibers—a finding reported both in the review document (Berman and Crump 2001) and a recent re-analysis of 17 cohort studies (Hodgson and Darnton 2000) that reported at least a 500-fold difference in potency. Two panelists commented further that the epidemiology literature provides no scientific support for chrysotile exposures having a role in causation of mesothelioma—an observation that is generally consistent with the meta-analysis in the proposed protocol, which failed to reject the hypothesis that chrysotile fibers have zero potency for mesothelioma.

The most notable response to this charge question was the agreement among most panelists that amphibole fibers are at least 500 times more potent than chrysotile fibers for mesothelioma, as supported by two separate reviews of epidemiological studies. The panelists made additional comments on specific matters when responding to this question, as summarized below, but the key point in this discussion was the agreement that chrysotile is a far less important cause of mesothelioma than are amphiboles.

Relative roles of chrysotile and amphibole. One panelist indicated that cohort studies with individual-level exposure-response data and the broader epidemiology literature both provide no evidence of increased mesothelioma risk due to chrysotile exposure. Further, this panelist noted that 33 of 41 mesothelioma cases previously identified as occurring among workers primarily exposed to chrysotile fibers (Stayner et al. 1996) were later reported as likely resulting from exposures to tremolite fibers found in the chrysotile mines (McDonald et al. 1997). This panelist noted that a recent finding of a small mesothelioma risk from chrysotile (Hodgson and Darnton 2000) results entirely on the assumption that the 33 mesothelioma cases mentioned above result entirely from chrysotile exposures. Based on these observations, this panelist indicated that the literature suggests that chrysotile exposures have limited, if any, role in causing mesothelioma. He nonetheless supported the relative potency attributed to chrysotile in the proposed protocol as a conservative measure in the overall risk assessment process.

Specific comments on the Connecticut friction products workers. Another panelist commented on an epidemiological study of a cohort of workers employed at a friction products plant in Connecticut. The panelist noted that the original study (McDonald et al. 1984) did not identify any deaths from mesothelioma, but review of the state cancer registry (Teta et al. 1983)

revealed that three Connecticut residents who died of mesothelioma were employed by the same friction products company. One of these employees had amphibole exposures during the time he worked for a textile plant that was under the same parent company that owned and operated the friction products plant. The other two cases, the panelist noted, were females who indeed worked at the friction products plant. A pathology review found that one of these cases was a woman with probable pleural mesothelioma and 5 years of exposure; the other case was a peritoneal mesothelioma in a woman who also had asbestosis, and worked as a clerk for 30 years. This panelist noted that it was questionable to attribute the latter two mesothelioma diagnoses to the chrysotile exposures at the friction products plant, though she added that this possibility cannot be definitively ruled out. This panelist encouraged that future review of this epidemiological study should be revised given this new information.

Comments on the proposed 500-fold difference in relative potency. The panelists had several comments on the finding in the proposed risk assessment methodology that amphibole fibers are 500 times more potent for mesothelioma than are chrysotile fibers. Several panelists noted that this finding is consistent with that of a recent re-analyses of 17 epidemiological studies (Hodgson and Darnton 2000). Though not disagreeing that amphibole fibers are clearly more potent, one panelist was concerned that the risk coefficients (K_M) were largely derived from data sets with inadequate exposure-response information for mesothelioma, and assumptions had to be made to determine critical inputs to the mesothelioma model (e.g., average exposure, duration of exposure).

Other panelists commented on specific sections in the proposed protocol. One panelist, for example, recommended that the authors check the accuracy of data presented in Table 6-16 and Table 6-29 of the report, which are not reported consistently. Another panelist suggested that the authors better explain why separate risk coefficients for amphiboles and chrysotile were calculated for some cohorts (e.g., Hughes et al. 1987) but not for others (e.g., Berry and Newhouse 1983), even though the exposure information available for the studies appears to be comparable. Finally, one panelist recommended that the authors of the proposed protocol consider questions recently raised (Rogers and Major 2002) about the quality of the exposure data originally reported for the Wittenoom cohort (De Klerk et al. 1989) when evaluating exposure-response relationships for mesothelioma.

3.2.2 Mesothelioma and Fiber Type: Inferences from Animal Toxicology and Mechanistic Studies

The panelists discussed the inferences provided by animal toxicology data and mechanistic data regarding relative mesothelioma potency of different asbestos fiber types. Overall, two panelists

commented that the human epidemiological data clearly establish that exposures to amphibole asbestos fibers pose a greater mesothelioma risk than do exposures to chrysotile fibers. They added that the animal toxicology data are generally supportive of this finding, but the animal data suffer from some limitations. Two panelists, for instance, noted that the utility of animal toxicology studies is limited by the fact that rodents are rather insensitive to mesothelioma. These panelists added that the animal toxicology studies involving intra-tracheal instillation or peritoneal injection are not directly relevant to the inhalation exposures that occur in humans. These limitations notwithstanding, the panelists raised the following points when discussing the animal toxicology and mechanistic studies:

One panelist referred to one of his earlier publications (Lippmann 1994) for further insights on the occurrence of mesothelioma in animal studies. At that time, this panelist noted, the animal inhalation studies found fewer than 10 cases of mesothelioma, and the number of cases appeared to be greatest among animals that were exposed to mixtures containing higher proportions of amphibole fibers. He found this consistent with the influence of fiber type observed in the human epidemiological data (see Section 3.2.1).

During this discussion, one panelist reviewed a publication (Suzuki and Yuen 2001) that was mentioned earlier in the workshop. The publication documents the amounts and types of asbestos fibers measured in samples of pleural plaques and tumor tissue collected for legal cases. These analyses reportedly found relatively large amounts of short, thin chrysotile fibers in the pleura, suggesting that these fibers should not be excluded from the group of fibers believed to induce mesothelioma. The panelist had several criticisms of the study. First, he indicated that the samples were analyzed using a non-standard technique, without any controls. Second, he questioned the major finding of fibers being detected in the pleura, because most of the samples analyzed were actually tumor tissue, in which he would not expect to find fibers. The panelist suspected that the chrysotile fibers reportedly found in the study likely result from specimen contamination—a bias that would have been more apparent had rigorous quality control procedures been followed. Finally, the panelist noted that a more rigorous study (Boutin et al. 1996) of

asbestos fibers in the parietal pleura found a mixture of fibers, including long amphibole fibers, among living patients with asbestos-related conditions. Based on these concerns, the panelist concluded that the publication of concern (Suzuki and Yuen 2001) is seriously flawed and its recommended should be excluded from EPA's analyses.

A specific issue raised regarding the analytical technique in the study (Suzuki and Yuen 2001) was that water was used during the digestion process. Noting that water may contain large amounts (>30,000 fibers/L) of small asbestos fibers, another panelist suspected that the fibers detected in the study might have resulted from contamination introduced during the digestion process. Because control samples were not analyzed, the panelist said the study offers no evidence that the fibers detected truly were in the original pleural plaques or tumor tissues. He added that studies of lung-retained asbestos fibers routinely detect primarily short, chrysotile fibers, and that the presence of the short fibers in the pleural tissue—even if the measurements from the study are valid—would not necessarily prove that short fibers cause mesothelioma.

3.2.3 Mesothelioma and Fiber Dimension: Inferences from the Epidemiology Literature

The panelists commented briefly on how the human epidemiological data characterize the role of fiber size on mesothelioma risk. Noting that exposure measurements in most every epidemiological study do not characterize fiber length distribution, one panelist indicated that these studies provide no direct evidence of how fiber length is related to mesothelioma. He added that the studies offer conflicting indirect evidence of the role of fiber length. Specifically, the higher mesothelioma risk coefficient among textile workers in South Carolina, when compared to that for the chrysotile miners and millers in Quebec, could be supportive of longer fibers being more potent, since exposures in South Carolina had a larger percentage of long fibers. However, a cohort of cement plant workers in New Orleans was found to have a higher mesothelioma risk coefficient than that of the South Carolina cohort, even though the South Carolina workers were exposed to higher percentages of long fibers. Finally, as indirect

evidence that carcinogenic potency increases with fiber length, this panelist noted that the mesothelioma risk model using the proposed exposure index, which is heavily weighted by long fibers, provided a considerably improved fit to the epidemiological data.

The panelists briefly revisited the inferences that can be drawn from studies of lung-retained fibers. One panelist again commented that results from a recent study (Suzuki and Yuen 2001) should be viewed with caution. He added that several other lung pathology studies (e.g., McDonald et al. 1989, Rogers et al. 1991, Rödelsperger et al. 1999) have been conducted using more rigorous methods, such as using appropriate controls for age, sex, and hospital. These studies all showed that risk of mesothelioma was considerably higher for individuals with larger amounts of long fibers retained in their lungs.

One panelist indicated that results from a study of lung-retained fibers (Timbrell et al. 1988) suggest fiber diameter plays a rule in mesothelioma risk: the study observed no mesothelioma cases among a population highly exposed to anthophyllite fibers, which tend to be thicker fibers. Citing his earlier review of mesothelioma cases (Lippmann 1988), the panelist also noted that crocidolite fibers are both thinner than and more potent than amosite fibers, which further supports the hypothesis that carcinogenic potency for asbestos decreases with increasing fiber diameter.

3.2.4 Mesothelioma and Fiber Dimension: Inferences from Animal Toxicology and Mechanistic Studies

The panelists made few observations on findings from animal toxicology studies regarding mesothelioma and fiber length. One panelist indicated that findings from the animal toxicology studies generally support the overall finding that mesothelioma risks are greatest for long, thin fibers. However, another panelist noted that his earlier review of mesothelioma risks (Lippmann 1988) hypothesized that the critical fibers for mesothelioma induction are those with lengths between 5 and 10 μm. This panelist added that fibers of this dimension are more likely to translocate to the pleura than are longer fibers, but

he acknowledged that it is unclear whether fibers must first translocate to the pleura in order to cause mesothelioma.

Some panelists indicated that fiber durability likely plays a role in inducing mesothelioma, based on the fact that mesothelioma is more easily induced in animals using administration methods (e.g., peritoneal injection) that remove the importance of dissolution.

3.3 Exposure Estimates in the Epidemiology Literature

The panelists raised numerous issues when responding to the third charge question: "To what extent are the exposure estimates documented in the asbestos epidemiology literature reliable?" Recognizing that the exposure estimates from the epidemiology studies are critical inputs to the exposure-response assessment, the panelists expressed concern about the exposure data: few studies provide detailed information on fiber size distribution; many studies report exposures using outdated sampling and analytical methodologies (e.g., midget impinger); individual-level data are not available for most studies; and many studies do not report detailed information on parameters (e.g., exposure levels, exposure duration) needed to evaluate exposure-response relationships, particularly for mesothelioma. Their specific concerns on these and other matters follow:

- ***Concerns regarding exposure estimates in specific studies.*** Some panelists expressed concern about the assumptions made to interpret the exposure data originally reported in the epidemiology studies. One panelist reviewed specific examples of these concerns:
  - The original study of workers at a Connecticut friction products plant (McDonald et al. 1984) reports exposures measured by midget impingers (in units of mmpcf), with no information on how to convert this to PCM measurements, and the original publication includes limited data on exposure duration.
  - The original study of workers at a New Jersey insulation factory (Seidman et al. 1986) did not report any exposure measurements from the factory studied, and data collected

from another plant with similar operations were used to characterize exposure-response for this cohort.

- The original study of workers at a Texas insulation factory (Levin et al. 1998) reported a range of exposure levels (15–91 fibers/mL), and the authors of the proposed protocol assigned an average exposure level (45 fibers/mL) to the entire cohort.

- The original study of U.S. insulation applicators (Selikoff and Seidman 1991) has no information on exposure. The proposed protocol assumes that all workers were exposed to 15 fibers/mL for 25 years, based on a separate review of exposures among insulation workers (Nicholson 1976).

- The original study of retirees from the U.S. Asbestos Products Company (Enterline et al. 1986) reported exposures based on midget impinger sampling, with no information on how to convert these exposures to PCM measurements.

- According to a recent letter to the editor (Rogers and Major 2002), the original study of the Wittenoom cohort (De Klerk et al. 1989) might have overestimated exposures, possibly by as much as a factor of 10.

The previous comments led to a discussion on whether certain studies should be excluded from the meta-analysis used in the proposed protocol (see next bulleted item). Prior to this discussion, one panelist expressed concern about being overly critical of the exposure estimates used for many of the studies listed above; he emphasized that all exposure estimates appear to be based on a critical review of the literature, and no estimates are completely arbitrary, as some of the panelists' comments implied.

***Comments on using study inclusion criteria for the meta analysis.*** Given the concerns about the quality of exposure data reported in some epidemiology studies, the panelists debated whether future revisions of the proposed protocol should exclude certain studies from the exposure-response analysis. The panelists were divided on this matter.

On the one hand, several panelists recommended that the authors develop and apply study inclusion criteria in the exposure-response evaluation, as is commonly done when conducting a meta-analysis. One panelist, for instance, recommended assessing exposure-response relationships for only those studies found to have adequate exposure data, and then using a sensitivity analysis to examine the effect of excluding studies with inadequate exposure data. These panelists clarified that they are not advocating disregarding the majority of studies; rather, they are suggesting simply that the authors of the proposed protocol use study inclusion criteria and sensitivity analyses to ensure that the conclusions are based on the best available exposure data.

On the other hand, several panelists supported the current approach of using as many studies as possible and accounting for the quality of the exposure measurements in the uncertainty factors. One panelist, for example, commended the authors for being as inclusive as possible when reviewing the studies; he supported the approach of recognizing the limitations of the available exposure data and accounting for these limitations in the uncertainty factors that were ultimately used to weight the studies in the meta-analysis. This panelist acknowledged that the exposure estimates in some of the epidemiological studies might be rough estimates, but he emphasized that the estimates are not worthless and should not be discarded. Other panelists concurred with these comments, and did not support applying overly restrictive study inclusion criteria.

Comments on the uncertainty factors assigned to each study. The panelists made several comments on the uncertainty factors that the authors assigned to each study. Dr. Berman first explained the four uncertainty factors: the first factor (F1) characterizes the confidence in exposure estimates; the second factor (F2) represents the confidence in the conversion to PCM measurements from other exposure metrics (typically midget impinger analyses); the third factor (F3) characterizes the confidence the authors had on worker history data; and the fourth factor (F4) was a non-exposure related factor to account for other uncertainties (e.g., lack of information on confounders, incomplete or inaccurate mortality ascertainment). Dr. Berman described generally how the individual uncertainty factors were assigned and noted that each factor could range from 1 to 5.

The panelists' comments primarily focused on the transparency of how uncertainty factors were presented and incorporated into the meta-analysis. Multiple panelists, for instance, recommended that future revisions to the proposed protocol include a table that lists the uncertainty factors assigned to each study. Further, one panelist suggested that the revised protocol describe the assumptions inherent in the uncertainty factor weighting approach, such as explaining why some factors are assigned values over a broader range than others (e.g., why F1 values span a broader range than F4 values) and describing why the individual uncertainty factors have equal weights in generating the composite uncertainty factor. Another panelist agreed, and added that the revised protocol should more explicitly describe how the uncertainty factors were combined into the composite factor and how this composite factors affects the weighting of studies in the meta-analysis. Expanding on this point, another panelist suggested that the final document more clearly explain that the final estimates of cancer risk coefficients (K_L* and K_M*) are actually weighted averages of the epidemiological studies, with the weights assigned to each study being a function of that study's uncertainty. This panelist also recommended that the revised document clearly state how, if at all, the fraction of amphibole fibers and the fraction of fibers longer than 10 μm are reflected in the uncertainty factors.

Some panelists debated the utility of alternate approaches that could be used to assign uncertainty factors. Two panelists noted that the approach used to assigning uncertainty factors is somewhat subjective, because different groups of analysts would likely assign different

uncertainty factors. To avoid the appearance of arbitrariness, these panelists suggested using alternate meta-analysis approaches that do not require using uncertainty factors. They noted, for example, that the authors could use a random effects model in which residual inter-study variation is estimated. Another suggestion was to conduct sensitivity analyses examining the effects of including or excluding studies, depending on the uncertainty factors assigned to them.

Another panelist disagreed with these comments and supported the analyses in the proposed protocol; this panelist indicated that the authors had no choice but to make judgments based on the information documented in the epidemiology literature. He suggested that EPA consider convening a separate expert panel to assign uncertainty factors, if panelists do not support those selected by Drs. Berman and Crump.

Assumptions made to convert exposure estimates from midget impinger sampling. Several panelists noted that the original publications for many epidemiology studies document exposure estimates based only on midget impinger sampling and do not include any information on how to convert these exposures to levels that would be measured by more modern methods (e.g., PCM, TEM). The panelists noted that the conversion factor (from mmpcf to fibers/mL) can vary considerably from one occupational setting to the next.

Interpretations of the study of South Carolina textile workers. The panelists had different opinions on interpretations of the study of South Carolina textile workers (Dement et al. 1994). One panelist, for instance, found this particular study to be an outlier among the other epidemiological studies, and he recommended that the authors exclude this study from the exposure-response analysis until the causes for the increased relative risks observed for this cohort are better understood. Another panelist suggested that the proposed protocol should classify the South Carolina cohort as being exposed to mixed asbestos fibers, rather than being exposed to chrysotile fibers. He indicated that some workers in the cohort were exposed to amosite and crocidolite, in addition to being exposed to chrysotile.[1]

Other panelists, however, did not think the South Carolina study should be excluded from EPA's analysis. One panelist was troubled about criticisms of the exposure estimates for this cohort, given that this is one of few studies in which co-located samples were collected and analyzed using different methods, thus providing site-specific data for converting midget impinger

[1] After reviewing a draft of this report, one panelist indicated that it is important to note that exposure data for the South Carolina cohort are available from more than just one reference (Dement et al. 1994). He suggested that EPA use data from studies conducted by McDonald in the 1980s of a parallel cohort in the same plant. However, he cautioned EPA against treating multiple studies of the same relatively small group of workers as separate studies, considering the large overlap of workers studied by the two groups of investigators. This panelist encouraged EPA to consider other data sources for this cohort, given that a recent re-analysis of epidemiological studies (Hodgson and Darnton 2000) severely criticized the data source EPA uses (Dement et al. 1994), to the point of those data being dropped from the recent re-analysis altogether.

sampling results to PCM measurements. Another panelist challenged suggestions that the South Carolina study is an outlier; he indicated that the South Carolina study is one of the more rigorous epidemiology studies available for asbestos exposures, and he found no valid scientific reasons for discarding it. During this discussion, one panelist point out in response that the South Carolina study is indeed an outlier among the textile cohorts, with a slope which is higher than either of the two textile cohorts; this panelist did acknowledge that the lung cancer risk among the textile cohorts is greater than that among the mining cohorts. This panelist added that scientists need a better explanation for why the lung cancer risk among the South Carolina cohort is greater than that of other cohorts before the South Carolina study can achieve credibility, especially considering that exposures in South Carolina were supposedly to "pure" chrysotile.

4. COMMENTS ON TOPIC AREA 2: THE PROPOSED EXPOSURE INDEX

This section summarizes the panelists' responses to the charge questions pertaining to the proposed exposure index. Section 4.1, 4.2, and 4.3 document the panelists' responses to charge questions 4, 5, and 6, respectively.

4.1 Responses to Charge Question 4

Charge question 4 asks: "The proposed exposure index does not include contributions from fibers shorter than 5 μm. Please comment on whether the epidemiology and toxicology literature support the conclusion that asbestos fibers shorter than 5 μm present little or no carcinogenic risk." The panelists discussed this matter earlier in the workshop (see Sections 3.1.3 and 3.1.4 for these comments), and provided additional insights on the matter. Overall, the panelists agreed that carcinogenic potency increases with fiber length, particularly for lung cancer. Most panelists supported assigning no potency to fibrous structures smaller than 5 μm. Some panelists agreed that the short fibrous structures are clearly less potent than long fibers, but they had reservations about assigning zero potency to the structures smaller than 5 μm; these panelists acknowledged that the toxicity of the short fibrous structures might be adequately addressed by EPA's air quality standards for particulate matter. Specific comments on this charge question follow:

- ***Reference to ATSDR's expert panel workshop on the role of fiber length.*** Two panelists noted that ATSDR convened an expert panel in October 2002 to discuss the role of fiber length on toxicity, and much of that discussion specifically addressed fibrous structures smaller than 5 μm. A main conclusion of that panel was that there is "a strong weight of evidence that asbestos and synthetic vitreous fibers shorter than 5 μm are unlikely to cause cancer in humans" (ERG 2003). The panelists encouraged EPA to review the summary report prepared for that workshop, which was officially released on March 17, 2003, and is available on-line at: www.atsdr.cdc.gov/HAC/asbestospanel.

- ***Evidence from epidemiological studies.*** One panelist indicated that the epidemiological studies do not provide direct evidence of the role of fibrous structures shorter than 5 μm.

However, the panelist indicated that a growing body of evidence suggests that the cohorts predominantly exposed to shorter fibers (e.g., friction brake workers, gold miners, taconite miners) do not have statistically significant increased cancer risks. This panelist added that the mechanistic studies provide the strongest evidence for assigning no potency to fibrous structures (see next bulleted item). Another panelist agreed with these statements, and added that his interpretation of data compiled by the National Cancer Institute provide additional indirect evidence of short fibrous structures presenting little or no carcinogenic risk (see page 102 of the premeeting comments in Appendix B).

The panelists briefly revisited the findings from a recent publication (Suzuki and Yuen 2001) that reported finding relatively large amounts of short, thin chrysotile fibers in malignant mesothelioma tissue. Several panelists encouraged that these findings not be considered in the risk assessment methodology for reasons cited earlier in the workshop (see Section 3.2.2).

Evidence from mechanistic studies. The panelists offered different interpretations of mechanistic studies. One panelist indicated that mechanistic studies have shown that shorter fibers are cleared more readily than long fibers from the alveolar region of the lung by phagocytosis, and therefore provide supporting evidence that short fibers play little or no role in carcinogenic risk. This panelist acknowledged that extremely high doses of particular matter and other non-fibrous structures can generate biological responses (e.g., inflammation), but he doubted that such "overload" conditions would be relevant to the environmental exposures that the proposed protocol will be used to evaluate.

Another panelist agreed that long fibers are clearly more potent than short fibrous structures, but he questioned the conclusion that short fibrous structures have no impact on carcinogenic risk. This panelist noted that mechanistic studies have demonstrated that short fibrous structures and spherical particles, like silica, can elicit the same toxic responses (e.g., generate reactive species, stimulate proliferative factors) identified for asbestos fibers. This panelist added, referring to his premeeting comments, that exposure to short fibers could cause inflammation and generation of oxidative species that might increase the response to long fibers (see Bellman et al. 2001). Overall, this panelist acknowledged that long fibers are more persistent than short fibers in the lung and should be weighted more heavily in the exposure index, but he was hesitant to assign the short fibrous structures zero potency.

Implications on sampling and analytical methods. One panelist commented on the practical implications, from a sampling perspective, of any changes to the exposure index. This panelist indicated that measuring all fibers (including structures shorter than 5 μm) in environmental samples would not only be expensive, but also would compromise the sensitivity of measuring the longer fibers that are most predictive of cancer risk. This panelist acknowledged that human exposure is predominantly to fibrous structures less than 5 μm, but he noted that the amounts of short fibrous structures retained by the lung tend to be very strongly

correlated with the amounts of long fibers retained by the lung. Due to this correlation, this panelist noted that measuring long fibers with sufficient accuracy would allow one to estimate amounts of short fibrous structures in a sample. This panelist added, however, that he sees no benefit of characterizing exposures to fibrous structures smaller than 5 μm, given the conclusion that such fibers do not cause cancer (ERG 2003).

4.2 Responses to Charge Question 5

Charge question 5 asks: "The proposed exposure index is weighed heavily by fibers longer than 10 μm. Specifically, Equation 7.13 suggests that the carcinogenic potency of fibers longer than 10 μm is more than 300 times greater than that of fibers with lengths between 5 and 10 μm. How consistent is this difference in carcinogenic potency with the epidemiology and toxicology literature?" The panelists' responses to this question follow:

- ***Consistency with epidemiological literature.*** The panelists noted that the original epidemiology studies did not collect exposure information that provides direct evidence of the relative potency assigned to the two different fiber length categories: fibers longer than 10 μm, and fibers with lengths between 5 and 10 μm. During this discussion, one panelist recommended that EPA consider the results of a case-control study (Rogers et al. 1991) that suggests that mesothelioma risks are greater for individuals with larger amounts of the shorter fibers (i.e., between 5 and 10 μm) retained in their lungs. Another panelist was not convinced of the findings from this study, due to possible biases from selection of controls not matched for hospital of origin. This panelist encouraged EPA to refer to more rigorous lung-retained fiber studies (e.g., McDonald et al. 1989, Rödelsperger et al. 1999) that have found that the majority of cancer risk for mesothelioma is attributed to exposures to longer fibers, even when measurements of short fibers are taken into account.

- ***Questions about the fiber length-dependence used for mesothelioma.*** Some panelists were not convinced that the relative potencies assigned to different fiber lengths were appropriate for mesothelioma. One panelist, for instance, noted that his previous review of the literature (Lippmann 1994) suggests that cancer risk for mesothelioma is most closely associated with exposure to fibers between 5 and 10 μm long. He indicated that this assessment is consistent with other human lung evaluations (e.g., Timbrell et al. 1988), which have reported that fibers retained by the lung tend to be longer than fibers that translocate to the pleura. This panelist added that the epidemiology literature clearly suggests that lung cancer and

mesothelioma have different risk factors, as the relative amounts of lung cancer and mesothelioma cases vary considerably from one cohort to the next. Based on these concerns, this panelist suggested that EPA consider developing separate fiber length weighting schemes for lung cancer and mesothelioma.

Another panelist indicated that the epidemiology studies provide indirect evidence that carcinogenic potency appears to increase with fiber length. Specifically, he noted that the studies consistently show that mesothelioma has a very long latency period—a trend that suggests that the most durable fibers (i.e., the longer fibers) are the most potent. The panelist added that the analyses in the proposed protocol provide further indirect evidence of mesothelioma risks increasing with fiber length: when the exposure index was used in the mesothelioma model, the proposed risk assessment methodology generated an improved fit to the epidemiological data.

During this discussion, a panelist cautioned about inferring that only those fibers that reach the pleura are capable of causing mesothelioma, because researchers have not determined the exact mechanisms by which mesothelioma is induced. Further, he cautioned about inferring too much from a single study (Timbrell et al. 1988), given that many additional studies are available on lung-retained fibers.

Questions about the relevance of animal toxicology data. Some panelists expressed concern about basing the proposed weighting factors for different fiber lengths on observations from animal data. First, one panelist noted that the weighting factors were derived strictly based on lung cancers observed in laboratory animals, and he questioned whether one can assume that the weighting factors can be defensibly applied to mesothelioma. Second, other panelists noted that extrapolating the weighting factors from rodents to humans also involves uncertainty, due to inter-species differences in respiratory anatomy, macrophage sizes, and sites of lung cancers.

Suggested follow-up analyses. Given the concerns about basing the proposed exposure index entirely on data from animal toxicology studies, two panelists recommended that EPA attempt to optimize the weighting factors applied to different fiber length categories using the available human epidemiological data. One panelist suggested that this optimization could be performed using the data compiled in Table 6-15 in the proposed protocol, which presents estimates of the fiber length distribution for different occupational cohorts. A panelist also suggested that EPA consider deriving separate weighting factors for lung cancer and mesothelioma, rather than assuming the same fiber length dependence for both outcomes.

4.3 Responses to Charge Question 6

Charge question 6 asks: "Please explain whether the proposed exposure index will allow meaningful comparisons between current environmental exposures to asbestos and historical exposures to asbestos that occurred in the work place." The panelists discussed several topics when addressing the question, because some panelists had different impressions of what the question was asking. Some panelists viewed the question as asking about the validity of low-dose linear extrapolations (see Section 3.1.5 for more information on this topic), and others viewed the question as asking about whether the proposed methodology is an improvement over EPA's current risk assessment model. A summary of the panelists' specific responses follows:

Is the proposed exposure index an improvement to asbestos risk assessment? When answering this charge question, multiple panelists focused on whether the proposed exposure index is an improvement over EPA's 1986 asbestos risk models. These panelists agreed that the proposed approach is more consistent with the overall literature on health risks from asbestos, which show that cancer risks vary with fiber type and fiber dimension. Two panelists were hesitant to call the proposed approach an improvement for evaluating mesothelioma risks, because the fiber length weighting factors are based entirely on lung cancer data in animals. These panelists were particularly concerned that the proposed methodology might assign lower risks for mesothelioma in certain circumstances, because the fiber-length dependence in the methodology is not based on any toxicological or epidemiological studies of mesothelioma.

Does the proposed risk assessment model support extrapolation from occupational exposures to environmental exposures? Some panelists commented on the applicability of the proposed risk assessment model to exposure doses below the ranges considered in the occupational studies. Referring to observer comments provided earlier in the workshop, two panelists indicated that some environmental exposures in areas with naturally-occurring asbestos do not appear to be considerably lower than those experienced by occupational cohorts. Another panelist agreed, and cautioned about distinguishing environmental exposures from occupational exposures; he instead encouraged EPA and the panelists to focus on the exposure magnitude, regardless of whether it was experienced in an occupational or environmental setting.

  One panelist recommended that EPA investigate how cancer risks for lung cancer and mesothelioma vary between EPA's 1986 model and the proposed risk assessment methodology: for different distributions of fiber types and dimensions, does the proposed methodology predict higher or lower risks than the 1986 model? Dr. Berman indicated that the proposed methodology, when compared to EPA's 1986 model, generally predicts substantially higher risks for environments with longer, thinner fibers and environments with larger amounts of

amphibole fibers and predicts somewhat lower risks for environments with shorter, thicker fibers and environments that contain only chrysotile fibers. One panelist recommended that future revisions to the proposed protocol include sample calculations, perhaps in an appendix, for several hypothetical environments to demonstrate how estimated cancer risks compare between the new methodology and the 1986 model.

5. COMMENTS ON TOPIC AREA 3: GENERAL QUESTIONS

This section summarizes the panelists' responses to charge questions 7–10 and 12. Responses to charge question 11 are included in Section 6, because this charge question sought the panelists' overall impressions of the proposed risk assessment methodology, rather than focusing on any one specific issue.

5.1 Responses to Charge Question 7

This charge question asks: "The proposed risk assessment approach assigns carcinogenic potency to individual fibers and to cleavage fragments (or 'bundles that are components of more complex structures'). Please comment on whether cleavage fragments of asbestos are as toxicologically significant as fibers of the same size range." The panelists raised the following points when responding:

- ***Terminology used in the charge question.*** One panelist took strong exception to the wording in this question (see pages 30–33 in Appendix B) and strongly recommended that the panelists use correct terminology during their discussions. This panelist noted, for instance, that cleavage fragments are not equivalent to bundles, nor do cleavage fragments meet the regulatory definition of asbestos, as the charge question implies. He clarified that he defines cleavage fragments as non-asbestiform amphiboles that are derived from massive amphibole structures. This panelist was concerned that none of the panelists at the workshop has the mineralogical expertise needed to address issues pertaining to cleavage fragments. Another panelist echoed these concerns and agreed that this charge question raises complex issues.

- ***Significance of cleavage fragments with respect to human health effects.*** The previous concerns notwithstanding, several panelists commented on the role of cleavage fragments in the proposed risk assessment methodology. One panelist, for example, indicated that there is no reason to believe that cleavage fragments would behave any differently in the human lung than asbestiform fibers of the same dimensions and durability; he added that this conclusion was also reached by the American Thoracic Society Committee in 1990 (Weill et al. 1990). This panelist acknowledged, however, that expert mineralogists have differing opinions on the role of cleavage fragments. Several other panelists agreed that it is reasonable to assume that cleavage fragments and asbestos fibers of the same dimension and durability would elicit similar toxic responses.

Review of selected epidemiological and toxicological studies. The panelists briefly discussed what information has been published on the toxicity of cleavage fragments. One panelist indicated that Appendix B in the proposed protocol (see pages B-3 through B-10) interprets results from an animal study (Davis et al. 1991) that evaluated exposures to six tremolite samples, including some that were primarily cleavage fragments. This panelist noted that the study provides evidence that cleavage fragments can cause mesothelioma in animals.

  Another panelist, however, cautioned against inferring too much from this animal study for several reasons: the study was not peer reviewed; the fiber measurements in the study reportedly suffered from poor reproducibility; and the mesotheliomas observed in the study might have reflected use of intra-peritoneal injection model as the dose administration method. This panelist recommended that EPA conduct a more detailed review on the few studies that have examined the toxicity of cleavage fragments, possibly considering epidemiological studies of taconite miners from Minnesota (Higgins et al. 1983) and cummingtonite-grunerite miners from South Dakota (McDonald et al. 1978); he noted that a pending publication presents updated risks among the taconite miners.

Practical implications of measuring cleavage fragments in environmental samples. One panelist added, and another agreed, that measuring cleavage fragments in environmental samples presents some challenges, because microscopists cannot consistently distinguish cleavage fragments from asbestiform fibers, even when using TEM.

5.2 Responses to Charge Question 8

Charge question 8 asks: "Please comment on whether the proposed cancer assessment approach is relevant to all amphibole fibers or only to the five types of amphibole fibers (actinolite, amosite, anthophyllite, crocidolite, tremolite) designated in federal regulations." The panelists made the following general comments in response:

Review of evidence from toxicological and epidemiological studies. The panelists identified few studies that address the toxicity of amphibole fibers other than actinolite, amosite, anthophyllite, crocidolite, and tremolite. One panelist indicated that animal toxicology studies have demonstrated that synthetic vitreous fibers with differing chemistry, but having similar durability and dimensions, generally exhibit similar potency for fibrosis, lung cancer, and mesothelioma. Another panelist added that lung cancer and mesothelioma exposure-response

relationships for a cohort of vermiculite miners from Libby, Montana, have been published for both asbestiform richterite and winchite.

Appropriateness of applying the model to non-asbestiform amphiboles. Several panelists agreed that the proposed risk assessment methodology is relevant to amphibole fibers other than those listed in the federal regulations. The panelists noted that, in the absence of more detailed information on the matter, it is prudent to assume that fibers of similar dimension and durability will exhibit similar toxic effects. Two panelists expressed some hesitation on applying the proposed model to the non-asbestiform amphiboles: one panelist asked how confidently one can apply the cancer risk coefficients to amphibole fibers that have not been studied, and another panelist indicated he was not convinced that the model should be applied to the other amphiboles, let alone for the amphiboles that are listed in the federal regulations.

Given the amount of naturally occurring amphiboles in the Earth's crust, one panelist suggested that the proposed protocol clearly state that the non-asbestiform amphiboles being evaluated are only those with the same dimensional characteristics and biodurability as the corresponding asbestiform amphiboles.

5.3 Responses to Charge Question 9

Charge question 9 asks: "The review document recommends that asbestos samples be analyzed by transmission electron microscopy (TEM) and count only those fibers (or bundles) longer than 5 μm. Such counting practices will provide no information on the amount of asbestos fibers shorter than 5 μm. To what extent would data on shorter fibers in samples be useful for future evaluations (e.g., validation of the cancer risk assessment methodology, assessment of non-cancer endpoints)?"

The panelists expressed varying opinions on this matter: some panelists saw no benefit of measuring fibrous structures shorter than 5 μm, based on responses to earlier charge questions (see Sections 3.1.3, 3.1.4, and 4.1); other panelists indicated that there is some utility to collecting information on shorter fibrous structures, particularly if the incremental analytical costs are not prohibitively expensive and if counting short fibers does not compromise accurate counts of longer fibers. The panelists raised the following specific issues when discussing measurement methods:

Support for using TEM in future sampling efforts. The panelists unanimously supported the recommendation in the proposed protocol of using TEM, rather than PCM or some other method, to characterize exposures in future risk assessments. The panelists also emphasized that future measurement methodologies must focus on generating accurate counts of the most biologically active fibers, or fibers longer than 5 μm.

Practical implications of counting fibers shorter than 5 μm. One panelist indicated that analyzing samples for fibrous structures shorter than 5 μm would compromise analysts' ability to accurately count the amounts of longer fibers that are of greater biological concern. Some panelists and an observer further discussed the costs associated with counting fibers in multiple length categories, including shorter than 5 μm. The panelists did not cite firm cost figures for these analyses. However, noting that environmental samples typically contain more than 90% short fibrous structures, one panelist suspected that counting the shorter structures would considerably increase the time a microscopist needs to analyze samples, and therefore also would considerably increase the cost of the analysis. A panelist indicated that the costs and benefits of counting fibers shorter than 5 μm might be more appropriately debated between microscopists and risk assessors, with inputs from industrial hygienists and mineralogists.

Relevance of fibers shorter than 5 μm for non-cancer endpoints. One panelist noted that exposures to fibrous structures shorter than 5 μm can contribute to asbestosis in occupationally exposed individuals (Lippmann 1988), but he doubted that the exposure levels found to be associated with asbestosis would be experienced in non-occupational settings. Another panelist added that the role of shorter fibrous structures for other non-cancer endpoints is not known, such as the pleural abnormalities and active pleural fibrosis observed in Libby, Montana. No panelists were aware of any authoritative statements made on the role that short fibers play, if any, on these other non-cancer endpoints. During this discussion, one panelist indicated that the toxicity of fibrous structures shorter than 5 μm might be adequately addressed by EPA's particulate matter standards.

5.4 Responses to Charge Question 10

Charge question 10 asks: "The proposed risk assessment methodology suggests that exposure estimates should be based only on fibers longer than 5 μm and thinner than 0.5 μm. Is this cut-off for fiber diameter appropriate?" Before the panelists responded to the question, Dr. Berman first clarified that the exposure index optimized from the animal studies (see Equation 7.12 in the proposed protocol)

assigns a far greater carcinogenic potency to fibers longer than 40 μm, with diameters less than 0.4 μm; he noted that the proposed diameter cut-off (0.5 μm) was based on an *ad hoc* adjustment.

The panelists agreed that the proposed cut-off for fiber diameter (0.5 μm) would likely include most fibers of health concern; however, they also unanimously agreed that the exposure index should not exclude thicker fibers that are known to be respirable in humans. The main argument given for increasing the cut-off is that fibers with diameters as large as 1.5 μm (or with aerodynamic diameters as large as 4.5 μm) can penetrate to small lung airways in humans. Other panelists provided additional specific comments, generally supporting inclusion of thicker fibers in the proposed exposure index. One panelist, for example, advised against basing the fiber diameter cut-off strictly on observations from rat inhalation studies, due to inter-species differences in respirability. Further, noting that the proposed cut-off for fiber diameter would likely exclude some amosite fibers and a considerable portion of tremolite fibers with known carcinogenic potency, another panelist encouraged that the proposed exposure index include contributions from thicker fibers.

The panelists noted that consideration of fibers thicker than 0.5 μm was viewed as being most important for the lung cancer risk assessment model, as risks for mesothelioma appear to be more closely linked to exposures to long, thin fibers (see Section 3.2.3). Further, some panelists suspected that increasing the fiber diameter cut-off in the exposure index should be accompanied by changes to the exposure-response coefficients in the risk assessment models, but the panelists did not unanimously agree on this issue.

5.5. Responses to Charge Question 12

Charge question 12 asks: "Section 8.2 of the review document presents three options for assessing cancer risks from asbestos exposure. Please comment on the technical merit of the proposed risk assessment options." The panelists briefly reviewed the strengths and weaknesses of the three options presented in the proposed protocol for assessing asbestos-related cancer risks. The panelists agreed that the first option—direct use of EPA's lung cancer and mesothelioma risk assessment models—allows for the greatest flexibility in evaluating site-specific exposure scenarios, particularly those with time-varying exposures. Dr. Crump indicated that he envisioned this option being coded into a computer program, into which users enter their site-specific exposure information. Most panelists endorsed developing such a program. The panelists did not reject use of the second and third options, provided that EPA ensures that all three options generate equivalent risk estimates for the same exposure scenario.

The one issue discussed in greater detail was how sensitive predictions using the first option are to the mortality rates used in the evaluation. Noting that mortality rates as functions of age and sex differ from one location to the next, this panelist encouraged EPA to consider carefully whether nationwide mortality estimates would be programmed into the risk assessment model or whether risk assessors would have the option of entering site-specific mortality rates. The panelist also suggested that the authors of the risk assessment conduct sensitivity analyses to quantify how strongly the mortality data affect cancer risk estimates. These comments also raised questions about the fact that two populations with different underlying mortality rates could have different cancer risks, even though their asbestos exposure levels are equivalent.

6. COMMENTS ON TOPIC AREA 4: CONCLUSIONS AND RECOMMENDATIONS

This section reviews the panelists' individual conclusions and recommendations regarding the proposed protocol (Section 6.1), as well as how the panelists developed their overall conclusions and recommendations that appear in the executive summary of this report (Section 6.2).

6.1 Responses to Charge Question 11

Charge question 11 asks: "Discuss whether the proposed cancer assessment approach, as a whole, is a reasonable evaluation of the available health effects data. What aspects of the proposed cancer assessment approach, if any, are inconsistent with the epidemiology or toxicology literature for asbestos?" The panelists offered individual summary statements, which were not discussed or debated among the panel. Following is a summary of the panelists' individual summary statements in the order they were given:

- ***Dr. Lippmann's summary statement.*** Dr. Lippmann commended Drs. Berman and Crump on developing the proposed risk assessment protocol and supported use of a model that accounts for the factors (e.g., fiber type and dimension) that are most predictive of cancer risk. Dr. Lippmann supported the authors' attempt to make full use of the existing data and to interpret the results from the epidemiological studies. He strongly recommended that EPA make every effort to obtain individual-level data from additional epidemiological studies. Dr. Lippmann suggested that a follow-up workshop with experts in exposure assessment could help EPA evaluate the uncertainties in exposure measurements from historic occupational data sets. Dr. Lippmann supported an observer's suggestion to conduct an animal inhalation study using tremolite cleavage fragments to help resolve the issue of these fragments' carcinogenic potency. Overall, he encouraged that future work on the proposed protocol continue, through use of additional expert panels, to make more informed usage of the human exposure data.

- ***Dr. Teta's summary statement.*** Dr. Teta indicated that the proposed protocol is an impressive integration of the animal toxicology data and the human epidemiology data. She commended the authors for developing a scientific methodology that successfully reduces the variability in results across the epidemiological studies, suggesting that the studies might be more consistent than were previously thought. Dr. Teta recommended improvements to the meta-analysis of

epidemiological studies, such as establishing and applying criteria for use of human data in characterizing exposure-response relationships. Overall, Dr. Teta found no inconsistencies between the proposed protocol and the larger body of epidemiology literature, including studies of cohorts (e.g., gas mask workers, railroad workers, friction brake workers) that do not have well-defined exposure information. Though not disagreeing with the utility of other panelists' recommendations, such as re-analyzing data from additional epidemiological studies and convening additional expert panels, Dr. Teta encouraged EPA to move forward expeditiously with completing the proposed protocol and discouraged implementing additional steps that might delay the overall project.

Dr. Hoel's summary statement. Dr. Hoel encouraged the use of more sophisticated modeling that incorporates data on exposure-response (including non-linear models), duration of exposure, cessation of exposure, and uncertainty in exposure. Dr. Hoel also strongly recommended that EPA attempt to obtain individual-level data from additional epidemiology studies, or at least obtain partial data sets. He encouraged Drs. Berman and Crump to use more sophisticated uncertainty analysis techniques, such as generating prior and posterior distributions of uncertainty. To ensure that the lung cancer model is not confounded by cigarette smoking, Dr. Hoel recommended that Drs. Berman and Crump more closely evaluate all available data on the interactions between asbestos exposure and cigarette smoking.

Dr. Steenland's summary statement. Dr. Steenland indicated that the proposed protocol is a step forward in asbestos risk assessment; however, he had several recommendations for improving the analysis of epidemiological studies. For instance, Dr. Steenland suggested that the authors conduct meta-regression analyses using the original exposure-response coefficients, in which predictor variables include fiber size, fiber type, the estimated percentage of amphiboles, percentage of fiber greater than 10 μm, and categorical grouping of studies according to quality. He indicated that these factors can be examined using both fixed effects and random effects models. Dr. Steenland recommended that the proposed protocol explicitly state and defend the basis for choosing the 10 μm cut-off for fiber length in the exposure index. He suggested that EPA should consider using Bayesian techniques or other methods to determine which relative potencies assigned to different fiber length categories optimize the model's fit to the epidemiological data.

Focusing on specific topics, Dr. Steenland indicated that he disagrees with the approach of assigning amphibole fibers five times greater lung cancer potency than chrysotile fibers, especially considering that the statistical analysis in the proposed protocol could not reject the hypothesis that amphibole fibers and chrysotile fibers are equally potent. Further, he advocated suggestions of exploring the adequacy of other exposure-response models (e.g., non-linear models). Finally, Dr. Steenland suspected that cigarette smoking likely will not be a confounding factor in exposure-response analyses for two reasons. First, he noted that differences in smoking practices between working populations and general populations typically do not cause

substantial differences in standardized mortality ratios. Second, he indicated that it is highly unlikely that prevalence of smoking varies with workers' exposure levels. Dr. Steenland encouraged that EPA refer to a recent publication (Liddell and Armstrong 2002) for similar insights on interactions between asbestos exposure and cigarette smoking.

Dr. Crapo's summary statement. Dr. Crapo complimented Drs. Berman and Crump on preparing the cancer risk assessment methodology, and he supported the general approach of expressing cancer risk as a function of asbestos fiber type and fiber dimension. Dr. Crapo indicated that the proposed protocol reaches several defensible conclusions, such as assigning greater mesothelioma potency to amphibole fibers and to longer fibers while assigning no risk to fibers less than 5 μm in length. However, he was concerned about some specific issues that are not yet adequately resolved. For instance, Dr. Crapo felt additional data are needed to rigorously define how mesothelioma potency varies with fiber length (i.e., fibers longer than 10 μm being 300 times more potent than fibers with lengths between 5 and 10 μm). Dr. Crapo recommended that EPA, when revising the proposed protocol, explore more sophisticated modeling techniques, including non-linear exposure-response models and consideration threshold effects. He supported more detailed analyses of interactions between asbestos exposure and cigarette smoking, again through the use of non-linear models.

Dr. Sherman's summary statement. Dr. Sherman first indicated that she concurred with several recommendations made by Drs. Hoel and Steenland. She focused her summary statements on the proposed exposure index, recommending that Drs. Berman and Crump use the epidemiology data to further investigate other formulations of an exposure index. Dr. Sherman recommended, for example, examining the goodness of fit of other formulations of the exposure index (e.g., assigning zero potency to all fibers shorter than 10 μm). Further, she recommended that the authors attempt to optimize the potency weighting factors in the exposure index to the epidemiological data. Finally, given that panelists expressed concern regarding how potency varies with fiber length for mesothelioma, Dr. Sherman suggested that Drs. Berman and Crump consider developing two different exposure indexes—one optimized for lung cancer, and the other for mesothelioma. Dr. Sherman added that she generally supported the lung cancer and mesothelioma exposure-response models, and questioned whether using more complicated models would necessarily lead to a better understanding of the data.

Dr. Castranova's summary statement. Dr. Castranova concluded that the proposed protocol is a significant advance in asbestos risk assessment methodology. He strongly supported the recommendation that future measurements be performed using TEM, rather than PCM. Dr. Castranova also supported the approach of assigning equal carcinogenic potency to cleavage fragments and asbestos fibers of similar dimension—a finding, he noted, that could be tested in an animal inhalation study. Further, Dr. Castranova agreed that non-asbestiform amphiboles and asbestos amphiboles of the same dimension should be assigned equal carcinogenic potency. Dr. Castranova indicated that the epidemiology and toxicology literature clearly indicate that

mesothelioma potency varies with fiber type, but he was not convinced that this literature supports a difference in lung cancer potency between amphibole and chrysotile fibers.

Dr. Price's summary statement. Dr. Price found the proposed protocol to be an impressive compilation of the epidemiology and toxicology literature into a cancer risk assessment model that addresses most, but not all, risk factors debated since EPA's 1986 model. Dr. Price urged EPA to explore exposure-response models other than the models that involve linear, low-dose extrapolations, which he viewed as being inconsistent with the epidemiology literature. Dr. Price indicated that future revisions to the protocol should definitely consider non-linear models and threshold effects.

As an additional comment, Dr. Price emphasized that the two main elements of the protocol—the proposed exposure index and the exposure-response analysis—are closely inter-related and subsequent changes to the proposed exposure index could affect the robustness of the overall modeling effort. As an example of his concern, Dr. Price noted that increasing the fiber diameter cut-off in the exposure index from 0.5 μm to 1.5 μm could (according to an observer comment) lead to dramatic differences in the number of cleavage fragments counted in environment samples; however, he indicated that the animal studies used to derive the original exposure index did not include cleavage fragments. Such scenarios raise questions about using an exposure index derived from very specific exposure conditions in animal studies to evaluate human health risks associated with exposures of an entirely different character. Dr. Price encouraged further study of cleavage fragments, perhaps in an animal inhalation study, to resolve the role of cleavage fragments.

Dr. Case's summary statement. Dr. Case congratulated Drs. Berman and Crump for compiling what he viewed as a reasonable evaluation of the available toxicology and epidemiology literature, and he strongly supported the general approach of factoring fiber type and fiber dimension into cancer risk assessment. Dr. Case indicated that he agreed with the finding that amphibole fibers have slightly greater lung cancer potency than do chrysotile fibers, although he believed that fiber dose, fiber length, and especially smoking history and type of industry have greater importance in this regard. Dr. Case recognized that how one views the differences between the Quebec and South Carolina cohorts affects the conclusions drawn on this issue, and he encouraged EPA to classify the cohort of South Carolina textile workers as being exposed to mixed asbestos fibers, rather than being exposed to only chrysotile fibers.[2]

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[2] When presenting the summary statements, one panelist (LS) indicated that NIOSH is re-analyzing filters that were collected in the 1960s from the South Carolina textile plant, and these re-analyses should indicate the distribution of fiber types in this cohort's exposures. Another panelist (BC) noted that these re-analyses will not characterize earlier exposures to amosite fibers, which are believed to have occurred primarily before 1950 (based on findings from studies of lung-retained fibers).

Dr. Case made several recommendations for further evaluating the existing epidemiological data and for collecting additional data. First, Dr. Case indicated that it is critically important for any lung cancer risk model to consider confounding effects of cigarette smoking, and he encouraged EPA to incorporate interactions with cigarette smoking into the lung cancer model to the greatest extent possible. Second, Dr. Case supported Dr. Lippmann's recommendation of convening an additional expert panel workshop to critically review inferences that should be drawn from the exposure measurements made in the epidemiological studies; such a panel, Dr. Case noted, would require inputs from experts in mineralogy, industrial hygiene, and measurement methodologies. Third, he supported comments recommending that EPA examine non-linear and threshold exposure-response models. Finally, Dr. Case agreed that conducting an animal inhalation study is probably the best way to examine whether tremolite cleavage fragments produce lung cancer, but did not advocate using rat inhalation studies to examine whether these fragments induce mesothelioma, because results from rat inhalation studies have been shown to be a poor model for mesothelioma in humans. He added, however, that it would quite probably be impossible to design an experiment in which rats were exposed only to "cleavage fragments" or "non-asbestiform fibers" with no asbestiform fibers present at all.

***Dr. Stayner's summary statement.*** Dr. Stayner supported the general concept of incorporating fiber type and fiber dimension into cancer risk assessment, but he recommended that additional work be conducted before EPA accepts the proposed protocol as a new risk assessment paradigm. Dr. Stayner indicated that his confidence in the proposed protocol varies between the lung cancer and mesothelioma models.

For lung cancer, Dr. Stayner indicated that the available epidemiological data should be able to support a new risk assessment model, but he recommended that EPA consider the panelists' many recommendations for how the meta-analysis can be improved (e.g., using different statistical models, developing and applying minimal study inclusion criteria, conducting additional sensitivity analyses). Concurring with Dr. Steenland's summary statement, Dr. Stayner added that cigarette smoking is very unlikely to be a confounding factor in the lung cancer model and he questioned whether the available data would support a quantitative assessment of the interaction effects. While Dr. Stayner supported the recommendation for evaluating non-linear exposure-response models, he noted that the individual-level data needed to construct these models are not available for most epidemiological studies. Dr. Stayner added that obtaining raw data from additional occupational cohorts would provide the best opportunity for more detailed exploration of non-linear exposure-response relationships.

Dr. Stayner expressed greater concern about the foundation of the mesothelioma risk model. He indicated, for instance, that the relative potencies included in the proposed exposure index are based entirely on toxicology studies for lung cancer, and not on any epidemiology or toxicology studies specific to mesothelioma. Despite these concerns about the biological basis for the proposed mesothelioma model, Dr. Stayner noted that the proposed model does provide an

improved fit to the findings from the epidemiological studies. He recommended that EPA consider optimizing the relative potencies in the exposure index to the human data, especially if EPA can access raw data from additional occupational cohorts to evaluate how exposure-response varies with fiber size and fiber type.

Dr. McClellan's summary statement. Dr. McClellan congratulated Drs. Berman and Crump for integrating the toxicological and epidemiological data into a reasonable evaluation of asbestos cancer risks. Overall, Dr. McClellan found the proposed protocol to be a substantial improvement over EPA's 1986 models and urged EPA to continue to move forward with completing the protocol based on the panelists' feedback. Though he found the presentation of information in the draft document to lack transparency on many important matters, Dr. McClellan indicated that the authors' presentations at the workshop addressed many of his concerns regarding the transparency of how the proposed model was developed. One suggested improvement to the protocol's transparency was to clearly describe what literature were reviewed and to specify what studies actually factored into the quantitative analyses.

Addressing specific topics, Dr. McClellan indicated that the analyses in the proposed protocol adequately characterize the general roles that fiber type and fiber dimension play in cancer risk. He supported suggestions for involving additional experts, perhaps in another expert panel review, to further review interpretations of the epidemiological studies. Further, Dr. McClellan agreed with other panelists' recommendation that EPA explore the utility of non-linear exposure-response models, consistent with the agency's proposed revised Cancer Risk Assessment Guidelines. If linear, low-dose extrapolation models are ultimately used, he suggested that EPA explicitly acknowledge the uncertainties associated with such an approach. Dr. McClellan indicated that obtaining raw data from additional epidemiological studies might be particularly helpful in the exposure-response modeling. Finally, Dr. McClellan emphasized that the exposure characterization in the proposed protocol is closely linked to the exposure-response assessment; thus, the authors must carefully consider how revisions to the exposure characterization affect the assumptions in the exposure-response assessment, and vice versa.

6.2 Development of Final Conclusions and Recommendations

After presenting their individual conclusions and recommendations, the panelists worked together to draft summary statements for the peer consultation workshop. Every panelist was asked to write a brief synopsis of a particular topic debated during the workshop. These draft statements were then displayed to the entire panel and observers, edited by the panelists, and then compiled into this document's

executive summary, which should be viewed as the expert panel's final conclusions and recommendations regarding the proposed protocol.

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Appendix A

List of Expert Panelists

Appendix B

Premeeting Comments, Alphabetized by Author (includes bios of panelists and the charge to the panelists)

Note: This appendix is a copy of the booklet of the premeeting comments that ERG distributed at the peer consultation workshop. One panelist (Dr. Bruce Case) submitted an edited form of his premeeting comments to ERG at the workshop. That edited version appears in this appendix.

Appendix C

List of Registered Observers of the Peer Consultation Workshop

Appendix D

Agenda for the Peer Consultation Workshop

Appendix E

Observer Comments Provided at the Peer Consultation Workshop

Note: The peer consultation workshop included three observer comment periods, one on the first day of the workshop and two on the second day of the workshop. This appendix includes verbatim transcripts (to the extent that specific remarks were audible from recordings) of the observer comments, in the order the comments were given.

Appendix F

Observer Post-Meeting Comments

Appendix A

List of Expert Panelists

Workshop to Discuss a Proposed Protocol to Assess Asbestos-Related Risk

Westin St. Francis
San Francisco, CA
February 25-27,2003

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Workshop to Discuss a Proposed Protocol to Assess Asbestos-Related Risk

Consultants' Premeeting Comments

February 2003

Notice

Premeeting comments were prepared by each consultant individually prior to the meeting. They are preliminary comments only, and are used to help consultants become familiar with the document and charge questions, develop the agenda, and identify key issues for discussion. During the meeting, consultants may expand on or change opinions expressed in their premeeting remarks and may introduce additional issues. For these reasons, premeeting comments should be regarded as preliminary and do not reflect the final conclusions and recommendations of individual consultants. These premeeting comments will be included as an appendix in the meeting summary report, along with other background materials.

Table of Contents

Workshop to Discuss A Proposed Protocol to Assess Asbestos-Related Risk

Charge to the Peer Consultants

The U.S. Environmental Protection Agency (EPA) is conducting a peer consultation workshop to solicit feedback from a panel of experts on issues related to the draft document, "Proposed Methodology for Conducting Cancer Risk Assessments for Asbestos" (Berman and Crump 2001). Eastern Research Group, Inc. (ERG), a contractor to EPA, is organizing the workshop. Discussions at the workshop will focus primarily on issues raised in this charge, which lists questions that EPA would like the peer consultants to discuss and answer. The charge questions are not intended to limit the peer consultants' discussions; they merely address issues that are important to EPA. Peer consultants are invited to raise and discuss additional relevant topics, as noted below. This charge provides background information, instructions to the peer consultants, and the charge questions.

Background

EPA's current assessment of asbestos toxicity is based primarily on an asbestos assessment completed in 1986 (EPA 1986), and EPA's assessment has not changed substantially since that time. The 1986 assessment considers all mineral forms of asbestos and all asbestos fiber sizes (i.e., all fibers longer than 5 micrometers) to be of equal carcinogenic potency. However, since 1986, there have been substantial improvements in asbestos measurement techniques and in our understanding of how asbestos exposure contributes to disease. To incorporate the knowledge gained over the last 17 years into the agency's toxicity assessment for asbestos, EPA has contracted with Aeolus, Inc. to develop a methodology for conducting risk assessments of asbestos. The proposed risk assessment methodology distinguishes between fiber sizes and fiber types in estimating potential health risks related to asbestos exposure. The proposed methodology and the charge issues (Berman and Crump 2001) are the subject of the peer consultation workshop.

A key step in the determination of whether the proposed risk assessment methodology can be used to support decisions at asbestos-contaminated sites is gaining feedback during this peer consultation workshop. During the two and one-half day workshop, EPA will seek feedback from the peer consultants on the technical issues outlined later in this charge. Time will be set aside each day to hear from observers. The Agency will consider feedback received at the workshop in making decisions as to the applicability of the updated risk assessment methodology.

Instructions to the Peer Consultants

ERG selected eleven scientists to serve as peer consultants for the workshop. The peer consultants have extensive expertise in related fields, such as inhalation toxicology, pulmonology, cancer risk assessment, and biostatistics. Before the workshop, each peer consultant will be asked to read the proposed methodology and technical support document for a protocol to assess asbestos-related risk (Berman and Crump 2001) and to prepare and submit pre-meeting comments, which are to be written responses to the charge questions listed in the next section. ERG will distribute a compilation of the pre-meeting comments to all peer consultants and will make copies of this compilation available at the peer consultation

workshop. At the workshop, the peer consultants will actively participate in discussions that will focus largely around the charge questions and they will help draft summary statements of their conclusions and recommendations. Following the workshop, a technical writer from ERG will prepare a draft summary report that documents the technical discussions at the workshop, including the observer comments. After the peer consultants review and comment on the draft summary report, ERG will submit a final summary report to EPA.

When preparing written comments, please write each question, followed by your comments (or state why you are not responding). Please include your name at the top of each page, but do not paginate. Please refer to the enclosed "Format Guidelines for Preparing Written Comments." Your written comments are due to ERG no later than February 14, 2003.

CHARGE QUESTIONS

Topic Area 1: Interpretations of the epidemiology and toxicology literature.

1) For *lung cancer*:

A] Influence of *fiber type*: Please comment on the extent to which the epidemiology literature and mechanistic studies suggest that carcinogenic potency varies from one *fiber type* to the next (e.g., chrysotile versus amphibole fibers). How adequate is the information in the epidemiology literature for supporting dose-response analyses for different *fiber types*? Specifically, to what extent do you think the proposed risk coefficients in Table 6-29 are supported by the epidemiology literature?

B] Influence of *fiber length*: Please comment on the extent to which the epidemiology literature and mechanistic studies suggest that carcinogenic potency varies with *fiber length*. How adequate is information in the epidemiology literature for supporting dose-response analyses for different *fiber lengths*? In general, is it appropriate to assess cancer risks using an exposure index (see Equation 7.13) that is weighed heavily by fibers longer than 10 micrometers (µm)? (Note: Topic area 2 includes more detailed questions on the proposed exposure index.)

C] To what extent do animal studies (e.g., studies by Davis and other researchers) suggest that carcinogenic potency varies with *fiber type* and *fiber length*?

D] Please comment on the extent to which carcinogenic potency is a function of fiber properties (e.g., diameter, aspect ratio, surface properties) *other than* fiber type and fiber length. How adequate is information in the epidemiology or toxicology literature for supporting these other properties into dose-response analyses?

2) For *mesothelioma*:

A] Influence of *fiber type*: Please comment on the extent to which the epidemiology literature and mechanistic studies suggest that carcinogenic potency varies from one *fiber type* to the next (e.g., chrysotile versus amphibole fibers). How adequate is the information in the epidemiology literature for supporting dose-response analyses for different *fiber types*? Specifically, to what extent do you think the proposed risk coefficients in Table 6-29 are supported by the epidemiology literature?

B] Influence of *fiber length*: Please comment on the extent to which the epidemiology literature and mechanistic studies suggest that carcinogenic potency varies with *fiber length*. How adequate is information in the epidemiology literature for supporting dose-response analyses for different *fiber lengths*? In general, is it appropriate to assess cancer risks using an exposure index (see Equation 7.13) that is weighed heavily by fibers longer than 10 micrometers (µm)? (Note: Topic area 2 includes more detailed questions on the proposed exposure index.)

C] To what extent do animal studies (e.g., studies by Davis and other researchers) suggest that carcinogenic potency varies with *fiber type* and *fiber length*?

D] Please comment on the extent to which carcinogenic potency is a function of fiber properties (e.g., diameter, aspect ratio, surface properties) *other than* fiber type and fiber length. How adequate is information in the epidemiology or toxicology literature for supporting these other properties into dose-response analyses?

3) To what extent are the exposure estimates documented in the asbestos epidemiology literature reliable?

Topic Area 2: The proposed exposure index.

4) The proposed exposure index does not include contributions from fibers shorter than 5 µm. Please comment on whether the epidemiology and toxicology literature support the conclusion that asbestos fibers shorter than 5 µm present little or no carcinogenic risk.

5) The proposed exposure index is weighed heavily by fibers longer than 10 µm. Specifically, Equation 7.13 suggests that the carcinogenic potency of fibers longer than 10 µm is more than 300 times greater than that of fibers with lengths between 5 and 10 µm. How consistent is this difference in carcinogenic potency with the epidemiology and toxicology literature?

6) Please explain whether the proposed exposure index will allow meaningful comparisons between current environmental exposures to asbestos and historical exposures to asbestos that occurred in the work place.

Topic Area 3: General questions.

7) The proposed risk assessment approach assigns carcinogenic potency to individual fibers and to cleavage fragments (or "bundles that are components of more complex structures"). Please comment on whether cleavage fragments of asbestos are as toxicologically significant as fibers of the same size range.

8) Please comment on whether the proposed cancer assessment approach is relevant to all amphibole fibers or only to the five types of amphibole fibers (actinolite, amosite, anthophyllite, crocidolite, tremolite) designated in federal regulations.

9) The review document recommends that asbestos samples be analyzed by transmission electron microscopy (TEM) and count only those fibers (or bundles) longer than 5 µm. Such counting practices will provide no information on the amount of asbestos fibers shorter than 5 µm. To what extent would data on shorter fibers in samples be useful for future evaluations (e.g., validation of the cancer risk assessment methodology, assessment of non-cancer endpoints)?

10) The proposed risk assessment methodology suggests that exposure estimates should be based only on fibers longer than 5 µm and thinner than 0.5 µm. Is this cut-off for fiber *diameter* appropriate?

11) Discuss whether the proposed cancer assessment approach, as a whole, is a reasonable evaluation of the available health effects data. What aspects of the proposed cancer assessment approach, if any, are inconsistent with the epidemiology or toxicology literature for asbestos?

12) Section 8.2 of the review document presents three options for assessing cancer risks from asbestos exposure. Please comment on the technical merit of the proposed risk assessment options.

Topic Area 4: Development of Conclusions and Recommendations

At the end of the workshop, the peer consultants will be asked to draft conclusion statements identifying their most notable findings on the proposed methodology. As a prelude to developing these statements, the peer consultants are invited to provide any additional comments or concerns, both strengths and weaknesses, on topics not specifically addressed in the previous charge questions. After completing the discussions the peer consultants will prepare their conclusions, and they will also be asked to develop recommendations for how EPA can improve the methodology. Please note that, although recommendations for future research projects are welcomed, the focus of this workshop is on the proposed risk assessment methodology and related charge questions and issues.

References

Berman DW and Crump K. 2001. Technical Support Document for a Protocol to Assess Asbestos-Related Risk. Final Draft. Prepared for U.S. Department of Transportation and U.S. Environmental Protection Agency. September 4, 2001.

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Dr. Case is a pathologist and epidemiologist at McGill University in Montreal, Canada. Following his residency in pathology at McGill University he obtained the Diploma in Occupational Hygiene at McGill, and worked as a post-doctoral fellow and instructor at the Mount Sinai School of Medicine, New York, from 1980–1983. While there, he performed some of the first studies on asbestos-mediated free radical release, with the help of the Young Investigator's Award of the American Lung Association. On his return to McGill he joined the Dust Disease Research Unit. The focus of this group was the epidemiological study of diseases related to mineral fiber exposure using lung-retained fiber in exposure assessment. In 1986, he received the National Health Scholarship of NHRDP (Canada) for his work in the field. In 1988, he moved to the University of Pittsburgh, where he succeeded Dr. Philip Enterline as Director of the U.S. EPA Center for Environmental Epidemiology, through their cooperative agreement with the University of Pittsburgh School of Public Health, where he was also associate professor of epidemiology. He returned to McGill in 1992 and continues research, teaching, and clinical work there in pathology, epidemiology, occupational health and in the McGill School of Environment. Dr. Case has participated in workshops, given lectures, and provided peer reviews and advice for many national and international agencies and professional societies on the subject of the exposure assessment and health affects of mineral fibers, including: EPA, CDC (through ATSDR and NIOSH), the U.S. Consumer Product Safety Commission (CPSC), the International Agency for Research on Cancer (IARC), the International Commission on Occupational Health (ICOH), the British Occupational Hygiene Society (BOHS), the American Thoracic Society (ATS), the Geological Society of America (GSA), and the Collegium Ramazzini. His research on asbestos and other mineral fiber and particle exposures and related diseases has been funded by American and Canadian public agencies including EPA, MRC (Canada) and NHRDP (Canada). Dr. Case has published over 100 papers on these subjects.

WORKSHOP TO DISCUSS A PROPOSED PROTOCOL TO ASSESS ASBESTOS-RELATED RISK: SAN FRANCISCO; FEBRUARY 25-27, 2003.
COMMENTS ARRANGED BY CHARGE QUESTIONS

Topic Area 1: Interpretations of the epidemiology and toxicology literature

1) For Lung Cancer:

Note 1: Lung cancer risk conveyed by asbestos exposure is principally related to degree of asbestos exposure and subsequent retained asbestos dose; to smoking habit; to type of industry (in occupational exposure situations), and to fiber type, in approximately that order of priority. Hence the following section is best addressed beginning with item (D), with some supplementation, rather than items (A) through (C), although many of these factors are inter-related.

Note 2: While it is not made clear what is meant by "mechanistic studies" in the questions below it is assumed that what is meant is *all* animal and toxicological studies, including both cell-free and in-vitro systems. In fact, in vitro and cell-free systems have not as yet proved successful in use in risk assessment, and should not be considered (these are given too much attention in the documentation of the proposed model). This has been established by a fairly recent consensus statement by IARC in Scientific Publication 140; the Consensus Statement has been circulated to the panelists (IARC 1996). Briefly, although a total of five possible mechanisms for asbestos carcinogenesis were considered in some detail**, "**The exact mechanisms leading to the development of cancer after exposure to asbestos fibers are poorly understood…Overall, the available evidence in favour of or against any of these mechanisms leading to the development of lung cancer and mesothelioma in either animals or humans is evaluated as weak". However, with respect to the two parameters principally considered in the risk assessment model under consideration by the panel, the IARC panel accepted as fact that "*Fiber dose, dimensions and durability are currently accepted as important parameters*". (Emphasis in the original).

In the following sections therefore "mechanistic studies" which do not rely on whole animal exposures will not be commented upon and (in this observer's view) should not have any input into current risk assessment. In addition, for whole animal studies, only those based on inhalation (which is the model most useful for human risk extrapolation) will be commented upon unless otherwise noted. Finally, what is described by the proposal as "(human) pathology studies" but is actually a subset of such studies which includes (but is not limited to) lung-retained internal dose studies (sometimes called "lung burden studies") will be commented upon here where relevant, as such studies are most directly relevant to human exposure assessment and have been (in this panelist's view) afforded too little emphasis by the authors, partially because of a assumption that the sampling for such studies is virtually always "opportunistic". The authors also appear to ignore the possibility of human exposure indices such as broncho-alveolar lavage (BAL) and sputum asbestos body analysis in living subjects; both relatively simple techniques with BAL being quite reproducible (sputum production on the other hand is highly affected by smoking status unless an "induction" technique is used; it has nevertheless proved useful in some situations and in at least one situation is a better predictor of asbestos-related radiological abnormalities than is estimated exposure (Sébastien P, Armstrong, B., Case, B.W. 1988 .).

A] Influence of *Fiber Type*: Please comment on the extent to which the epidemiology literature and mechanistic studies suggest that carcinogenic potency varies from one *fiber type* to the next (e.g. chrysotile versus amphibole fibers). How adequate is the information in the epidemiology literature for supporting dose-response relationships for different *fiber types*? Specifically, to what extent do you think the proposed risk coefficients in Table 6-29 are supported by the epidemiology literature?

This is a much more difficult question for lung cancer than it is for mesothelioma, where there is a clear preponderance of the evidence for a very large effect of fiber type. This panelist

agrees with the authors of the proposal and with the recent analysis of Hodgson and Darnton (Hodgson JT and Darnton A 2000) of seventeen cohorts for which exposure data are available that (even having accounted for smoking, dose, and industry type) there is at least a tenfold increase in lung cancer asbestos-related risk for amphibole asbestos exposures over chrysotile asbestos exposures; it is difficult to differentiate however between amphibole fiber types, and also difficult to differentiate between "asbestiform" and "nonasbestiform" or "cleavage fragments of massive amphiboles" and "asbestiform" exposures *if the latter exposures are to structures having similar dimensions, regardless of their crystal structure.* An effective test of this is provided in the data on chrysotile miners, millers and factory workers of Liddell et al. (Liddell FD, McDonald AD and McDonald JC 1998), in which "it is now clear that for all practical purposes (lung cancer risk) was confined to (one mining area), probably due largely to fibrous tremolite and in dust conditions (averaging)…7 mpcf or very roughly 24 fibers/ml".

The proposed risk coefficients in Tables 6-29 and 6-30 appear to be highly conservative with respect to what is known about the differential effects of fiber type for lung cancer risk, with only a five-fold difference. Since others have suggested that there is in fact a difference that is somewhere between ten and fifty-fold, this seems reasonable. Given the extreme importance of the other factors noted above and described in more detail in section D] below (dose, smoking habit, and type of industrial setting (the latter perhaps being related to fiber length); a coefficient which is conservative for lung cancer risk and fiber type seems reasonable, as long as the other factors are taken into sufficient account by the risk model.

B] Influence of *Fiber Length*: Please comment on the extent to which the epidemiology literature and mechanistic studies suggest that carcinogenic potency varies with *fiber length.* How adequate is information in the epidemiology literature for supporting dose-response relationships for different *fiber lengths*? In general, is it appropriate to assess cancer risks using an exposure index (see equation 7.13) that is weighted heavily by fibers longer than 10 micrometers (μm)?

This question was recently explored *in part* by an expert panel for ATSDR, the report of which is pending. Specifically, the latter panel was asked to assess charge questions which addressed any proven or putative risk for "short fibers", which were defined operationally as

those having length *less than 5 μm* (ATSDR 2002), for both cancer and non-cancer endpoints. The aim was not a consensus statement but to use the information presented during the expert panel meeting to aid in developing scientifically sound public health evaluations for exposures to "short fibers" defined as above. Because the final draft of this document has not been released it cannot be cited or quoted, but hopefully it will be made available to the current expert panel for EPA as it is directly relevant to issues of fiber length and risk. There is no reason to "reinvent the wheel" for the part of the current discussion which overlaps the previous panel's deliberations, although additional input from panel members not involved in the ATSDR-convened panel will be a valuable addition to this discussion. While the ATSDR-convened panel was not charged with looking at the converse proposition that *longer fibers* convey greater risk of the endpoints in question (including lung cancer), this is the other side of the same coin and was certainly discussed.

As acknowledged by the authors of the current proposal to EPA, there is little epidemiological data available which specifically assesses the role of fiber length on lung cancer risk. Most of the available epidemiological data on lung cancer risk for which any exposure assessment is available comes from occupational cohorts in which that exposure was assessed either by midget impinger counts (which historically counted all particles as million particles per cubic foot (MPCF); isometric particles as well as fibers). This method dealt with *all* particles visible by light microscopy and had a low resolution of approximately 1 μm diameter, with *no information on particle length.*

Some epidemiological studies have as indices of exposure to asbestos data derived from the membrane filter method through counting via phase contrast optical microscopy (PCOM). Results are expressed as fibers per cubic centimeter or milliliter (fibers/ ml.), *but are always limited to fibers longer than 5 μm.* As noted by the authors of the current proposal to EPA, a principal weakness of the membrane filter method and of PCOM counts is that they are not capable of determining whether the structures being counted are actually "asbestos" at all (although the authors do not appear to address the use of dispersion staining techniques in this regard. *It is important that EPA receive competent mineralogical or industrial hygiene advice as to the suitability of dispersion staining techniques in association with PCOM/ membrane filter counts to improve upon the identification of "asbestos", and individual types of asbestos fiber*

using light microscopy alone, especially given the increased costs (and perhaps decreased sensitivity) of transmission electron microscopic techniques.

Some epidemiological studies combine both types of exposure index (MPCF and fibers/ ml), using data-derived conversion factors from MPCF which vary from an approximate threefold to an approximate eightfold multiplication of the MPCF value in question to derive an analogous value in fibers/ ml. The conversion factors appear to be to some degree study and workplace-specific, are by definition approximations, and should be used with caution; the most commonly used conversion factor is an approximate threefold multiplication of MPCF.

Since all situations in which there is exposure to asbestos fibers comprise a *size distribution* with respect to fiber length rather than a specific fiber length compartment, it is not surprising that epidemiological studies have not addressed this issue to a great extent. It should be emphasized however that all existing risk assessment models, including the 1986 EPA risk assessment, are largely derived on the exposure assessment side from measurements of, or approximations of measurements of, or conversions of other measurements to, exposures to fibers *longer than 5* μ*m.* In addition it is well known both from studies of size distributions of asbestos exposures and of asbestos retained-dose that there is good correspondence of asbestos concentrations (even when broken down into individual fiber types) across fiber-length categories.

Some data does exist from epidemiological studies which may inform as to effects of fiber length on lung cancer incidence or mortality. There are two extremes for fiber length in epidemiological studies which *have* been examined with respect to the shape of distributions. Studies of workers in asbestos textile industries, in which there is some evidence that there is more skew of exposure fiber-length distributions to longer fibers, have generally shown a higher dose-response gradient for lung cancer risk (Knox JF, Holmes S, Doll R et al. 1968; Newhouse ML, Berry G, Wagner JC et al. 1972; Peto J, Doll R, Howard SV et al. 1977; Peto J 1980; McDonald AD, Fry JS, Woolley AJ et al. 1983; McDonald AD, Fry JS, Woolley AJ et al. 1983; Paci E, Buiatti E and Geddes M 1987; Sebastien P, McDonald JC, McDonald AD et al. 1989; Dement JM and Brown DP 1994; Dement JM, Brown DP and Okun A 1994; McDonald JC 1998;

Case BW, Dufresne A, McDonald AD et al. 2000; Hodgson JT and Darnton A 2000) .

Conversely, studies of studies of gold mine workers in South Dakota and taconite miners in Minnesota suggested no lung cancer risk for a largely short (< 5 μm) fiber distribution. The South Dakota workers were exposed to cummingtonite-grunerite material with 94% of airborne fibers being less than 5 microns in length. Gilliam et al.(Gillam JD, Dement JM, Lemen RA et al. 1976) found increased mortality from malignant respiratory disease among workers with at least 5 years of exposure. However, a follow-up study of this cohort which considered longer latency and the most highly exposed workers found no such increase at estimated average exposure concentrations of 4.83 fibers per cubic centimeter (McDonald JC, Gibbs GW, Liddell FD et al. 1978). A later study of 3,444 men employed for at least 3 months in Minnesota taconite mining operations (also believed to be exposed to a short-fiber distribution) during the years 1947 to 1958 (86,307 person-years of observation) found 41 deaths from respiratory cancer - an SMR of only 61 to 85 (for US white male rates or Minnesota rates respectively) (Cooper WC, Wong O and Graebner R 1988).

It seems reasonable to weight the exposure indices in question to assign greater risk for greater fiber length. It also seems *un*reasonable based on current knowledge to assign any weight at all to fibers of less than 5 μm in length. Finally, while it seems clear from what we know of mechanistic studies that tumor hazard is related to increasing length, a coefficient that assigns incrementally increasing weight to fibers in a continuous length distribution would be preferable to one that simply categorizes lengths. This however may be quite impractical for real-world assessments of hazard. Having said all this, the paucity of direct data on fiber length in the epidemiological studies makes it imperative to answer the question as posed – "…is it appropriate to assess cancer risks using an exposure index (per equation 7.13) that is weighted heavily by fibers longer than 10 micrometers (μm)?" in the negative, *if one is referring to the supporting evidence from epidemiological studies alone.* Nevertheless, the very heavy weight put on the longest fibers for lung cancer risk in this equation does seem reasonable taking *all of* the available data into account. Strictly speaking, an equation which put greater weight on increasing length intervals would be better, and it must be remembered that the vanishingly small

coefficient for fibers between 5 and 10 μm in length will be modified by the fact that those fibers are far more numerous (and more likely to be disproportionately counted by any available technology, including transmission electron microscopy).

C] To what extent do animal studies (e.g. studies by Davis and other researchers) suggest that carcinogenic potency varies with *fiber type* and *fiber length?*

These studies are clearly outlined in the protocol provided by the authors of this proposal. In general, inhalation studies support the role of fiber length (especially fiber length greater than 10 μm, or in some studies greater than 20 μm) in lung cancer risk and also support the assertion that there is no excess lung cancer risk in these models under 5 μm.

D] Please comment on the extent to which carcinogenic potency is a function of fiber properties (e.g., diameter, aspect ratio, surface properties) *other than* fiber type and fiber length. How adequate is information in the epidemiology and toxicology literature for supporting these other properties into dose-response analyses?

Aspect ratio is simply the ratio of length to width and therefore should have no role in risk assessment independent from length and width. Surface properties, especially surface iron, may well be related to lung cancer risk through the mechanisms of lung cancer production (such as, for example, free radical generation and cell signaling mechanisms), but in my view are insufficiently developed or understood at this time to be useful for risk assessment, and are certainly not ready to be incorporated into dose-response analyses. This was also in essence the conclusion of the IARC panel, which was convened in order to determine *whether* mechanistic studies could contribute to risk assessment protocols and in the consensus statement concluded in effect that current evidence is “weak”(IARC 1996) .

As noted above the principal factors driving risk for lung cancer related to asbestos exposure, in approximate order of priority, are not fiber factors *per se* but ***asbestos dose, degree of smoking co-exposure, type of industry (in an industrial setting), and fiber type.*** With the exception of the latter, which was dealt with above, these are ***not*** necessarily directly related to fiber factors, and are ***more important than fiber factors*** (particularly fiber type and length) and

should to the degree possible be accounted for in any risk assessment model. They are in fact accounted for in one way or another in the proposed model.

Fiber dose (derived from *fiber exposure)* is so obviously related to risk that little further need be said here; in fact the charge questions *assume* the importance of this factor, while "jumping the gun" to assess the effect of other factors on "dose-response analysis". One cannot begin without a discussion of the influence of (externally measured) exposure, and subsequently of retained dose, *per se.* The authors of the proposal in fact do so in a number of ways, although their model itself is highly dependent on fiber factors *in addition to* dose. The question of linear extrapolation, the general use of the linear model (as opposed to other models), and the question of threshold, also arises in relation to the issue of total exposure and resultant total dose.

Individual smoking history is the second most important factor in risk after absolute exposure and absolute dose. The previous (1986) EPA model *and* the current model appear to assume through the derivation of the terms that risk for smoking and asbestos are multiplicative, with both assessments being heavily reliant on an early and flawed analysis of this relationship by Selikoff and Hammond ((Selikoff IJ, Hammond EC and Seidman H 1979) This is assumed through the use of a model which uses relative risk (to the underlying population) in which most of the absolute risk is due to smoking. This may overestimate lung cancer risk as the actual synergism between smoking and asbestos exposure is now generally thought to be less than multiplicative, although still more than additive (Liddell FD and Armstrong BG 2002) .

Type of industry remains a powerful influence in risk. It is often assumed that fiber factors (perhaps especially fiber length) may be important in this regard, but this remains unproven and based largely on some assumptions about the large differences in the dose-response analyses between asbestos textile cohorts and asbestos mining cohorts, particularly those commonly associated with chrysotile. In fact, while there is no doubt that large differences in the slope of lung cancer risk exist between these industries, it remains unproven that these can be accounted for entirely by differences in fiber length, and recent thinking on this subject suggests a more complex explanation (McDonald JC 1998; Case BW et al. 2000; Hodgson JT and Darnton A 2000) in which other factors (including but not limited to fiber type, and including other processing steps in industrial settings) play a role. For example, it is clear that

while exposure (externally measured) may show a greater proportion of longer fibers in the textile than in the mining setting, for **any given fiber length interval** the lung-retained *concentration* of fibers is *greater in the mining situation* – and it is the mining situation which shows lesser lung cancer risk. It does appear from close examination of the data however that the ratio of retained dose to exposure is higher in the textile situation for the longest fibers (unpublished analysis of data from (Case BW et al. 2000)).

It is hard to say how, if at all, this element which is a powerful one in industrial settings can be translated into risk assessments for environmental settings *unless* it is possible to determine for a given environmental setting (or site) which industrial cohort is most similar. For most superfund sites dealing with former mine sites, for example, mining cohorts (those with a lower slope of lung cancer risk) should clearly be those applied and the textile data is of little relevance. The model offered does not account for this possible discrepancy between sites.

Finally, as noted above, fiber type does play an apparent role in risk for lung cancer, with a ten to fifty-fold excess risk having been suggested by the best available analysis (Hodgson JT and Darnton A 2000) for commercial amphibole exposure as opposed to chrysotile, and for virtually all of the excess lung cancer risk in the chrysotile *mining situation* being explained by co-exposures to tremolite, at least in those with exceptionally heavy exposure (specifically greater than 300 million particle per cubic foot - years (MPCF-Y). (Liddell FD et al. 1998).

2) For *mesothelioma:*

A] Influence of *Fiber Type:* Please comment on the extent to which the epidemiology literature and mechanistic studies suggest that carcinogenic potency varies from one *fiber type* to the next (e.g. chrysotile versus amphibole fibers). How adequate is the information in the epidemiology literature for supporting dose-response relationships for different *fiber types*? Specifically, to what extent do you think the proposed risk coefficients in Table 6-29 are supported by the epidemiology literature?

The epidemiology literature provides definitive evidence that carcinogenic potency varies from one *fiber type* to the next. Indeed, there is currently no real scientific support for the proposition that

chrysotile is a cause of malignant mesothelioma from available epidemiological studies. This is true across a wide range of industries and studies, including cohort studies of workers in a variety of asbestos industries, case-control studies of mesothelioma and occupation, and a variety of studies of non-occupational exposure to asbestiform amphiboles, including but not limited to tremolite asbestos and to "cleavage fragments" of massive tremolite amphibole having dimensions similar to those of asbestiform tremolite fibers. Even efforts to gather together all reported "cases" of mesothelioma related "mainly" to chrysotile exposure inevitably come up with small numbers of such cases limited mainly to chryostile miners and millers also exposed to tremolite (e.g. (Stayner LT, Dankovic DA and Lemen RA 1996) .

Mesothelioma is related to amphibole asbestos exposure in approximately 80% of cases in epidemiological and pathological studies (the attributable risk varies from about 60% (McDonald AD and McDonald JC 1980; Yeung P and Rogers A 2001) to about 88% (Spirtas R, Heineman EF, Bernstein L et al. 1994) depending on the population and time period covered. This is supported by studies which assess exposure to humans directly through lung-retained fiber content (what the authors of the proposal call "pathology studies"; for example (McDonald JC, Armstrong B, Case B et al. 1989; Rogers AJ, Leigh J, Berry G et al. 1991; Rodelsperger K, Woitowitz HJ, Bruckel B et al. 1999) or by occupational inquiry (McDonald AD and McDonald JC 1980; Teta MJ, Lewinsohn HC, Meigs JW et al. 1983; Spirtas R et al. 1994; Woitowitz HJ and Rodelsperger K 1994; Teschke K, Morgan MS, Checkoway H et al. 1997) (if properly conducted in a true analytical epidemiological study as opposed to a survey, "registry", or collection of "cases").

The percentage is higher in occupations with heavy amphibole asbestos exposure, and in relatives of those in some such occupations, or occasionally in areas of endemic exposure such as the neighborhood of some shipyards, factories, and mines. It is important to note in this regard that exposures thought to be "nonoccupational" may first of all simply have inadequate occupational history, and secondly may be truly "nonoccupational" but nonetheless be associated with exceptionally high dose. An example of both of the latter is offered by a recent case control study of pleural mesothelioma among women living in the neighborhood of chrysotile mines: of ten cases discovered, all had worked outside the home, five were known to have worked in the industry, nine had at lived with at least one and more frequently more than one asbestos worker, and all lived in the highest-tremolite area (Case BW CM, Richardson L, Parent M-É, Désy M, and Siemiatycki J 2002) . In addition exposures were very high, estimated among cases on average at over 200 fiber/ml – years and never under 100 fiber-ml years. A

similar situation for environmental exposure to crocidolite has recently been reported from China (Luo S, Liu X, Mu S et al. 2003), where crocidolite was found in the surface soil in a rural county where the average number of mesothelioma cases was 6.6 per year in the 1984-95 period and 22 per year in the 1996-99 period, in a population of 68 000. The annual mortality rate for mesothelioma was reported as 85 per million, 178 per million, and 365 per million for three separate cohort studies, and there here were no cases of mesothelioma in comparison groups where no crocidolite was known to exist in the environment. This provides an object lesson for parts of California in which asbestiform tremolite has been identified in the surface soil and there has been a large degree of recent and planned housing development.

Most exposed mesothelioma cases in other studies either worked with, or more rarely had relatives who worked with commercial amphiboles , whether crocidolite (Armstrong BK, de Klerk NH, Musk AW et al. 1988; de Klerk NH, Armstrong BK, Musk AW et al. 1989; de Klerk NH, Armstrong BK, Musk AW et al. 1989; de Klerk NH, Musk AW, Cookson WO et al. 1993; Hansen J, de Klerk NH, Eccles JL et al. 1993; Hansen J, de Klerk NH, Musk AW et al. 1998) and/ or amosite(Sluis-Cremer GK 1991; Sluis-Cremer GK 1991; Sluis-Cremer GK, Liddell FD, Logan WP et al. 1992), although large quantities of non-commercial amphibole fiber (tremolite or other minerals in the tremolite-actinolite series) associated with chrysotile in mining occupations, mined as industrial "talc" (Abraham JL, Hull, M., Case, B.W. 2002) or vermiculite (McDonald JC, McDonald AD, Armstrong B et al. 1986; Amandus HE and Wheeler R 1987; Wright RS, Abraham JL, Harber P et al. 2002) may also be causative. Relatives of such workers who are subject to domestic (household) exposure to mining or milling fibers brought home on clothes or shoes are also subject to mesothelioma risk.

Mesothelioma was first conclusively linked to “asbestos” by J.C. Wagner in South Africa in 1960 (Wagner JC, Sleggs CA and Marchand P 1960) in a large study of cases taken from the Cape crocidolite mines. Some pathologists including the late Dr. Wagner still believe that crocidolite is the most important or even the only causative fiber, but most now accept amosite as responsible for as many or more cases (at least in the United States), and lung-retained fiber surveys of cases by Churg and by Roggli et al. (Churg A and Green F 1990; Roggli VL, Pratt PC and Brody AR 1993; Churg A and Vedal S 1994) have established that the less potent amosite fiber is responsible for the largest percentage of cases in the United States, at least among plaintiffs in lawsuits from which their cases were mainly drawn.

A recent meta-analysis of 17 cohorts with established exposure histories has reconfirmed the over-arching importance of amphibole exposure in mesothelioma causation, including in cases of exposure to mixed fiber types, including situations where chrysotile is by far the most prevalent exposure (Hodgson JT and Darnton A 2000) These authors estimate the relative risks of fiber types for mesothelioma as crocidolite: amosite: chrysotile 500:100:1, even making the conservative assumption that the chrysotile-related fraction includes the mining cases.

Crocidolite, the form first shown to cause mesothelioma, remains the most potent cause, although use has been essentially banned in North America and Europe and the number of future cases has been overestimated according to the most recently available data. More North American workers (at least insulation workers and those in allied trades) have now been exposed to amosite, and therefore more cases are produced by it, even though, given equal exposures, the proportion of workers developing mesothelioma is higher among those exposed to crocidolite.

Studies of chrysotile miners and millers in Quebec (well-described by the proposal's authors, in general) show a mesothelioma death rate of approximately 0.4% (33[1]/8009 or 1 in 240 deaths in recent years (Case BW, Churg, A., Dufresne, A. Sébastien,P. McDonald, A.D. and McDonald, J.C. 1997; McDonald AD, Case BW, Churg A et al. 1997). Lung tissue analytic study of miners from different locations show unequivocally that what was thought to be "chrysotile-related" mesothelioma occurs only in mining and milling situations where tremolite is present in sufficient quantity to produce high levels of long, thin, high aspect-ratio tremolite or tremolite-actinolite fiber in the lungs of workers.

In these studies the area in which mesothelioma risk was in greatest excess was that where the amphibole tremolite was (a) geologically likely to be present in highest concentration and (b) present in excess (compared to other chrysotile mines) in the lungs of miners and millers.

Commercial amphiboles, on the other hand, have long been known to cause mesothelioma, and at far lower dose. Wagner established the causal relationship between "asbestos" and mesothelioma in a crocidolite mining region, as noted above. Work by Hansen and colleagues have shown at the Witenoom

[1] This applies to the 33 of 38 cases in this study who were miners and millers of chrysotile. Another 5 cases worked in a factory producing asbestos products and used crocidolite asbestos. The total number of deaths given however also includes deaths among the small number of factory workers)

mine in Australia the causation of mesothelioma by crocidolite exposures as brief as one week and as small as 0.4 fiber-years (Hansen J et al. 1998). Similar work in South Africa has produced comparable results, both for crocidolite and for amosite, although the quantification of exposure is not as good as that observed in the Australian studies (Hodgson and Darnton 2000). Recent work from China suggests that in one rural province there the situation may be similar (Luo S et al. 2003).

Surveys of individual asbestos industries have confirmed that *within* those industries fiber type remains the key factor in mesothelioma production: effectively, wherever crocidolite or amosite have been used commercially some mesothelioma risk has been introduced. Acheson and others (Acheson ED, Gardner MJ, Pippard EC et al. 1982) looked at female respirator manufacturers: groups followed for 40 or more years. One group made "civilian" respirators containing chrysotile and showed no mesothelioma excess (and only one case, who had worked in the other plant as well). The other made "military" respirators (containing crocidolite) and had increased mesothelioma mortality. Similar results were observed for Canadian workers making military gas masks using crocidolite (McDonald AD and McDonald JC 1978).

A similar pattern was demonstrated for two asbestos cement plants in Louisiana by Hughes and Weill (Hughes JM, Weill H and Hammad YY 1987). Mesothelioma risk occurred in the plant in which crocidolite was used in one manufacturing process. Similarly, Gardner observed one case of mesothelioma in a cement plant using mainly chrysotile, but noted that the case was believed to be due to exposure elsewhere (Gardner MJ, Winter PD, Pannett B et al. 1986). A very recent study from Norway has again demonstrated the importance of a proportion of crocidolite in the cement manufacturing process in inducing mesothelioma risk (Ulvestad B, Kjaerheim K, Martinsen JI et al. 2002).

The manufacture of friction products is a particularly useful area in which to look at the distinctive differences in epidemiologic risk by fiber type. This is because for the most part these products were made with chrysotile asbestos, with only occasional “special contracts” in some plants having used crocidolite. Mesothelioma risk has been limited to those situations. This is true whether the studies have been of the plants in which friction materials were manufactured (for example (McDonald AD and Fry JS 1982; Newhouse ML, Berry G and Skidmore JW 1982; Berry G and Newhouse ML 1983; McDonald AD, Fry JS, Woolley AJ et al. 1984; Newhouse ML and Sullivan KR 1989; Berry G 1994)), or whether the studies were case-control studies of mesothelioma in which end-product users (including

identified groups of workers who worked with brake linings in garage settings) were included (McDonald AD and McDonald JC 1980; Teta MJ et al. 1983; Spirtas R et al. 1994; Woitowitz HJ and Rodelsperger K 1994; Teschke K et al. 1997). A recent meta-analysis has added statistical power to the latter analyses by combining them and again finding no mesothelioma risk for end-users of automotive friction products (Wong O 2001).

"Mechanistic" studies of mesothelioma add little of value to the question of fiber type. This is because of the large degree of interspecies difference as well as the technical difficulty of performing inhalation experiments with mesothelioma as an endpoint. One intriguing mechanistic point that has come to the fore with recent in vitro and cell-free work has been the question of the presence of iron and its effect on free radical generation and related effects. While this appears at first blush to be relevant due to the "structural" iron content of the commercial asbestiform amphiboles (crocidolite and amosite) (as well as the ferruginous "asbestos bodies"!), it does not explain the effects of some of the other amphiboles. Furthermore, chrysotile is not always "iron-free", as iron may be substituted in its structure or absorbed onto its surface.

The proposed risk co-efficients in Table 6-29 are quite consistent with the enhanced effect of amphibole fiber types on mesothelioma risk observed in epidemiological studies. The coefficients appear to be conservative in that they assign any mesothelioma risk at all to chrysotile asbestos for mesothelioma. It is interesting that although a different method was used than that of Hodgson and Darnton (2000), the "bottom line" in this model appears to be the same or even greater: an approximate five-hundred fold increase in risk for the amphiboles on a fiber-for-fiber basis.

B] Influence of *Fiber Length:* Please comment on the extent to which the epidemiology literature and mechanistic studies suggest that carcinogenic potency varies with *fiber length.* How adequate is information in the epidemiology literature for supporting dose-response relationships for different *fiber lengths*? In general, is it appropriate to assess cancer risks using an exposure index (see equation 7.13) that is weighted heavily by fibers longer than 10 micrometers (μm)?

For the most part, epidemiology studies do not inform with respect to carcinogenic potency for mesothelioma for fiber length. This is because, as pointed out by the authors, the existing epidemiology

studies have not used methods for exposure assessment which are capable of assessing fiber length, other than (if PCOM is used with the membrane filter method or an approximation of or conversion to PCOM values used from MPCF) limiting exposures to those longer than 5 μm. Of "mechanistic" studies which inform as to fiber length, the classic studies remains those of Stanton (Stanton MF and Wrench C 1972; Stanton MF 1974; Stanton MF, Laynard M, Tegeris A et al. 1977; Stanton MF, Layard M, Tegeris A et al. 1981), although the method of "exposure" in those experiments was neither physiologic nor in any way related to actual human exposure. Nevertheless, no discussion of mesothelioma and fiber length can ignore the Stanton model, for which there has been additional support in many animal studies since. It must be realized however that the classic Stanton "carcinogenic" fiber dimension (fibers having length greater than 8 μm and diameter less than 0.25 μm) were not met by *all* carcinogenic fibers, and with specific respect to tremolite – a fiber for which two preparations produced a 100% tumor response in the model – Stanton specifically reported that his model *did not* fit the response, and that "…relatively high correlations (with tumor response) were also noted with fibers in other size categories having diameters up to 1.5 micrometer and lengths greater than 4 micrometer" (Stanton MF et al. 1981). On the other hand, there is no evidence that structures having the same chemistry and crystalline structure as "asbestos" but length less than 5 μm behave as fibers rather than in the same way as isometric particles, nor is there evidence that such particles convey any risk for malignant mesothelioma. There is also a great deal of animal data which suggests the converse, much of which is listed by the authors of the proposal.

C] To what extent do animal studies (e.g. studies by Davis and other researchers) suggest that carcinogenic potency varies with *fiber type* and *fiber length?*

Animal studies are of little value in assessing the carcinogenic potency of fiber type. Animal studies which assess mesothelioma risk using the exceptionally sensitive peritoneal injection model in rats are in my view of little value, and intra-tracheal instillation models are similarly flawed, in the latter case in part because of the difficulty of assessing either the size or the nature of the administered dose in terms of fiber number or morphology. Even animal inhalation models have proved disappointed in assessing the risk posed by different fiber types, principally because rats are rather insensitive in this model. A recent review (Muhle H and Pott F 2000) summarizes this well: "Inhalation experiments with rats need fiber exposure concentrations…about 1,000 times higher (than those of asbestos workers) to reach the same mesothelioma risk. Also, the striking difference between the low lung burden of

amphibole fibers of asbestos workers with mesothelioma and the more than 1,000 times higher lung burden of rats with a low mesothelioma risk demonstrates the low sensitivity of the inhalation test model for the carcinogenic potency even of crocidolite fibers." Fortunately the effect of fiber type *for mesothelioma* is established beyond question by the epidemiology studies, at least for the relative effects of chrysotile as compared to commercial amphiboles and tremolite asbestos.

To the degree that fiber length categories can be separated for the purposes of exposures in animals (there is no such thing as a perfect preparation in which there are "no long fibers" or "no short fibers") the animal studies do indicate increasing mesothelioma risk with increasing fiber length, although the fiber length varies somewhat from study to study. The fiber length most often mentioned above which a mesothelioma response was observed is 20 μm in more recent studies. These are well-described in the proposal and will not be repeated here: key references include those with sized fiber preparations, with characterized length distributions, and with theoretical calculations (Davis JM, Addison J, Bolton RE et al. 1986; Davis JM and Jones AD 1988; Lippmann M 1990; McConnell EE, Axten C, Hesterberg TW et al. 1999; Miller BG, Searl A, Davis JM et al. 1999). While the same problems exist for studies using the intraperitoneal injection model in the rat with length as the independent variable as those for fiber type, one study that was not peer-reviewed prior to publication of six naturally occurring tremolite preparations does suggest some effect (Davis JM, Addison J, McIntosh C et al. 1991). However the main purpose of this study was to test the relative effects of "asbestiform" versus "nonasbestiform" tremolite preparations (see below).

D] Please comment on the extent to which carcinogenic potency is a function of fiber properties (e.g., diameter, aspect ratio, surface properties) *other than* fiber type and fiber length. How adequate is information in the epidemiology and toxicology literature for supporting these other properties into dose-response analyses?

It is important here to distinguish between respirability and carcinogenicity, with respect to fiber diameter. As noted above, the original Stanton studies actually showed effects at diameters of less than 1.5 μm, not 0.5 μm. A cutoff of 0.5 μm is probably inappropriate, although it is quite true that almost all chrysotile and crocidolite fibers will be included. This is somewhat less true for amosite and is not acceptable at all for tremolite, which in many situations will almost reach an *arithmetic average* of 0.5 μm diameter. In general, as demonstrated by Berry (unpublished data on Witenoom and (Berry G 1999)

), who has shown that “the incidence of mesothelioma after exposure to asbestos is proportional to the intensity of exposure (fibers per milliliter of air) and the duration of exposure, and to the time that has elapsed since the exposure. The incidence increases with time since exposure to a power of between 3 and 4”.

The latter variable – time since first exposure – is a very powerful component of mesothelioma risk in epidemiological studies across the board, if they are large enough and have long enough follow-up. No model which ignores this timing factor can be considered adequate for predicting risk. In addition Berry has recently demonstrated a large effect of elimination time on mesothelioma risk by applying this model to Witenoom mesothelioma mortality data (Berry G, unpublished data presented at International Mesothelioma Interest Group meeting, Perth, Australia, December 2002).

I will take the opportunity here to separately and briefly discuss lung-retained fiber studies in human subjects for mesothelioma - a separate category of study which is called “pathology studies” by the authors which is capable of isolating effects of fiber type and length with the understanding that analyses are performed at an endpoint (either lung biopsy, pneumonectomy, or autopsy) which integrates lifetime dose and clearance at a single point in time. It is nonetheless useful, although to some degree dismissed by the authors of the model for a number of theoretical reasons, chief among them what the authors call “opportunistic” sample site selection and what the authors believe is poor repeatability of results. In fact, if such studies are well-controlled, sample selection is *not* opportunistic, in that samples from cases and controls, taken at the same time and in the same way by the same pathologists in the same hospitals, are very likely to be comparable. Similarly, there is little evidence other than a few studies based on very small numbers of samples that there is in fact significantly poor reliability in such measurements so long as they are compared within rather than across laboratories. Reliability is at least as good as that for TEM fiber measurements in air. In fact, in Quebec, this is the method used *routinely* to characterize exposure for workman’s compensation purposes (when lung tissue sections are available). We have had the experience of hundreds of such analyses and our results do well in cross-disciplinary validation studies in comparison with semiquantitative job-based indices of asbestos exposure. We have not encountered difficulties with reliability; our published studies in fact are capable of distinguishing trends of fiber retention with age, with rural-urban gradient, and with distance lived from and time lived in mining areas for environmentally-exposed individuals (Case BW and Sebastien P 1987; Case BW, Sebastien P and McDonald JC 1987; Case BW and Sebastien P 1989; Case BW 1991; Case BW 1994;

Takahashi K, Case BW, Dufresne A et al. 1994). Here for example are results from our most recently analyzed mesothelioma case; note the consistency across samples.

Sample site	Asbestos body concentration (AB/ gram dry lung, PCOM at 320X, detection limit 40 AB/ gram dry lung)	Crocidolite fiber concentration* (and number)	Other asbestos fibers detected; detection limit 35 fibers/ mg dry lung.
Right lower lobe #1	31,520 AB/ gram dry lung	722 fibers/ mg dry lung (N=22)	None detected
Right middle lobe	26,880 AB/ gram dry lung	620 fibers/ mg dry lung (N=18)	None detected
Right lower lobe #2	28,320 AB/ gram dry lung	790 fibers/ mg dry lung (N=23)	None detected
Right upper lobe	26,920AB/ gram dry lung	550 fibers/ mg dry lung (N=16)	None detected

* Fibers (longer than 5 μm, aspect ratio greater than 3:1) identified and counted by transmission electron microscopy at 13,500 X magnification and by energy dispersive x-ray spectrometry (EDS).

With specific reference to mesothelioma causation, several case-control studies using this type of exposure index have produced interpretable results which lend strong support to both the role of (amphibole) fiber type and of increasing fiber length. In one such example, McDonald et al. studied 78 case-control pairs of lung samples from mesothelioma victims and controls matched for age, sex, hospital, and time of acquisition of sample. (McDonald JC et al. 1989). There were "substantial differences…between cases and referents for amosite, crocidolite, and tremolite. Much less difference was noted for anthophyllite, talc, and chrysotile…Statistical analysis indicated that short fibers were not associated with increased risk for mesothelioma." It should be noted that no special care was taken to match sample sites for cases and controls or across cases or controls; this is in fact not necessary if cases and controls are matched by hospital and era as it is the routine practice of pathologists which determines sample site selection; in other words, while the authors of the proposal were justified to in their *belief* that such studies might use "opportunistic" samples which are not from similar sites within the lung, the *actual practice of pathologists taking lung samples from autopsy or from resected lung tissue is quite consistent in this regard, with most taking central parenchymal samples from fixed sites in a manner learned during any pathology residency.*

3) To what extent are the exposure estimates documented in the asbestos epidemiology literature reliable?

This question is unclear, and may not be the most relevant to ask. More important than the reliability of exposure estimates is their validity, which in general is excellent within the largest and best studies that have been generally used for risk assessment (combining them in meta-analyses has proved more difficult and controversial). Similarly, reliability is good across the largest individual studies but much poorer between studies, due to the differences in methodology employed. This is well discussed by the authors of the proposal and they suggest some additional work which might help to ameliorate this difficulty. However, the authors do appear to be unaware of some of the controversies extant about these estimates[2]. For example, they make use the Witenoom data without referring to the controversy and debate between Australian researchers about these (***because of their exceptional importance these comments are attached to these comments as appendix A***). The authors do note the exclusion of the Charleston (textile) data by Hodgson and Darnton but choose to include it; in my view this is not critical to their conclusions although the Charleston data is clearly an anomaly even *within* the studies of textile workers and should be viewed with extreme caution. It should only be used if balanced with use of the Quebec data on exposures in the mining and milling of chrysotile. Finally, the set of Quebec data, as well, has attracted both positive and negative comment, the latter usually based on its exclusive use of midget impinger (MPCF) data. The latter are unavoidable (that was the data available); the data are extensive and internally consistent, and the authors of the current proposal do a good job of discussing this type of data.

For purposes of risk assessment my own opinion is that the operative question is "Can exposure be measured in such a way in sites which require evaluation that the exposure assessment is both valid and repeatable". Again, this is somewhat controversial. Rogers for example is on record as feeling that "A 'clear dose-response relationship' does not validate the actual exposure values used, but the decision about exposure values of course determines the slope, which influences the apparent potencies of different fiber types". My own view is that a clear dose-response relationship *does* validate *the use of* the exposure values; if the data are good enough to establish a dose-response relationship then they have internal validity. However,

[2] See the letter, reply, and editorial comment recently published as regards the Witenoom exposure data attached to these comments as Appendix A: (1) Rogers A and Major G. Letter to the Editor. Ann Occup Hyg (2002) **46**: 127-128 ; (2) A.W. MUSK and N.H. DE KLERK. Reply. Ann Occup Hyg (2002) **46**: 128-129; The Editors, Ann Occup Hyg: (3) Editorial Response. Ann Occup Hyg (2002) **46**: 129.

it is quite true that in absolute terms *none* of the studies can give absolute confidence as to what the *actual exposure levels* were in these historical cohorts.

Analytical sensitivity, however, is also especially important. Use of transmission electron microscopy coupled with energy dispersive spectrometry of x-rays and in some instances selected area electron diffraction should allow, at a minimum, the detection of fiber types and lengths in any such situation at a specified detection limit. At the Oakland conference of May 2001, Dr. Patrick Sebastien suggested that for environmental exposures the best use of TEM/ EDS is the qualitative identification of the presence of individual fiber types rather than their full characterization in quantitative terms. The authors of the proposal appear to believe that "environmental" sites may be less homogeneous in their asbestos content, and perhaps more dilute in their asbestos content, than exposures in occupational settings. While this is no doubt true in sites where little is known about past use or exposures, it is certainly *not necessarily true* in superfund sites such as old mine sites.

The **method of sampling** is the key factor for evaluating environmental exposure (for example, Superfund) sites: for example, simple measurement of air samples in an undisturbed area which contains low concentrations of amphibole fibers will mislead the investigator of a site. One example is offered by a study of vermiculite insulation in the ceilings of a Canadian army base which unfortunately has been published only as the following abstract (and which is directly relevant to the exposure situations in Libby and to the question of exposures to amphibole from attic insulation) note the extreme effect of *conducting the air sampling* ***during*** *the demolition work*: concentrations of "asbestos" which were generally less than 0.1% by weight became tremolite levels by TEM of up to 172 fibers/ ml

Cowan BW [1997]. Elevated Asbestos Exposures from a Building Demolition Which Contained Vermiculite Insulation. Proceedings of the American Industrial Hygiene Conference and Exposition (AIHCE 1997). Paper 65.

B.W. Cowan, Government of Manitoba, Brandon, MB, Canada

Vermiculite is a silicate mineral which has been installed in many attics as a building insulation. An asbestos consultant collected bulk insulation samples from several locations scheduled for demolition on a Canadian Forces base. Asbestos concentrations ranging from less then 0.1% to

5-10% Actinolite and/or Tremolite were detected in this proactive survey. The majority of test results were quite low; generally less than 0.1% asbestos, however, the potential existed for asbestos fibers to become airborne during a routine demolition project. Air monitoring was conducted during the demolition work, which utilized no dust suppression, to determine representative worker exposures to airborne asbestos dust. Ten samples were analyzed by transmission electron microscopy (TEM) in accordance with NIOSH Method 7402 and concentrations ranged from 13 to 172 fibers per mL. The results of this study indicated elevated levels of airborne asbestos fibers were generated during the ceiling demolition and appropriate asbestos abatement procedures had to be initiated. These included the installation and operation of a negative pressure ventilation system and a decontamination facility, the wearing of adequate personal protective equipment, the prewetting of the asbestos contaminated material, the proper bagging of all asbestos waste, and regular on-site air monitoring to record the levels of airborne fiber concentrations.

TOPIC AREA 2: The proposed exposure index

4) The proposed exposure index does not include contributions from fibers shorter than 5 μm. Please comment on whether the epidemiology and toxicology literature support the conclusion that asbestos fibers shorter than 5 μm present little or no carcinogenic risk.

Such structures (they are not fibers and it stretching a point to call them "asbestos") present little or no carcinogenic risk. This was dealt with fully in the recent ATSDR workshop (ATSDR 2002) and will not be repeated here, although the panelists should if possible be provided with the current report from the ATSDR meeting in lower Manhattan in the fall of 2002, even though it has not yet been published. I sincerely hope we do not waste much time on this.

5) The proposed index is weighted heavily by fibers longer than 10 μm. Specifically, equation 7.13 suggests that the carcinogenic potency of fibers longer than 10 μm is more than 300 times greater than that of fibers between 5 and 10 μm. How consistent is this difference in carcinogenic potency with the epidemiology and toxicology literature?

It cannot be said to be "consistent with the epidemiology literature" since as the authors themselves point out that the epidemiology literature lacks such data (with the exception of lung-retained fiber studies or what are described by the authors as "pathology studies"). On the other hand it is quite consistent with the toxicology literature, and indeed an argument could be made that the critical length should be 20 μm rather than 10. The use of the more conservative 10 μm, although it will make many mineralogists unhappy (since they would not even regard such structures as "fibers"), is actually quite conservative in this regard.

Ultimately however the proof of the model (and of the index) is in its predictive ability; the authors do provide convincing evidence of this.

6) Please explain whether the proposed exposure index will allow meaningful comparisons between current environmental exposures to asbestos and historical exposures to asbestos that occurred in the workplace.

This will be exceptionally difficult since, as the authors note, virtually all of the published literature on workplace exposures (at least in the context of the epidemiological studies referred to) do not use similar methodology. In a broad qualitative sense the proposed exposure index will offer better estimation of *exposure* than do the exposure measures offered in the historical workplace exposure measurements, since they include the biologically important descriptions of fiber type and length (with fiber type in particular being of proven importance in the epidemiology studies, although *not* from the historical measures of exposure but more from the qualitative descriptions of exposure offered in those studies; for example comparisons across similar industries having differences in fiber type which are not necessarily quantified.

Topic Area 3: General Questions.

7) The proposed risk assessment approach assigns carcinogenic potency to individual fibers and to cleavage fragments (or "bundles that are components of more complex structures"). Please comment on whether cleavage fragments of asbestos are as toxicologically significant as fibers of the same size range.

This question must be withdrawn and reworded. It is badly mis-stated and contains errors of fact within its structure.

First, it is not clear whether the person or persons writing this question do not understand the distinction between "cleavage fragments" and "fiber bundles" (which are completely different animals), whether they are asking *only* about "cleavage fragments", or whether they are asking about *both* cleavage fragments and fiber bundles. Second, "cleavage fragments" are, by definition (as is clearly pointed out in the proposal), ***not "asbestos", although this does NOT mean they are without effect.*** **Third,** the limitation of the question to *toxicological* significance ignores the published data on human exposure to "cleavage fragments" which is of greater importance than toxicological data (for example it has recently been estimated in a very detailed mineralogical study at the mine site that the nonasbestiform portion of the Quebec tremolite associated with one mine (the Jeffrey mine at Asbestos, Quebec) is 99% "nonasbestiform"). **Fourth**, the expert panel as constituted has no mineralogists or geologists, making any discussion of these points somewhat perilous. **Thus this question, which is an exceptionally important one that has been addressed by the authors of the proposal, should be reworded.** ***The question commented upon by this observer is reworded as the following: I recommend that this or a consensus rewording, preferably with expert mineralogical input, be substituted BEFORE the meeting:***

7 REVISED) The proposed risk assessment approach assigns carcinogenic potency to individual fibers and to cleavage fragments derived from massive amphibole structure (that is, nonasbestiform amphiboles). Please comment on whether cleavage fragments of this nature are as significant with respect to human health effects as fibers of the same size range, including reference to the toxicological and epidemiological literature.

Again, cleavage fragments are NOT "bundles that are components of more complex structures". The question of cleavage fragments of massive amphibole is a very important one, and the question of the assessment of complex bundles (which may or may not be composed of aggregates of asbestiform structures, nonasbestiform structures, or both) is an important but entirely separate issue. The phrase **(or "bundles that are components of more complex structures")** must be removed from this charge question before the meeting. If it is not the discussion of the exceptionally important issues surround

exposure assessment to cleavage fragments of massive amphibole, "nonasbestiform" amphibole, and so-called "transitional fibers" will be confused by this error. The following discussion responds to the restated charge question above (**7 REVISED)**: it makes no mention of and does not apply to "bundles that are components of more complex structures".

This (inclusion of cleavage fragments of massive amphibole on the strict basis of structure dimension) is one of the greatest strengths of the proposed risk assessment approach, and may make up for the catastrophically inadequate approach taken by OSHA in their removal of such fibers from the asbestos standard in 1992. It may be recalled that the latter action was taken against the advice of NIOSH, of the scientific branch of OSHA itself (OSHA scientific staff, personal communication) and of the ATS Committee on the Health Effects of Tremolite (Weill HW AJ, Balmes J, Case BW, Churg AM, Hughes J, Schenker M and Sébastien P 1990; Case BW 1991a; Case BW 1991b). The critical problems with excluding "cleavage fragments" and/or "nonasbestiform" amphiboles (of size and shape similar to analogous asbestiform amphiboles) from risk assessment were

(a) That as a practical matter there was a debate as to whether there was a "bright line" separation between them;
(b) That they often occur together, sometimes with only a small proportion of "asbestiform" structures;
(c) That they are difficult to separate analytically (in fact they cannot be separated by the microscopist with certainty, not even with high-magnification transmission electron microscopy: on this point for example Patrick Sébastien has stated "***To be able to tell whether fibers are asbestiform or not under the microscope is quite impossible. To me, the concept of "asbestiform" is not a microscopic one. Geologists may tell us whether a fiber is asbestiform, but certainly the microscopist cannot".***
(Sébastien P, Discussion Part 14, Ann NY Acad Sci **643:** page 505).

(d) That most important, there is no convincing evidence that given similar dimensions and similar durability in the lung there is any reason to believe that "cleavage fragments" might be less toxic. Reproducing the ATS Committee document from page 1 on **"Mineralogic Issues"** and from the Conclusion:

Mineralogic Issues

As noted above, the focus on tremolite has raised the issue of the importance of cleavage fragments as opposed to asbestiform fibers. The fundamental issue is whether two fibrous particles of identical size and shape will have different biologic properties if the particles are pieces of mineral that have broken off a larger sample parallel to a crystal face (i.e., cleavage fragments) as opposed to particles that have originally grown in a fibrous habit (i.e., asbestiform fibers).

It became apparent, both from our review of the literature and from submissions made to this committee by experienced mineralogists, that the distinction between cleavage fragments and asbestiform fibers, although theoretically clear, is in practice extremely murky. Some mineralogists believe that these two types of particles are always distinct, whereas others believe that they shade off one into the other and that intermediate forms (byssolite) exist. Further, these same submissions were at odds with each other in identifying particular samples used in various experiments as asbestiform fibers or cleavage fragments. To complicate matters, it was also suggested to us that the important distinction is not that between cleavage fragments and asbestiform fibers but between nonasbestiform and asbestiform fibers.

Because of the lack of consensus among mineralogists, as well as the limited information about the minerals present in most published human and animal data (i.e., whether the particles used or observed really are fibers or cleavage fragments), we have to a great extent ignored the distinction and ended up treating most of the data as based on "fibers" of various sizes. The committee recognizes that this is not an ideal solution, and where stronger evidence of the cleavage fragment or asbestiform nature of a particular fiber exists, we have noted it. However, until there is reasonable mineralogic unanimity both on

(continues as "general definition and the classification of specific samples, and then animal experimentation with such classified materials, it appears to us impossible to draw general conclusions about biologic effects based on the distinction between cleavage fragments and asbestiform fibers"

and from the conclusion:

" 3. The evidence for biologic effect distinctions based on mineralogic parameters, other than fiber dimension and fiber number, is currently inadequate.

4. At present, the prudent public health policy course is to regard appropriately sized tremolite "fibers," in sufficient exposure dose (concentration and duration), as capable of producing the recognized asbestos-related diseases, and they should be regulated accordingly"

(Note: It is strongly recommended that panelists read the full statement in the American Review of Respiratory Medicine as referenced. Panelists should also be aware that the Environmental and Occupational Health Assembly of the American Thoracic Society has recently obtained funding to reconvene a new panel to update this statement, which is currently working on revisions and will meet in Seattle in May, 2003).

8) Please comment on whether the proposed cancer assessment approach is relevant to all amphibole fibers or only to the five types of amphibole fibers (actinolite, amosite, anthophyllite, crocidolite, tremolite) designated in federal regulations.

The proposed cancer assessment approach is certainly relevant to all amphibole fibers which have been identified as capable of producing the recognized asbestos-related disease. In addition to the five designated types these include richterite, winchite, and possibly edenite in one location in Italy. Given the very large number of amphiboles (over 50) it seems likely that others may be found to have forms which may act in similar ways, but I am not aware of any at present. It should also be noted that "amphiboles" comprise a huge portion of the earth's crust, and it would be totally impractical to try to regulate all forms of all amphiboles. In this regard the authors' proposal is very useful in that it ***limits*** the nonasbestiform amphiboles assessed to those which *have the same dimensional characteristics as the analogous asbestiform varieties.*

9) The review document recommends that asbestos samples be analyzed by transmission electron microscopy (TEM) and count only those fibers (or bundles) longer than 5 μm. Such counting practices will provide no information on the amount of asbestos fibers shorter than 5 μm. To what extent would data on shorter fibers in samples be useful for future evaluations (e.g., validation of the cancer risk assessment methodology, assessment of non-cancer endpoints)?

This was answered above, with the exception of the point on "assessment of non-cancer endpoints". Again the panelists should be referred to the as yet unpublished ATSDR 2002 document which deals specifically with this issue; there is a general consensus that such short structures are not important in

non-cancer endpoints – specifically lung fibrosis – but there are (unlike the case for cancer endpoints) at least a few studies which contradict this.

10) The proposed risk assessment methodology suggests that exposure estimates should be based only on fibers longer than 5 μm and thinner than 0.5 μm. Is this cut-off for fiber *diameter* appropriate?

While the use of this cutoff would include most chrysotile and crocidolite fibers of concern, it would not count some amosite fibers and would not count a substantial portion of tremolite fibers of proven toxicity. Hence this cutoff is *not* appropriate; perhaps a weighted index could be applied similar to that for fiber length for thicker fibers, but ultimately it must be realized that no single technique for assessing exposure by electron microscopy in this regard will be equally applicable to all waste sites, and the hazard may be severely underestimated in some locations should such a liberal definition of diameter be adopted. In particular, it is not appropriate to exclude tremolite fibers under 1.5 μm in diameter from concern and from inclusion in assessments of sites where tremolite is the major mineral of concern.

11) Discuss whether the proposed cancer assessment approach, as a whole, is a reasonable evaluation of the available health effects data. What aspects of the proposed cancer assessment approach, if any, are inconsistent with the epidemiology or toxicology literature for asbestos?

As a whole the proposed cancer assessment approach does appear to be a reasonable evaluation of the available health data, although it is mistaken in some details. These were described in previous sections. The emphasis on fiber type in risk assessment is long overdue; evidence for fiber length criteria in the approach is perhaps less solid, although certainly it is true that structures having length less than 5 μm need not be assessed, and indeed (through the fact of skewed length distributions) inclusion of this size category actually would provide risk assessment which may either overstate or understate health effects. Use of the greater-than-10 μm criterion as the most heavily weighted fraction, and the exact weight to attach to it (or to some other fraction), requires discussion by the panel.

12) Section 8.2 of the review document presents three options for assessing cancer risks from asbestos exposure. Please comment on the technical merit of the proposed risk assessment options.

I will leave this to the actual panel discussion.

Topic Area 4: …the peer review consultants are invited to provide any additional comments or concerns, both strengths and weaknesses, on topics not specifically addressed in the previous charge questions. …the focus of this workshop is on the proposed risk assessment methodology and how it may be used to support decisions at asbestos-contaminated sites.

(signed)

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Monday, February 17, 2003

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CHARGE QUESTIONS

Topic Area 1: Interpretations of the epidemiology and toxicology literature.

1) For *lung cancer:*

A. Influence of *fiber type*: Please comment on the extent to which the epidemiology literature and mechanistic studies suggest that carcinogenic potency varies from one *fiber type* to the next (e.g., chrysotile versus amphibole fibers). How adequate is the information in the epidemiology literature for supporting dose-response analyses *fiber types*? Specifically, to what extent do you think the proposed risk coefficients in Table 6-29 are supported by the epidemiology literature?

Response: A large body of data exist comparing rate constants for the in vitro dissolution of fibers of different chemical compositions. A good correlation exists between these in vitro dissolution data and biodurability data collected in animal models. Furthermore, a correlation exists between durability values and the potency of fibers to cause fibrosis, lung cancer and mesothelioma in animal models. In vitro dissolution data indicate that chrysotile is less durable than amphibole fibers. However, in vitro toxicology data and animal studies do not consistently fine chrysolite to be less bioactive (in vitro) or less fibrogenic or carcinogenic (in animal models) than amphibole fibers. The report proposes that the time frame of in vitro studies (hours-days) and animal studies (2 years) is too short for the dissolution of chrysotile to become a significant factor. In contrast, the 30 year time frame for asbestos-induced lung cancer is sufficiently long for chrysotile dissolution to influence the results. This is a reasonable argument, and it is supported by the modeling of the epidemiology data. The risk coefficients for lung cancer given in Table 6-29 and 6-30 suggest a 5 fold greater risk from amphibole exposure than from exposure to chrysotile. My view is that the epidemiological data support a greater risk coefficient for lung cancer with amphiboles than chrysotile. However, a 5 fold difference in risk is debatable considering the uncertainties inherent in the data used in this model.

B. Influence of *fiber length*: Please comment on the extent to which the epidemiology literature and mechanistic studies suggest that carcinogenic potency varies with *fiber length.* How adequate is information in the epidemiology literature for supporting dose-response analyses for different *fiber lengths*? In general, is it appropriate to assess cancer risks using an exposure index (see Equation 7.13) that is weighed heavily by fibers longer than 10 micrometers (μm)? (Note: Topic area 2 includes more detailed questions on the proposed exposure index.)

Response: In vitro mechanistic data generally support the hypothesis that long fiber are more bioactive than short fibers. Animal data for fibrous and lung cancer support this conclusion. Modeling of epidemiology also supports the hypothesis that long fibers are more potent in inducing lung cancer than short fibers. Equation 7.13 heavily weighs the contribution of fibers > 10 μm vs those between 5-10 μm in length by a factor of greater than 300:1. The equation dismisses particles < 5 μm in length as having no influence of pulmonary response. Mechanistic in vitro data on cell proliferation, generation of reactive species, and cytokine and growth factor production indicate that short particles are not without an effect. Indeed, although long fibers have been shown to activate transcription factors and increase cytokine production form cultured cells to a greater extent than short fibers, a relationship to surface area was noted (Ye et al. Am J Physiol 276: L426-L434, 1999; J Biol Chem 276; 5360-5367, 2001). Animal and epidemiological studies of asbestos toxicity indicate that short fibers are relatively less potent than long fibers. However, these were relatively pure exposures. In a mixed exposure condition, where exposure to short or non-fibrous particles is high, short particles may potentiate the pulmonary reaction to long fibers. The World Trade Center site is an example of an exposure to high levels of short particles along with fiber exposure. The potency factor of 300:1 for fibers longer than 10 μm seems high.

C. To what extent do animal studies (e.g., studies by Davis and other researchers) suggest that carcinogenic potency varies with *fiber type* and *fiber length*?

Response: Animal studies do not support the 5:1 difference in lung cancer potency of amphiboles to chrysotile. The report's suggestion that a 2 year animal study is too short for dissolution of chrysotile to be an important factor has merit. Animal studies support the hypothesis that lung fibers are more potent carcinogenesis than short fibers. However, animal studies do not support the hypothesis that short fibers or spherical particles are essentially inert.

D. Please comment on the extent to which carcinogenic potency is a function of fiber properties (e.g., diameter, aspect ratio, surface properties) *other than* fiber type and fiber length. How adequate is information in the epidemiology or toxicology literature for supporting these other properties into dose-response analyses?

Response: The major influence of fiber chemistry is expressed as differences in fiber durability. Surface properties, such as the ability of chrysotile vs amphiboles to generate reactive oxygen species, have not proven to greatly influence fiber carcinogenicity in animal models. Diameter and aspect ratio affect fiber deposition in the lung. However, the influence on carcinogenicity in animal models as independent of deposition has not been adequately evaluated.

2) For *mesothelioma:*

A. Influence *fiber type*: Please comment on the extent to which the epidemiology literature and mechanistic studies suggest that carcinogenic potency varies from one *fiber type* to the next (e.g., chrysotile versus amphibole fibers). How adequate is the information in the epidemiology literature for supporting dose-response analyses for different *fiber types*? Specifically, to what extent do you think the proposed risk coefficients in Table 6-29 are supported by the epidemiology literature?

Response: Intraperitoneal instillation data do not support a great difference between the potency of chrysotile and amphiboles to induce mesothelioma. In vitro mechanistic data do not support a great difference in potency by fiber type. However, animal data strongly indicate that chrysotile is less potent than amphiboles in producing mesothelioma. This is supported by epidemiological data. The relative risk coefficients of amphiboles vs chrysotile for mesothelioma in Table 6-29 and Table 6-30 are 500-600:1. Data support a large difference in risk.

B. Influence of *fiber length*: Please comment on the extent to which the epidemiology literature and mechanistic studies suggest that carcinogenic potency varies with *fiber length*. How adequate is information in the epidemiology literature for supporting dose-response analyses for different *fiber lengths*? In general, is it appropriate to assess cancer risks using an exposure index (see Equation 7.13) that is weighed heavily by fibers longer than 10 micrometers (μm)? (Note: Topic area 2 includes more detailed questions on the proposed exposure index.)

Response: Intraperitoneal instillation data support a strong dependence on fiber length. In vitro mechanistic data support a relationship between potency and fiber length, although the relationship is not all or none. Modeling epidemiologic data strongly support that long fibers are more potent than short fibers in inducing mesothelioma. Equation 7.13 indicates that fibers >10 μm should be weighed 300:1 over fibers 5-10 μm in length for mesothelioma. The weighing for length and mesothelioma is mechanistically stronger than for lung cancer.

C. To what extent do animal studies (e.g., studies by Davis and other researchers) suggest that carcinogenic potency varies with *fiber type* and *fiber length*?
Response: The difference in potency of chrysotile vs amphiboles and long vs short fibers to cause mesothelioma is supported by animal inhalation studies.

D. Please comment on the extent to which carcinogenic potency is a function of fiber properties (e.g., diameter, aspect ratio, surface properties) *other than* fiber type and fiber length. How adequate is information in the epidemiology or toxicology literature for supporting these other properties into dose-response analyses?

Response: The major influence of fiber chemistry is expressed as differences in fiber durability. Surface properties, such as the ability of chrysotile vs amphiboles to generate reactive oxygen species, have not proven to greatly influence fiber carcinogenicity in animal models. Diameter and aspect ratio affect fiber deposition in the lung. However, the influence on carcinogenicity in animal models as independent of deposition has not been adequately evaluated.

3) To what extent are the exposure estimates documented in the asbestos epidemiology literature reliable?

Response: The problem with these data have been adequately discussed in the report. Fiber characterization is not complete. Exposure levels for past exposures are often estimates. These uncertainties don't affect the conclusion that long fibers are more potent than short fibers or that amphiboles are more potent than chrysotile. However, they do make absolute quantitation of the potency differences difficult.

Topic Area 2: The proposed exposure index.

4) The proposed exposure index does not include contributions from fibers shorter than 5 μm. Please comment on whether the epidemiology and toxicology literature support the conclusion that asbestos fibers shorter than 5 μm present little or no carcinogenic risk.

Response: Cohorts for epidemiologic studies were chosen for the absence of major mixed dust exposure. Animal studies were controlled for fiber exposure alone. Therefore, the burden to particles less than 5 μm in length was minimized in the experimental designs. At such low burdens, long fiber toxicity would dominate. However, one could envision situations were high exposures to spherical particles or short fibers could occur. Mechanistic data is consistent with the hypothesis that such burden would elevate the oxidant/inflammatory set point and increase the response to long fibers. This point was discussed in 1B.

5) The proposed exposure index is weighed heavily by fibers longer than 10 μm. Specifically, Equation 7.13 suggests that the carcinogenic potency of fibers longer than 10 μm is more than 300 times greater than that of fibers with lengths between 5 and 10 μm. How consistent is this difference in carcinogenic potency with the epidemiology and toxicology literature?

Response: See response 1B and 4.

6) Please explain whether the proposed exposure index will allow meaningful comparisons between current environmental exposures to asbestos and historical exposures to asbestos that occurred in the work place.

Response: It seems possible that current and future exposures of environmental concern would be to mixed dusts rather than pure fibers. The proposed exposure index would dismiss what might be a high exposure to spherical particles or short fibers. The World Trade Center site is an example of such a mixed dust exposure. There are in vitro mechanistic data which would suggest that the responsiveness to long fibers might be enhanced if the system was under particle-induced oxidative stress and inflammation.

Topic Area 3: General questions.

7) The proposed risk assessment approach assigns carcinogenic potency to individual fibers and to cleavage fragments (or "bundles that are components of more complex structures"). Please comment on whether cleavage fragments of asbestos are as toxicologically significant as fibers of the same size range.

Response: Assigning equivalent potency to individual fibers and cleavage fragments of equal dimension is a reasonable approach. Data from in vitro mechanistic studies do not indicate that cells can discern a difference between a single fiber or a bundle of equivalent dimensions.

8) Please comment on whether the proposed cancer assessment approach is relevant to all amphibole fibers or only to the five types of amphibole fibers (actinolite, amosite, anthophyllite, crocidolite, tremolite) designated in federal regulations.

Response: Response to fibers is governed by dose, durability and dimensions. No mechanistic or animal data exist which would suggest that two types of fibers which were similar in the three characteristics noted above would exhibit a different biological response in the lung. Therefore, long durable fibers not currently labeled as asbestos if inhaled at a similar dose would be expected to result in a similar degree of pathology.

9) The review document recommends that asbestos samples be analyzed by transmission electron microscopy (TEM) and count only those fibers (or bundles) longer than 5 μm. Such counting practices will provide no information on the amount of asbestos fibers shorter than 5 μm. To what extent would data on shorter fibers in samples be useful for future evaluations (e.g., validation of the cancer risk assessment methodology, assessment of non-cancer endpoints)?

Response: Use of TEM rather than PCM allows thin fibers to be counted. This is appropriate, since long thin fibers would be expected to be highly potent. In evaluating risk of fiber inhalation as part of a mixed dust exposure, it is possible that particles less than 5 μm in length could enhance the response to long fibers. The proposed assessment approach would ignore this possibility.

10) The proposed risk assessment methodology suggests that exposure estimates should be based only on fibers longer than 5 μm and thinner on 0.5 μm. Is this cut-off for fiber *diameter* appropriate?

Response: Since fibers up to 0.7 μm can be deposited in the respiratory zone of the lung, it seems more appropriate to raise the cut-off to this value.

11) Discuss whether the proposed cancer assessment approach, as a whole, is a reasonable evaluation of the available health effects data. What aspects of the proposed cancer assessment approach, if any, are inconsistent with the epidemiology or toxicology literature for asbestos?

Response: The concepts that amphiboles are more potent than chrysotile and long fibers are more potent than short are reasonable. The debate is the weighing of these potencies. The approach used to model existing epidemiologic and animal data is reasonable. However, uncertainty of the weighing factors exists due to the uncertainty of exposure and size characterization in the individual studies used in the model.

12) Section 8.2 of the review document presents three options for assessing cancer risks from asbestos exposure. Please comment on the technical merit of the proposed risk assessment options.

Response: All three options assume that the weighing factors for fiber dimension and fiber type are adopted. Given that assumption option 2 appears to be simple to apply to environmental conditions. Each option suffers from the uncertainty of the weighing factors and each option ignores the situation of a significant mixed particle exposure.

Topic Area 4: Development of Conclusions and Recommendations

At the end of the workshop, the peer consultants will be asked to draft conclusion statements identifying their most notable findings on the proposed methodology. As a prelude to developing these statements, the peer consultants are invited to provide any additional comments or concerns, both strengths and weaknesses, on topics not specifically addressed in the previous charge questions. After completing the discussions the peer consultants will prepare their conclusions, and they will also be asked to develop

recommendations for how EPA can improve the methodology. Please note that, although recommendations for future research projects are welcomed, the focus of this workshop is on the proposed risk assessment methodology and how it may be used to support decisions at asbestos-contaminated sites.

Response: The proposed methodology is founded strongly on the premise that lung cancer risk due to asbestos is independent of other exposures. This is not the case with smoking and asbestos exposure. Mechanisms for asbestos-induced cancer include oxidant damage, disregulation of growth control, production of inflammatory cytokines and proliferation factors, down regulation of apoptosis, etc. Considering the current mechanistic understanding of fiber-induced cancer induction, it is not unreasonable to propose that lung burden to short fibers or spherical particles might change the oxidant stress and/or inflammatory set point of the lung and alter the responsiveness to long fibers.

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Workshop to Discuss a Proposed Protocol to Assess Asbestos-Related Risk - Response to Charge Questions

Topic Area 1: Interpretations of the epidemiology and toxicology literature.

1) For *lung cancer*:

A] Influence of fiber type: Please comment on the extent to which the epidemiology literature and mechanistic studies suggest that carcinogenic potency varies from one fiber type to the next (e.g., chrysotile versus amphibole fibers). How adequate is the information in the epidemiology literature for supporting dose-response analyses for different fiber types? Specifically, to what extent do you think the proposed risk coefficients in Table 6-29 are supported by the epidemiology literature?

I concur that the epidemiology literature and mechanistic studies now strongly suggest that the carcinogenic potency varies between fiber types. With respect to commercially used asbestos products, the research supports the carcinogenic potency as being: crocidolyte > amosite >> chrysotile The recent review done by Hodgson and Darton and the analysis prepared by Drs. Berman and Crump provide two approaches to assessing the relative potency of fiber types with similar outcomes. The epidemiologic data is now sufficient to support developing different risk coefficients for different fiber types. The coefficients shown on Table 6-29 are supported by the literature but are conservative. If the analysis done by Hodgson and Darton were used, it would result in larger differences in the risk coefficients than shown in Table 6-29.

B] Influence of fiber length: Please comment on the extent to which the epidemiology literature and mechanistic studies suggest that carcinogenic potency varies with fiber length. How adequate is information in the epidemiology literature for supporting dose-response analyses for different fiber lengths? In general, is it appropriate to assess cancer risks using an exposure index (see Equation 7.13) that is weighed heavily by fibers longer than 10 micrometers (µm)? (Note: Topic area 2 includes more detailed questions on the proposed exposure index.)

The epidemiology and mechanistic literature shows that the carcinogenic potential of asbestos is strongly correlated with fiber length. There is sufficient literature to support the development of dose-response relationships for different fiber lengths. The mechanistic literature shows that fibers less than 10-15 microns in length are cleared by macrophage action. The epidemiology literature supports the conclusion that the longer the fiber, the greater the carcinogenic potential, with fibers longer than 20 microns in length carrying most of the associated risk for carcinogenicity. Based on the additional studies generated over the past 15 years, it would now be appropriate to develop cancer risk estimates that are heavily weighted toward fibers longer than 10 or 20 microns.

C] To what extent do animal studies (e.g., studies by Davis and other researchers) suggest that carcinogenic potency varies with fiber type and fiber length?

Animal studies also suggest that carcinogenic potency varies with fiber type and fiber length, although the differences are often less than that suggested by human epidemiologic studies. This difference is likely due to the fact that animal studies are commonly done using extremely high doses (often given by injection or instillation) and shorter periods of observation (limited by the animal's life span). These differences have the effect of removing fiber durability and clearance as substantial factors in determining carcinogenic risk. Thus, differences in carcinogenic potency between fibers based on fiber durability are not adequately evaluated in animal studies. In spite of this, animal work in general supports the concept that carcinogenic potency varies with both fiber type and fiber length.

D] Please comment on the extent to which carcinogenic potency is a function of fiber properties (e.g., diameter, aspect ratio, surface properties) other than fiber type and fiber length. How

adequate is information in the epidemiology or toxicology literature for supporting these other properties into dose-response analyses?

Fiber diameter is an important element in carcinogenic potency probably by influencing the ability of the fiber to be inhaled into the deep lung. The recommendation by Berman and Crump that risk assessments should be focused on fibers with diameters of 0.5 microns or less is reasonable. Aspect ratio does not appear to be a factor in determining carcinogenic risk. Aspect ratio is a valuable function in characterizing fibers from other inhaled materials, but there is no evidence that aspect ratio is an important factor in predicting fiber toxicity. There is some evidence that other fiber characteristics, which include surface properties or chemical composition, may influence carcinogenic potential although this has not yet been sufficiently defined to be used in developing specific risk estimates. The current epidemiology and toxicology literature would support using fiber diameter as an important factor in determining carcinogenic potency, but would not support using aspect ratio as a factor, and is insufficient to develop specific risk estimates for other fiber properties.

One factor not adequately considered in the current document is the interrelationship between smoking and asbestos exposure in causation of lung cancer. Many historical studies were not appropriately controlled for smoking. Smoking is a higher risk factor for causation of cancer than is asbestos exposure and thus can easily confound risk estimates that focus only on asbestos exposure. The epidemiologic literature assessing the ability of asbestos exposure to contribute to cancer causation in the absence of smoking is weak. Another important issue in developing correct estimates for asbestos exposure contribution to lung cancer risk is whether or not asbestosis is required before cancer risk is elevated. There is a substantial body of literature suggesting that formation of asbestosis is required before asbestos exposure will increase lung cancer risk.

2) For mesothelioma:

A] Influence of fiber type: Please comment on the extent to which the epidemiology literature and mechanistic studies suggest that carcinogenic potency varies from one fiber type to the next (e.g., chrysotile versus amphibole fibers). How adequate is the information in the epidemiology literature for supporting dose-response analyses for different fiber types? Specifically, to what extent do you think the proposed risk coefficients in Table 6-29 are supported by the epidemiology literature?

My comments for mesothelioma are similar to those for lung cancer. The carcinogenic potency varies between fiber types. The epidemiologic literature shows a much larger difference in carcinogenic potential (based on fiber type) for mesothelioma than for lung cancer. The risk coefficients shown in Table 6-29 are conservative estimates based on current literature. A critical question not fully resolved by current literature is whether common human occupational exposures to chrysotile result in a low risk of mesothelioma or whether such chrysotile exposure carries no risk. It is possible that amphibole contaminants in chrysotile (commonly tremolite) create the low level risk of mesothelioma recorded in "chrysotile only cohorts." Most mesotheliomas found in chrysotile exposed cohorts are associated with the mining environment. MacDonald and colleagues have suggested that the mesothelioma risk in chrysotile mining cohorts is primarily associated with tremolite contamination. Based on current literature, I would concur that the conservative approach would be to use risk coefficients for mesothelioma such as those proposed in Table 6-29.

B] Influence of fiber length: Please comment on the extent to which the epidemiology literature and mechanistic studies suggest that carcinogenic potency varies with fiber length. How adequate is information in the epidemiology literature for supporting dose-response analyses for different fiber lengths? In general, is it appropriate to assess cancer risks using an exposure index (see Equation 7.13) that is weighed heavily by fibers longer than 10 micrometers (μm)? (Note: Topic area 2 includes more detailed questions on the proposed exposure index.)

I concur with the assessment by Berman and Crump that longer fibers carry the primary risk for development of mesothelioma. It is appropriate to use exposure indices heavily weighted for fibers longer than 10 microns (or 20 microns). Fibers less than 5 microns in length have not been shown to carry significant potency.

C] To what extent do animal studies (e.g., studies by Davis and other researchers) suggest that carcinogenic potency varies with fiber type and fiber length?

Animal studies, in general, support that there are differences in carcinogenic potency with fiber type and fiber length. Depending on study design, those differences may be under-estimated or not present due to the dose and/or route of administration of the asbestos and due to the shorter duration of animal studies. The effects of fiber durability in determining carcinogenic potency are not adequately assessed in animal studies.

D] Please comment on the extent to which carcinogenic potency is a function of fiber properties (e.g., diameter, aspect ratio, surface properties) other than fiber type and fiber length. How adequate is information in the epidemiology or toxicology literature for supporting these other properties into dose-response analyses?

Carcinogenic potency has clearly been shown to be a function of fiber diameter which influences the respirability of the fibers. There is no data associating aspect ratio with carcinogenic potency other than its ability to identify a fiber as opposed to a particle. Other factors such as surface property and chemical composition likely play an effect, but this is not adequately defined by current literature. For example, Faux et al. (2001) showed using rat pleural mesothelial cells that crocidolyte had an impact on growth factor expression not seen with chrysotile and which was removed by milling the crocidolyte. I would expect mechanistic studies to eventually define chemical or surface characteristics of fibers which could be included in risk estimates.

3) To what extent are the exposure estimates documented in the asbestos epidemiology literature reliable?

Most of the asbestos epidemiology literature contains relatively crude estimates of exposure. Most estimates are qualitative and, at best, contain only intermittent assessments of exposure levels under specific work conditions. Even in those cases, exposure conditions are not generally well characterized as to fiber type, fiber length, or fiber diameter. The exposure estimates in the epidemiology literature are adequate for general conclusions but do not commonly allow rigorous comparison between studies. It would be advisable to recommend new criteria for assessing exposures which would include time-weighted exposure conditions and greater characterization of the fibers, including a more complete assessment of fiber length and fiber diameter distributions.

Topic Area 2: The proposed exposure index.

4) The proposed exposure index does not include contributions from fibers shorter than 5 μm. Please comment on whether the epidemiology and toxicology literature support the conclusion that asbestos fibers shorter than 5 μm present little or no carcinogenic risk.

The epidemiology and toxicology literature support the conclusion that fibers shorter than 5 microns in length do not significantly contribute to carcinogenic risk. There are sufficient epidemiologic studies at the present time to exclude fibers shorter than 5 microns in length from carcinogenic risk estimates for asbestos exposures.

5) The proposed exposure index is weighed heavily by fibers longer than 10 μm. Specifically, Equation 7.13 suggests that the carcinogenic potency of fibers longer than 10 μm is more than 300 times greater than that of fibers with lengths between 5 and 10 μm. How consistent is this difference in carcinogenic potency with the epidemiology and toxicology literature?

The fiber length coefficients used in Equation 6.7 and Equation 7.13 are consistent with the epidemiology and toxicology literature.

6) Please explain whether the proposed exposure index will allow meaningful comparisons between current environmental exposures to asbestos and historical exposures to asbestos that occurred in the work place.

The proposed exposure index will be somewhat difficult to apply to historical exposures in the workplace because data regarding fiber length and width characteristics are not consistently available in that literature. However, many reasonable assumptions can be made based on known fiber characteristics from different products. Use of the proposed exposure index should enable a re-evaluation of historical workplace exposures and may help reconcile some of the unexplained risk differences between various workplace environments. Changing to a new exposure index will lead to problems in comparing to historical data, but this should not inhibit moving to a more correct exposure index. One problem not adequately considered in the current document is the relationship of smoking and asbestos exposure in lung cancer causation. When considering comparisons of current environment conditions to historic conditions, one must also recognize that there are major changes in the smoking characteristics of today's workers. This will confound interpretation of risk estimates related to asbestos exposures when comparisons are done to historical studies.

Topic Area 3: General questions.

7) The proposed risk assessment approach assigns carcinogenic potency to individual fibers and to cleavage fragments (or Abundles that are components of more complex structures@). Please comment on whether cleavage fragments of asbestos are as toxicologically significant as fibers of the same size range.

My interpretation of the existing literature is that cleavage fragments of asbestos are toxicologically significant only if the fragments remain of sufficient length (10-20 microns or longer). I am aware of no data showing that short cleavage fragments of asbestos show carcinogenic potential.

8) Please comment on whether the proposed cancer assessment approach is relevant to all amphibole fibers or only to the five types of amphibole fibers (actinolite, amosite, anthophyllite, crocidolite, tremolite) designated in federal regulations.

It is my general assumption that the proposed cancer assessment approach would be relevant to all amphibole fibers, however, there is rigorous data only on a limited number of amphibole types – most of the data is focused on crocidolyte, amosite and tremolite.

9) The review document recommends that asbestos samples be analyzed by transmission electron microscopy (TEM) and count only those fibers (or bundles) longer than 5 μm. Such counting practices will provide no information on the amount of asbestos fibers shorter than 5 μm. To what extent would data on shorter fibers in samples be useful for future evaluations (e.g., validation of the cancer risk assessment methodology, assessment of non-cancer endpoints)?

Based on current literature, I would not expect counting asbestos fibers shorter than 5 microns in length to significantly enhance one's ability to validate cancer risk assessment methodology or known cancer endpoints. It is, however, difficult to make firm statements about data one does not have. The critical question is the cost of including short fiber counts vs. the potential future value of the data. If costs were low, I would include such counts. The current data do not support including counts of short asbestos fibers at a high economic cost.

10) The proposed risk assessment methodology suggests that exposure estimates should be based only on fibers longer than 5 μm and thinner than 0.5 μm. Is this cut-off for fiber diameter appropriate?

The use of counting methodology identifying only fibers longer than 5 microns in length and thinner than 0.5 microns in width is appropriate. This proposed change in methodology would be a substantial advance over the current use of a 3:1 aspect ratio.

11) Discuss whether the proposed cancer assessment approach, as a whole, is a reasonable evaluation of the available health effects data. What aspects of the proposed cancer assessment approach, if any, are inconsistent with the epidemiology or toxicology literature for asbestos?

The proposed cancer assessment approach is consistent with the epidemiology and toxicology literature for asbestos. My primary concerns relate to the absence of an adequate assessment of the confounding impact of smoking on lung cancer risk assessments and the absence of evaluating the role of asbestosis as a factor in determining lung cancer risk. The epidemiology literature shows that both of the above factors are major components in determining lung cancer risk in asbestos exposed cohorts. Neither of these factors have been clearly shown to have a linear correlation with asbestos exposure alone. Table 8-xxx on page 8-10 makes an attempt to assess smoking impact on both chrysotile and amphibole exposures. This assessment should be expanded and internal inconsistencies in the table resolved. Duration and intensity of smoking need to be more fully characterized. Looking at Table 8-xxx, why would a male nonsmoker who is not exposed to an amphibole have a 4 times higher lung cancer risk than a male nonsmoker not exposed to chrysotile?

12) Section 8.2 of the review document presents three options for assessing cancer risks from asbestos exposure. Please comment on the technical merit of the proposed risk assessment options.

All three proposed options have significant limitations. The use of a risk table is simpler for general use but is limited by factors such as the assumption of a constant exposure in both intensity and fiber characteristics. It is also limited by crude grouping with other characteristics such as smoking. Intensity and duration of smoking are also huge factors that modify the risk assessment. I would, in general, favor estimating risk using a unit risk factor if this approach were adequately developed and expanded, particularly if this unit factor could be accurately integrated with other major factors in cancer causation such as smoking, other exposures, and the formation of asbestosis.

Topic Area 4: Development of Conclusions and Recommendations

My initial recommendations are included in the previous comments.

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Response to the Charge Questions

This is a very interesting and a very complex risk assessment. I am in support of what the authors and the agency are attempting to due. The question is whether relevant analysis and review can be accomplished in the short time period we have. I have restricted myself to the area of epidemiological data and the quantitative models being used with this data.

The general comments I have so far are as follows.

Models:

For both lung cancer and mesothelioma, two specific risk models are used. These models are applied to the fitting of grouped epidemiological data using Poisson regression. The models appear to describe the epidemiological data in a reasonable manner. I have several questions concerning the adequacy of these models and the impact they make on the final risk estimates.

For lung cancer, a simple relative risk model using cumulative exposure is used. For this type of data, one often sees the estimation of internal rates without the need of incorporating external lung cancer mortality rates. The authors are not clear as to why they prefer the use of external rates followed by an estimation of the alpha parameter, which allows an adjustment for the difference between the background lung cancer rates of the cohort and those of the general population.

Another issue is the choice of a linear relationship of cumulative exposure to risk as opposed to the separation into exposure rates and duration of exposure. For example, the lung cancer and cigarette smoking modeling of Peto and Doll find a linear quadratic effect of smoking rate with a 4^{th} to 5^{th} power of duration of smoking.

For mesothelioma, the model assumes that risk is proportional to cumulative exposure. Further, the effect is proportional to the 3^{rd} power of time since first exposed, with a ten-year latency. Again, the question is whether this model is the appropriate one for dealing with the various cohorts that report mesothelioma.

It may be that the quantitative results of the overall analysis of the epidemiological data are fairly robust with respect to these two cancer risk models. If this is not the case, then it is important to understand the impact of the quantitative risk results on the choice of these two very specific cancer models.

Risk Estimates:

The optimized risk coefficients for pure fiber types are given in Tables 6-29. Table 6-30 gives conservative values. It would be more informative if simulations incorporating the estimated model uncertainties could be carried out and used in place of table 6-30.

Topic Area 1.

1) Lung Cancer: At this point in my review I believe that the epidemiological data is supporting the questions raised in A) & B). I have not reviewed the animal data so I have no answer for C). Based on the human data I do not believe we know beyond fiber type and length as in D). But I am still looking at this question.
2) Mesothelioma: Same answers as with Lung cancer.
3) Not my area of expertise.

Topic Area 2-4.

I hope to have answers for a number of these questions as we get closer to the meeting time.

In general, to appropriately answer many of the specific charge questions will necessarily require reviewing a large amount primary research papers.

CHARGE QUESTIONS

Topic Area 1:

Interpretations of the epidemiology and toxicology literature.

1)

For *lung cancer*:

A] Influence of *fiber type*: Please comment on the extent to which the epidemiology literature and mechanistic studies suggest that carcinogenic potency varies from one *fiber type* to the next (e.g., chrysotile versus amphibole fibers). How adequate is the information in the epidemiology literature for supporting dose-response analyses for different *fiber types*? Specifically, to what extent do you think the proposed risk coefficients in Table 6-29 are supported by the epidemiology literature?

Answer: A meta type analysis was used to group studies of similar fiber type from the epidemiological literature. These studies appeared to be fairly heterogeneous and the weighting factors were modified by incorporating ad hoc measures of study quality which resulted in increased confidence intervals. The resulting weighted potency estimates with confidence intervals by fiber type were not specifically given. However there did appear to be a difference in potency by fiber type (pure chrysotile v. amphiboles) although they may not necessarily be statistically different.

They linear RR model fits the South Carolina (Chyrsotile) example very well while it was necessary to include an additional parameter (alpha) in order to fit the Wittenoom miner data (crocidolite) which continued to appear to be nonlinear. The reason for assuming that the spontaneous rate for lung cancer in this cohort being twice that expected is not clear other than the data is poorly fit

without the additional parameter. How well the linear model describes the data for other cohorts is not described with respect to residual patterns.

The risk estimates in Table 6-29 depend upon the concept that potency for a given asbestos type depends primarily length and diameter of the fibers. This is the result of animal inhalation studies (Davis et al.) which are assumed to directly apply to man. If this is correct the one can say that the Table 6-29 results are not inconsistent with the epidemiological data. The estimates can not apparently be derived solely from epidemiological findings.

B] Influence of *fiber length*: Please comment on the extent to which the epidemiology literature and mechanistic studies suggest that carcinogenic potency varies with *fiber length*. How adequate is information in the epidemiology literature for supporting dose-response analyses for different *fiber lengths*? In general, is it appropriate to assess cancer risks using an exposure index (see Equation 7.13) that is weighed heavily by fibers longer than 10 micrometers (μm)? (Note: Topic area 2 includes more detailed questions on the proposed exposure index.)

Answer: As stated above the epidemiology literature does not provide adequate information on fiber length and potency. Using the animal data to develop the exposure index 7.13 and applying it to the epidemiology data does not change greatly the forest plots given in Figures 6-3 and 6-4 with regard to heterogeneity.

C] To what extent do animal studies (e.g., studies by Davis and other researchers) suggest that carcinogenic potency varies with *fiber type* and *fiber length*?

Answer: It would be useful to have Appendix C available to answer this question. Based on the information from the animal studies it is clear that potency varies with fiber type and length.

D] Please comment on the extent to which carcinogenic potency is a function of fiber properties (e.g., diameter, aspect ratio, surface properties) *other than* fiber type and fiber length. How adequate is information in the epidemiology or toxicology literature for supporting these other properties into dose-response analyses?

Answer: The epidemiology data does not provide adequate information on these measures with regard to cancer risk.

2)

For *mesothelioma*:

A] Influence of *fiber type*: Please comment on the extent to which the epidemiology literature and mechanistic studies suggest that carcinogenic potency varies from one *fiber type* to the next (e.g., chrysotile versus amphibole fibers). How adequate is the information in the epidemiology literature for supporting dose-response analyses for different *fiber types*? Specifically, to what extent do you think the proposed risk coefficients in Table 6-29 are supported by the epidemiology literature?

Answer: The epidemiological data is somewhat limited for mesothelioma, however the available data shows a strong difference in potency by fiber type. Because of the limited data, potency is necessarily assumed to be linear in concentration. The model which assumes a third power of lagged duration since exposure is not specifically used. The exact method employed by the authors is as I understand a nonparametric description of time since exposure component. This is a reasonable approach which should be better than the parametric approach. The data is too limited to determine whether the parametric model is realistic. The coefficients in Table 6-29 are reasonable but because of limited data I have less confidence than for the lung cancer values.

B] Influence of *fiber length*: Please comment on the extent to which the epidemiology literature and mechanistic studies suggest that carcinogenic potency varies with *fiber length*. How adequate is information in the epidemiology literature for supporting dose-response analyses for different *fiber lengths*? In general, is it appropriate to assess cancer risks using an exposure index (see Equation 7.13) that is weighed heavily by fibers longer than 10 micrometers (μm)? (Note: Topic area 2 includes more detailed questions on the proposed exposure index.)

Answer: As with lung cancer the epidemiological data are insufficient to estimate potency based on fiber length.

C] To what extent do animal studies (e.g., studies by Davis and other researchers) suggest that carcinogenic potency varies with *fiber type* and *fiber length*?

Answer: The Davis data does show length and type differences but only a total of 13 tumors are available from the 18 experimental groups for the estimation of the differences. There are therefore large uncertainties which are not estimated and incorporated into the model. There seems to be the assumption that the fiber length and width effects for lung cancer are similar for mesothelioma.

D] Please comment on the extent to which carcinogenic potency is a function of fiber properties (e.g., diameter, aspect ratio, surface properties) *other than* fiber type and fiber length. How adequate is information in the epidemiology or toxicology literature for supporting these other properties into dose-response analyses?

Answer: The epidemiology data does not provide adequate information on these measures with regard to mesothelioma risk.

3)

To what extent are the exposure estimates documented in the asbestos epidemiology literature reliable?

Answer: I am not qualified to comment on the industrial hygiene aspect of the epidemiological studies. However, it seems that the comparisons between lung burden and air concentrations are reasonable given assumptions concerning retention of the fibers.

Topic Area 2:

The proposed exposure index.

4)

The proposed exposure index does not include contributions from fibers shorter than 5 μm. Please comment on whether the epidemiology and toxicology literature support the conclusion that asbestos fibers shorter than 5 μm present little or no carcinogenic risk.

Answer: The animal data is clear that there is no cancer risk for exposures to fibers less than 5um. The epidemiological data provides no information on this issue due to the mixed fiber sizes in the occupational exposures. The epidemiological data is not inconsistent with this animal finding.

5)

The proposed exposure index is weighed heavily by fibers longer than 10 μm. Specifically, Equation 7.13 suggests that the carcinogenic potency of fibers longer than 10 μm is more than 300 times greater than that of fibers with lengths between 5 and 10 μm. How consistent is this difference in carcinogenic potency with the epidemiology and toxicology literature?

Answer: The analysis of the animal inhalation data produces this finding. What is not given is the statistical uncertainty of this result. Also there may be physiological differences between rat and man that suggests that the species extrapolation may not be valid. This I simply do not know would like to see a discussion of the issue.

6)

Please explain whether the proposed exposure index will allow meaningful comparisons between current environmental exposures to asbestos and historical exposures to asbestos that occurred in the work place.

Answer: Since the historical exposures are the basis for the risk models it should be reasonable to estimate risk from current environmental exposures. One issue I have is whether or not the simple linear assumptions are appropriate for relatively low current exposures. If not the environmental risks may be over estimated. There is simply no way of knowing this unless mechanistic data can provide an answer.

Topic Area 3:

General questions.

7)

The proposed risk assessment approach assigns carcinogenic potency to individual fibers and to cleavage fragments (or Abundles that are components of more complex structures@). Please comment on whether cleavage fragments of asbestos are as toxicologically significant as fibers of the same size range.

Answer: At this point I have no opinion on the concept of cleavage fragments.

8)

Please comment on whether the proposed cancer assessment approach is relevant to all amphibole fibers or only to the five types of amphibole fibers (actinolite, amosite, anthophyllite, crocidolite, tremolite) designated in federal regulations.

Answer: I simply do not know enough about asbestos fibers to say whether an extrapolation beyond the five types is reasonable. I feel that the risk estimates using the types reported in the animal and epidemiology data are reasonable.

9)

The review document recommends that asbestos samples be analyzed by transmission electron microscopy (TEM) and count only those fibers (or bundles) longer than 5 μm. Such counting practices will provide no information on the amount of asbestos fibers shorter than 5 μm. To what extent would data on shorter fibers in samples be useful for future evaluations (e.g., validation of the cancer risk assessment methodology, assessment of non-cancer endpoints)?

Answer: Obviously data on shorter fibers would be useful in future studies in order to confirm the currently proposed risk analysis.

10)

The proposed risk assessment methodology suggests that exposure estimates should be based only on fibers longer than 5 μm and thinner than 0.5 μm. Is this cut-off for fiber *diameter* appropriate?

Answer: Based upon the limited animal and epidemiological data this seems reasonable to me. If this is not correct the contribution to risk for fibers outside this range would be very small at best.

11)

Discuss whether the proposed cancer assessment approach, as a whole, is a reasonable evaluation of the available health effects data. What aspects of the proposed cancer assessment approach, if any, are inconsistent with the epidemiology or toxicology literature for asbestos?

Answer: The only issue I have is whether effects are proportional to exposure. The alternative approach has been to consider the specific 2-stage model of Moolgavkar. I would also be interested in seeing an application of the more traditional Armitage –Doll multistage model as has been used recently with diesel exhaust and lung cancer.

12)

Section 8.2 of the review document presents three options for assessing cancer risks from asbestos exposure. Please comment on the technical merit of the proposed risk assessment

options.

Answer: I prefer the second method since it is an estimate of the actual risk for a individual classified by gender and smoking status. It should be extend to cover scenarios of varying or terminated exposures and smoking status. The other approaches are crude general estimates of increased risk.

Topic Area 4:

Development of Conclusions and Recommendations

At the end of the workshop, the peer consultants will be asked to draft conclusion statements identifying their most notable findings on the proposed methodology. As a prelude to developing these statements, the peer consultants are invited to provide any additional comments or concerns, both strengths and weaknesses, on topics not specifically addressed in the previous charge questions. After completing the discussions the peer consultants will prepare their conclusions, and they will also be asked to develop recommendations for how EPA can improve the methodology. Please note that, although recommendations for future research projects are welcomed, the focus of this workshop is on the proposed risk assessment methodology and how it may be used to support decisions at asbestos-contaminated sites.

Answer: For both lung cancer and mesothelioma, two specific risk models are used. These models are applied to the fitting of grouped epidemiological data in a Poisson regression manner. The models appear to describe the epidemiological data in a reasonable manner. I have several questions concerning the adequacy of these models and the impact they make on the final risk estimates.

For lung cancer, a simple relative risk model using cumulative exposure is used. For this type of data, one often sees the estimation of internal rates without the need of incorporating external lung cancer mortality rates. The authors are not clear as to why they prefer the use of external rates followed by an estimation of the alpha parameter, which allows an adjustment for the difference between the background lung cancer rates of the cohort and those of the general population.

Another issue in the model is the choice of cumulative exposure as opposed to the separation into exposure rates and duration of exposure. For example, the lung cancer and cigarette smoking modeling of Peto and Doll find a relationship of a linear quadratic effect of smoking rate and a 4^{th} to 5^{th} power of duration of smoking.

For mesothelioma, the model assumes that risk is proportional to cumulative exposure. Further, the effect is proportional to the 3^{rd} power of time since first exposed, with a ten-year latency. Again, the question is whether this model is the appropriate one for dealing with the various cohorts that report

mesothelioma.

It may be that the quantitative results of the overall analysis of the epidemiological data are fairly robust with respect to these two cancer risk models. If this is not the case, then it is important to understand the impact of the quantitative results on the choice of these two specific cancer models.

Finally, as I mentioned in response to question 11, I would be interested in the use of the multistage model as it describes degrees of initiation and promotion. Also the meta-analyses used appear to correctly use random effects model due to the heterogeneity of the studies. Publication bias was not considered i.e. funnel plots etc.

References

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Responses to Charge Questions

Topic Area 1: Interpretations of the epidemiology and toxicology literature.

1) For *lung cancer*:

A] Influence of *fiber type*: Please comment on the extent to which the epidemiology literature and mechanistic studies suggest that carcinogenic potency varies from one *fiber type* to the next (e.g., chrysotile versus amphibole fibers). How adequate is the information in the epidemiology literature for supporting dose-response analyses for different *fiber types*? Specifically, to what extent do you think the proposed risk coefficients in Table 6-29 are supported by the epidemiology literature?

Response: The epidemiology literature, controlled animal inhalation exposure studies, and mechanistic studies cited by Berman and Crump are among the most appropriate for representing the differential potency of chrysotile and amphibole fibers for causing increased rates of lung cancer. The K_L coefficients listed in Table 6-29 represent the best estimates currently available and are based on a reasonable interpretation of the available literature.

B] Influence of *fiber length*: Please comment on the extent to which the epidemiology literature and mechanistic studies suggest that carcinogenic potency varies with *fiber length*. How adequate is information in the epidemiology literature for supporting dose-response analyses for different *fiber lengths*? In general, is it appropriate to assess cancer risks using an exposure index (see Equation 7.13) that is weighed heavily by fibers longer than 10 micrometers (μm)? (Note: Topic area 2 includes more detailed questions on the proposed exposure index.)

Response: The epidemiology literature and controlled animal exposure studies that have provided adequate data on fiber length and diameter distributions in the exposure atmospheres and/or delivered tissue dose clearly demonstrate that fiber length is a critical determinant of carcinogenic potency. The conclusion was firmly supported by the recent ATSDR Workshop Report: "Report on the Expert Panel on Health Effects of Asbestos and Synthetic Vitreous Fibers: The Influence of Fiber Length" (Draft Final of 12/23/02). The epidemiology literature supporting exposure-response analyses for different ranges of fiber lengths is still quite sparse, but a formulation that is weighted heavily for fibers longer than 10 μm is certainly justified. It may need further refinement in the future (e.g., giving greater weight to fibers longer than 20 μm) but the

proposed formulation is clearly superior to the pre-existing formulation that makes us distinction beyond length > 5 μm.

C] To what extent do animal studies (e.g., studies by Davis and other researchers) suggest that carcinogenic potency varies with *fiber type* and *fiber length*?

Response: The controlled exposure studies in animals (rats) by the John Davis group in Edinburgh and the Chris Wagner group in Penarth are among the most informative concerning the influence of fiber type (e.g., amosite, other amphiboles, chrysotile, and erionite) and fiber size (length and width), as summarized by Lippmann (1988, 1994), and the discussion Berman and Crumps document would have been strengthened by a more complete reference to the analyses cited in those papers.

D] Please comment on the extent to which carcinogenic potency is a function of fiber properties (e.g., diameter, aspect ratio, surface properties) *other than* fiber type and fiber length. How adequate is information in the epidemiology or toxicology literature for supporting these other properties into dose-response analyses?

Response: Carcinogenic potency can be influenced by fiber diameter and surface properties, but aspect ratio, per se, has no biological significance. Fiber diameter can be influential in two different ways. One is that fiber diameter is closely related to aerodynamic diameter, which in turn largely determines deposition probabilities in the conductive airways and lung parenchyma. The mucociliary and macrophage mediated clearance pathways and residence times at deposition sites are determinants of toxic potential. The other way that fiber diameter affects carcinogenic potency is that very thin fibers appear to be able to penetrate through pores in the respiratory epithelium and thereby gain more ready access to interstitial lung cells and lymphatic drainage pathways.

Surface properties can affect dissolution rates and thereby biopersistence, the generation of reactive oxygen species, and the release of mediators from lung cells, and all of these factors may be important to carcinogenic potency for lung cancer.

Aspect ratio, i.e., the ratio of fiber length to fiber width, has no known biological significance in and of itself. Fiber lengths and widths themselves are the critical determinants of toxicity, as discussed above and in the Berman and Crump document. The information in the epidemiology and toxicology literature

provides quite adequate support for these conclusions in regard to exposure-response relationships for lung cancer.

2) For *mesothelioma*:

A] Influence of *fiber type*: Please comment on the extent to which the epidemiology literature and mechanistic studies suggest that carcinogenic potency varies from one *fiber type* to the next (e.g., chrysotile versus amphibole fibers). How adequate is the information in the epidemiology literature for supporting dose-response analyses for different *fiber types*? Specifically, to what extent do you think the proposed risk coefficients in Table 6-29 are supported by the epidemiology literature?

Response: The epidemiology literature, controlled animal inhalation exposure studies, and mechanistic studies cited by Berman and Crump are among the most appropriate for representing the differential potency of various fiber types for causing mesothelioma. It is clear that, in terms of potency, erionite fibers > amphibole asbestos fibers > chrysotile fibers for given ranges of fiber diameter and fiber length. Table 6-29 provides coefficient estimates for mesothelioma (K_M) associated with amphiboles and chrysotile fibers that are based on an incomplete evaluation of the relevant literature, and need to be adjusted to reflect the influence of fiber length, as discussed below.

B] Influence of *fiber length*: Please comment on the extent to which the epidemiology literature and mechanistic studies suggest that carcinogenic potency varies with *fiber length*. How adequate is information in the epidemiology literature for supporting dose-response analyses for different *fiber lengths*? In general, is it appropriate to assess cancer risks using an exposure index (see Equation 7.13) that is weighed heavily by fibers longer than 10 micrometers (μm)? (Note: Topic area 2 includes more detailed questions on the proposed exposure index.)

Response: The epidemiology literature and contolled animal inhalation exposure studies clearly indicate that fiber length is a critical determinant of potential to cause mesothelioma. As discussed by Lippmann (1988), short amphibole fibers (< 5 μm long) are essentially innocuous, in both studies in human lungs (Timbrell, 1983) and rats (Davis, 1986), and the critical fibers for mesothelioma induction are those between 5 and 10 μm in length. Fibers longer than 10 μm are not effectively translocated to the mesothelioma. Thus, for

mesothelioma, it is not appropriate for the exposure index to be heavily weighted for fibers longer than 10 µm.

C] To what extent do animal studies (e.g., studies by Davis and other researchers) suggest that carcinogenic potency varies with *fiber type* and *fiber length*?

Response: Potency for mesothelioma induction clearly varies with both fiber length and fiber type. As noted above (in 2B), the critical fiber lengths are those between 5 and 10 µm, and, as noted (in 2A), fiber type is also a critical determinant, with erionite > amphibole > chrysotile. In fact, as noted by Lippmann (1994), the mesothelioma associated with exposure to commercial chrysotile are most likely due to the tremolite component of the commercial chrysotile.

D] Please comment on the extent to which carcinogenic potency is a function of fiber properties (e.g., diameter, aspect ratio, surface properties) *other than* fiber type and fiber length. How adequate is information in the epidemiology or toxicology literature for supporting these other properties into dose-response analyses?

Response: As noted in 1D above, surface properties can affect dissolution rates and thereby biopersistence, the generation of reactive oxygen species, and the release of mediators from lung cells, and all of these factors may be important for carcinogenic potency. Accessible internal surfaces within fibers, such as that characteristic for erionite fibers, may account for the exceptional potency of erionite for producing mesothelioma in rats (Wagner et al., 1985) and humans (Baris et al., 1987).

As noted in 1D above, aspect ratio, per se, has no influence on carcinogenic potency.

3) To what extent are the exposure estimates documented in the asbestos epidemiology literature reliable?

Response: The exposure estimates documented in the asbestos epidemiology literature clearly have weaknesses associated with: a) the different exposure indices measured (total dust count, PCM counts of fibers > 5 µm in length that could not detect very thin fibers and could not discriminate among fiber types, SEM, and TEM); b) the lack of information on fiber length and fiber diameter distributions in the PCM, SEM and TEM measurements; c) the relatively few long fibers seen in SEM and TEM measurements, resulting

in limited statistical validity for long-fiber counts. A significant contribution made in the Berman and Crump document was its ability to locate, access, analyze, and document better fiber distribution data from archived sampling filters collected during past epidemiology and controlled animal inhalation studies.

4) The proposed exposure index does not include contributions from fibers shorter than 5 μm. Please comment on whether the epidemiology and toxicology literature support the conclusion that asbestos fibers shorter than 5 μm present little or no carcinogenic risk.

Response: The recent ATSDR Workshop Report: "Report on the Expert Panel on Health Effects of Asbestos and Synthetic Vitreous Fibers: The Influence of Fiber Length" (Draft Final of 12/23/02) clearly indicates that fibers shorter than 5 μm present little or no carcinogenic risk.

5) The proposed exposure index is weighed heavily by fibers longer than 10 μm. Specifically, Equation 7.13 suggests that the carcinogenic potency of fibers longer than 10 μm is more than 300 times greater than that of fibers with lengths between 5 and 10 μm. How consistent is this difference in carcinogenic potency with the epidemiology and toxicology literature?

Response: The heavy weighting of fibers > 10 μm in length is quite appropriate for risk assessments for lung cancer, as documented in the literature review provided by Berman and Crump. On the other hand, as noted in my response to charge question 2B), such weighting is not appropriate for risk assessments for mesothelioma, where the risk is most closely associated with fibers between 5 and 10 μm in length

6) Please explain whether the proposed exposure index will allow meaningful comparisons between current environmental exposures to asbestos and historical exposures to asbestos that occurred in the work place.

Response: The proposed exposure index is based largely on analyses of the past relationships between cancer incidence in asbestos exposed populations in the mines and mills in Quebec, a textile plant in South Carolina and crocidolite exposed workers at Wittenoom in Australia, and historic and retrospective analyses of the airborne fiber concentrations in those work environments. The extrapolation of that experience to the carcinogenic hazards associated with contemporary environmental exposures to people exposed to tremolite

fibers in Libby, Montana, various California communities around surface deposits of serpentine, people exposed to dust from the World Trade Center collapse in New York and New Jersey, and other places is reasonable and prudent insofar as the exposure concentrations in these communities are within about two orders of magnitude of those in the historic occupational cohorts.

7) The proposed risk assessment approach assigns carcinogenic potency to individual fibers and to cleavage fragments (or bundles that are components of more complex structures). Please comment on whether cleavage fragments of asbestos are as toxicologically significant as fibers of the same size range.

Response: The toxic potential of inhaled mineral and vitreous fibers has been shown to depend most strongly on fiber length, fiber diameter, and biopersistence. There is very little evidence that amphibole asbestos cleavage fragments in the fiber diameter and fiber length range of concern are less hazardous than comparably sized asbestiform fibers. In fact, the only directly relevant comparison, i.e., the Davis et al. (1991) comparative study of six tremolite asbestos samples (three asbestiform fibers, and three cleavage fragment dusts), which was discussed in some detail in the Berman and Crump document (pp. B-3 through B-10), showed that the risks from the tremolite cleavage fragments, when appropriately adjusted according to their protocol structure formulation, had quite comparable potency to the asbestiform tremolite.

8) Please comment on whether the proposed cancer assessment approach is relevant to all amphibole fibers or only to the five types of amphibole fibers (actinolite, amosite, anthophyllite, crocidolite, tremolite) designated in federal regulations.

Response: Since all amphibole asbestos fibers can be expected to be biopersistent and be found in diameters and lengths that are associated with cancer causation, there is no good reason, based on biology, to limit regulations to the five specific types now regulated.

9) The review document recommends that asbestos samples be analyzed by transmission electron microscopy (TEM) and count only those fibers (or bundles) longer than 5 μm. Such counting practices will provide no information on the amount of asbestos fibers shorter than 5 μm. To what extent would data on

shorter fibers in samples be useful for future evaluations (e.g., validation of the cancer risk assessment methodology, assessment of non-cancer endpoints)?

Response: Fibers shorter than 5 μm can contribute to asbestosis in occupationally exposed individuals (Lippmann, 1988). However, the asbestosis risk is not closely related to fiber number, but rather to fiber surface area. The counting of fibers < 5 μm in length would serve no purpose in cancer risk assessment, and asbestosis requires exposures to asbestos at concentrations far higher than any likely to be encountered in nonoccupational environments.

10) The proposed risk assessment methodology suggests that exposure estimates should be based only on fibers longer than 5 μm and thinner than 0.5 μm. Is this cut-off for fiber *diameter* appropriate?

Response: There is no good reason to exclude fibers between 0.5 μm and 1.5 μm in diameter (~ 5 μm in aerodynamic diameter) in a risk analysis for lung cancer. Such fibers can penetrate to small lung airways, and same asbestos minerals produce many fibers in this range of diameter (especially anthophyllite). On the other hand, there is little risk for mesothelioma for fibers thicker than 0.15 μm (Lippmann, 1988).

11) Discuss whether the proposed cancer assessment approach, as a whole, is a reasonable evaluation of the available health effects data. What aspects of the proposed cancer assessment approach, if any, are inconsistent with the epidemiology or toxicology literature for asbestos?

Response: The Berman and Crump cancer assessment approach is quite reasonable for lung cancer risk assessment. However, as discussed in my responses to charge questions 2B and 5, it is not optimized for mesothelioma risk assessment.

12) Section 8.2 of the review document presents three options for assessing cancer risks from asbestos exposure. Please comment on the technical merit of the proposed risk assessment options.

Response: The three different risk assessment options proposed by Berman and Crump are all usable, albeit with some variation in the convenience with which they can be applied. The easiest to use would be Option 2 (Risk Table), but as acknowledged by Berman and Crump, this could lead to errors for short-duration exposures.

For application of any of these options, reliance on Equation 7-13 may be appropriate for lung cancer risk estimation. However, it is almost certainly misleading for mesothelioma risk assessment, where its emphasis on fibers longer than 10 μm is not warranted.

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Timbrell V. 1983. Fibres and carcinogenesis. J. Occup. Health Sci. 3:3-12.

Wagner JC, Skidmore JW, Hill RJ, and Griffiths DM. 1985. Erionite exposure and mesothelioma in rats. Br. J. Cancer 51:727-730.

Some General Comments on the Berman and Crump Technical Support Document

This document needs a lot of editing for both technical content and organization. For example, there are numerous places where a statement in an earlier chapter relies on text in a later chapter. The text is overly encyclopedic and cites many papers whose relevance to the issues of concern in relation to the development of a better model for asbestos fiber risk assessment is not apparent. Also, there are indications of references to be supplied (see pp. 5.7, 5.8, and 5.10) as well as incomplete references in the reference list. Who is to do the needed work to make this document a better support for the recommendations offered? How much help for

this needed work is the responsibility of the Workshop's Peer Consultants? The merits of the basic formulations and recommendations of the Berman & Crump document should not be discarded because of the quite sloppy presentation in their document.

Some Specific Technical Comments on the Berman and Crump Document

1) Replace “dose-response“ with “exposure-response“ in all of the numerous places where the epidemiology and controlled animal inhalation exposure results are discussed.

2) Replace “asbestos-related risks“ with “asbestos fiber-related risks“. Nonfibrous asbestos dust exposures are a different issue.

3) The discussion of dust counts based on midget impinger samples on p. 4.6 needs to be clarified for most potential readers of this document.

4) Their reliance on Raabe (1984) for a discussion on the quantitative aspects of particle deposition, and of Figure 7-1 from that paper to illustrate it, is inappropriate as an up-to-date and authoritative reference. A more appropriate reference is ICRP Publication 66: Human Respiratory Tract Model for Radiological Protection, Ann. ICRP,Vol. 24, Nos. 1-3, 1994.

5) The 4th, 5th, and 6th bullets in Section 7.1.4 are wholly or partially incorrect statements.

6) The first paragraph on p. 7.16 misspells “mucus“ five times.

7) The last bullet on p. 7.18 indicates, incorrectly, that diffusional transport influences asbestos retention in the lung and other tissues.

8) There are various places where the authors have notes to themselves to reconsider or complete the text (see pp. 7.48 , 7.65, and 7.103).

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Preliminary Comments for Workshop on "Proposed Protocol to Assess Asbestos-Related Risk"

A. General Comments

In addition to responding to the 12 specific charge questions formulated by the U.S. Environmental Protection Agency I believe it is appropriate to respond to a more general over-arching question. Specifically, "Has the Agency, and its Contractor, reviewed all of the relevant information on the carcinogenic risks of asbestos and interpreted, synthesized and integrated the information in a scientifically adequate manner for regulatory decision making"? In the following comments I will address the over-arching question I have posed.

1. The material provided by the Agency as background material for the Workshop does not reflect a comprehensive and thorough review of the literature. Neither does the material provide a high degree of confidence that all the relevant literature has been reviewed, interpreted, synthesized and integrated in a scientifically sound manner that lends confidence to the finished product meeting the high standards required for use in regulatory decision making. Three primary documents were provided to the Panel in sequential fashion; (a) a document labeled, "Final Draft – Technical Support Document for a Protocol to Assess Asbestos-Related Risk" prepared by D.W. Berman and K. Crump dated September 4, 2001, (b) a document labeled "Final – Methodology for Conducting Risk Assessments at Asbestos Superfund Sites, Part 1: Protocol, Interim Version" prepared by D. W. Berman and K. Crump dated February 15, 1999, and (c) a document, EPA/600/8-84/003F, June 1986, Airborne Asbestos Health Assessment Update prepared under the auspices of the Environmental Criteria and Assessment Office, Office of Health and Environmental Assessment, Office of Research and Development, U.S. Environmental Protection Agency.

Taken in aggregate these documents do not represent an up-to-date summary of the voluminous literature available on the health effects of asbestos and, specifically, the lung cancer and mesothelioma risks of exposure to asbestos. The base document, "Airborne Asbestos Health Assessment Update" was prepared by an EPA contractor, Dr. William J. Nicholson, nearly two decades ago and reviewed at that time by the Environmental Health Committee of EPA's Science Advisory Board. In the intervening years, numerous additional papers on the health effects of asbestos, including new epidemiological analyses and mechanistic studies on the carcinogenicity of asbestos, have been published. New and improved analytical methods for characterizing exposure to asbestos have also been

developed and adopted.

The two other documents noted above are also dated. Despite the intervals from September 4, 2001 (the Support Document) and February 15, 1999 (the Methodology) to present, the documents remain "works in progress" with incomplete references and omissions. It is a challenge to the reader to follow the logic being used to synthesize very complex data sets into relative simple algorithms to describe exposure-response relationships for lung cancer and mesothelioma induction by exposure to different types of asbestos fibers with varying dimensions.

The apparent haphazard and protracted approach to developing a scientifically sound approach to characterizing the risks of asbestos exposure is clearly not related to this being a "back burner" issue. During the last two decades, the issue of asbestos-related health effects has received substantial attention in the courts and resulted in the bankruptcy of some 60 companies.

To get the "asbestos-risk characterization" train on the track, so to speak, the Agency might consider using an approach that has served the Agency well in dealing with the criteria air pollutants. That approach is multi-phased. In the first phase, a criteria document is prepared periodically for each criteria pollutant by the Agency's National Center for Environmental Assessment, Office of Research and Development, with input from knowledgeable scientists both from within and outside the Agency. These encyclopedic documents describing all that is currently known about the pollutant are reviewed by the Clean Air Scientific Advisory Committee (CASAC), a part of the Agency's Science Advisory Board. CASAC notifies the Administrator by a "closure letter" when it has reached a consensus that the criteria document provides a scientifically adequate review of all the available information in the pollutant.

In a second phase, the Agency's Office of Air Quality Planning and Standards, Office of Air and Radiation Programs, prepares a Staff Position Paper, that draws exclusively on information in the criteria document, to critically assess the information specifically germane to assessing the risks of exposure to the pollutant in question. The Staff Position Paper is also reviewed by CASAC and when a consensus is reached by the Committee that the document provides a scientifically adequate basis for regulatory decision making, a "closure letter" is issued to the Administrator. The agency then proceeds to use the resulting information to set National Ambient Air Quality Standards and take other regulatory actions.

The process described above is transparent, open, and engages the scientific community, interested parties and the public. The process is not without controversy. However, the open and

participatory nature of the process results in controversy focusing on scientific issues. Legislative mandates for review of criteria pollutants every five years have rarely been met. Nonetheless, steady progress has been made in reviewing new information on a regular schedule.

Without question, the Agency would benefit from having an up-to-date comprehensive review of the current state of knowledge on the health effects of asbestos. The credibility and scientific and public acceptance of the review would be enhanced by obtaining input from a number of knowledgeable scientists in addition to Drs. Berman and Crump and having rigorous peer review by the Agency's Science Advisory Board.

A subsequent risk assessment prepared using information included within the health assessment document would have enhanced credibility if it were based on the input of a number of knowledgeable scientists. This statement is not intended to question the credibility and scientific credentials of Drs. Berman and Crump who are clearly two of the world's experts on the subject at hand. Despite their credentials, I submit that involvement of other scientists in a participatory and transparent manner would enhance the scientific credibility and acceptance of the final product.

As a third step, it would be appropriate for the Agency to provide a brief document detailing how the asbestos risk assessment will be used by the Agency in fulfilling its regulatory and enforcement agenda. The present documents leave these important matters open to speculation. This includes the scientific reviewers who do not know how the science, the associated uncertainties and the various assumptions will be used. For some applications a high degree of uncertainty and the use of many assumptions may be scientifically defensible. For other applications, this may not be the case.

2. Using only the three documents provided, it is difficult to assess if all the relevant information on asbestos-related health risks has been considered. Without question, the 1984/1986 Assessment is out of date. Thus, attention focuses on the two other documents. The manner of presentation in these documents is such that I am uncertain if other knowledgeable scientists could reproduce the calculations and quantitative results. The basic assumptions used in the various calculations are not always clearly spelled out. This leads to uncertainties as to the linkages between the various tables and related text as the document builds to summary conclusions (Tables 6-29 and 6-30).

3. The documents in numerous places acknowledge the substantial uncertainty in developing quantitative estimates of exposure-response coefficients for various types of asbestos (with

varied size characteristics) producing lung cancer and mesothelioma. Nonetheless, these uncertainties are rarely quantified and are absent from the summary conclusions (Tables 6-29 and 6-30).

4. Two key inter-related uncertainties that are not adequately addressed in the documents relate to (a) the shape of the exposure-response relationship over the range of observations from epidemiological studies of occupationally exposed populations, and (b) the basis of extrapolation from observations at high levels of generally prolonged occupational exposure to much lower levels of environmental exposure. These issues have been a focus of attention in EPA's revised cancer risk assessment guidelines. It is of interest that the Agency's proposed revised cancer risk assessment guidelines are not even referenced in either document.

The proposed revised cancer risk assessment guidelines emphasize the importance of using a two-step process. First, characterize exposure-response relationships over the range where observations can be made. Then in a second step, extrapolate to lower exposure levels. Neither step is adequately documented in the material at hand. Intuitively, one would anticipate considerable variation in extrapolated risk at environmental levels of exposure. To the extent it is possible the uncertainty should be quantified.

5. During the last two decades substantial progress has been made in understanding the mechanisms by which fibers may induce cancer. The present documents focus on advances in understanding the role of fiber dimensions as determinants of carcinogenic potency.

However, the documents do not adequately address a related issue, biopersistence, and especially the role of fiber solubility in biopersistence. Advances in this area have been extraordinary with regard to man-made fibers and have led industry to make revolutionary changes in commercial man-made fibers, i.e., increasing solubility and, thus, reducing their potential for causing human cancer. This body of science should be reviewed in the document because it may have applicability to some situations involving asbestos fibers. Specifically, provision should be made for changes in risk coefficients for asbestos fibers if it can be shown that the solubility of the fibers differs from the solubility of the asbestos fibers purported to induce cancer in the epidemiological studies used as the basis for the exposure-response models that have been advanced.

6. I am uncertain at this juncture if the proposed risk assessment approach is sufficiently

well developed and validated and the associated assumptions and uncertainties identified to warrant its use in the field for regulatory decision making. However, I do see substantial merit to the approach and urge the Agency to continue with development and validation of the approach on an accelerated basis. This accelerated process should include provision for broader scientific community participation in the development process and more peer-review than has occurred in the past.

B. Specific Comments

Topic Area 1: Interpretations of the epidemiology and toxicology literature.

1) For lung cancer.

> a] Influence of fiber type: Please comment on the extent to which the epidemiology literature and mechanistic studies suggest that carcinogenic potency varies from one fiber type to the next (e.g., chrysotile versus amphibole fibers). How adequate is the information in the epidemiology literature for supporting dose-response analyses for different fiber types? Specifically, to what extent do you think the proposed risk coefficients in Table 6-29 are supported by the epidemiology literature?

It is my professional opinion that the epidemiological literature and mechanistic studies provide strong evidence for the hypothesis that carcinogenic potency varies from one fiber type to another; crocidolite > amosite > chrysotile. There is also evidence that within a fiber type, differences in carcinogenic potency may also exist.

The proposed "optimized risk coefficients" in Table 6-29 may well be appropriate. However, the document in its present form does not clearly relate the origins of the "representative values" in Table 6-15 and their linkage to the "optimized risk coefficients" in Table 6-29 and the "recommended risk coefficients" in Table 2-1 of the protocol document. The Hodgson and Darnton (2000) analysis, cited in the document, provides different coefficients. The basis for the difference is not clear.

In future reports on this topic, it is important that additional attention be given to clarity of presentation including the origin of any values and associated assumptions and uncertainties. Whenever possible uncertainties should be quantified.

> b] Influence of fiber length. Please comment on the extent to which the epidemiology literature and mechanistic studies suggest that carcinogenic potency varies with fiber length. How adequate is information in the epidemiology literature for supporting dose-response analyses for different fiber lengths? In general, is it appropriate to assess cancer risks using an exposure

index (see Equation 7.13) that is weighed heavily by fibers longer than 10 micrometers (μm)? (Note: Topic area 2 includes more detailed questions on the proposed exposure index.)

It is my professional opinion that the epidemiological literature and mechanistic studies clearly show a strong correlation between fiber length and carcinogenic potency for asbestos. If an integrated exposure index is developed and used, it is appropriate to give substantially greater weight to fibers greater than 10 μm in length as Berman and Crump have done.

c] To what extent do animal studies (e.g., studies by Davis and other researchers) suggest that carcinogenic potency varies with fiber type and fiber length?

The animal studies are clearly informative on the topics of fiber type and fiber length. This includes the early work of the Wagner group and the more recent work of the Davis group. This section of the report would be strengthened by more careful consideration of previous analyses including those of Lippmann (1988 and 1994).

d] Please comment on the extent to which carcinogenic potency is a function of fiber properties (e.g., diameter, aspect ratio, surface properties) other than fiber type and fiber length. How adequate is information in the epidemiology or toxicology literature for supporting these other properties into dose-response analyses?

Fiber diameter is an important determinant of the carcinogenic potency of fibers. Fiber diameter is a major determinant of the aerodynamic diameter of fibers which strongly affects the deposition probability of fibers. In contrast, fiber length has only a small influence on aerodynamic diameter. The diameter of fibers influences the surface area of fibers which, along with surface chemistry, influences the dissolution rate of fibers and the interaction of fiber constituents with biological systems.

The aspect ratio is of importance in defining what is or is not characterized as a fiber. The definition of a fiber as an elongated particle with an aspect ratio of greater than 3 to 1 as typically used seems reasonable.

2) For mesothelioma:

a] Influence of fiber type: Please comment on the extent to which the epidemiology literature and mechanistic studies suggest that carcinogenic potency varies from one fiber type to the next (e.g., chrysotile versus amphibole fibers). How adequate is the information in the epidemiology literature for supporting dose-response analyses for different fiber types? Specifically, to what

extent do you think the proposed risk coefficients in Table 6-29 are supported by the epidemiology literature?

The results of epidemiological investigations supported by mechanistic studies provide substantial support for a variation in mesothelioma induction potency associated with fiber type: erionite > tremolite/crocidolite > chrysotile. Because of difficulties in interpreting the various studies, it is not possible to rule out the hypothesis that pure chrysotile exposures are not associated with mesothelioma induction.

The proposed "optimized risk coefficients" for mesothelioma in Table 6-29 may be appropriate. However, the linkage to the individual studies from which they are derived is not always clear nor is the linkage to the "representative values" in Table 6-15 or the "recommended risk coefficients" in Table 2-1 of the protocol document.

In future reports, it is important that additional attention be given to clarity of presentation including the origin of all values, explicit statements as to assumptions used and statements of the underlying uncertainties. Whenever possible uncertainties should be quantified.

b] Influence of fiber length. Please comment on the extent to which the epidemiology literature and mechanistic studies suggest that carcinogenic potency varies with fiber length. How adequate is information in the epidemiology literature for supporting dose-response analyses for different fiber lengths? In general, is it appropriate to assess cancer risks using an exposure index (see Equation 7.13) that is weighed heavily by fibers longer than 10 micrometers (μm)? (Note: Topic area 2 includes more detailed questions on the proposed exposure index.)

The epidemiological literature, supported by the results of controlled animal exposure studies, clearly indicate that fiber length is a major determinant of the potential for fibers to cause mesothelioma. In my professional opinion, fibers less than 5 μm in length are unlikely to induce mesotheliomas. The role of fibers 5 to 10 μm in length is less clear. Fibers 10 μm to 20 μm in length are most likely to induce mesothelioma. However, my statement as to the role of fiber lengths must be coupled with knowledge of the fiber type.

c] To what extent do animal studies (e.g., studies by Davis and other researchers) suggest that carcinogenic potency varies with fiber type and fiber length?

It is apparent that erionite and the amphobiles have the potential to induce mesothelioma. The available literature is not persuasive that pure chrysotile induces mesothelima.

d] Please comment on the extent to which carcinogenic potency is a function of fiber properties (e.g., diameter, aspect ratio, surface properties) other than fiber type and fiber length. How adequate is information in the epidemiology or toxicology literature for supporting these other properties into dose-response analyses?

As the diameter of fibers decreases the relative surface area for a given mass of fibrous material increases. Thus, there is a greater opportunity for the surface of fibers to interact with the biological systems. Surface area will also influence the rate of dissolution of fibers. And, clearly, surface characteristics will influence the interactions between fibers and the biological system. Unfortunately, the specific surface properties of concern are not yet well understood.

As noted earlier, knowledge of exposure-response relationships extending from the high occupational exposure levels studied epidemiologically to environmental levels of exposure is lacking. The linear extrapolations from epidemiological studies of occupationally exposed populations to environmental levels of exposure have major uncertainties that have not been adequately stated in the Berman and Crump documents.

3) To what extent are the exposure estimates documented in the asbestos epidemiology literature reliable?

The exposure estimates for asbestos reported in the occupational exposure asbestos epidemiology literature, are highly uncertain. In some cases, there is considerable uncertainty as to the fiber types to which the individuals were exposed. In other cases, major uncertainty exists as to the physical dimensions of the fibers because of the variety of evolving techniques used to characterize asbestos fibers. The extent to which other particulate matter or other toxicants were present is not always known. And for most studies there are only a relatively few exposure concentration measurements available for populations exposed for many years making estimates of cumulative exposure highly uncertain.

To the extent occupational exposures are under-estimated, the estimated risk coefficients will be too high, i.e., over-estimate the true potency. Conversely, if the occupational exposures have been over-estimated, the estimated risk coefficients will be under-estimates of true potency. For each study used to develop risk coefficients, the authors should provide a clear statement of their confidence in the exposure estimates and, if possible, provide a quantitative estimate of the uncertainty associated with the exposure estimates. These estimates of uncertainty for exposure should be carried over into estimates of uncertainty for the potency values.

4) The proposed exposure index does not include contributions from fibers shorter than 5 μm. Please comment on whether the epidemiology and toxicology literature support the conclusion that asbestos fibers shorter than 5 μm present little or no carcinogenic risk.

In my professional opinion, the asbestos fibers less than 5 μm in length do not pose a carcinogenic risk. Thus, it is appropriate to exclude them from the exposure-response index for asbestos-induced cancer.

5) The proposed exposure index is weighed heavily by fibers longer than 10 μm. Specifically, Equation 7.13 suggests that the carcinogenic potency of fibers longer than 10 μm is more than 300 times greater than that of fibers with lengths between 5 and 10 μm. How consistent is this difference in carcinogenic potency with the epidemiology and toxicology literature?

In my professional opinion, it is appropriate for the exposure-response index for lung cancer to be weighted toward the long fibers. The human literature is less certain with regard to mesothelioma induction.

6) Please explain whether the proposed exposure index will allow meaningful comparisons between current environmental exposures to asbestos and historical exposures to asbestos that occurred in the work place.

Embedded in this question are several issues. Historical exposure assessments are what have been reported. Whatever the technique and the reporting criteria used is what we have to work with, if it was phase contrast that is what we must work with. The second issue is the extent to which these measurements are truly reflective of the historical exposures of the population. The third issue following from the above is the degree of uncertainty in the derived estimates of exposure-response relationships. A fourth issue is whether these exposure-response relationships are valid for contemporary environmental exposures. A key consideration in this matter is the substantial extrapolation involved in going from historical occupational exposure levels to contemporary environmental levels including levels established for clean-up.

Topic Area 3: General questions.

7) The proposed risk assessment approach assigns carcinogenic potency to individual fibers and to cleavage fragments (or "bundles that are components of more complex structures"). Please comment on whether cleavage fragments of asbestos are as toxicologically significant as fibers of the same size range.

In my professional opinion, the cleavage fragments have toxicological significance to the same extent as intact fibers of the same dimensions.

8) Please comment on whether the proposed cancer assessment approach is relevant to all amphibole fibers or only to the five types of amphibole fibers (actinolite, amosite, anthophyllite, crocidolite, tremolite) designated in federal regulations.

The proposed exposure-response index, if appropriately validated, would be appropriate for use in assessing the risks of asbestos fibers equivalent in type and size to those on which the index was based. Use of the index with other asbestos fiber types would involve an extrapolation of unknown uncertainty. It should also be emphasized that use of the index with asbestos or other fibers that have biopersistence characteristics different from those of the fibers used to develop the index would be inappropriate.

9) The review document recommends that asbestos samples be analyzed by transmission electron microscopy (TEM) and count only those fibers (or bundles) longer than 5 μm. Such counting practices will provide no information on the amount of asbestos fibers shorter than 5 μm. To what extent would data on shorter fibers in samples be useful for future evaluations (e.g., validation of the cancer risk assessment methodology, assessment of non-cancer endpoint)?

The document makes the point at several places that the output of the assessment of exposure must be matched to the exposure-response model being used. I strongly agree with this statement. Thus, if the Berman-Crump exposure-response indices are to be used, then it is appropriate to analyze samples by transmission electron microscopy and count only those fibers (particles with an aspect ratio of greater than 3 to 1) or bundles longer than 5 μm. This approach is justified if the only use of the exposure data is to match it to the Berman-Crump exposure-response indices.

However, it must be recognized that for many situations, exposures may be evaluated for multiple purposes. For example, the exposure estimates may be used as input to an epidemiological investigation of a specific population. In such a situation, it may be very useful to have a more comprehensive assessment of exposure. This might include enumeration of fibers by different increments of length, i.e., less than 5 μm, 5-10 μm, 10-20 μm, etc. Indeed, in some cases it may be

advantageous to have information collected in a manner that allows characterization of the variability of both fiber diameter and fiber length analyzed independently or in a linked manner along with electron diffraction analysis to provide information on chemical composition. The specific information must be matched to its intended use and also the cost of collecting the additional increments of information.

10) The proposed risk assessment methodology suggests that exposure estimates should be based only on fibers longer than 5 μm and thinner than 0.5 μm. Is this cut-off for fiber diameter appropriate?

This question addresses the inter-play between the definition of a fiber (an elongated particle with an aspect ratio [length to diameter] of 3 to 1), fiber length and diameter, and fiber aerodynamic diameter. Fibers with a length of 5.0 μm or longer and diameters up to about 1.5 μm could still meet the traditional definition of a fiber and have an aerodynamic diameter of about 5.0 μm. Such objects would still have a low probability of being inhaled and deposited in the pulmonary region. On this ground, there is no basis for excluding them from consideration. On the other hand, the proposed exposure-response index appears to have merit when only fibers under 0.5 μm in diameter are included.

11) Discuss whether the proposed cancer assessment approach, as a whole, is a reasonable evaluation of the available health effects data. What aspects of the proposed cancer assessment approach, if any, are inconsistent with the epidemiology or toxicology literature for asbestos?

This issue is addressed in my general comments.

12) Section 8.2 of the review document presents three options for assessing cancer risks from asbestos exposure. Please comment on the technical merit of the proposed risk assessment options.

It is appropriate for the document, and any subsequent versions, to provide multiple options for assessing cancer risks for different situations dependent on the information available. However, it would be appropriate for the document to more clearly define the circumstances under which it is appropriate to use each of the options. The “decision rules” for selection of options should be crafted to avoid providing the opportunity for a regulator to attempt to select an option to gain a particular pre-selected outcome.

I strongly favor retaining an approach that matches exposure-response risk coefficients to the particular type of asbestos fiber under consideration and calculation of risks separately for smokers and non-smokers.

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CHARGE QUESTIONS

Topic Area 1: Interpretations of the epidemiology and toxicology literature.

I. For *lung cancer*:

A] Influence of *fiber* to which the epidemiology literature and mechanistic studies suggest that carcinogenic potency varies from one *fiber type* to the next (e.g., chrysotile versus amphibole fibers). How adequate is the information in the epidemiology literature for supporting dose-response analyses for different *fiber types*? Specifically, to what extent do you think the proposed risk coefficients in Table 6-29 are supported by the epidemiology literature?

Answer: The epidemiology literature suggests that carcinogenic potency for lung cancer varies across fiber types, but the evidence is scattered throughout the literature and is not overwhelming. A unified analysis that incorporates all the lung cancer epidemiology data and that is focused specifically on the hypothesis - "potency for lung cancer varies with mineral type" is needed to answer this question. The Berman & Crump report (B&C) provides such an analysis. I am not aware of any other unified analysis of the lung cancer epidemiology data. The B&C analysis is innovative and, by necessity, employs various assumptions and interpretations of incomplete data. Before accepting the B&C conclusion, we need a better understanding of the B&C assumptions and data interpretations. A more detailed evaluation is needed of the B&C assumptions and applications of incomplete data than was possible at this time. (Note: Access to raw data used in B&C would be required for a detailed evaluation.) Since there is no competing unified analysis of the lung cancer epidemiology data that concludes otherwise, the "potency for lung cancer varies with mineral type" hypothesis should be accepted.

Concerning the risk coefficients for lung cancer in Table 6-29, the only way to determine if they are supported by the epidemiology literature is to conduct the type of unified analysis I mentioned above. Note that these risk coefficients are determined not only by the epidemiology data, but they depend also on the new proposed exposure index, the fiber size distribution adjustments to K_L, and the assumptions and data that were used to determine those entities. The B&C unified analysis, if

it survives more detailed peer review than was possible at this time, is itself a statement that the epidemiology literature supports the risk coefficients in Table 6-29.

However, the recorded values of the lung cancer risk coefficients in Table 6-29 are very likely incorrect because the B&C analysis relies on linear extrapolation of risk to low-exposure levels. An alternative unified analysis needs to be conducted that incorporates "threshold" models for lung cancer risk. Some researchers claim that epidemiology and clinical data suggest an exposure threshold for lung cancer of 25 f-yr/cc. Although there may be no asbestos exposure level where the risk of lung cancer is an absolute zero, the size of the potency coefficient for exposures below 25 f-yr/cc, or an appropriately determined alternative "threshold" exposure, is likely to be substantially less than the size of the potency coefficient for exposures greater than the "threshold."

The epidemiology literature supports the existence of this type of "threshold." Most, if not all the epidemiology data from studies used in B&C indicate “no statistically significant elevation of lung cancer cases” for exposure categories with exposures less than 15 to 20 f-y/cc. (As an example, my calculations applied to the Dement data analyzed in B&C (Table 6-2) indicate no statistically significant elevation of lung cancer risk below the exposure interval, [28-60) f-yr/cc. A simple linear-linear fit to these data picks a "threshold" exposure at 21.3 f-yr/cc.)

The “threshold” approach needs to be explored. However, simply fitting a standard exposure-risk equation to the full set of data from an epidemiology study will not necessarily solve the low-exposure problem adequately. Standard exposure-risk equations lack flexibility. The risk values at high exposures tend to pull the curve upward even at low exposure levels and it is likely that a statistical test will not be able to differentiate an s-shaped curve from a linear model due to the limited number of data points. Therefore, other approaches may be required, similar to the general approach in B&C that combines judgment based on information from animal studies, lung burden studies, and cellular studies with epidemiology data and statistical analysis. The “threshold’ – low exposure linear extrapolation issue must be resolved before adopting new values for lung cancer potency.

B] Influence of *fiber length*: Please comment on the extent to which the epidemiology literature and mechanistic studies suggest that carcinogenic potency varies with *fiber length*. How adequate is

information in the epidemiology literature for supporting dose-response analyses for different *fiber lengths*? In general, is it appropriate to assess cancer risks using an exposure index (see Equation 7.13) that is weighed heavily by fibers longer than 10 micrometers (μm)? (Note: Topic area 2 includes more detailed questions on the proposed exposure index.)

Answer: Fiber length and fiber dimensions in general are extremely important factors in asbestos risk assessment. The epidemiology literature alone does not contain adequate data to determine the effects of different fiber lengths. Information concerning the lung cancer potencies of different fiber dimensions can be determined from animal studies and lung burden studies. An exposure index that weights long fibers more heavily than short fibers is justified for assessing lung cancer risk associated with asbestos exposure.

C] To what extent do animal studies (e.g., studies by Davis and other researchers) suggest that carcinogenic potency varies with *fiber type* and *fiber length*?

Answer: These studies indicate that carcinogenic potency varies with *fiber length*.

D] Please comment on the extent to which carcinogenic potency is a function of fiber properties (e.g., diameter, aspect ratio, surface properties) *other than* fiber type and fiber length. How adequate is information in the epidemiology or toxicology literature for supporting these other properties into dose-response analyses?

Answer: The epidemiology literature does not contain adequate data to determine the risk effects of fiber properties such as diameter, aspect ratio, and surface dimensions.

2) For *mesothelioma*:

A] Influence of *fiber type*: Please comment on the extent to which the epidemiology literature and mechanistic studies suggest that carcinogenic potency varies from one *fiber type* to the next (e.g., chrysotile versus amphibole fibers). How adequate is the information in the epidemiology literature for supporting dose-response analyses for different *fiber types*? Specifically, to what extent do you think the proposed risk coefficients in Table 6-29 are supported by the epidemiology literature?

Answer: The epidemiology literature clearly establishes the significance of *fiber type* for mesothelioma potency and supports different exposure-risk analyses for different *fiber types*.

Concerning the risk coefficients for mesothelioma in Table 6-29, the only way to determine if they are supported by the epidemiology literature is to conduct a unified analysis such as the B&C unified analysis. (For a more complete explanation, refer to my discussion above of a unified analysis for lung cancer). To answer this question, a more detailed peer review than was possible at this time would be required to test B&C assumptions and to dissect how supporting data were used (e.g., the calculation of fiber size adjustment factors for K_M). In addition, the "threshold" concept that I described above for lung cancer risk assessment also needs to be considered for mesothelioma risk assessment to avoid problems associated with low-exposure linear extrapolation.

B] Influence of *fiber length*: Please comment on the extent to which the epidemiology literature and mechanistic studies suggest that carcinogenic potency varies with *fiber length*. How adequate is information in the epidemiology literature for supporting dose-response analyses for different *fiber lengths*? In general, is it appropriate to assess cancer risks using an exposure index (see Equation 7.13) that is weighed heavily by fibers longer than 10 micrometers (μm)? (Note: Topic area 2 includes more detailed questions on the proposed exposure index.)

Answer: Fiber length and fiber dimensions in general are extremely important factors in asbestos risk assessment. The epidemiology literature alone does not contain adequate data to determine the effects of different fiber lengths. Information concerning mesothelioma potencies of different fiber dimensions can be determined from animal studies and lung burden studies. An exposure index that weights long fibers more heavily than short fibers is justified for assessing mesothelioma risk associated with asbestos exposure.

C] To what extent do animal studies (e.g., studies by Davis and other researchers) suggest that carcinogenic potency varies with *fiber type* and *fiber length*?

Answer: These studies indicate that carcinogenic potency varies with *fiber length*

D] Please comment on the extent to which carcinogenic potency is a function of fiber properties

(e.g., diameter, aspect ratio, surface properties) *other than* fiber type and fiber length. How adequate is information in the epidemiology or toxicology literature for supporting these other properties into dose-response analyses?

Answer: The epidemiology literature does not contain adequate data to determine the risk effects of fiber properties such as diameter, aspect ratio, and surface dimensions.

3) To what extent are the exposure estimates documented in the asbestos epidemiology literature reliable?

Answer: "Reliable" is a relative term. To answer this question, the word "reliable" has to be interpreted in a context. The context is “decision-making based on risk estimates derived, in part, from exposure estimates documented in the asbestos epidemiology literature.” I am referring to decision-making applied to selecting exposure limits, managing or removing asbestos-containing materials in buildings, cleaning asbestos waste sites, or implementing product bans. The decision-making process must account for uncertainty in risk estimates, which is due, in part, to the uncertainty (i.e., the reliability or lack thereof) in the underlying exposure data used to develop the risk estimation method. B&C describe most and possibly all the well-known problems with exposure estimates in the epidemiology literature. We cannot claim to know the exact airborne fiber concentration or makeup of fiber types and sizes for any particular worker who is a subject in an epidemiology study. However, the collection of exposure estimates associated with the epidemiology studies, which have been developed from various and often disparate sources of information, appear to provide a relatively consistent characterization of exposure that is sufficient for developing a risk assessment method. Provided the uncertainty in risk estimates is treated with an appropriate degree of respect in decision-making, the exposure estimates documented in the asbestos epidemiology literature may be characterized as "reliable."

Topic Area 2: The proposed exposure index.

The proposed exposure index does not include contributions from fibers shorter than 5 µm. Please comment on whether the epidemiology and toxicology literature support the conclusion that asbestos fibers shorter than 5 µm present little or no carcinogenic risk.

Answer: The epidemiology literature alone does not contain adequate data to determine the effects of different fiber lengths. The toxicology literature supports the conclusion that long asbestos fibers are associated with greater carcinogenic risk than short asbestos fibers. The assertion that the 5 µm limit is a "bright line" separating carcinogenic fibers from non-carcinogenic fibers is doubtful, but it is clear that fibers shorter than 5 µm have diminishing potency.

An evaluation of the carcinogenic potential of short fibers also can be addressed from a completely different perspective, using a different set of epidemiology data – cancer incidence data collected by the National Cancer Institute in its Surveillance, Epidemiology, and End Results (SEER) program. Briefly, the trend over time of mesothelioma incidence for US women does not reflect the pattern that would be expected if exposure to short fibers posed a significant carcinogenic risk. These data indicate that although exposures to short fibers may have increased over time, they have not resulted in an epidemic of asbestos-related cancer.

5) The proposed exposure index is weighed heavily by fibers longer than 10 µm. Specifically, Equation 7.13 suggests that the carcinogenic potency of fibers longer than 10 µm is more than 300 times greater than that of fibers with lengths between 5 and 10 µm. How consistent is this difference in carcinogenic potency with the epidemiology and toxicology literature?

Answer: The epidemiology literature alone does not contain adequate data to determine the effects of different fiber lengths. The toxicology literature generally supports the conclusion that long asbestos fibers are associated with greater carcinogenic risk than short asbestos fibers. The proposed exposure index is consistent with the toxicology literature. There exist no data at this time other than those used in B&C to further confirm the use of the proposed classification of lengths and numerical weights.

6) Please explain whether the proposed exposure index will allow meaningful comparisons between current environmental exposures to asbestos and historical exposures to asbestos that occurred in the work place.

Answer: I believe the question should be - Can the proposed exposure index be used to evaluate cancer risk associated with current environmental exposures, given that the index was derived from animal data and the risk models were derived from data collected in occupational studies? The answer is "yes" with qualifications. "Yes" because the potency factors in the proposed risk models were adjusted to be applied with the proposed index. The qualifications are the uncertainties concerning the methodology and use of data to derive the adjustments as discussed in answers to earlier questions.

Topic Area 3: General questions.

7) The proposed risk assessment approach assigns carcinogenic potency to individual fibers and to cleavage fragments (or bundles that are components of more complex structures). Please comment on whether cleavage fragments of asbestos are as toxicologically significant as fibers of the same size range.

Answer: From my reading of the scientific literature, it appears that cleavage fragments may be less potent for asbestos-related cancer than asbestos fibers. As a practical matter, it would be very difficult to evaluate the proportion of structures that were cleavage fragments in historical exposure measurements. Therefore it would be difficult to use a current exposure measurement that was adjusted for cleavage fragments in a risk assessment model.

8) Please comment on whether the proposed cancer assessment approach is relevant to all amphibole fibers or only to the five types of amphibole fibers (actinolite, amosite, anthophyllite, crocidolite, tremolite) designated in federal regulations.

Answer: The proposed cancer assessment approach is applicable only to the mixture of fibers that constituted exposure in the epidemiology studies. If it were subsequently confirmed that other mineral types were, in fact, included in the exposures (e.g., winchite and richterite at the Libby mine), the proposed cancer assessment approach, subject to adjustment of potency factors, could accommodate other amphiboles.

9) The review document recommends that asbestos samples be analyzed by transmission electron

microscopy (TEM) and count only those fibers (or bundles) longer than 5 µm. Such counting practices will provide no information on the amount of asbestos fibers shorter than 5 µm. To what extent would data on shorter fibers in samples be useful for future evaluations (e.g., validation of the cancer risk assessment methodology, assessment of non-cancer endpoints)?

Answer: The evidence is reasonably strong that asbestos fibers with lengths less than 5 µm have minimal potency for asbestos-related cancers. Also, there is no history of an association between low level environmental exposures, which probably included a high percentage of short fibers, and asbestosis. There is no reliable evidence at this time that other non-cancer endpoints are associated with low level asbestos exposure or short fibers. Counting fibers shorter than 5 µm would increase the cost of measuring airborne asbestos. The cost would not be justified if the only use of the data were to validate the fiber length component of the cancer risk assessment. We need more information through a debate that has not yet been conducted to determine if the risk of specific non-cancer endpoints potentially associated with exposures to short fibers is sufficiently established to justify the extra cost of including short fibers in asbestos measurements.

10) The proposed risk assessment methodology suggests that exposure estimates should be based only on fibers longer than 5 µm and thinner than 0.5 µm. Is this cut-off for fiber *diameter* appropriate?

Answer: Determining the correct weights for fiber lengths is more important than fixing a specific diameter limit. The cut-off for fiber diameter should account for fiber respirability and clearance mechanisms. I do not have a recommendation at this time.

11) Discuss whether the proposed cancer assessment approach, as a whole, is a reasonable evaluation of the available health effects data. What aspects of the proposed cancer assessment approach, if any, are inconsistent with the epidemiology or toxicology literature for asbestos?

Answer: As a whole the proposed cancer assessment approach is an impressive analysis of a wide-ranging collection of data to produce an asbestos cancer risk model that addresses almost all the significant risk issues that have been debated over the past 20 years. It is a reasonable evaluation of the available health effects data with one extremely important exception. It does not address the

"threshold" - "low exposure linear extrapolation" issue. The analysis, by virtue of this exception, is inconsistent with the epidemiology literature for asbestos.

12) Section 8.2 of the review document presents three options for assessing cancer risks from asbestos exposure. Please comment on the technical merit of the proposed risk assessment options.

Answer: Each of the three proposed options is an approach with a counterpart that is currently available and has been available since 1988 when EPA last updated its Asbestos IRIS file. The simple equation reported in IRIS (counterpart of B&C Option 3) that determines asbestos cancer risk to be 0.23 risk units for each PCM fiber/cc measured in units of lifetime average daily exposure (LADE) is usually identified as "the EPA asbestos risk assessment." However, it is not the only option available to a risk assessor today. One may choose to utilize Tables 6-1 through 6-3 in the EPA Asbestos Health Assessment Update (1986) for separate risk estimates of lung cancer and mesothelioma by sex and smoking status (counterpart of B&C Option 2), or may use the underlying equations for lung cancer and mesothelioma with life-table data to estimate risks (counterpart of B&C Option 1). The changes in the currently available approaches that define the three proposed options are: (i) use of a new exposure index that explicitly accounts for fiber dimensions; and (ii) differential potencies based on mineral type that also are different for lung cancer and mesothelioma. These B&C innovations are significant, but more is needed.

Option 3 does not distinguish lung cancer from mesothelioma, and requires averaging over smoking status and sex. Option 3 may have some merit for "quick" asbestos risk comparisons, but is inflexible and subject to error. B&C does not explain how to implement Option 3. EPA should not rely on Option 3 for estimating risk.

Option 1 and Option 2 need to address "the low-exposure linear extrapolation" issue. EPA's risk assessment is intended to evaluate risk at low exposures. The currently available risk assessment methods lead to questionable risk estimates at low exposures. For example, using the current EPA unit risk equation published in IRIS, the incremental risk of asbestos-related cancer corresponding to a cumulative lifetime exposure of 0.30 f-y/cc is approximately 1 in 1000 ($1x10^{-3}$). However, epidemiology data suggest an exposure threshold that may be as large as 25 f-y/cc for lung cancer. Although there may be no exposure level where the risk of cancer is an absolute zero, it is highly

unlikely that 0.30 f-y/cc lifetime exposure would lead to a $1x10^{-3}$ risk of cancer. Option 1 and Option 2 are likely to overstate risks at low exposures because they incorporate low exposure linear extrapolation risk assumptions.

Finally, Option 1 and Option 2 require estimates of mortality due to all other causes in order to produce risk estimates for lung cancer and mesothelioma. B&C provides mortality data that they use to create risk tables for Option 2. Since mortality patterns have been shifting (i.e., survival to older ages) and mesothelioma has a long latency period, the mortality data used in the model may be an important factor, especially for Option 2. (For example, using 1970 mortality data may lead to different risk estimates than mortality data from 2000.) The effect may be small, but it needs to be assessed before a particular set of data are locked-in to Option2.

Topic Area 4: Development of Conclusions and Recommendations

At the end of the workshop, the peer consultants will be asked to draft conclusion statements identifying their most notable findings on the proposed methodology. As a prelude to developing these statements, the peer consultants are invited to provide any additional comments or concerns, both strengths and weaknesses, on topics not specifically addressed in the previous charge questions. After completing the discussions the peer consultants will prepare their conclusions, and they will also be asked to develop recommendations for how EPA can improve the methodology. Please note that, although recommendations for future research projects are welcomed, the focus of this workshop is on the proposed risk assessment methodology and how it may be used to support decisions at asbestos-contaminated sites.

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Dr. Sherman received her B.S. in mathematics from Pennsylvania State University, her M.A. in Biostatistics from the University of California-Berkeley, and her Ph.D. in statistics from the University of Waterloo. She is a Biostatistician with California Environmental Protection Agency, where she specializes in quantitative cancer risk assessment. She has served in various positions at NIEHS as a Biostatistician and has co-authored a number of papers with Dr. Christopher Portier including "Multistage stochastic models of the cancer process: a general theory for calculating tumor incidence," "The two-stage model of Carcinogenesis: overcoming the nonidentifiability dilemma," The utility of the Kolmogorov backward equations in stochastic Carcinogenesis modeling," and " Numerically calculating the cumulative distribution function for the time to an observable tumor in multistage models of Carcinogenesis." She is the author of a book chapter entitled "the potential effects of chemical mixtures on the carcinogenic process with in the context of the mathematical multistage model," in Risk Assessment of Chemical Mixtures: Biological and Toxicological Issues, R. Yang (1994). She serves as a reviewer for several professional journals, including Biometrics, Environmental Health Perspectives, Journal of the American Statistical Association, and The Journal of Toxicology and Applied Pharmacology. She has presented numerous papers for government agencies and universities including "Assessing Cancer Risk from large Epidemiologic Cohorts: Tumor Incidence, Hazard Functions, and Identifiability," Improving the mathematical modeling of Carcinogenesis via intermediate events and biomarker data." She is a member of the American Statistical Association, the International Biometrics Society, and the New York Academy of Sciences.

Prior to submitting these written comments, I would like to acknowledge the invaluable assistance and guidance of my colleagues at California EPA/OEHHA. Drs. John Budroe, Stan Dawson, and Melanie Marty have (probably) collectively spent more years working on the subject of asbestos than the number of years that I have been on this earth. Without their support, many of the questions that have been addressed would have been without comment. My only regret is that we did not have ample time to more thoroughly answer all of the questions within the charge.

Topic Area 1: Interpretations of the epidemiology and toxicology literature.

1) For lung cancer:

A] Influence of fiber type: Please comment on the extent to which the epidemiology literature and mechanistic studies suggest that carcinogenic potency varies from one fiber type to the next (e.g., chrysotile versus amphibole fibers). How adequate is the information in the epidemiology literature for supporting dose-response analyses for different fiber types? Specifically, to what extent do you think the proposed risk coefficients in Table 6-29 are supported by the epidemiology literature?

As has been documented throughout the asbestos literature and conditional on the relative risk model that has been used to describe asbestos induced lung cancer, carcinogenic potency varies for chrysotile and amphibole fiber types. What has not been reconciled are the results of Hodgson and Darnton (2000) with this report's conclusions regarding fiber type. Hodgson and Darnton (2000) determined differences in carcinogenic potencies for crocidolite, amosite and chrysotile. In this report, carcinogenic potency differences between the amphiboles are not reported nor is there a discussion to settle this disparity.

The overall values of KL of Table 6-29 appear to be in an appropriate relation to the adjusted individual values in Fig. 6-4 for pure chrysotile and pure amphibole and even for mixed fibers, suggesting agreement with the central tendencies in the epidemiological literature. This approach, however, does not give sufficient recognition to the high chrysotile

coefficients obtained in the South Carolina studies, a recognition that is needed for adequate health protection.

B] Influence of fiber length: Please comment on the extent to which the epidemiology literature and mechanistic studies suggest that carcinogenic potency varies with fiber length. How adequate is information in the epidemiology literature for supporting dose-response analyses for different fiber lengths? In general, is it appropriate to assess cancer risks using an exposure index (see Equation 7.13) that is weighed heavily by fibers longer than 10 micrometers (mm)? (Note: Topic area 2 includes more detailed questions on the proposed exposure index.)

The adjustment of the risk coefficients for fiber length seems to be an appropriate concept applied to the animal studies. However, extrapolation to humans who have different airway geometry than rodents and may well respond differently to the same fiber dimension requires justification. The report needs some substantial basis for an extrapolation that will ultimately require a complex model to fit the human data.

C] To what extent do animal studies (e.g., studies by Davis and other researchers) suggest that carcinogenic potency varies with fiber type and fiber length?

Hesterberg et al. (1998) exposed Fischer rats to chrysotile asbestos and several man-made fibers by nose-only inhalation for 6 h/day, 5 days/week for 2 years. The chrysotile asbestos inhalation concentration was 10,600 WHO fibers/ml (WHO fibers defined as being 5 µm in length and > 3 µm in diameter and having a length/diameter ratio > 3). The geometric mean length and width of the dispersed fibers was 1.2 and 0.08 µm, respectively, suggesting that the non-WHO fiber concentration was higher than the WHO concentration. Additionally, no fibers were > 20 µm in length, and very few were > 10 µm in length. The geometric mean length and width of the lung burden of deposited chrysotile fibers after 104 weeks of exposure and 23 weeks of recovery were 1.6 µm and 0.07 µm, respectively.

Chrysotile asbestos caused significantly increased incidences of both lung cancer (12/69, 17.4%, adenomas and carcinomas combined), and pleural mesothelioma (1/69, 1.4%) compared to controls (lung cancer incidence 2/130, 1.5%; mesothelioma incidence 0/130). These results suggest that relatively short chrysotile asbestos fibers are capable of inducing both lung cancer and mesothelioma in rats. The authors stated that "fiber-induced lung toxicity is not always strictly dependent upon the numbers of long fibers retained in the lung", and "these data demonstrate that the toxic potential of chemically different fiber types cannot be predicted solely by the dimensions of the fibers retained in the lung. In the induction of fiber-induced pathogenesis, sheer numbers of fibers may thus be able to compensate for a lack of long fibers".

D] Please comment on the extent to which carcinogenic potency is a function of fiber properties (e.g., diameter, aspect ratio, surface properties) other than fiber type and fiber length. How adequate is information in the epidemiology or toxicology literature for supporting these other properties into dose-response analyses?

No comment.

2) For mesothelioma:

A] Influence of fiber type: Please comment on the extent to which the epidemiology literature and mechanistic studies suggest that carcinogenic potency varies from one fiber type to the next (e.g., chrysotile versus amphibole fibers). How adequate is the information in the epidemiology literature for supporting dose-response analyses for different fiber types? Specifically, to what extent do you think the proposed risk coefficients in Table 6-29 are supported by the epidemiology literature?

As stated in Section 8.1.2, Hodgson and Darnton (2000) find substantially different carcinogenic potencies for ampiboles and chrysotile. Even though the report agrees with the conclusions of Hodgson and Darnton (2000) on this point, there have been references

in the literature over the years to differences in potency between crocidolite and all other asbestos minerals.

The overall values of KM appear to be substantially less than the individual values in Fig. 6-6 not only for pure chrysotile and pure amphiboles, but also for the mixtures. This appears to represent an irreconcilable difference between the optimal values given in Table 6-29 and the individual values for the epidemiology studies.

B] Influence of fiber length: Please comment on the extent to which the epidemiology literature and mechanistic studies suggest that carcinogenic potency varies with fiber length. How adequate is information in the epidemiology literature for supporting dose-response analyses for different fiber lengths? In general, is it appropriate to assess cancer risks using an exposure index (see Equation 7.13) that is weighed heavily by fibers longer than 10 micrometers (mm)? (Note: Topic area 2 includes more detailed questions on the proposed exposure index.)

Nolan et al. (1994) examined the lung contents of six workers who had been occupationally exposed to chrysotile asbestos. Five were lung cancer cases from Quebec, Canada. The sixth case was an American worker who had developed pleural mesothelioma. An analysis of two parenchymal lung tissue specimens from the pleural mesothelioma of the American worker demonstrated that the predominant fiber type was chrysotile. Chrysotile fiber length percentages in those parenchymal lung tissue specimens are described in Table 1. Fibers < 0.5 µm in length were not counted.

Table 1: Length distribution of chrysotile fibers from two parenchymal lung tissue specimens from an American pleural mesothelioma case (from Nolan et al., 1994)

Specimen	Percentage of fiber length		
	< =4.99µm	5 – 7.99 µm	>=8 µm
A	96.7	2.5	0.8
B	98.8	1.2	0

The authors stated that "the fiber length distribution of the chrysotile recovered from the U.S. mesothelioma case was indistinguishable from that of chrysotile specimens known to produce mesotheliomas in rats". These data suggest that short fiber chrysotile may be capable of inducing mesothelioma in humans.

A study by Suzuki and Yuen (2001) characterized asbestos fibers in the lung and mesothelial tissues (mesotheliomatous tissue and hyaline plaque) taken from 151 human malignant mesothelioma cases. The most common asbestos types seen in the lung were a mixture of chrysotile with amphiboles followed by amphiboles alone and chrysotile alone. The majority of asbestos types seen in the mesothelial tissues were chrysotile alone, followed by chrysotile plus amphibole and amphibole alone. The majority of asbestos fibers detected in the lung and mesothelial tissues were shorter than 5 µm in length. Only 4% of the fibers found were 8 µm in length or greater. The authors stated that chrysotile asbestos can induce human malignant mesothelioma, since, in some of the mesothelioma cases, asbestos fibers detected in both the lung and mesothelial tissues, or lung tissue alone or mesothelial tissues alone were exclusively chrysotile fibers. Additionally, the authors concluded that "such short, thin asbestos fibers should not be excluded from those contributing to the induction of human malignant mesothelioma".

These studies suggest that short fiber chrysotile asbestos is capable of inducing both lung cancer and mesothelioma in rats, and may be capable of inducing mesothelioma in humans.

Similar to the case of lung cancer, the adjustment of the risk coefficients for fiber length suffers from inadequate data applied to the animal studies. Use of the same fiber-length adjustment obtained for lung cancer to mesothelioma, though not contraindicated, is not supported in the asbestos literature. Extrapolation to humans who have different airway geometry than rodents and may well respond differently to the same fiber dimension requires justification as well.

C] To what extent do animal studies (e.g., studies by Davis and other researchers) suggest that carcinogenic potency varies with fiber type and fiber length?

See lung cancer section, part c.

D] Please comment on the extent to which carcinogenic potency is a function of fiber properties (e.g., diameter, aspect ratio, surface properties) other than fiber type and fiber length. How adequate is information in the epidemiology or toxicology literature for supporting these other properties into dose-response analyses?

No comment.

III. To what extent are the exposure estimates documented in the asbestos epidemiology literature reliable?

The exposure estimates documented in the asbestos epidemiology literature suffer from many of the exposure uncertainties inherent in occupational epidemiological studies. Exposure uncertainties related to non-representative sampling, poor evaluation of job exposures, retrospective estimation of exposure levels, and the conversion of samples from counted particles (particle concentrations in million particles per cubic foot) to fiber concentrations (fibers per milliliter).

Topic Area 2: The proposed exposure index.

IV. The proposed exposure index does not include contributions from fibers shorter than 5 mm. Please comment on whether the epidemiology and toxicology literature

support the conclusion that asbestos fibers shorter than 5 mm present little or no carcinogenic risk.

The authors assume asbestos fibers shorter than 5 mm present little or no carcinogenic risk when insufficient information exists to validate this assumption. Potential counter-examples to this assumption would include Nolan et al. (1994) and Suzuki and Yuen (2001). Their conclusions were that short fiber chrysotile (< 5mm) may be capable of inducing mesothelioma in humans.

5) The proposed exposure index is weighed heavily by fibers longer than 10 mm. Specifically, Equation 7.13 suggests that the carcinogenic potency of fibers longer than 10 mm is more than 300 times greater than that of fibers with lengths between 5 and 10 mm. How consistent is this difference in carcinogenic potency with the epidemiology and toxicology literature?

Equation 7.12 adequately fit tumor incidence data across 13 separate animal studies, but there is no justification for using the proposed exposure index to evaluate asbestos-related cancer risks for humans. Furthermore, as has been cited in earlier questions relating to fiber length, the induction of fiber-induced pathogenesis can be the result of the sheer numbers of fibers when there is a lack of long fibers.

VI. Please explain whether the proposed exposure index will allow meaningful comparisons between current environmental exposures to asbestos and historical exposures to asbestos that occurred in the work place.

Given the lack of justification for the proposed exposure index in human studies, it is difficult to answer this question.

Topic Area 3: General questions.

VII. The proposed risk assessment approach assigns carcinogenic potency to individual fibers and to cleavage fragments (or bundles that are components of more complex

structures). Please comment on whether cleavage fragments of asbestos are as toxicologically significant as fibers of the same size range.

Cannot comment.

VIII. Please comment on whether the proposed cancer assessment approach is relevant to all amphibole fibers or only to the five types of amphibole fibers (actinolite, amosite, anthophyllite, crocidolite, tremolite) designated in federal regulations.

In the absence of better information, it seems prudent to use the existing amphibole numbers, obtained from crocidolite or amosite studies or both, for other fibrous amphiboles. Based upon the study data of Amandus et al. (1987), tremolite has a potency between crocidolite and chrysotile for mesothelioma. For lung cancer, the potency of tremolite is more similar to chrysotile.

IX. The review document recommends that asbestos samples be analyzed by transmission electron microscopy (TEM) and count only those fibers (or bundles) longer than 5 mm. Such counting practices will provide no information on the amount of asbestos fibers shorter than 5 mm. To what extent would data on shorter fibers in samples be useful for future evaluations (e.g., validation of the cancer risk assessment methodology, assessment of non-cancer endpoints)?

Data on shorter fibers would certainly be useful to validate any cancer risk assessment methodology that is in current practice or development. Suzuki and Yuen (2001) characterized asbestos fibers in the lung and mesothelial tissues and noted that a majority of the asbestos fibers detected were shorter than 5mm in length. They concluded that short, thin asbestos fibers should not be excluded from those contributing to the induction of human mesothelioma.

e proposed risk assessment methodology suggests that exposure estimates should be based only on fibers longer than 5 mm and thinner than 0.5 mm. Is this cut-off for fiber diameter appropriate?

Cannot comment.

XI Discuss whether the proposed cancer assessment approach, as a whole, is a reasonable evaluation of the available health effects data. What aspects of the proposed cancer assessment approach, if any, are inconsistent with the epidemiology or toxicology literature for asbestos?

The proposed assessment is predicated on the adjustment for fiber length, i.e. interim exposure index given by Equation 7.13, to be reasonable for humans. Without adequate justification, one cannot determine whether the approach outlined within the report is a

reasonable evaluation of the available health effects data. In addition, the proposed approach for developing coefficients has two serious problems: (i) For lung cancer, the potencies of the South Carolina textile studies for workers exposed to chrysotile are not adequately recognized. These should be included to afford greater health protection. (ii) For mesothelioma, the overall optimized coefficients are substantially below the trends of the coefficients for the individual studies.

X. Section 8.2 of the review document presents three options for assessing cancer risks from

asbestos exposure. Please comment on the technical merit of the proposed risk assessment options.

All three options could be used, depending on the application. Option 3, Estimating Risk from a Unit Risk Factor, has the advantage of being the most simple to apply and has been traditionally implemented. Option 3 would be particularly useful for inexpensive screening calculations.

Technical Comments:

Comment: Table 6-12 and Figure 6.3 display the likely ranges for the KL estimates. However, the uncertainty factors used to derive these "likely ranges" are not defined in a manner that allows one to replicate these analyses. A protocol that provides decision rules for assigning such factors is needed as well as the range for each factor. Thus, the text that describes the variation in the KL estimates could be misleading since the confidence intervals are effectively expanded.

Pg. 6.35:Among "pure" amphibole studies, the lowest and highest of the best-estimate KL values vary by a factor of approximately 20…. However, these two estimates are not statistically difference (based on comparison of their confidence intervals).

Comment: The inference suggested above can be statistically tested via likelihood-ratio tests. By confining the slopes of the "pure" amphibole studies to be equal and then comparing the likelihood from this model to a model where the slopes may vary, one can objectively assert whether there is a statistically significant difference in the KL estimates.

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Dr. Stayner has been selected to co-chair the workshop. He recently served as a visiting scientist for the International Agency for Research on Cancer, where he worked with Dr. Jerry Rice on monographs for man-made mineral fibers and numerous other epidemiologic projects. He is the Chief of the Risk Evaluation Branch, which includes working on research on characterization of occupational health and safety risks and the development of better methods to characterize theses risks. He was the 2000 recipient of the NIOSH Special Act Award for organizing a workshop 9on "Future Research for Improving risk Assessment Methods." He has lectured and served as an instructor on risk assessment and risk management for academia and professional societies, and international organizations. He has published numerous papers including "Exposure Response Analysis of Respiratory Disease Risk Associated with Occupation Exposure to Chrysotile Asbestos," "Silica, Asbestos, Man-Made Fibers, and Cancer," "Occupational Exposure to Chrysotile Asbestos and Cancer Risk: A review of the 'Amphibole Hypothesis," "Concordance of Rat and Human-based Risk Estimates for Particle Related Lung Cancer," Exposure to Crystaline Silica, Silicosis and Lung Disease other than cancer in Diatomaceous Earth Industry workers: A Quantitative Risk Assessment." He has made numerous presentations at symposia, seminars, and workshops including "Using Epidemiologic Data for a Risk Assessment of Silica Exposure, 2001," "The Molecular Epidemiology of Asbestos and other Fibers, Harvard SPH, 1996, and "An Exposure-Response Analysis of Respiratory Disease risk Associated with Occupational Exposure to Chrysotile Asbestos."

1) For *lung cancer*:

A] Influence of *fiber type*: Please comment on the extent to which the epidemiology literature and mechanistic studies suggest that carcinogenic potency varies from one *fiber type* to the next (e.g., chrysotile versus amphibole fibers). How adequate is the information in the epidemiology literature for supporting dose-response analyses for different *fiber types*? Specifically, to what extent do you think the proposed risk coefficients in Table 6-29 are supported by the epidemiology literature?

The epidemiologic literature does not provide compelling evidence that the carcinogenic potency differs by fiber type for lung cancer. This was the conclusion of a review that I authored about 5 years ago [Stayner et al. 1997], and I have not seen anything in this document or elsewhere that has changed my position. In fact, the epidemiologic literature provides in many cases evidence that chrysotile is just as potent as amphibole for inducing lung cancer The studies of textile workers provide very similar estimates of potency (K_L), despite the fact that some of these studies involved pure chrysotile exposures [Dement et al. 1994], and others had mixed exposures [Peto 1985, and McDonald et al. 1983b]. In a study of cement workers, Hughes et al. [1987] observed an exposure-response for lung cancer that was nearly identical for workers exposed to chrysotile or to mixed fibers [In fact K_L = 0.4 in both plants, see Table 6-16 of this report]. The "meta-analysis of K_Ls presented in this report does not provide support for the hypothesis that chrysotile has lower potency for lung cancer than the amphiboles. In Table 6-21 the test for the hypothesis that the ratio of potencies (RPC) differs by fiber type was rejected (p=0.42 or p=0.14 depending on whether K was adjusted or not). Although this analysis resulted in a potency estimate for chrysotile that was either approximately 2 times (unadjusted K_L), or 5 times (adjusted K_L) lower than amphiboles these difference were not statistically significant, and therefore could be explained by chance.

In the end, I strongly suspect that decision of whether or not chrysotile is as potent as amphiboles for lung cancer is highly influenced by the disagreement between the Quebec miners and millers study, and the South Carolina textile study. It would be highly informative if a sensitivity analysis could be performed in which each of these studies as well as other studies were dropped from the analysis. I also suspect that differences in slopes may be more a function of industry type than fiber type, and it would interesting to see the analysis attempt to adjust for this factor.

While there are some mechanistic arguments that have been advanced to suggest that chrysotile may be less potent for lung cancer than amphiboles [e.g., Mossman et al. 1993], it is difficult to accept these arguments given that we do not presently know the mechanism and that these arguments appear to conflict with the empirical evidence from the epidemiologic literature discussed above (and toxicologic literature discussed below).

In summary, I do not believe that the choice of using separate lung cancer risk coefficients for chrysotile and amphiboles is well justified.

B] Influence of *fiber length*: Please comment on the extent to which the epidemiology literature and mechanistic studies suggest that carcinogenic potency varies with *fiber length*. How adequate is information in the epidemiology literature for supporting dose-response analyses for different *fiber lengths*? In general, is it appropriate to assess cancer risks using an exposure index (see Equation 7.13) that is weighed heavily by fibers longer than 10 micrometers (μm)? (Note: Topic area 2 includes more detailed questions on the proposed exposure index.)

There is substantial evidence that fiber length is a critical factor in the carcinogenic potency for lung cancer. Unfortunately, this evidence is from toxicologic studies and there is little available information from epidemiologic studies. This is because the epidemiologic studies have not generally included characterizations of the fiber size distributions. There is some indirect evidence from epidemiologic studies. For example, Dement and Wallingford [1990] reported that the percentage of fibers greater than 10 μm was higher in the South Carolina textile facility than what had previously been reported in the Quebec mines and mills, or in asbestos cement manufacturing facilities. Thus differences in the fiber size distributions is a possible explanation for why a higher carcinogenic potency for lung cancer was observed in the South Carolina textile facility than in the Quebec mines and mills, and the cement manufacturing facilities.

Although there is limited epidemiologic evidence to support the need for an exposure index that gives greater weight to fibers longer than 10 μm, there is inadequate epidemiologic evidence to support the choice of the specific cutoff and exposure index that is proposed in this report [Equation 7.13].

There is also mechanistic data to support the increased carcinogenecity of long fibers. Davis and others have demonstrated that short-fiber preparations are cleared more rapidly from rat lungs than long-fiber preparations. As described in this report, a mechanistic hypothesis has been advanced that relates this difference in clearance to the inability of an alveolar macrophage to engulf fibers that are longer than the diameter of the macrophage. However, this mechanistic argument may imply a different choice of cutoffs for the exposure index than what is proposed in this report. The report lists 13.1 µm as the average diameter for a rat alveolar macrophage (AM), versus 21.2 µm for a human AM (p. 4.20). Therefore, based on this one might expect that model should use a fiber size cut-point in the model that would be around 13 µm for the rat model, and around 21 µm for the human model. Instead, the "optimum" rat model in the paper by Bernstein et al. 1995] uses 40 µm as a fiber size cut-point, and the "ad hoc" human model uses 10 µm as a fiber size cut-point

Berman and Crump also cite studies suggesting that long fibers interfere with cellular division in a way that short fibers do not. There is evidence presented in some of these studies that specifically it is fibers longer than 15 µm that interfere with mitosis [Jensen CG and Watson M, Cell Biology International 23(12): 829-840, 1999, and Jensen CG et al., Carcinogenesis 17(9): 2013-2021, 1996) specifically refer to this as an effect of long fibers - either 15-80 µm long, in the 1999 paper, or 15-55 µm long, in the 1996 paper. Thus based on this mechanistic information one might suggest a cutoff of about 15 µm.

C] To what extent do animal studies (e.g., studies by Davis and other researchers) suggest that carcinogenic potency varies with *fiber type* and *fiber length*?

There is little if any evidence from animal studies that carcinogenic potency for lung cancer by fiber type. The statistical analyses of the toxicologic data by Berman et al. [1995] failed to demonstrate any significant difference in carcinogenic potency for lung cancer by fiber type. It is suggested in this report [page 7-151] and elsewhere that this may be a reflection of the fact that animals have a much shorter lifespan than humans, and that given the long half-life of amphiboles the difference in potency might only be observable in humans. However, this arguments seems to conflict with the fact that the analysis by Berman et al. [1995] was able to detect a difference in potency by fiber type for mesothelioma.

There is extensive evidence from toxicologic studies that fiber size is an important determinant of carcinogenic potency. The inhalation studies of Davis and co-workers [Davis et al. 1986; Davis and Jones, 1988] clearly demonstrated the effect of fiber size on potency. The total exposure concentration was held constant in these studies, and the preparations that contained a high proportion of long fibers were markedly more potent than the same fiber type with a short fiber length. The long amosite (with fibers up to 100 µm long) produced 11 lung tumors and 3 mesotheliomas in 40 rats; the short-fiber preparation (with fibers only up to 10 µm) produced no lung tumors and 1 mesothelioma in 43 rats. The long and short chrysotile preparations were not as different in lengths as the amosite, but Davis and Jones stated that the long-fiber preparation had over 80 times as many fibers > 30 µm than the short-fiber preparation. In this case the long-fiber preparation produced approximately three times as many pulmonary tumors as the short-fiber preparation. Similar differences in pathogenicity were seen for mesotheliomas, as well, in intraperitoneal injection studies comparing long and short fibers. There are other studies in the tox literature that also suggest greater pathogenicity for long fibers, but the Davis et al. studies are sufficient to demonstrate the magnitude of the response differences that have been seen.

D] Please comment on the extent to which carcinogenic potency is a function of fiber properties (e.g., diameter, aspect ratio, surface properties) *other than* fiber type and fiber length. How adequate is information in the epidemiology or toxicology literature for supporting these other properties into dose-response analyses?

There is no epidemiologic data available to address this question.

Toxicologic evidence that carcinogenic potency for lung cancer is associated with fibers > 0.15 µm in diameter was reviewed by Lippmann, Environ Res 46: 86-106, 1988. In addition, the analysis of Berman et al., Risk Anal 15: 181-195, 1995 suggests that fibers as large as 5 µm in diameter may be carcinogenic in the rat. In contrast, mesothelioma has primarily been associated with very thin fibers; Stanton et al., J. Nat'l Cancer Inst. 67: 965-975, 1981; reviewed by Lippmann, Environ Res 46: 86-106, 1988

2) For *mesothelioma*:

A] Influence of *fiber type*: Please comment on the extent to which the epidemiology literature and mechanistic studies suggest that carcinogenic potency varies from one *fiber type* to the next (e.g., chrysotile versus amphibole fibers). How adequate is the information in the epidemiology literature for supporting dose-response analyses for different *fiber types*? Specifically, to what extent do you think the proposed risk coefficients in Table 6-29 are supported by the epidemiology literature?

I believe that the hypothesis that the risk of mesothelioma varies by fiber type is pretty well established. The epidemiologic literature clearly demonstrates much higher incidence of mesothelioma among workers exposed to amphiboles than to chrysotile. For example the percentage of deaths in South African miners exposed to crocidolite is approximately 4.7% [Sluis-Cremer, 1992], and 2.4% among vermiculite miners [McDonald et al. 1986]; whereas, the percentage of deaths from mesothelioma among Quebec chrysotile miners and millers was only 0.4% [McDonald et al. 1993] and only 0.2% among South Carolina textile workers exposed to chrysotile [Dement et al. 1983]. In contrast to lung cancer, the meta-analysis performed in the report of the K_ms for mesothelioma indicated that the ratio of potencies for chrysotile and amphiboles was highly statistically different ($p < 0.001$) than 1 (See Table 6-21).

Although there are clear differences in mesothelioma risk by fiber type, the actual values of the risk coefficients presented in Table 6-29 have limited support from the epidemiologic literature. Exposure-response information for estimating slopes (K_ms) was generally not available in these studies, and the K_ms could only be crudely estimated with assumptions about the average

exposures for most of these cohorts. True exposure-response relationships could only be determined from the studies by Liddell et al. [1997] and Dement et al. [1994], since these investigators made their data available to the authors of this report.

I am not aware of mechanistic data that indicates carcinogenic potency for mesothelioma varies by fiber type, although I must confess here that I am not totally up to date on my reading of this literature.

B] Influence of *fiber length*: Please comment on the extent to which the epidemiology literature and mechanistic studies suggest that carcinogenic potency varies with *fiber length*. How adequate is information in the epidemiology literature for supporting dose-response analyses for different *fiber lengths*? In general, is it appropriate to assess cancer risks using an exposure index (see Equation 7.13) that is weighed heavily by fibers longer than 10 micrometers (μm)? (Note: Topic area 2 includes more detailed questions on the proposed exposure index.)

There is virtually no data available in the epidemiologic literature to evaluate how the carcinogenic potency for mesothelioma varies by fiber length. It is interesting to note, however, that the K_ms (0.013 for Asbestos, and 0.021 for Thedford) derived in this report from the analysis of raw data from the Quebec study of miners and millers [Liddell et al. 1997], was nearly an order of magnitude lower than the K_m (0.11) derived from analysis of the raw data from the South Carolina textile cohort. This may be consistent with the argument that the exposures in South Carolina had a larger percentage of long fibers, than in the Quebec mines and mills [Dement and Wallingford 1990], and thus with the hypothesis that longer fibers have higher carcinogenic potency for mesothelioma. On the other hand, the fact that the K_m for the cement plant study by Hughes et al. [1987] was higher than the South Carolina textile plant would seem to contradict this hypothesis, since Dement and Wallingford [1990] also suggested that the exposures at the South Carolina textile facility had a higher percentage of long fibers than the exposures at the cement factory.

There is no epidemiologic evidence to support the choice of the specific exposure index that is proposed in this report [Equation 7.13].

C] To what extent do animal studies (e.g., studies by Davis and other researchers) suggest that carcinogenic potency varies with *fiber type* and *fiber length*?

The toxicological evidence to suggest that the carcinogenic potency for mesothelioma varies by fiber type is limited. There is considerable evidence from the toxicologic studies using fiber implantaion that fiber length is an important determinant of carcinogenic potency for mesothelioma, but there is very limited data from inhalation studies. Part of the problem with answering this question is that very few mesotheliomas are produced in rodent studies where the route of exposure is via inhalation. The inhalation studies by Wagner et al. [1974] and the studies by Davis et al. produced small numbers of tumors, and overall provide little evidence [see review by Stayner et al. 1996]. The analysis by Berman et al. [1995] does suggest that chrysotile is approximately 3 times less potent than amphiboles. However, there too few cases (n=13) to perform a direct evaluation of this question and it was evaluated by testing whether a direct constant of proportionality could be applied to the probability of lung cancer and mesothelioma. It was found that this proportionality constant was weakly significantly (p=0.032) for chrysotile and amphiboles. It should be noted that this analysis does not take into account differences in the fiber size distributions, and only indirectly the exposure level.

D] Please comment on the extent to which carcinogenic potency is a function of fiber properties (e.g., diameter, aspect ratio, surface properties) *other than* fiber type and fiber length. How adequate is information in the epidemiology or toxicology literature for supporting these other properties into dose-response analyses?

There is no data from epidemiologic studies to evaluate these questions.

3)To what extent are the exposure estimates documented in the asbestos epidemiology literature reliable?

The potential for exposure misclassification in many of the epidemiologic studies is extremely large, and possibly introduces far more uncertainty than the adjustments used by the authors of this report. Exposure intensity and even duration of exposure had to be estimated for many of the studies included in this analysis. For example, the study by Selikoff and Seidman of U.S. insulators did not include information on duration of exposure, and the US EPA (and this report) simply assumed that all workers in this study were exposed for 25 years, and to 15 f/ml in order to calculate a K_l.

There are also large uncertainties in the exposure estimates for studies that included analyses by cumulative or average asbestos exposure. One of the key issues is the conversion of measurements from impingers (mpcf) to the more modern methods based on PCM or TEM.

This may in fact be an explanation for the differences in potency between the South Carolina chrysotile textile cohort, and the Quebec chrysotile miners and millers study, which is a critical issue in this risk assessment. The South Carolina textile worker study included extensive side by side measurements for the conversion. It is noted in the report (page 5.3) that the conversion factors for the Quebec study came from studies at other facilities. It is also noted in this report (page 6.43) that in the mining environment there is a large potential for interference in using the impinger method and even the PCM method from non-asbestos dust and cleavage fragments. This suggests the possibility that fiber counts may have been over estimated in the Quebec study, which may explain in part the lower carcinogenic potency observed in this facility relative to the South Carolina cohort.

Topic Area 2: The proposed exposure index.

4) The proposed exposure index does not include contributions from fibers shorter than 5 µm. Please comment on whether the epidemiology and toxicology literature support the conclusion that asbestos fibers shorter than 5 µm present little or no carcinogenic risk.

The epidemiologic literature does not have any information to contribute to this question. The toxicologic literature does, and it does strongly indicates that fibers shorter than 5 µm have little if any carcinogenic risk. For example, the multivariate analyses by Berman et al. (1995) indicated zero potency for fibers shorter than 5 µm. However, I think we need to be somewhat cautious here about overinterpreting these findings. It is still possible that short fibers (<5 µm) have a very low carcinogenic potency, and that the toxicologic studies did not have adequate statistical power to detect the level of risk associated with exposures to these fibers. One might expect short fibers to have similar carcinogenic potency as has been observed for other particles such as titanium dioxide or carbon black.

5) The proposed exposure index is weighed heavily by fibers longer than 10 µm. Specifically, Equation 7.13 suggests that the carcinogenic potency of fibers longer than 10 µm is more than 300 times greater than that of fibers with lengths between 5 and 10 µm. How consistent is this difference in carcinogenic potency with the epidemiology and toxicology literature?

There is virtually no information in the epidemiologic literature to address this question. There is also very limited information from the toxicological literature with the exception of the paper by Berman et al. [1995], and even this paper does not clearly support the factor of 300, which appears to have been chosen somewhat arbitrarily (i.e., using an "ad hoc method"). Unfortunately, the Berman et al. paper did not present a model comparable to the proposed index. The closest model shown is the "intermediate" analysis, and in this analysis the potency of fibers that are 5 to 10 µm long is only approximately 1/4th less than 10-20, 1/10th less than 20-40, and 900 times less than >40 µm. Based on this model it would seem that assuming a factor of 300 in potency between fiber 5 and 10 µm, and > 10 µm would only make sense if a very larger percentage of the fibers > 10 µm were > 40 µm. It would be very informative if the analysis by Berman et al. could be repeated using the proposed exposure index.

One also must be concerned that this formula is based solely on the analysis of toxicological data. One might expect that humans might show a very different pattern in risk related to fiber size, given species difference in respiratory anatomy and the size of human and rat macrophages. The site of lung tumors is also different with rats developing tumors in the alveoli, and humans in the bronchus. Given these species differences, one would strongly suspect that the relationships between fiber size and carcinogenic potency could be species specific.

6) Please explain whether the proposed exposure index will allow meaningful comparisons between current environmental exposures to asbestos and historical exposures to asbestos that occurred in the work place.

At this time, it is not possible to use the exposure index to make meaningful comparisons between current environmental exposures and workplace because the workplace studies have not included the exposure measurements needed to use the index.

Topic Area 3: General questions.

7) The proposed risk assessment approach assigns carcinogenic potency to individual fibers and to cleavage fragments (or "bundles that are components of more complex

structures"). Please comment on whether cleavage fragments of asbestos are as toxicologically significant as fibers of the same size range.

I am unaware of any epidemiologic or toxicologic studies that have direct bearing on this question. It is interesting to note the concern raised in this report that studies of miners may have included counting of cleavage fragments, and that this might account for the very low lung cancer risk detected in these studies.

7) Please comment on whether the proposed cancer assessment approach is relevant to all amphibole fibers or only to the five types of amphibole fibers (actinolite, amosite, anthophyllite, crocidolite, tremolite) designated in federal regulations.

I am not convinced that the proposed methodology is even relevant for the amphiboles designated in federal regulation let alone for other fiber types.

8) The review document recommends that asbestos samples be analyzed by transmission electron microscopy (TEM) and count only those fibers (or bundles) longer than 5 µm. Such counting practices will provide no information on the amount of asbestos fibers shorter than 5 µm. To what extent would data on shorter fibers in samples be useful for future evaluations (e.g., validation of the cancer risk assessment methodology, assessment of non-cancer endpoints)?

I think its obvious that if we ever want to be able in the future to answer the question as to whether or not fibers < 5 µm are carcinogenic, than we will need to have studies in which these fibers are measured.

9) The proposed risk assessment methodology suggests that exposure estimates should be based only on fibers longer than 5 µm and thinner than 0.5 µm. Is this cut-off for fiber *diameter* appropriate?

In the "optimum" model in the paper by Berman et al., fibers longer than 40 µm, and > 5 µm in diameter showed a relatively high carcinogenic potency. This would suggest that 0.5 µm is not an appropriate cutoff, particularly when you have long fibers.

11) Discuss whether the proposed cancer assessment approach, as a whole, is a reasonable evaluation of the available health effects data. What aspects of the proposed cancer assessment approach, if any, are inconsistent with the epidemiology or toxicology literature for asbestos?

I believe what this report has done is clearly identify weaknesses in the current methodology using for measuring asbestos exposure, and for assessing risk. The choice of a 5 μm cutoff with a 3 to 1 aspect ratio was clearly arbitrary, and not based on biologic principles as much as on the available sampling methodology. However, I am afraid the proposed methodology is also quite arbitrary, and lacks a solid scientific basis. I am most concerned that lower index for chrysotile and lung cancer risk is not supported by the analysis of the epidemiologic data. I am also concerned that while the proposed exposure metric may have more plausibility than the current one, that it still needs further evaluation before being adopted. In particular, I think that there is a real need to reanalyze some of the key epidemiologic studies using this index and other possible indices based on TEM analysis to determine what an appropriate index is.

12) Section 8.2 of the review document presents three options for assessing cancer risks from asbestos exposure. Please comment on the technical merit of the proposed risk assessment options.

Obviously the first option (using the dose-response model and a life table) is the most accurate, but the second (estimating risk from a life table) should be reasonably accurate under most circumstances (i.e., excess risks less than 1 per 100). As far as ease of use, of course the 3rd option is the easiest although the least reliable. All three methods may be useful for different audiences. EPA officials would probably want in most cases to use the first option since it is the most accurate. On the other hand, the unit risk option might be most appropriate for the lay public and this is what EPA might want to continue to use in its IRIS database.

Other Comments:

This document is in serious need of editing, and in many ways is a very rough draft. I have the following editorial and other minor comments to offer:

1) Page 4.21 – It seems that a bullet should be added stated that there are important species differences in the morphology of the lung and pleura, and these differences may have important implications for risk assessment.

2) Page 5.7, next to last paragraph – There is a missing reference (REF).

3) Page 6.17, last paragraph – it is stated that the animal data suggests that tumorigenecity is a function of in-vivo durability. However, this statement seems to be inconsistent with the fact that the animal studies have generally failed to demonstrate a difference carcinogenic potency between chrysotile and the amphiboles. The section 7.2.4 that is referred to is merely a discussion of differences in dissolution rates and does not provide any evidence to support this statement.

4) Chesson et al 1989, which is a critical reference cited several times in this document (e.g. page 6.46), is listed in the references as "Submitted for Publication 1989"?

5) In the meta-analyses of K_L and K_m I hope that they have not included both the McDonald and Dement analyses of the South Carolina cohort. This would obviously be a mistake.

6) Page 6.61 -The improvement in the range of K_L from when adjustments were made is not very impressive and seems to be due to improvements solely in the agreement between the South Carolina textile and Quebec miners studies. I am not sure that this can be interpreted as providing justification for the new index as the report does.

7) Page 6.65, formula 6-12 – the symbols for this formula need to be defined.

8) Page 6.69, last paragraph – It should be noted that the differences in mesothelioma risk was not statistically significant, which is clear in the presentation in the appendix.

9) Page 6.70 – It should be noted that the model does not fit locations 2 or 3&4 very well.

10) Page 6.90 – For the conservative risk coefficients why not use the largest value for chrysotile rather than only using the largest values for crocidolite and then scaling chrysotile?

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EPA asbestos document (Berman and Krump), comments by Kyle Steenland, 2/10/03

Summary of approach

Exposure-response estimates based on a linear relative risk model for lung cancer, and an absolute risk model for mesothelioma, were re-calculated on summary data from the 15-20 epidemiologic studies in the literature with exposure-response data. For lung cancer, these analyses were based on SMRs comparing exposed populations to large non-exposed populations with background rates, and in the re-calculation an additional parameter was estimated as a multiplier of background rates. Using the results of these analyses, a meta-analysis of exposure-response coefficients was then conducted, for both lung cancer and mesothelioma. A correction was applied to exposure-response coefficients for lung cancer and mesothelioma based on fiber size (more weight on long thin fibers) and on fiber type (more weight on amphiboles vs chrysotile). The fiber size correction was taken a priori from animal data tempered by limitations in available exposure data, while the adjustment for fiber type was estimated from the data. The fiber type adjustment results in separate exposure-response estimates for chrysotile and amphiboles, a major difference from the current EPA approach. The fiber size correction has fewer implications.

The authors have done a thorough and competent job synthesizing a large body of literature and data, and have taken inventive approaches to old questions. Nonetheless, I have some questions and disagreements as outlined below. My comments are focused on epidemiologic issues, which is my area of expertise.

General comments

I. Style of the document.

It is actually quite difficult to de-cipher the text, the heart of what was done is contained in a few pages of a very long document. This document could be simplified. For example, pages 6.1-6.30 could be put in an appendix, as their results are essentially never used by the authors. I have put my comments on page 6.1-6.30 at the end of this document. Similarly, the animal data in section 7 seems to be summarized at the end on pages 7.148 through 7.158, and it is not clear to me that the preceding pages could not be reduced in size.

II. Meta-analysis of exposure response coefficients.

The meta-analysis differed from customary meta-analyses (DerSimonian and Laird, 1986) in which a random effects model is used (in the presence of heterogeneity) and an inverse-variance weighted average of study-specific exposure-coefficients is calculated (with the variance reflected in the confidence interval of each study-specific estimate), along with the addition of a variance component for between study heterogeneity. Here, in contrast, the between-study

variance component was estimated via a likelihood approach, a parameter for weighting fiber-type was also estimated via likelihood, and the individual study variance (confidence interval) was inflated in a way described in the Appendix.

This approach is not unreasonable, and is of importance in the estimation of the fiber-type weighting parameter from the data. One thing not clear, however, is the inflating of confidence intervals for each study as indicated in the Appendix. First, it should be made clear in the text that these inflated confidence intervals are used uniformly throughout the text, which I believe is the case – it would be better to consistently give them a different name altogether (eg, 'reasonable range' which is used sometimes). More importantly, Appendix A is not clear on how these inflated confidence are in fact calculated. They seem rather arbitrary. There appears to be an assumed value of 1.0 for up to 4 factors. This value would not appear to make sense as the formula in Appendix A has the logarithm of these factors, which would then be 0. I must be missing something here.

A different and more traditional approach, perhaps more transparent, would be estimate the weighting factor for fiber type from the data and then use it in a traditional meta-analysis, in which the traditional study-specific variances (CIs) are used, and an additional variance component (which would cover all the factors in Appendix A) was taken as the between study variance.

III. Why SMRs in the lung cancer re-analysis?

For lung cancer, why were internal analyses not considered, rather than SMRs?. Use of SMRs leads to correction of background rates (estimation of 'alpha') for background rates, which in turn changes the estimated exposure-response coefficients. The raw data for the meta-analysis given in the Appendix uses a Poisson-SMR model in which background rates are incorporated. It is not clear why a Poisson model could not be used in internal analyses without recourse to national rates, which would get rid of the need to estimate the extra parameter alpha (background correction).

IV. Why these models (the usual EPA models for lung cancer and mesothelioma)?.

Given that the authors have re-calculated exposure-response data for each study, why were models restricted largely to the usual EPA models? Why not the more common statistical models, such as the usual log-linear relative risk model for lung cancer?

For mesothelioma, the usual EPA model was originally based on animal data and mechanistic considerations. It is not a model used for any other disease, to my knowledge. The model, which is based on absolute risk rather than relative risk, is based on an average intensity

and time since first exposure, with no consideration of cumulative exposure. Cumulative exposure is the metric of interest in most occupational cancer studies. For example, it is the metric of interest used here for lung cancer (and lung cancer models do not include time since first exposure). This discrepancy between these two models could be mentioned.

If there is a reason to accept the EPA models a priori for historical reasons this should be stated. Of course, one reason is to simplify the task.

V. Throw out the outliers?

Another suggestion would be to throw out outliers, such as any plant where there is no exposure-response for lung cancer (this contradicts the great bulk of the evidence) and perhaps the Ontario plant for mesothelioma, where mesothelioma deaths were almost as numerous as lung cancer deaths.

Comments on adjustment for fiber size and fiber type.

The charge for peer reviewers primarily relate to these two questions.

The authors claim that 'by adjusting for fiber type and fiber size, the existing data base of studies can be reconciled adequately to reasonably support risk assessment'. The basis of this statement is not clear. Adjusting for fiber type and fiber size reduces somewhat the heterogeneity of the data; nonetheless, the heterogeneity remaining within the categories of amphibole and chrysotile studies remains very large, and any decision to accept a common risk coefficient across such heterogenous data is more a policy than a statistical decision (the authors do not do any tests for heterogeneity, referring rather to non-overlapping confidence limits, but tests are somewhat superfluous in the face of large and apparent heterogeneity.)

Adjustment for fiber type. Mesothelioma. It would appear that there is reasonable evidence that adjustment for fiber type is worthwhile for mesothelioma, in that the amphibole cohorts appear to have considerably higher risks than the chrysotile cohorts. However, there is great heterogeneity within the amphibole cohorts, making prediction within them quite difficult (the controversy over Whitenoom exposure estimates further increases uncertainty here, see below under 'minor points'). Furthermore, the chrysotile cohorts are also quite different, ie, between Quebec and S. Carolina/N. Orleans. The Carolina and New Orleans cohorts show high risk, and approach the lower bounds of some of the amphibole cohorts. Nonetheless, given the general increase in risk for all the amphibole cohorts vs the chrysotile cohorts, some adjustment for fiber type appears justified.

Animal data also apparently tends to support an increased risk of mesothelioma for amphiboles.

Adjustment for fiber type. Lung caner. The evidence for adjustment for fiber type for lung cancer is more problematic, in that it relies almost exclusively on the low risk among Quebec chrysotile miners, or conversely on the high risk for Carolina textile workers and New Orleans cement workers exposed to chrysotile. The discrepancy of results these results for these 3 cohorts is unresolved, and yet upon it rests the conclusion that the lung cancer risk as substantially different between amphiboles and chrysotile. The evidence is weak, in my view, to make an adjustment for fiber type for lung cancer risk.

The animal data do not clearly indicate that lung cancer risk is higher for amphiboles vs chrysotile, further weakening the case for adjustment for fiber type for lung cancer. Theories about the short life of rats and the over-whelming of clearance mechanisms have been proposed to explain the lack of difference in rats by fiber type, but these explanations do not appear to have explained away the issue.

Adjustment for fiber size. The adjustment for fiber size on page 6.50 (a re-weighting of traditional exposure measures used in the current standards, which are based on fibers longer than 5 um and with a 3:1 aspect ratio and greater than 0.25 um diameter) is taken from the animal data in which long thin fibers (>40 um) appear to be more carcinogenic, plus an ad hoc recognition that the epidemiologic studies permit exposure measures only based on a dichotomy of greater or less than 10 um in length (so that a re-weighting using 40 um cannot be done).

The data supporting the carcinogenicity of long and thin fibers appear reasonably uncontroversial. The application of this adjustment in fact does not change much the observed heterogeneity in the data. Another possible approach to adjusting for fiber size is to pick the weighting (currently 0.3% for <10 um, 97.7% for >10 um) such that heterogeneity in the data is maximally reduced. In practice so little weight is given to fibers <10 um that their weighting could simply be 0.

More minor points

a) Specific comments on pages 6.1-6.30.

While they are interesting exercises, it is not clear to me why the analyses of raw data for two specific cohorts was done, given the limited inferences which can be drawn about the universe of asbestos studies (a pooled analysis of all existing data, as opposed to a met-analysis, would be ideal but very time-consuming and possibly impractical). Tentative conclusions about the current EPA model are drawn based on these two studies, based on sparse data, which do not strike me as valid. In particular inferences about the pattern of rate ratios after employment termination strike me as unwarranted, as they are based on very sparse data. Time-related patterns of RRs, eg, stratified by time since termination, are affected by other variables involving the healthy worker survivor effect, independent of cumulative dose. Estimation of models using various assumptions about internal dose vs external dose are focused on patterns for time-since-termination. It might be more interesting to first evaluate dose-response by cumulative dose using estimates of internal dose vs external dose. But in any case, if only two cohorts can be studied using raw data, it does not seem worth the effort, as no generalizations can be extrapolated to other studies.

Similarly, it was not clear to me why the multi-stage model was included in the analysis of two cohorts . Again, while this was an interesting exercise, it could have been predicted that this model – which has not been adopted by epidemiologist conducting occupational studies – is complex and involves estimating a large number of parameters based on biological assumptions. It is difficult to interpret these parameters

b) There is a dispute about exposure levels in Whitenoom which is not reflected in this document, whereby exposure levels may have been overestimated by 4-10 times (see Hodgson and Darnton, 2000). This becomes relevant (see below), given the large weight of this study (large numbers of cases).

c) As a general comment, it would be worthwhile if the authors were to add the observed numbers of cancers to Table 6.12. These would enable an immediate appreciation of the strength of evidence provided by each study.

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CHARGE QUESTIONS

Topic Area 1: Interpretations of the epidemiology and toxicology literature.

1) For *lung cancer*:

A] Influence of *fiber type*: Please comment on the extent to which the epidemiology literature and mechanistic studies suggest that carcinogenic potency varies from one *fiber type* to the next (e.g., chrysotile versus amphibole fibers). How adequate is the information in the epidemiology literature for supporting dose-response analyses for different *fiber types*? Specifically, to what extent do you think the proposed risk coefficients in Table 6-29 are supported by the epidemiology literature?

There is compelling evidence from epidemiologic and mechanistic studies that carcinogenic potency varies by fiber type with chrysotile being a less potent lung carcinogen than the amphiboles. The formal analysis of the cohort studies included in the Berman/Crump report illustrates this fact, even after adjustment for fiber size. There are 16 cohort studies with quantitative data upon which to base these analyses and published studies with average TEM fiber size distributions relevant to all but two of them. This is adequate information. While uncertainties remain related to some of the assumptions and adjustments made in this methodology, the end result is much greater homogeneity among the studies within each fiber type and a clear distinction in risk between chrysotile and the amphiboles.

The analysis of relative risk (RR) with time, using raw data from Wittenoom (crocidolite) and SC (primarily chrysotile), is also informative with respect to potency variability. The RR remains constant after exposure for the Wittenoom miners but diminishes with time since last exposure for the textile workers. This is consistent with the findings of Finkelstein and Dufrensne (1999) that chrysotile splits both longitudinally and transversely in the human lung and that lung burdens decrease substantially with cessation of exposure. The breakdown of chrysotile and its greater solubility has an inverse relationship with tumorgenicity. Although fiber size is the stronger influence on biopersistence, both rodent and human pathology studies indicate that in vivo durability (solubility) is a predictor of clearance and it is dependent on fiber mineralogy.

While unable to distinguish the effects of fiber size and type, the large body of asbestos epidemiologic studies, not included in this report because of inadequate exposure data for exposure-response modeling, is very consistent with the lesser potency of chrysotile. For example, Camus et al., (New England Journal of Medicine 1998; 338: 1565-71) reported no excess risk of lung cancer in a population of women with relatively high levels of nonoccupational asbestos exposure from two chrysotile asbestos mining regions. However, there are numerous examples of bystander and domestic amphibole exposures [e.g., shipyard, asbestos cement] linked with increased lung cancer rates. There is no clear evidence of increased lung cancer risk among vehicle mechanics despite potential exposure to chrysotile in brake dust and little or no risk associated with manufacture of (chrysotile) friction products. Similar fiber type risk differences have even been observed within the same cohort (e.g., Ohlson et al. 1984 Mortality among asbestos-exposed workers in a railroad workshop. Scand J Work Environ Health 10: 283-291) or industrial group (chrysotile v. amosite cement cohorts). The contrast in lung cancer risk among female gas mask workers follows a similar clear pattern of lower risk among those exposed to chrysotile than crocidolite. The exception of course is the textile manufacturing studies, where fiber size and the extent of mixed exposures to amphiboles confound the ability to address variability in risk due to mineralogy.

As Berman and Crump point out, the existing EPA model provides an adequate description of lung cancer mortality for the Wittenoon cohort but may not be adequate for the SC cohort. These findings, in addition to the differences observed in the optimized coefficients upon adjustment for fiber size (Table 6-29) and the consistent mechanistic data, provide compelling evidence that the dose-response curves for chrysotile and the amphiboles are too disparate to be represented by one curve or model.

The optimized coefficients for pure fiber types with a ratio of 5.3:1 (amphiboles to chrysotile) in Table 6-29 successfully reduce study potency variability (33% from a factor of 90 (based on 18 studies) to 60 (based on 16 studies)). Since the coefficients have been

adjusted for fiber type and size, a straightforward quantitative assessment of consistency with epidemiology studies may not be feasible. Furthermore, since the most informative epidemiology studies have been used to derive these values, they cannot be used as an independent test of consistency. This might have been possible, had some studies been excluded from the derivation of the coefficients. In this case, predictions based on the coefficients could have been compared to what was observed in the study cohorts. The disadvantage, of course, would be the reduction in the number of studies and the associated increased uncertainty in the optimization procedure. Would it be possible, however, to examine the observed number of lung cancer cases in each study against predicted, using the optimized coefficients to evaluate the goodness of fit?

B] Influence of *fiber length*: Please comment on the extent to which the epidemiology literature and mechanistic studies suggest that carcinogenic potency varies with *fiber length*. How adequate is information in the epidemiology literature for supporting dose-response analyses for different *fiber lengths*? In general, is it appropriate to assess cancer risks using an exposure index (see Equation 7.13) that is weighed heavily by fibers longer than 10 micrometers (μm)? (Note: Topic area 2 includes more detailed questions on the proposed exposure index.)

Epidemiology and mechanistic studies provide convincing evidence that fiber size and shape (length and diameter) are important predictors of carcinogenic risk. Mechanistically, fiber dimension is related to respirability, deposition, degradation, clearance and translocation and, therefore, is a major determinant of cumulative dose to the lung. Attempts to relate potency to asbestos air concentrations or worse, measures of dust containing asbestos, results in extreme variability in potencies, both among different fiber types and within the same fiber type.

The detailed review of experimental data from rodents and humans in the Berman/Crump report show that: short fibers (<10 um) are cleared much more quickly than long (>20 um) insoluble fibers, short fibers do not induce fibrosis, long fibers produce substantial inflammation, and deposition and translocation depend predominately on fiber size, while durability depends mostly on fiber type. Even longer fibers may be cleared efficiently if

they are soluble. Studies were examined that included varying fiber lengths within the same fiber type to enable distinctions to be made, free of confounding. Both the epidemiology and mechanistic data support using a weighted exposure index that recognizes the predominant influence of fibers longer than 10um.

The analysis of the lung cancer crude potencies (not adjusted for fiber size) based on the Quebec miners and SC textile worker studies, together with a re-analysis of the lung pathology results of workers from these two locations are very informative. Higher measured concentrations in Quebec do not translate to higher lung cancer potency; in fact the epidemiology studies confirm higher lung cancer risks in the textile workers. The Berman/Crump analyses show that airborne concentration ratios between the two work settings are not predictors of lung burden (relative ratios of fiber types [chrysotile or tremolite]). More importantly, size distribution comparisons indicate that textile dust in SC may have been highly enriched with long tremolite fibers (>20 um). The published size distributions in these environments (Gibbs and Hwang, 1975, 1980) and knowledge of the raw fiber purchased by the textile plant further support these findings.

The absence of a clear increase in lung cancer in epidemiology studies of auto and brake mechanics, after adjustment for smoking, may be explained in part by the potential exposure to short fiber chrysotile, in contrast with the long fiber types in textile settings needed to facilitate weaving of the fibers.

Table 6-15 shows a clear correlation between fiber length and lung cancer potency coefficients. Wittenoom, however, seems to be an exception, with a predominance of shorter fibers and one of the higher potencies. Potencies adjusted for fiber size (by using the new exposure metric) are presented in Table 6-15. All coefficients increase by factors of 2 to 7, with the exception of Wittenoom, whose increase is less than 2, dropping it down to 9th most potent (of 20 cohorts). The Wittenoom results merit some discussion and clarification.

The Berman/Crump approach to adjusting the lung cancer potencies for fiber size (length and width) is very effective in reconciling the variability in the unadjusted estimates. This body of epidemiological data is adequate for supporting these dose-response analyses. The approach of using relevant TEM size distributions from the published literature to implement the size adjustment is both rational and innovative. The uncertainty values assigned, however, need to be more clearly explained and justified. The range of uncertainty values should be described for each consideration and the criteria used clarified.

C] To what extent do animal studies (e.g., studies by Davis and other researchers) suggest that carcinogenic potency varies with *fiber type* and *fiber length*?

As an epidemiologist, I will defer to the toxicologists on this issue.

D] Please comment on the extent to which carcinogenic potency is a function of fiber properties (e.g., diameter, aspect ratio, surface properties) *other than* fiber type and fiber length. How adequate is information in the epidemiology or toxicology literature for supporting these other properties into dose-response analyses?

Fiber diameter is a more important characteristic with respect to respirability (0.02-2um) than fiber length. In addition, experimental studies clearly show that long, thin fibers have the greatest potency. Few fibers thicker than 0.7 um appear to reach the deep lung. Berman and Crump make a persuasive case that maximum diameter is more important than aspect ratio as a criteria for an exposure metric. I do not think epidemiology informs this issue.

2) For *mesothelioma*:

A] Influence of *fiber type*: Please comment on the extent to which the epidemiology literature and mechanistic studies suggest that carcinogenic potency varies from one *fiber type* to the next (e.g., chrysotile versus amphibole fibers). How adequate is the information in the epidemiology literature for supporting dose-response analyses for different *fiber types*? Specifically, to what extent do you think the proposed risk coefficients in Table 6-29 are supported by the epidemiology literature?

The evidence from epidemiologic and mechanistic studies that carcinogenic potency varies by fiber type with chrysotile being less potent than the amphiboles is even more dramatic for mesothelioma than for lung cancer. The formal analysis of the cohort studies included in the Berman/Crump report illustrates this fact, even after adjustment for fiber size. There are 12 cohort studies with quantitative data upon which to base these analyses and published studies with average TEM fiber size distributions relevant to all but one of them. This is adequate information. (See 1A for comments regarding the mechanistic evidence.) While uncertainties remain related to some of the assumptions and adjustments included in this methodology, the end result is much greater homogeneity among the studies within each fiber type and a clear distinction in mesothelioma risk between chrysotile and the amphiboles (about 600 times more potent).

The percentages of deaths from mesothelioma in amphibole-exposed cohorts greatly exceed what is seen among workers primarily exposed to chrysotile. Paraoccupational and bystander mesothelioma excesses examined in formal epidemiology studies have been associated with amphibole exposures. In a recent publication, Case et al. identified six mesothelioma cases among women in the Quebec chrysotile mining region. All resided in Thetford, where the mines have a higher tremolite concentration and none in Asbestos. The ubiquitous uses of crocidolite in Australia have led to the highest rates of mesothelioma in the world. The clear increased rate of lung cancer in the SC textile cohort contrasts with the few observed suspect deaths from mesothelioma. The cases of mesothelioma identified in the Quebec miners and millers study track with the crocidolite exposure at location 2 and the higher tremolite content at Thetford. In a mostly chrysotile friction products plant, the 11 cases of mesothelioma were attributable to uses of crocidolite at the plant or other employment (e.g., Berry and Newhouse, 1983). The contrast in

lung cancer risk among female gas mask workers follows a similar clear pattern of lower risk among those exposed to chrysotile than crocidolite.

In addition, the current EPA model, which applies potency derived from cohorts heavily exposed to amphiboles, has been shown to overpredict mesothelioma in a chrysotile-exposed population (Camus et al., 2002).

The CT friction product plant studied by McDonald et al. (1984) with no reported deaths due to mesothelioma based on death certificates is worthy of comment, since it has had special treatment in this report. There were 3 deaths due to mesothelioma that were employed at this location, identified from the CT Tumor Registry as part of a case/control study (Teta et al., 1983; Letters to the editor, JOM 1986 28: 808-809). One man worked at an asbestos textile plant, 1921-32, which was the parent company to the friction products plant studied by McDonald. His hire date preceeded the start of her cohort, 1938, and involved amphibole exposure. There were two women whose cause of death on their death certificates did not list mesothelioma. One was classified as probably pleural mesothelioma and the other as a confirmed case of peritoneal mesothelioma during a pathological review. There were issues related to possible domestic exposures and possible involvement of other jobs, so it is not known whether these cases are attributable to exposure at the friction products plant. Peritoneal mesothelioma is virtually unheard of due to chrysotile exposure. The Berman/Crump report included in their analyses suspected mesothelioma cases from the SC textile cohort and cases in other studies for which there was possible involvement of other employment. This seems reasonable, given the under-reporting of cases in the past on death certificates. In this same spirit, perhaps the two women might be included in the analysis of the McDonald cohort.

The treatment, in general, of uncertain mesothelioma cases should be evaluated for consistency in computing Km values. For example, in Hughes, 1987, Kms were derived for chrysotile and amphibole cohorts separately. However, no Kms were calculated for Berry and Newhouse (1983), although the study had 0 cases exposed to chrysotile and 8-11 for crocidolite. Neither study permitted CIs to be computed directly.

The optimized coefficients for pure fiber types with a ratio of 600:1 (amphiboles to chrysotile) in Table 6-29 successfully reduce study potency variability, a remarkable reconciliation from a factor of 1000 to about 26. Since the coefficients have been adjusted for fiber size, a straightforward quantitative assessment of consistency with epidemiology studies may not be feasible. Furthermore, since the most informative epidemiology studies have been used to derive these values, they cannot be used as an independent test of consistency. This might have been possible, had some studies been excluded from the derivation of the coefficients. In this case, predictions based on the coefficients could have been compared to what was observed in the study cohorts. The disadvantage, of course, would be the reduction in the number of studies and the associated increased uncertainty in the optimization procedure. Would it be possible, however, to examine the number of observed mesothelioma cases in each study against predicted, using the optimized coefficients to evaluate the goodness of fit?

> B] Influence of *fiber length*: Please comment on the extent to which the epidemiology literature and mechanistic studies suggest that carcinogenic potency varies with *fiber length*. How adequate is information in the epidemiology literature for supporting dose-response analyses for different *fiber lengths*? In general, is it appropriate to assess cancer risks using an exposure index (see Equation 7.13) that is weighed heavily by fibers longer than 10 micrometers (µm)? (Note: Topic area 2 includes more detailed questions on the proposed exposure index.)

Epidemiology and mechanistic studies provide convincing evidence that fiber size and shape (length and diameter) are important predictors of carcinogenic risk. Mechanistically, fiber dimension is related to respirability, deposition, degradation, clearance and translocation and, therefore, is a major determinant of cumulative dose to the lung. Attempts to relate potency to asbestos air concentrations or worse, measures of dust containing asbestos, results in extreme variability in potencies, both among different fiber types and within the same fiber type.

As with lung cancer, it is evident from Table 6-15 that the unadjusted mesothelioma potencies for the 12 cohort studies correlate with fiber size, with the exception of Wittenoom, which ranks #2 in potency but #10 in total fibers > 10um. The most dramatic changes after adjustment are in the insulating manufacturing and insulator cohorts, whose potencies dramatically increased, due to the highest proportion of long fibers. The smallest change occurred for Wittenoom, consistent

with a distribution favoring short fibers (crocidolite). (Note: the KL values for Wittenoom and SC in Table 6-16 don't seem to agree to the values in Tables 6-1 and 6-2.)

The Berman/Crump approach to adjusting the mesothelioma potencies for fiber size (length and width) is very effective in reconciling the variability in the unadjusted estimates. This body of epidemiological data is adequate for supporting these dose-response analyses. The approach of using relevant TEM size distributions from the published literature to implement the size adjustment is both rational and innovative. The uncertainty values assigned, however, need to be more clearly explained and justified. The range of uncertainty values should be described for each consideration and the criteria used clarified. The authors might consider a section describing each decision in the process that was made to account for uncertainty, in both the use of TEM values from other studies and the F1-F4 factors related to exposure and other uncertainties.

> C] To what extent do animal studies (e.g., studies by Davis and other researchers) suggest that carcinogenic potency varies with *fiber type* and *fiber length*?

As an epidemiologist, I will defer to the toxicologists on this issue.

> D] Please comment on the extent to which carcinogenic potency is a function of fiber properties (e.g., diameter, aspect ratio, surface properties) *other than* fiber type and fiber length. How adequate is information in the epidemiology or toxicology literature for supporting these other properties into dose-response analyses?

I have nothing to add beyond my brief comment in 1 D.

3) To what extent are the exposure estimates documented in the asbestos epidemiology literature reliable?

Obviously, some studies have more complete and more accurate exposure estimates and the amount of error and imprecision is a function of time, with estimates of historical exposures being the most difficult to reconstruct. In the past they are more likely, however, to be worst case, with representative sampling becoming routine around the mid to late 1970s, if the chemical industry pattern in the U.S. holds. The authors used uncertainty factors (F1-F3) to account for uncertainties in exposure estimates for each of the studies: F1 for uncertain recreation

of past exposures, F2 for conversion and F3 for use of a crude estimate of average exposure. F4 was used for other types of uncertainties.

While these issues capture the key exposure factors, the choice of F values ("at least 1.5 and is at least 2 or more in most cases") is inadequately explained and appears arbitrary. Furthermore, the formula for the overall uncertainty factor (A.6), the square root of the exponent of the sum of the logs squared of the factors, needs more justification than the reasonable one that it accounts for errors in different directions. In addition, the factors are only applied to the confidence intervals (CI), as if the only influence on the coefficients would be related to random variability or precision. It is unclear how the CIs impact the final coefficients in Tables 6-29 and 6-30.

I would disagree with the use of F3 as an uncertainty factor and argue that use of an overall cohort average exposure is too uncertain and studies with this severe a limitation should not be used for exposure-response. It appears this occurs for only one study, Selikoff and Seidman, 1991. The limitation of this study is even greater because the average exposure concentration did not even come directly from the study itself. (A case study by Nicholson, 1976, is cited in the 1986 EPA Health Assessment). Furthermore, there were no data on duration of exposure, requiring another outside average to be used. This was a very important study with respect to identification of asbestos hazards, but the available information is not adequate for use in exposure-response analyses. Another study I would reconsider including in the exposure-response is Lacquet et al., 1980. The follow up is much to short and the exposure information inadequate.

Topic Area 2: The proposed exposure index.

4) The proposed exposure index does not include contributions from fibers shorter than 5 µm. Please comment on whether the epidemiology and toxicology literature support the conclusion that asbestos fibers shorter than 5 µm present little or no carcinogenic risk.

There is adequate evidence that fibers shorter than 5um present little or no risk. Experimental data confirm that clearance of fibers is dependent on fiber length and that short fibers do not produce fibrosis. Mechanistic and other experimental studies show fibers < 5 um clear readily

and the small proportion that do not clear are sequestered in alveolar macrophages. Fibers shorter than 10-20 um are almost completely handled by macrophages. The strongest evidence comes from Berman's re-analysis of the toxicological studies of Davis et al. using TEM based fiber length distribution data. None of the epidemiology studies have TEM data and there is no way to identify workers in the studies that are exposed only to fibers < 5 um. Therefore, epidemiology cannot specifically address this issue. There is corroborative epidemiology, however, in studies of vehicle and brake mechanics, who have potential exposure to short fiber asbestos (chrysotile) and have not been found to be at increased risk of mesothelioma in numerous studies examining this issue.

5) The proposed exposure index is weighed heavily by fibers longer than 10 µm. Specifically, Equation 7.13 suggests that the carcinogenic potency of fibers longer than 10 µm is more than 300 times greater than that of fibers with lengths between 5 and 10 µm. How consistent is this difference in carcinogenic potency with the epidemiology and toxicology literature?

This difference is based on the re-analysis of the Davis et al. studies, using TEM based fiber distributions. Other experimental evidence is corroborative indicating that fiber lengths shorter than 10 to 20 um are readily handled by macrophages. In addition, the optimum exposure index indicates little impact of exposures as high as 40 um in length.

As indicated in #4 above, epidemiology cannot offer specific guidance on this issue.

6) Please explain whether the proposed exposure index will allow meaningful comparisons between current environmental exposures to asbestos and historical exposures to asbestos that occurred in the work place.

Current environmental exposures to asbestos can be fully characterized by fiber type and size using TEM. Berman and Crump have characterized the exposures of workers in the cohort studies used for exposure-response by these same characteristics. Factors have been introduced, however, to address uncertainty in the exposure data from the studies and in the derivation of fiber size distributions from these studies for purposes of potency calculations and their CIs. Therefore, if I understand the question correctly, direct comparisons of exposure would not be a meaningful

exercise. However, use of the models with the new potency estimates can be effectively employed to estimate lifetime risk associated with the particular environmental circumstance.

Topic Area 3: General questions.

1) The proposed risk assessment approach assigns carcinogenic potency to individual fibers and to cleavage fragments (or Abundles that are components of more complex structures@). Please comment on whether cleavage fragments of asbestos are as toxicologically significant as fibers of the same size range.

   This issue is beyond my area of expertise.

2) Please comment on whether the proposed cancer assessment approach is relevant to all amphibole fibers or only to the five types of amphibole fibers (actinolite, amosite, anthophyllite, crocidolite, tremolite) designated in federal regulations.

I am not familiar with any other amphibole fibers and doubt that there is any epidemiology to inform the issue.

3) The review document recommends that asbestos samples be analyzed by transmission electron microscopy (TEM) and count only those fibers (or bundles) longer than 5 µm. Such counting practices will provide no information on the amount of asbestos fibers shorter than 5 µm. To what extent would data on shorter fibers in samples be useful for future evaluations (e.g., validation of the cancer risk assessment methodology, assessment of non-cancer endpoints)?

Since fibers shorter than 5 um do not contribute to fibrosis, there would be no value in collecting these data for non-cancer endpoints. To validate the risk assessment methodology, more research would be needed. The only circumstance I could think of that would be of interest is where there is an exposure scenario (e.g., work environment, environmental source) where exposures are limited to < 5 um and there is an ability to identify increased risk, if it existed for lung cancer and mesothelioma. It would be extremely difficult, however, to design a valid study with reasonable precision. Power issues and confounding exposures would likely be insurmountable.

4) The proposed risk assessment methodology suggests that exposure estimates should be based only on fibers longer than 5 µm and thinner than 0.5 µm. Is this cut-off for fiber *diameter* appropriate?

With the exception of mouth breathing, few fibers > 0.7 um in diameter reach the deep lung. And not all those that do will adhere to the lung surface. Experimental data also indicate that it is the fibers thinner than 0.7 um and longer than a minimum of 10 um that likely contribute to disease. Timbrell (1982) reported complete clearance of short (< 4 um) fibers with diameter less

than 0.6um. (Berman and Crump make another argument supporting 0.5 um as the cut-off related to diffusional diameter. This discussion is outside the scope of my expertise.) Reliance on the re-analyses of the Davis et al. toxicology studies using TEM based exposure results in an adequate fit of the data with a cut-off of 0.3 um diameter for structures between 1 and 40 um in length. Adequate fit was also seen with a 0.4 um cut-off. In light of this evidence 0.5 um seems appropriate.

5) Discuss whether the proposed cancer assessment approach, as a whole, is a reasonable evaluation of the available health effects data. What aspects of the proposed cancer assessment approach, if any, are inconsistent with the epidemiology or toxicology literature for asbestos?

This is a very impressive piece of work that considers all the evidence and integrates it effectively. The methodological approach is supported by a solid foundation of scientific evidence and data. Uncertainties in the human data are considered and factored into the method. The experimental data is carefully scrutinized and reasonably evaluated in a balanced fashion.

The variability in the results of the epidemiology studies are well described, but no standards are provided to judge the acceptability of the studies for risk assessment.

I found the epidemiology data to be accepted at face value as evidenced by the placement of study summaries in the Appendix. The information from these studies is fundamental to the methodology. Justification for the uncertainty factors needs to be clearer (see response to question #3). What criteria were used for acceptability of the studies for inclusion (see prior discussion of Selikoff and Seidman and Lacquet et al.)? I support the use of human data and the methodology proposed but question whether study quality and the suitability of each study for exposure-response was measured against any standard. I am not convinced that introducing the uncertainty factor, F4, for example, solves all the limitations unrelated to exposure, such as a sizeable proportion of subjects lost to follow up. Would it be more appropriate to exclude the study?

I see no substantive inconsistencies with the existing epidemiology and toxicology literature. The extreme variability in estimates of risk from the epidemiology studies has troubled scientists for

some time. It is well accepted in the scientific community that asbestos fiber size and type are key determinants of risk. More specifically, it is well recognized that the long, thin fibers are the most potent and that amphiboles have greater potency than chrysotile. This scientific understanding and a practical approach to applying it has been captured in the Berman/Crump proposed methodology. The result is a vast improvement in reconciling the differences in the epidemiology studies.

This is an innovative piece of work that vastly improves the risk assessment methodology for asbestos and makes excellent use of all the currently available scientific information.

6) Section 8.2 of the review document presents three options for assessing cancer risks from asbestos exposure. Please comment on the technical merit of the proposed risk assessment options.

I support options #1 and #2 as appropriate approaches to assessing cancer risks for asbestos exposure. They are both technically correct with option #1 being more flexible (e.g., can handle time-varying exposure), being the more general case; but option #2 being easier to implement (only need estimates of long-term exposure). Choosing between these options depends on the circumstances of the population of interest. To make a judgment about lifetime risk to an urban U.S. population with a relatively constant exposure, option #2 would be the easiest to use and would provide the same result, had option #1 been employed. If a demolition project is under consideration in which exposure concentrations might vary by task and workers would have various fixed durations of employment, then option #2 would not be suitable, but the more general case, option #1 would be.

I would not recommend option #3, some sort of combined unit risk, because it defeats the purpose of taking into account how potencies vary by fiber size and type and introduces an additional weighting procedure. While single unit risk estimates have the advantage of simplicity, the disadvantages in this case outweigh the advantage, particularly with the ease of use of the risk table.

Topic Area 4: Development of Conclusions and Recommendations

At the end of the workshop, the peer consultants will be asked to draft conclusion statements identifying their most notable findings on the proposed methodology. As a prelude to developing

these statements, the peer consultants are invited to provide any additional comments or concerns, both strengths and weaknesses, on topics not specifically addressed in the previous charge questions. After completing the discussions the peer consultants will prepare their conclusions, and they will also be asked to develop recommendations for how EPA can improve the methodology. Please note that, although recommendations for future research projects are welcomed, the focus of this workshop is on the proposed risk assessment methodology and how it may be used to support decisions at asbestos-contaminated sites.

Additional comments:

- It is noted in 6.65 that background cases of mesothelioma are rare in the general population. Is 2 per million, the estimate for the U.S. small enough to not impact the model?
- Why are 90% CI preferred in this document?
- Discussion of two-stage model may be better placed in the Appendix, since it didn't turn out to be useful
- Very long section on factors governing cellular and tissue response (i.e., mechanism of carcinogenicity) should be substantially shortened (with more detail in Appendix), since it resulted mostly in hypotheses that were not integral to methodology.
- Clarify how CIs are incorporated into final coefficients, if in fact they are. If not, how do the uncertainty factors make a difference?
- Would incorporation of a maximum latency period into the EPA model improve its performance?
- There is little discussion of peritoneal mesothelioma – would potency estimates be any different for this endpoint?
- P. 5.6 notes one needs incidence of meso. by "age at first exposure" to implement EPA model. Is this correct or should it be "time since first exposure"?
- P. 6.65, description of equation 6-12. "assuming that exposure remains constant" may be incorrect.
- P. 8.7 notes consistency with Stayner yet he concludes that with respect to lung cancer, epidemiology doesn't support lower potency for chrysotile?

- Is there any mechanistic data to understand why chrysotile is closer in potency to amphiboles for lung cancer but so much less potent than amphiboles for mesothelioma?

References

Berman DW and Crump K. 2001. Technical Support Document for a Protocol to Assess Asbestos-Related Risk. Final Draft. Prepared for U.S. Department of Transportation and U.S. Environmental Protection Agency. September 4, 2001.

EPA 1986. Airborne Asbestos Health Assessment Update. U.S. Environmental Protection Agency. EPA 600/8-84-003F. 1986.

Appendix C

List of Registered Observers of the Peer Consultation Workshop

Workshop to Discuss a Proposed Protocol to Assess Asbestos-Related Risk

Westin St. Francis
San Francisco, CA
February 25-27,2003

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Workshop to Discuss a Proposed Protocol to Assess Asbestos-Related Risk

Westin St. Francis
San Francisco, CA
February 25–27, 2003

Agenda

Workshop Co-Chairs: *Roger McClellan, Toxicology & Human Health Risk Analysis*
Leslie Stayner, National Institute for Occupational Safety and Health

Facilitator: *Jan Connery, Eastern Research Group, Inc.*

T U E S D A Y , F E B R U A R Y 2 5 , 2 0 0 3

8:00AM **Registration/Check-In**

8:30AM **Welcome and Announcements** . . . . . *Jan Connery*

8:35AM **Opening Remarks** . . . . . *Richard Troast*
U.S. Environmental Protection Agency (U.S. EPA)
Office of Solid Waste and Emergency Response (OSWER)
Office of Emergency and Remedial Response (OERR)

8:45AM **Peer Consultant Introductions and Conflict-of-InterestDisclosure** . . . . . *Facilitated by Jan Connery*

9:00AM **Goals, Purpose, and Ground Rules** . . . . . *Jan Connery*

9:10AM **Background on the Proposed Protocol to Assess Asbestos-Related Risk** . . . . . *Wayne Berman, Aeolus, Inc. and Kenny Crump, ENVIRON*

10:10AM B R E A K

10:30AM **Charge to the Peer Consultants**

T U E S D A Y , F E B R U A R Y 2 5 , 2 0 0 3 (c o n t i n u e d)

10:40AM **Topic Area 1: Interpretations of the Epidemiology and Toxicology Literature**
Discussions facilitated by Roger McClellan (Animal Toxicology and Mechanistic studies) and Leslie Stayner (Epidemiology)

LUNG CANCER

(1) Fiber Type
- *a. Epidemiology*
- *(b) Animal Toxicology and Mechanistic Studies*

12:00 Noon L U N C H (on own)

1:00PM **Observer Comment Period** . . . . . *Facilitated by Jan Connery*

2:00PM **Topic Area 1: Interpretations of the Epidemiology and Toxicology Literature**

LUNG CANCER (continued)

II. Fiber Dimensions and Surface Properties (length and other considerations)
- *a. Epidemiology*
- *b. Animal Toxicology and Mechanistic Studies*

3:30PM B R E A K

3:45PM **Topic Area 1: Interpretations of the Epidemiology and Toxicology Literature**

MESOTHELIOMA

II. Fiber Type
- *a. Epidemiology*
- *b. Animal Toxicology and Mechanistic Studies*

II. Fiber Dimensions and Surface Properties (length and other considerations)
- *a. Epidemiology*
- *b. Animal Toxicology and Mechanistic Studies*

5:30PM A D J O U R N

W E D N E S D A Y , F E B R U A R Y 2 6 , 2 0 0 3

8:00AM **Observer Comment Period**

9:00AM **Review of Day One Discussions and Day Two Charge to Peer Consultants**

W E D N E S D A Y , F E B R U A R Y 2 6 , 2 0 0 3 (continued)

9:10AM **Topic Area 1: Interpretations of the Epidemiology and Toxicology Literature**

EXPOSURE ESTIMATES . . . . . *Facilitated by Leslie Stayner*

9:40AM **Topic Area 2: The Proposed Exposure Index**

Question #4 . . . . . *Facilitated by Roger McClellan*

10:10AM B R E A K

10:30AM **Topic Area 2: The Proposed Exposure Index**

Question #5 . . . . . *Facilitated by Leslie Stayner*

11:15AM **Topic Area 2: The Proposed Exposure Index**

Question #6 . . . . . *Facilitated by Roger McClellan*

12:00Noon L U N C H

1:00PM **Topic Area 3: General Questions**

Question 7 . . . . . *Roger McClellan*
Question 8 . . . . . *Leslie Stayner*
Questions 9 . . . . . *Roger McClellan*
Question 10 . . . . . *Leslie Stayner*
Question 12 . . . . . *Leslie Stayner*
Questions 11 . . . . . *Roger McClellan*

3:15PM B R E A K

3:30PM **Discussion of Other Key Issues** . . . . . *Facilitated by Roger McClellan and Leslie Stayner*

4:50PM **Wrap Up of Day Two Discussions and Review of Goals for Thursday**

5:00PM A D J O U R N

T H U R S D A Y , F E B R U A R Y 2 7 , 2 0 0 3

8:00AM **Topic Area 4: Development of Conclusions and Recommendations**

10:15AM B R E A K

10:30AM **Topic Area 4: Development of Conclusions and Recommendations**

11:35AM **Closing Remarks**

11:45AM A D J O U R N

Appendix E

Observer Comments Provided at the Peer Consultation Workshop

Note: The peer consultation workshop included three observer comment periods, one on the first day of the workshop and two on the second day of the workshop. This appendix includes verbatim transcripts (to the extent that specific remarks were audible from recordings) of the observer comments, in the order the comments were given.

Appendix E
Observer Comments Provided at the Peer Consultation Workshop

Day 1, Comment 1: Jenny Bard, American Lung Association of California

I actually signed up today as a private citizen, but since I am listed with the American Lung Association, I would just say that we are keenly interested in the work you are doing for obvious reasons. Any time you look at cancer risks, and indeed lung-disease risk, from exposure to asbestos, our organization has been intimately involved with providing resources and assistance to people with lung disease and asbestos-related lung disease. So, we want to thank you for all the time and effort you are doing on this very important issue.

In fact, the American Lung Association of California and the California Thoracic Society have actually requested, just for the record, that due to public health concerns from naturally occurring asbestos (and, in particular, tremolite asbestos) in California; and, in fact, maybe I could just help you orient a little bit. This map shows all the locations of asbestos deposits in the state of California. We can post this. I'll leave it here for the three days. I will only be attending for today. The green on that map is considered asbestos, but it includes all the forms of asbestos. There is a yellow marker indicating the areas of specifically tremolite asbestos, and it is a very localized tiny little area, but you will see it up there.

We remain concerned that a public health threat from naturally occurring asbestos may exist to residents who live in these areas, especially in areas where tremolite out-croppings have been identified. In order to fully understand the public health impacts from naturally occurring asbestos, and to better characterize areas of potential concern for naturally occurring asbestos exposure, we support additional research, including air monitoring, soil sampling, and exposure studies in these areas. We are particularly concerned about tremolite and other types of amphibole asbestos fibers, because recent research has demonstrated that amphiboles pose the greatest public health threat, and indeed that is somewhat supported by the methodology that you are reviewing. We have asked for expanded and aggressive air monitoring and soil sampling for amphibole asbestos fibers, especially tremolite, in areas where soil has been disturbed due to construction or where out-croppings of tremolite asbestos have been identified, such as the Sierra foothills. We support additional research on exposure to naturally occurring asbestos to fill information gaps on naturally occurring asbestos exposure in non-occupational settings and to better characterize the risks to the general population in areas with this mineral fiber. And we support conducting epidemiological investigations of the health effects of tremolite and other amphibole exposure in order to identify the unique health impacts potentially associated with such exposures, including low-level.

So, that's my American Lung Association of California hat. Now I'm going to put on my private citizen hat. The proposed risk assessment recommends two additional studies to fill in the gaps in the findings. I believe it is an amphibole-only cohort and a chrysotile-only cohort. These are mostly occupational studies that you have been reviewing, but I'm hoping that you can begin to

think about environmental exposures as they are taking place in California. The Lung Association gets so many questions about exposure: is it harmful? is it harmful to be around a serpentine rock? should I have it covered? The same kinds of questions that we used to get inside the homes in terms of insulation, we are now getting regarding outside exposures: how much is in the dirt? when you disturb it, how many fibers are going to get into the air?

As an example of the types of potential exposures I am describing, I would like to hand out some pictures. To describe one scenario, I'm not trying to be site-specific, I'm bringing this up so perhaps you can visualize a real-life scenario where environmental exposures are taking place. You are looking at a dirt parking lot. The dirt parking lot is where the students park. This school and adjoining neighborhood have been built on top of tremolite asbestos veins. The soil testing at this school and in the neighborhood: school results have routinely tested positive for tremolite asbestos in every soil sample. There was dirt from a pile of dirt cut out for a road that was 5–95% tremolite asbestos. Many generations of students have had potentially ongoing episodic exposures during human and natural activities on these soils, due to construction, vehicles driving, wind and weather, running, sports, and riding bicycles.

I am here to tell you there has never been a single breathing zone exposure study to determine how many fibers are airborne during these activities. This is not acceptable. Based on your methodology, this is something we would like to see changed. The soil samples collected from the school grounds, including dirt from the parking lot and the soccer field, have had long, thin fibers with aspect ratios up to 1000:1. In the methodology, this would no doubt be considered the most lethal form of asbestos. We have a situation with daily exposures. I guess to summarize, what I am trying to bring to your attention, is that we need the science. We need to know what these exposures are in the environmental situations to know if we are indeed producing a mesothelioma epidemic as we speak, if there is one already under way. The buildings in these areas are 20 to 30 years old; some of the people in the audience may correct me. If there is a mesothelioma epidemic that's going to show up, it will probably be another 20 years. I urge you to use your scientific expertise, your resources, to help get the human exposure studies that are so needed. Thank you.

Day 1, Comment 2: Eric Chatfield, Chatfield Technical Consulting, Ltd.

My name is Eric Chatfield. I am president of Chatfield Technical Consulting, Ltd., in Toronto, Canada. As Bruce said, coming here from Canada, I may be perceived as having a conflict of interest. I have often said that if you understood the relationship between Quebec and the rest of Canada, you wouldn't make remarks like that.

I've got two basic comments at this stage in the game. I am signed up for a comment tomorrow, but I'm pleased to see we have got far enough for me to make a comment now. One is that I've been vaguely uncomfortable for a long time about this protocol. Wayne and myself have discussed it a number of times. One of the principal problems I have is that the original animal

work, because there were not enough malignant tumors, the animal work was done on the basis of total tumors, including all of the benign tumors. The benign tumors were somewhat of the majority in the Davis work. So, we derived an exposure index based on total tumors. We then build on that to create an exposure index for humans and we build on it further to refer to only cancer. So, somewhere we have a shift here. To me, that scientifically doesn't seem acceptable to derive an index on one class of particles and then to extend it to another class of particles.

The second problem I have is the so-called change from 40 μm from the animal studies down to 10 μm. The absence of scientific data doesn't mean to say that should be an accepted group. If we don't have the data, we don't have the data. If we simply make a change from 40 μm down to 10 μm for this critical transition where we apply the increased weighting, and, by the way, there was also another change made, it was 0.4 μm in the animal studies that was increased to 0.5 μm for the index. These changes are both arbitrary and some folks might say capricious. We have a problem here that we don't have the basis to make that change, and I don't see how one can then push a thing like this through into legislation with this kind of departure from a scientific method incorporated in there. And that bothers me. So, I'm just throwing that out for discussion. I know that Wayne and Kenny probably disagree with me, but I think it should be addressed. Thank you.

Day 1, Comment 3: Chris Anaya, resident of El Dorado Hills, California

I've got some issues. There are so many questions, and it's too bad the audience can't participate with some of the questions. I know I'm supposed to make a statement and not ask questions, but there are so many questions that I have that unfortunately that I can't ask. Hopefully, I can put them in writing and one of the panelists can present them later on.

I noticed to look at chrysotile, one of the studies we looked at is the Quebec studies. It bothers me knowing that there is predominantly chrysotile there, but there are also traces of tremolite. Yet, we are assuming the mesotheliomas are from the chrysotile because it is the predominant fiber there, and that bothers me because there are studies showing that traces of amphibole is what is causing the mesothelioma, and not necessarily the chrysotile. The last I read, maybe I'm not followed up with the latest science, but that's what I understand.

Fiber length is an issue, just like what Eric said. My goodness, you can't just change these numbers to force that round peg fit into the square hole, and that's what we're doing, in my view. Before you start doing that, you need to come up with studies that support the scientific basis for doing that. Less than 5 μm is not going to be included, yet talc workers with fibers less than 5 μm are known to have GI cancer; but we are not talking about any kind of cancer, but lung cancer. Why is that? If this is for IRIS, we are supposed to be looking at all cancers, but, no, all I hear about is mesothelioma and lung cancer, and that's good. There's enough evidence showing that GI cancers do exist, do take place. Selikoff's name has been mentioned; he was the first to bring this up. Now, maybe somebody has turned around and said all his research was unfounded, I don't know. But I think we need to look at GI cancers as well. I know for a fact, based on what I

read, if the information is correct, talc workers in fact have received GI cancer from asbestos or talc less than 5 µm.

The Libby lung burden study show that the majority of fibers in the people that have been evaluated are less than 5 µm. So, basically, it wouldn't even meet the definition of asbestos, and yet, tell those people that. Look at the health problems they are having. I believe it's 60% of the fibers they found in the lung burden studies were all less than 5 µm. On the air sampling, I can't see how a body can determine these nice little formulas. I tell you what, formulas are great, but when I see numbers that the coefficient for chrysotile is a number of 3 and the coefficient for amphiboles is going to be 15. That's a 5-times difference. Well, according to Dr. Whitehouse from Spokane who studied Libby, Montana, residents as well as other people exposed to chrysotile and other fibers for the last 30 to 35 years, he said in testimony that, in fact, you have a 100 times greater chance of receiving mesothelioma with tremolite than you do with chrysotile. Yet, this formula here only shows 5-times more greater chance. Dr. Whitehouse is a pulmonary disease specialist, from what I understand, and I think we have a pulmonologist here. I don't know if you have ever seen his research or talked to Dr. Whitehouse, but that is what he has said in testimony based on his evaluation of all the patients and people he has had to deal with, and I'll be happy to provide you with his testimony. I have a copy of it.

There is lack of information regarding asbestiform tremolite. Very few studies that you mentioned up here even address it. And yet, where I'm from, in El Dorado County, we have a significant problem, and yet it is not being addressed because there aren't any studies that show it's a hazard: a little trace of tremolite here in this study, a little trace of tremolite in this study. But all the other amphiboles are studied. But yet nothing there, and so it doesn't bring comfort to me to know that we're going to plug these numbers in and it's not going to be representative of what the environment is that I'm placing my children in.

Another thing is air sampling; that's what I was starting to get to. We have a formula also for converting the exposures based on how air sampling is conducted. Well, if somebody places a monitor in an improper place, where they get zero detects, this nice little neat formula you have is going to have zero exposures. Yet, that is exactly what happened in Libby: you had zero detects on all these people and yet they had many people dying from exposures to tremolite or a form of tremolite asbestos. And they couldn't figure it out; it was because the methodology for sampling was wrong, faulty, and it gave them the wrong data. So, my question is: how do you know every study that we are comparing, these 100s of studies, how exactly did they perfect their monitoring to determine that everyone of them had the same quality of exposure. In my neighborhood, where I'm from, the state, supported by EPA, places their air monitors for tremolite asbestos on top of rooftops; yet, the children, who are 3 feet off the ground, that's supposed to be representative of people on the ground. They are nicely getting zero detects, yet our soil content is 1 to 3%, 5%, or even higher in some cases, depending on the grab sample you take. You know there's exposure, but, when you place a monitor on a rooftop at 2 liters a minute, you're going to get no detects every time. So, I have a problem with plugging in these numbers without having a consistent way of monitoring the air to see exactly what those exposures are.

I don't believe any of these studies that you are using from 20 to 30 years ago really do anybody any justice. The animal studies, for one, are flawed in many cases; this is guesswork. And you are using PCM in many cases, when we should be using TEM. I know that is another thing is that we are finding out now that these ultra-fine fibers are not detected with the methods we used to use. Some of these bulky fibers, you can see them under the older type of methods, but the fibers that I'm dealing with are ultra-fine. You cannot see the fibers in bulk sampling. The same thing occurred in Libby. They could not find any sampling. I think somehow, to sum it up, we need more data. We need to be able to make sure that these methods are not just plugging in numbers to make a nice linear graph, because that's not going to get it for me. I hope it doesn't get it for you. We need scientific information to support what we have. And I'll just close with this: how can this study only claim mesothelioma to be 5 times greater risk than chrysotile when evidence looking at bodies essentially shows different?

Day 1, Comment 4: Stan Dawson, CalEPA

I would like to present an alternative view that gives some perspective on the studies that have been done on mesothelioma and lung cancer and just concentrate on the potencies from the published data. Basically, this is going back before the Crump/Berman report, using data that was available in about 2000, mainly in an article by Hodgson and Darnton, which is a review article that is mentioned in the Berman/Crump report, and also some data by [authors' names inaudible]. Anyway, what I want to emphasize here is another way of looking at this rather than just thinking about averages and standard deviations of distributions of potencies. I wanted to look at the full spectrum of potencies for each mineral. In particular [referring to a graph shown to the panelists], we have crocidolite here, we have amosite here, the mixtures are here, chrysotile is here, and the one Libby study of tremolite. What's plotted on the horizontal access is the lifetime unit risk, which is just the factor K_L multiplied by a few things to get it into the usual regulatory units for lifetime unit risk.

You can see that one of the advantages of this is that, instead of just looking at the average value or the central tendency, which you can talk about the median here, you can look at the 90^{th} percentile here and see the somewhat convergence of the amphiboles and chrysotile. Of course, each one of these is a study, for example, this one is South Carolina (Dement et al.) and that one is, of course, the Quebec study. And, of course, I'm using the previous designation of South Carolina as a chrysotile study, which may be a little simplistic.

OK, well I'll have to use my powers of description to tell you about the mesothelioma result. There are, I believe, copies being made of this, so at least you can see it on the copy. Anyway, the basic result is that, in the case of mesothelioma, the studies of the various minerals are much more separate than they were in the case of lung cancer, but you still can see the perspective you get from looking at the 90^{th} percentile, because these curves are bent over so much, that it's quite a ways away from the central tendency. So, it gives you this spectrum. You know, one of the points I wanted to emphasize, we hear about the differences between the Quebec and the South Carolina study, which is great, but what I'm trying to do is place this into perspective that, for

one reason or another, there is one result in Quebec and there is another result in South Carolina and there is a spectrum of stuff in between. And that's the way it is. So, if we are going to go on to risk assessment, we need to take that into account, that, sure enough, chrysotile can be pretty potent. So, that's it.

Day 1, Comment 5: Jay Turim, Sciences International, Inc.

My name is Jay Turim, and I'm with the consulting company called Sciences International, Inc., in Alexandria, Virginia. I wanted to make one point, and it turns out to be an elaboration of a point made by Dr. Chatfield, and that is a question of the exposure index. I know it is one of the charge questions to the panel. It was spoken about by Wayne this morning, and there was some questions asked by the panel. I'd just like to elaborate and not take too much of the 8 minutes allotted to me.

In the 1995 paper by Berman/Crump/et al. in Risk Analysis, a very important paper and a very good paper, they re-analyzed animal data and came up with an exposure index showing most of the risk is in fibers greater than 40 μm. Wayne, in his comments this morning, made the point well, that although 40 μm turns out to be the number that the statistical analysis of the re-analysis of the animal data showed, we can't expect it to be a step function, and, if anything, probably the potency increases from a number less than 40 μm and it goes up. But, because of limitations and the availability of certain data, the analysis showed 40 μm to be the break point used. It's been known, Stanton and others showed, that fiber length is an important determinant of cancer. 40 μm was the number shown in the 1995 paper. When Wayne was giving his comments this morning, he said he believes that maybe 20 μm is a better figure than 40 μm, and I think other people believe 20 μm might be an interesting break point for where most of the potency of long fibers comes into play. And yet the Berman/Crump report, the report that this panel is examining, has a break point of 10 μm.

The difference between 10 and 20 and 40 μm can be enormous in a practical sense, depending on the characteristics of a dust cloud in a practical situation. If you have fibers between 10 and 15 μm, using a 20 μm break point and a 10 μm break point can dwarf the difference in K_L and K_M. That exposure index, to me, is an extraordinarily important aspect of what this panel is to deliberate. Going from the 40 μm number that the 1995 paper developed to the 10 μm break point in the Berman/Crump report, the only explanation in that very voluminous document was a couple of paragraphs that said, for *ad hoc* reasons and for risk conservatism reasons, we are going to use 10 μm as a break point. It appears to me, IRIS is supposed to be a scientific document; this is supposed to be a scientific document. Questions about using policy decisions of conservatism to base a break point is not what this report is supposed to be about. This, I understood, is to be a scientific report. As far as I can tell, the data shows 40 μm. There might be some questions about 40 μm, but I ask the panel to consider very, very carefully whether 10 μm is the important break point. Thank you.

Day 1, Comment 6: Eileen Kempel, NIOSH

I'm Eileen Kempel from NIOSH, and I have a couple of comments for the panel to consider. The first one concerns the estimation of the risk coefficient for chrysotile versus the amphiboles. I noticed that, based on the statistical tests, the hypothesis that the risk coefficient for chrysotile and the amphiboles could not be rejected as being equal, which suggests that the risk coefficients should be equal for chrysotile and amphiboles, and it seems like there is not a good justification for having the risk coefficient for the amphiboles as being five times greater than chrysotile when the statistical test could not rule out the possibility that they are, in fact, equal. That's the first comment.

The second one concerns the proposed revised exposure index, and I think it's very important to keep in mind that the basis for this is from animal studies that were performed with exposures for 12 months, which is half the standard chronic bioassay according to the criteria that are used in cancer bioassay studies. So, it is uncertain whether the relative potency by fiber size that was seen after 12 months exposure, and they were followed for an additional 12 months without exposure, but whether that would be consistent with what would be seen after a full 2-year chronic bioassay. I think it is very important to keep that in mind. There has been a more recent study by Hesterberg et al. in 1998 in which they used chrysotile with a geometric mean length of 1.6 μm. That was a full 2-year bioassay. In that study, they found statistically significant increases in both lung cancer and mesothelioma. And, again, the mean length of that chrysotile was 1.6 μm. So, I think it will be very important to include this more recent study that was a full 2-year chronic bioassay and see what influence inclusion of those data may have on the proposed revised exposure index. And it's also important to keep in mind that the human data do not include any information on exposures to fibers less than 5 μm, so there is no way to test the hypothesis in the human studies as to whether there is a risk of exposure to the short fibers. So there's a lot of uncertainty in the assumption of the proposed revised exposure index of zero potency for the shorter fibers. And, in fact, the vast majority of fibers in airborne exposures, both in terms of mass and number, are the shorter fibers. So the risk index is being based on a very small proportion of the fibers that people would be exposed to and there are no human data that we can use to evaluate that. And the rodent study, the more recent one that is based on the 2-year study, that used the shorter fibers has not been included in that proposed revised exposure index.

There's also a number of mechanistic studies in rodents showing that there are adverse health effects from exposure to the shorter particles or fibers, including pulmonary inflammation and lung cancer. So, therefore, I think that there is considerable uncertainty and there should be a lot of concern about assuming a zero potency for the shorter fibers. Thank you.

Day 1, Comment 7: John Budrow, California Office of Environmental Health Hazard Assessment

My colleague from NIOSH over here stole some of my comments about both the length of exposure in the Davis studies and the Hesterberg study. And one point to note with the

Hesterberg study is that there were exactly zero chrysotile fibers in that study that the animals were exposed to that were longer than 20 µm, so you are looking at pretty much exclusively a short chrysotile exposure that caused both lung cancer and mesotheliomas.

There is a couple of other recent human lung burden studies also that I would like to call the panel's attention to. [Author name inaudible] 1994 and Suzuki and Yuen 2001. [Author name inaudible] looked at 5 or 6 cases of mesotheliomas; looked at lung burden in parenchymal lung tissue specimens. In one of the American cases, found primarily short chrysotile fibers. And Suzuki and Yuen did a study with, I think, 114 American mesothelioma cases and found that the predominant fiber type in the mesothelial tissue was short chrysotile. I think only something like 4% of the fibers were 8 µm in length or longer. So, this collection of more recent data suggests two things: one is that maybe the half-life of chrysotile in humans is not that short and that it may not necessarily be a good idea to establish a very small potency for chrysotile fibers in the 5 to 10 µm range and to assign a zero potency for chrysotile fibers shorter than 5 µm.

Day 1, Comment 8: Suresh Moolgavkar, Fred Hutchinson Cancer Research Center

First of all, I'd like to commend Drs. Berman and Crump for taking on this formidable task of trying to synthesize this huge literature on asbestos and cancer. And I think, by and large, they have done an excellent job. I've got to say that I understood their approach to this problem much better today, after their presentations, than from the draft document that I was able to get off the Web. I think it is unfortunate that it was posted there in the first place, because today's talks were just so much clearer than that document.

They've already done a lot of work, and I'd hate to ask them to do any more, but I see this as an opportunity. It's been almost 20 years since EPA reviewed the asbestos literature in 1986, and I see this as a real opportunity for detailed epidemiological understanding and analysis of the asbestos data, not only to setting risk but also to understanding some of the mechanisms by which asbestos might be causing lung cancer and mesothelioma. So, I think there is a real opportunity for a detailed exploration of exposure-response relationships. Note, I say exposure here and not dose-response. And a real opportunity to look at the temporal evolution of risks, particularly after exposure stops, and to try and understand if there is any difference between the chrysotiles and amphiboles in this regard and, if there is a difference, what it might be attributable to. And also an opportunity to study the interaction with other carcinogens, particularly tobacco smoke. I think in large part the report misses the opportunity to examine these issues detail. As Dr. Crump said, the main goal of the report was simply to see if the 1986 EPA model did a good job of describing the data. So, much of the epidemiological analysis were restricted to minor extensions of the methods used in 1986. It began in Chapter 6—the exploration of temporal evolution of risk—but abandoned this exploration because of lack of time. There was no real exploration of interaction with other carcinogens. There was some discussion of interaction with tobacco smoke with the panel this morning, but it is not at all clear that this interaction results in a multiplicative relative risk. It seems to me that, despite this opportunity for a thorough epidemiological analysis, the main thrust of the report is a proposal

for a new index of asbestos exposure based on TEM measurements and the defense of this exposure measure.

As to specific comments for the epidemiology study, they used mainly minor extensions of the 1986 EPA models. There is a linear excess relative risk model with a multiplicative constant to adjust for background rates. But even with this limited linear ERR formulation, there are various possibilities. One could do linear regression, or weighted linear regression, which is the way that apparently Nicholson did the analyses in 1986; or one could use generalized linear models with Poisson variance and the offsets are the expected numbers, and this is I think what Dr. Crump did. This is what you will get if you explicitly take into account the Poisson variance. Now one would imagine that, looking at one of two, there would be very small differences in the results, but this is not true. With small numbers of cases, there can be substantial differences in the results using other linear regression or Poisson regression. Or one can use generalized linear models with Poisson variance, but a log link, so that you will have log-linear excess relative risk. And this is in fact what Kyle Steenland was talking about this morning; he asked why this process was not adopted here. And if this is done, one can ask the question: is the multiplicative factor α necessary with this formulation? And all the above models could be done repeated with exposure-response formulations that are not linear, for example, linear quadratic exposure response relationship. It would add only one more parameter, but you would get rid of the α.

In addition to the group-level data, they also had individual-level data in two cohorts, in South Carolina and Wittenoom. Here, there was a real opportunity to investigate the separate contributions made by the intensity of exposure and duration of exposure, rather than just cumulative exposure. Now, if as is generally believed, asbestos is a promoter, then you would expect duration of exposure—and you see this for mesothelioma anyway—to be a much stronger fact than intensity of exposure, and you should see this for lung cancer as well if you do the analyses. So the temporal evolution of risk, including the risk after exposure stops, could also have been examined. [Sentences not recorded at end of tape.] And this hypothesis could be examined, albeit crudely, in the epidemiology data sets that they have, had they pursued the ideas based on multi-stage carcinogenesis.

So, with the individual-level data that they have, they can investigate the above questions with at least two approaches: either use the Cox proportional hazards regression or use hazard functions based on ideas of multi-stage carcinogenesis. I personally prefer the latter approach. I think it is better than the Cox proportional hazards for this problem, and Drs. Berman and Crump did try the latter approach, but there are a number of technical problems with the approach that I cannot go into now that are detailed in my written report, which I will send as an e-mail attachment to ERG. This attempt was abandoned for lack of time.

Now, consideration of other carcinogens: There was an opportunity to update interaction of asbestos and tobacco smoking causing lung cancer and possibly mesothelioma—that's a question out there. If smoking information, for example, was available on some sub-cohort, there was a possibility of doing a case cohort analysis of this data. And I think it very important, I think Stan

Dawson brought up the report by Hodgson and Darnton earlier today, that a comparison of results with those reported in other recent reviews, for example Hodgson and Darnton, would have been very useful.

What about the new exposure index? I'm not an expert on exposure, but it seems like to me a couple of points can be made here. Clearly to translate potencies from epi studies based on PCM measurements to the new exposure index, you need to set up a mapping from the old to new indices. When I saw the document, I could not understand what was being done. I must say that, after the talk today, I understood this conversion factor much better, but clearly any new index must be risk-neutral for existing data. What I'm trying to suggest is that this is a reality check. Dr. Berman presented a table in which he looked at ratios of K_Ls and so on and indicated that the new index is less likely to underestimate risk than the old index. That may be true, but I think a direct reality check might be the following: you use the new index in the existing cohorts that you already have to generate exposures and see whether the risks that you obtain are in the same ballpark, because clearly any new index must be risk-neutral. And, as I said, I cannot follow the chain of reasoning used, but I understood it much better today. Thank you. I'll stop there.

Day 2 (morning), Comment 1: Drew Van Orden, RJ Lee Group

My name is Drew Van Orden. I'm a senior scientist with RJ Lee Group. I'm here representing Rich Lee, who is a bit under the weather and sends his regards. A couple of short comments: PCM equivalent, as I understand it, is used in the model, refers only to asbestos concentrations. In a mixed-fiber environment, such as what you would find in the insulators or the shipyard workers, the PCM and the PCM-E concentrations are not equivalent, and I think you have got to account for that. I would like to see an appropriate reference to proper mineralogy in the model, such as the International Mineralogical Association. You know, the ones we use in the ASTM meetings. I think there should be a limitation on the upper size, in the analytical protocol, of matrices and clusters. As it stands now, we would count asbestos particles that are embedded in clearly non-respirable particles. And then, the epidemiology studies present good evidence that there is a difference between cleavage fragments and asbestiform fibers. I use cleavage fragments here as the non-asbestiform varieties; the protocol does not discriminate between the two of them, and I would like to see that added in. Thank you.

Day 2 (morning), Comment 2: Eric Chatfield, Chatfield Technical Consulting, Ltd.

Good morning. I did mean to make this remark yesterday, actually: the documents that are on the Web, which I downloaded, didn't have any tables in them. As a result, it is a bit difficult to review a document with none of the tables which are referred to frequently in the text. Is there any way that we can get those tables? That's number one question.

The main point I want to address this morning is the topic of cleavage fragments as it relates to the selection of this *ad hoc* break point, above which fibers are assigned the 300-times increased potency, in particular, the effect of the change from the 40 µm, predicted by the animal work, to either 20 or 10 µm, as it now stands. The population of cleavage fragments in all amphiboles, as far as I'm aware, will largely be excluded by this index, but the use of the lower 10 µm break point will have some consequences. In looking at populations of cleavage fragments derived from known fragments of obviously [inaudible] amphiboles, I have never seen a cleavage fragment longer than 30 µm, with a width of 0.5 µm. However, there is a small proportion that have widths close to 0.5 µm, and lengths between 10 and 20 µm. This means that, under the current proposal, some will be assigned this increased potency of 300 times potent. Now, given the analytical sensitivity considerations that we have with air sampling, the observation of even one cleavage fragment in the increased potency range could decide a significant risk, where there is no evidence that any risk exists. As an analyst, I'm called upon almost daily to discriminate between asbestos and non-asbestiform cleavage fragments, and I welcome the procedure that relieves me of that responsibility. At the moment, we have no guidance.

However, the current proposal doesn't meet the requirements of the U.S. courts, in some respects: in particular, the application of the new exposure index, derived from asbestos, which is one kind of material, and then applied to non-asbestiform amphibole, which is a different material; the *ad hoc* selection of the 10 µm value for the transition to the high potency range simply because there is insufficient data. Those are two points, and neither of them, neither of these actions, are likely to meet [inaudible] the rules of evidence in U.S. courts nowadays. This legal stuff won't likely arise if there is no reason to challenge the protocol. For this reason, I urge the panel to consider lowering the 40 µm transition predicted by the animal exposures to 20 µm, rather than 10 µm. In my experience, this would relieve a load of problems and minimize the possibility of legal problems. Make no mistake about this, it doesn't mean that we are excluding the cleavage fragments from counting; just that they are less likely that any will be assigned this increased potency of 300 times. We have got little evidence, if any, that cleavage fragments themselves in these size ranges are potent, and those studies of cleavage fragments were used in deriving the new exposure index.

To resolve this issue in the future, EPA can do the community a great service by commissioning an animal inhalation study using elutriated cleavage fragments of several amphiboles. By elutriated, I mean prepared from some large amounts of material, those fractions that are less than 0.5 µm and longer than 5 µm, and do the animal inhalation work. These amphibole samples, however, have to be carefully characterized mineralogically to ensure the absence of true asbestos. I believe that such a study would resolve this issue once and for all. At the moment, you can't do an inhalation study of cleavage fragments, because you can't get enough of them in; they're too thick. So, you want to separate the thin ones, and try that.

I want to finish up with a few comments about chrysotile, and in particular, the Coalinga calidria chrysotile, which is the trade name for it. The mine is about 100 miles south of here. There are some remarks about this in the protocol. This chrysotile is quite unique, and it is a different

geological origin from the more traditional types. Unlike other chrysotiles, when this is dispersed in air, the fiber bundles are much thicker as the lengths increase. So, as you pick a long body, it is generally thick, and it is not very long before you get to a non-respirable diameter. That doesn't happen with the other kinds of chrysotile; they all stay thin. So, much of the material from Coalinga, in fact, ends up being non-respirable. On the other hand, it disperses very readily in water to single fibrils. I have never seen a calidria single fibril longer than about 30 µm. It just simply does not exist. I have been using this material as a reference standard since the 1970s to simulate water dispersion, and it is a very different material from other chrysotiles, and I think that should be recognized in the protocol as far as possible. Thank you.

Day 2 (morning), Comment 3: Chris Anaya, resident of El Dorado Hills, California

Good morning. The citizens of El Dorado County have become students, I guess, about asbestos and unfortunately that's nothing I really like doing. But myself, and a number of other people, have read a number of studies, researched this greatly, so that we have a firm grasp on if we have a problem on our hands where we are from. And I can tell you we do. I'm saying this because that's why I'm here. That's why a lot of people showed up. So, I think we have a fairly firm grasp on tremolite versus chrysotile, and matters such as that, but I think there needs to be a change in the current methods for determining exposures for determining risk assessment. I know the studies or the current methods are flawed, as proven in Libby, because, statistically, Libby residents should never have had the problems they faced. 25% of the people afflicted were non-occupational exposures. I believe 5%—and I'm sure some of you will correct me, maybe I'm wrong—they couldn't find any exposure pathway whatsoever. And this is pretty common with the tremolite fiber, which is a solid core fiber, versus the chrysotile, which is a hollow cord fiber; and it acts differently in the air.

Our concern, because I don't understand the modeling here, it may be good, but I would like this panel to address, maybe when the time is there: this current proposal, does it lessen chrysotile's risk on paper and keep the amphibole the same? Or, does it keep chrysotile risk assessment the same, and raises the bar on amphibole above where it is now? And that's unclear to me, what this study does, because I believe amphibole needs to be raised above where it is now, not remain the same; and lessen the severity of chrysotile. So, I want to leave that thought in your mind, to review that for me please.

All studies that you guys are faced with were animal studies—short term exposures and injections—and occupational workers—40 hours a week, 8 hours a day, 5 days a week. Well, we're in a situation, where I live, we have exposures 24/7. There are no studies that show what that's going to do. We have the proposed analytical method, and I know we touched on this a little bit, but we need to be consistent on how we are going to measure the air, how many fibers per cubic centimeter, how are we going to get that data to plug into this formula? Because, unless we do that, we are going to come up with information that is inconsistent between one study and another, and I'll give you an example. On my former address, there are a couple of air monitors;

monitoring real close to a point source came up with, the lowest was 0.2250 fibers per cubic centimeter; the highest level happened to be 100 feet away from the point source, 93.967 fibers per cubic centimeter. Now, this is in a residential area. There is no study that shows what 93.967 fibers per cubic centimeter for chrysotile will do. This is off the chart, but yet it is not supposed to exist, but yet it does. So, what does that tell us, the residents? What's going to happen to us or our children? We don't know. We have to come up with our own little formula.

Likewise, the tremolite, I mentioned, is a different fiber: acts differently, behaves differently. New Caledonia, Turkey, Cypress, Libby, El Dorado County. We don't get detects in the air because the way the fiber behaves. You cannot put a monitor on top of the roof of a building, as you would for ozone measurement, and expect to find what kind of exposures are at ground level. Likewise with the chrysotile, you put the monitor at a different location from a point source, you're going to get different readings. And so, whatever method you folks come up with, there has to be a consistency with how you gather that data. I would probably guarantee you, and I don't know this, but those monitors placed on the workers in occupational exposures probably had them strapped to their waist, I'm guessing, or had the monitor close by to see exactly what the true exposure was at the breathing zone level. But yet, it's not required to perform it that way, here in California, at least. EPA accepts putting these monitors on the rooftops. To me, it's unacceptable. OSHA would require it—OSHA would cite somebody, if these children are workers; the people that hired these children, or workers in this case, would be cited. But yet, it's OK because there is nothing in the regulations that say you have to measure breathing zone levels where the children are being affected.

I want to close with: I'm a firefighter. When people call us for medical aid, we have to err on the side of public safety. Whether it's a fire, if we are not sure, if we think the fire is extinguished, we are going to take the extra step and open up a wall to make sure it hasn't extended in the wall. We don't want to assume that everything is OK. Likewise, you have a stomach pain, we're not going to assume it's indigestion. We are going to treat you for heart attack, if there is a chance for that, because it is not going to hurt anything. This formula is very important that you have before you. You have to make sure that you are going to err on the side of public safety. Because if you don't, somebody is going to pay dearly for it later on. So, this is very, very important. Make sure that you err on the side of public safety.

Day 2 (morning), Comment 4: Lance McMahan, private citizen

I'm a private citizen, registered civil engineer, though, with some experience with environmental issues. What I want to talk about this morning is background levels of mesothelioma, lung cancer, and asbestos-induced illnesses. It was Mary Jane over here who mentioned that, I believe, it was Australia had a risk of 8 in 1,000,000 currently in the background level; that's what they're measuring. Now, I don't know why that is. Maybe they are moving people onto asbestos deposits, and they are not keeping track of those people, so they are not accounting for them. Personally, I don't think that kind of risk is appropriate. It is extremely high. If you are getting

that much mesothelioma, imagine how much lung cancer you might getting along with that.

I lived in El Dorado Hills, and I have seen these veins of tremolite asbestos that are out there. Department of Toxics went out and found up to 96.5%, period, in a residential area, kids on their bikes in the area. This dirt, mixed in with this vein, was used to make the pads that the homes are built on. You know, the mass padding—take the top of the mountain, move the dam, build homes on top of it. I don't think I want my children to be part of that background level, because no one is looking at this. Having said that, that really doesn't bear directly on what you are looking at, necessarily, but it does provide an opportunity. There has only been in existence for 15 years since they started doing that grading in that particular area. Some of the residents are still there from the initial home purchase. There is a fair number of people that leave, of course; it's a very high turnover area generally. New people come in. So, exposures are 24/7 for the kids, for the school next door, for the community center across the street where the kids some of their summertime.

I believe you have an opportunity to do an epidemiological study that looks at this area, looks at the soil concentrations, gets breathing zone monitoring data. This has been going on for at least 7 years that I'm aware of. Of course, it's been going on since before the work, before they began the construction work out there. No one is doing anything about it. They are not doing breathing zone monitoring. I've asked EPA to do it. I've asked CalEPA to do it. I've asked the county to do it. They won't do it. So you may as well go ahead and let all the folks continue to live there, and take the opportunity over the next 10–15 years, to actually collect information on what people are being exposed to, to track the residents, to see how ill they become, and make use of this experiment that we're conducting. It's better than lab rats—actual human beings. So, you folks may as well get started, before people realize exactly what it is they are living on, and make use of lab rats. Is there any questions?

Note: At this point, one panelist (BC) addressed issues raised in the previous two comments. The panelist concurred that exposure assessment is a critical aspect of the proposed methodology, and he added that the expert panel did not have the expertise necessary to review thoroughly how occupational exposures were interpreted in the proposed protocol. Regarding the situation in El Dorado County, the panelist indicated that further research is needed to understand the health implications of exposures, and he encouraged regulatory agencies, government officials, and other entities to support such research.

Day 2 (morning), Comment 5: Terry Trent, El Dorado County resident

I'm Terry Trent. I'm a biologist. I'm from El Dorado County. Thank you, Bruce. I don't have to say very much now. I'm perhaps, on the topic of El Dorado again, Wayne Berman's most vociferous critic in the private sector. Me and my family, through asbestosis and lung cancer, have nearly paid the ultimate price—have lost most of what we own in the world—due to abuses of philosophy, measurement, and risk assessment in El Dorado County. At this point in time, it

remains to be seen what else we might loose. However, in reviewing Wayne's formula and the math last night, and in comparison to the literature and my own investigations in El Dorado County and elsewhere in California, I have to congratulate Wayne in his development of this risk formula. This is very eloquent, Wayne. My concern now becomes measurement techniques, how they are to be plugged into this formula, the mineralogy and how it is to be plugged into this formula. I have a few comments on the formula, and the variables in it, which I will submit in writing. And my largest concern is that it is a formula, as all formulas would be, that is ripe for abuse; and that is simply not your fault.

I'd like to comment a little bit on El Dorado County and my personal home in El Dorado County. In my front yard, I had one vein of slip fiber tremolite asbestos that weighed about 27 tons. It was one of thousands of veins in residential neighborhoods. I have discovered about ten additional areas in El Dorado County that are similar. My estimate is that there is about 10,000 people in El Dorado County being exposed to these fibers in their everyday activities around their homes, and their homes are simply full of the fibers. I'd just like you to consider that with your considerations here. Thank you very much.

Day 2 (morning), Comment 6: Suresh Moolgavkar, Fred Hutchinson Cancer Research Center

I am Suresh Moolgavkar, Fred Hutchinson Cancer Research Center, and University of Washington. I just wanted to reiterate a few of the points I made yesterday. Because it's 20 years since EPA looked at asbestos, I think this is a real opportunity for a thorough evaluation of the epidemiological literature, and there are three points I would like to make.

First, exposure-response relationships. I think these need to be investigated in detail and Drs. Berman and Crump need to go beyond just showing that the EPA models used in 1986 are adequate. There needs to be a thorough evaluation. This is a real opportunity to do so. For example, for mesothelioma, there is a 1999 paper in *Inhalation Toxicology* by G Berry, who applies a dose-response model to the Wittenoom data and considers what the evolution of risk might be after exposure to asbestos stops. Certainly, considerations of this type and other models that have been developed should be looked at in this document.

Related to that is the issue of the proper exposure metric for asbestos. Now, it's clear that, for mesothelioma, duration of exposure, or time since first exposure, is an extremely important variable, and it's probably more important than the daily intensity of exposure. Now this has been seen for cigarette smoking as well, and it's characteristic. This kind of an exposure-response function is characteristic of any agent that is believed to be a promoter in the carcinogenic process. And so it is quite possible that the same kind of exposure-response relationship, namely one in which the duration of exposure is more important than the intensity of exposure, might operate with lung cancer as well, as mesothelioma. So the fact that the cumulative exposure provides a satisfactory fit to the data is not sufficient. One has to show that

a model that considers daily intensity of exposure and duration of exposure does not do a better job. And, with grouped data, this is extremely difficult to do, because you lose a lot of information in grouped data. But, Drs. Berman and Crump do have two data sets with individual-level data. I wish they could get more. I wish they could get the Libby data to look at this problem as well, but I encourage them to pursue their analyses of the Wittenoom and South Carolina data sets and not abandon the analysis at this point. The write-up that we pulled off the Web indicates that they ran out of time, and they could not complete their analyses. I would be happy to help them, collaborate with them, in the analyses of these data sets.

And, finally, I think again that it is extremely important to look at the interactions of this carcinogen, asbestos, with other lung carcinogens, and most importantly, cigarette smoking. The perceived wisdom here, based on work done by Hammond in the 1970s, is that the relative risk for the two exposures is multiplicative. But, as Dr. Case point out yesterday, there is a very recent paper by Liddell and Armstrong, which I have not had the opportunity to look at, but apparently it indicates that the risk is probably much closer to additive, than multiplicative. Now, if this is true, then all the risk tables for smokers are going to change considerably, and so I think it is extremely important to investigate to the extent possible the interaction of asbestos with other carcinogens. Thank you.

Day 2 (morning), Comment 7: Eileen Kempel, NIOSH

Eileen Kempel from NIOSH. I wanted to make some general comments and also follow up on a few things from yesterday, and first I wanted to thank EPA and the organizers, the panelists, and Drs. Crump and Berman for putting this all together. It's clearly a tremendous amount of effort on a very important topic, and I think it really provides an excellent opportunity to interpret the scientific data, both animal and human, to make very important public health recommendations, which clearly are of great impact. At the same time, I think it's also very incumbent upon us to use the best available science in doing that, and so I agree with comments that have been made that it's important to use some of the methods that have been suggested to evaluate how robust the proposed method is to the data and assumptions and models that have been used.

I think it is encouraging that the proposed revised index does provide improved risk estimation, at least for the mesothelioma. But, at the same time, we are dealing with imperfect data, particularly with the human data, where the exposures in the epidemiological studies are very poorly characterized, and that's clearly an area in exposure estimation that needs to be looked into. So, we are relying on the animal data, to a large extent, because we don't have size-specific data in humans, and I think that's appropriate. That's a good example of using all the available science in the risk assessment. But, at the same time, I agree with the comments that it's important to look at, in the extrapolation from rat to human, what the appropriate dose metrics are in humans. For example, what's respirable in a rat is not the same as what's respirable in humans, and that comment was well taken.

Another area we mentioned yesterday is there is a lot of question about—we just don't know—there's lacking data on what the role of the short fibers are, and the reality of "short" meaning, you know, less than 5 µm. Of course, the 5 µm cut-off was established primarily because of convenience in the analytical method and didn't have a direct biological connection, but those are the data that we have to deal with. But there are still questions on what are the role of the particles or fibers below that size range, whether it's a direct effect or an indirect effect involving increased inflammation, cell proliferation, and fibrosis. We just don't know. And, in reality, humans are going to be exposed to the mixed fiber or particle situation, and we really ought to consider our area of uncertainty in that.

And also with regard to dosimetry, it's important to realize that lung clearance in humans is about an order of magnitude slower than it is in rats, and this gives increased opportunity for the particles to be translocated into the interstitium. And this has been shown in lung dosimetry models for humans, as well as in a study by [inaudible author name] and colleagues, where they found that the pattern of particle retention in humans was preferentially in the interstitial area, as opposed to rats, where it was in the alveolar lumen. So, this increases the probability that, for a given exposure, the dose in humans over long term may be greater than predicted from the rat studies. So there is an opportunity to use the dosimetric information that we have in the risk assessment, and this has been done for risk assessment for fibers recently. Dr. Moolgavkar and Dr. Yu have done that, for example. So, I think it's just very important to consider the dosimetry in going from rats to humans.

And then finally, with regard to the rat data that are used, the Davis studies from the 1970s and 1980s, which were used to derive the exposure index, they're very good in their own right. But, again, they were only exposed for 12 months, and there are some additional studies as I mentioned yesterday. There's one by Bernstein with short chrysotile in 1998, and I understand there's—and I'm sorry, there is one by Bernstein, yesterday I mentioned one by Hesterberg. The point is, there have been some more recent studies since the 1995 evaluation, and that these really should be considered in the revised exposure index, because those animal studies and the data from that are what are being used to derive the exposure index for humans. And, with regard to the exposure in those studies, the Hesterberg study used almost 11,000 fibers per cubic centimeter, but the Davis study used up to about 6,000 fibers per cubic centimeter. And, from what I understand, the reason for that is that it is very difficult to get fibers into the lungs in rats, and that's because of the complex nasal structures, and that's why the fiber concentrations have to be so high. But given that the main crux of this proposed method is this revised exposure index based on fiber length, and that this is relying heavily, and exclusively, on the studies from Davis and others, which use the 12-month exposure, and there have been some more recent studies which use the full 2-year bioassay, I think it's very important to include the additional recent data and see what influence they might have on the derivation of the human exposure index. Thank you.

Day 2 (morning), Comment 8: Betty Anderson, affiliation not stated

Good morning. Just a couple of comments, the first two, historical in context. I was director of EPA's carcinogen assessment group, with Roy Albert as chairman, when this work in 1985 was done. One point that I think gets lost in this historical context is the insistence that we had agreement we had with science advisory boards at the time that, whenever we were using the linear, non-threshold model, there would be—mine which that was quite descriptive, and I can certainly share it with you—that would recognize that where there was no model that could confidently describe the data, we would be certain to include language that described the results as establishing a plausible upper-bound on the risk, meaning the risk would be considerably less, even approaching zero. So, I think this gets lost, and when we use the model for background levels, we lose the context for what we were talking about. Now I fully endorse trying to go forward with getting some better modeling results so that we can go beyond the 1985 work.

I think also, the historical context of the 1985 work, we had an exposure metric. It was the PCME metric. Now, for sure, what was captured in that metric were the bond fibers and whatever else was not being seen by PCM, but then we were in search of using the metric with the incidence to do a dose-response work for risk assessment. As we now change to finding a different exposure metric, we are shifting the focus to that exposure metric, and I think we have to be certain that we are almost flipping the coin and taking the exposure metric in search of the right incidence relationships for risk assessment. And so, therefore, I think this committee needs to really focus on that exposure metric and what it means in terms of the incidence data, because we are shifting.

A couple of other points just from some recent work we've done. I think when we are looking at this *ad hoc* or whatever bright line we choose for the cut-off point, whether it is 10 µm or 20 µm, we have to be very careful. I think Eric has said it very well earlier today. We have seen in several data sets high risk if we use what Wayne and Kenny, their model; and very low risk if we use ours. Now, we shouldn't have these discrepancies, unless we are going to have a way to explain them. So, I think we certainly don't want to have a method that gives us some very high risks and we don't have a scientific basis for having chosen that 10 µm or that 20 µm level. So I certainly think the committee will, and certainly needs to, focus on how we, and as well as Kenny and Wayne, can get some information to better describe how to deal with something below 40 µm.

And, finally, I think the committee was charged with looking at the role of cleavage fragments. I wonder how compelling a discussion we can have based on the document that's in review here, since I believe this document doesn't go into that discussion. As many of you know, and many of you I'm sure have been involved, there is a lot of information, a lot of data, the OSHA hearings being a part of that record. So, I'm not quite certain how this committee at this point can fully address that particular issue. It may take another convening of another committee with that information to fully address the role of cleavage fragments and health effects. Thank you.

Day 2 (morning), Comment 9: Stan Dawson, CalEPA

Good morning. I wanted to follow up on yesterday's presentation with somewhat improved technology on the slides; they came out better this morning. [Referring to a figure displayed on an overhead.] I'll just explain a little bit, the diagram; maybe some of you have had a chance to look at the handout with the methodology on it. Basically, what we are plotting here is the cumulative proportion of expected total deaths in the studies versus the potency of each study in terms of lifetime unit risk. This is a little bit reminiscent of when we were taking courses and had the final exams and the teacher gave your grades and your teacher made a cumulative distribution of the scores and then you could find the median score and the 90th percentile score, and this is a way of displaying this data. I should explain that this total deaths, expected total deaths, is used to kind of weight the size of the study, as it were. For example, the last time I said that incorrectly that this was the Liddell study. In fact, that is the [inaudible author name] study—a tiny, tiny study; it only has that much, a tiny amount, of this y-axis. The Liddell study has this whole sweep in here; it's the Liddell point. Anyway, there are the chrysotile studies, the mixture studies, the amosite, and crocidolite. And also, tremolite has been mentioned a couple of times; it's right there. The point I made yesterday is that at the 50th percentile you see quite a spread here. At the 90th percentile, the spread is very, very much less. Dement is not the only study that has a fairly high potency, which gives a little bit above 0.1 of unit risk. And I know surely that the CalEPA potency from 1986, which followed U.S. EPA, was 0.1. So, this is, for lung cancer, the unit risk that is being used right now in California. Are there any questions on the lung cancer slide? [Several questions of clarification regarding the lung cancer plot followed.]

Then we have mesothelioma. Now this is a somewhat similar picture. I want to emphasize that, if this was a log-normal distribution, we would have seen the classical sigmoid shape. And, of course, I have plotted these things that if they were log-normal they would come in on straight lines and they don't, by a long shot. Anyway, here are the values of lifetime unit risk of mesothelioma, and the whole thing is shifted up by almost a factor of 10 for chrysotile. And you can see again that the chrysotile studies come up pretty high with Dement here, compared to the rest. And then there's the mixtures. The amosite now is separated much more from crocidolite than before. Of course, this is consistent with Hodgson and Darnton, as it should be. And if you then look at something like the 90th percentile, and you have to extrapolate up a bit here, you can see there is about a factor of ten difference between crocidolite and amosite, and then another factor of ten down to the 90th percentile for chrysotile. And then tremolite is hanging out here by amosite. [Several questions of clarification regarding the mesothelioma plot followed.]

Day 2 (afternoon), Comment 1: Leonard Burelli, Environmental Profiles

I'm Leonard Burelli. I'm with Environmental Profiles in Baltimore, Maryland. Currently, I'm an industrial hygienist, so I get involved with sampling and writing reports. In my past life, I was a microscopist. I worked in a micro-analytical lab, so I am somewhat sensitive to sampling and preparation and analytical techniques. In the report, specifically the conclusions and

recommendations section, there is a call for addressing the validity of the risk assessment in the protocol, and what's pointed out is to use a TEM method—ISO method 10312—and then later on it says that indirect preparation could be used: ". . . should indirect preparation be required due for example to problems with overloading, a sufficient number of paired samples will need to be collected and analyzed." I just want to point out that indirect preparation could artificially create higher structure counts, and you might want to revisit the idea about indirect. I have one question, too: Will there be opportunity to have written questions presented, because I'm going to get back to Baltimore tomorrow and think of something else? Will there be an opportunity to submit additional comments, observations, that sort of thing, in writing? And who would we direct those to? [A representative from EPA indicated how observers could submit follow-up comments on the proposed protocol.]

Day 2 (afternoon), Comment 2: Chris Anaya, resident of El Dorado Hills, California

Thank you. I think my fears are unfounded. When talking about age and how long people live, it made me a little nervous, and I wasn't sure where you were going with that, and I just want to get clarification: is this just a matter for determining lifetime exposures, I'm assuming? Because, surely we're assuming that a child, maybe 1-year-old, crawling on the floor in asbestos and growing up in this stuff is going to probably live long enough for the mesothelioma, or whatever it may be, to take effect if something was to take effect. I just want to make sure that we are taking into consideration the worst-case scenario. I know with the drinking water, they do; they have orders of magnitude to allow for the sensitive populations. I just want to make sure I understood you correctly. I think you should assume that the exposures take place at the youngest age and then determine how long that person is expected to live from there. That's all.

Day 2 (afternoon), Comment 3: Jay Turim, Sciences International, Inc.

Just a very quick comment. When I first became aware of the work that Wayne and Kenny were doing, it started back in 1995 in that paper—the *Risk Analysis* paper. That paper had the 40 µm break point; I spoke about that yesterday a little bit. And also the 0.4 µm diameter. We said that the paper showed that, in terms of the animal data, most risks was long fibers greater than 40 µm and fibers less than 0.4 µm. Each one of those numbers has seemed to been hacked away by this committee, and I just wanted to call the committee's attention to that. The 40 µm went down to 10 µm, and that was debated, and I think the consensus of the committee was, well, 10 or 20 µm. Not on the basis of the animal data, but on the basis of other considerations. A half an hour ago, you debated the 0.5 µm with the 0.4 µm. Wayne said he made it 0.5 µm because it was easier to read; Eric said, well, 0.4 µm or 0.5 µm can be read equally easily. Dr. Lippmann and others said 1.5 µm is a break point. Fair enough. But I think everyone has to realize that the whole underpinning of the 1995 paper has been abandoned. The 40 µm; the 0.4 µm is gone. Everything is going to rely now upon Table 6-15, coming up with K_L's and K_M's. And, fair enough, that's a way of doing it, but I think we all have to admit that this is the way you are going, and this is the way the Berman/Crump method is going. I just wanted to point out which, to me, seemed a

different take on the way things started out. What had been the basis or the genesis, which was the animal data with some very concrete numbers, have been completely abandoned, and I wanted to bring that point to the attention of the panel. Thank you.

Day 2 (afternoon), Comment 4: Eric Chatfield, Chatfield Technical Consulting, Ltd.

I guess my comment is very similar to that in that the discussions of respirability this afternoon indicated that we should be measuring widths up to 1.5 µm, or thereabouts. The problem with that is that if we retain the 10 µm cut-off again, we then bring in a whole population of cleavage fragments in places where there basically is no risk because there is no asbestos. So, I would point out that one of the recommendations I made at a Denver conference some time back—one of the Libby meetings—was that you can use whatever model you like to estimate risks, but, for the purposes of comparability with past data and with the IRIS method to doing things, then there was very little incremental cost to measuring all widths up to 3 µm, in the longer than 5 µm count. The actual extra cost going from just, say, the 0.4 µm or the 0.5 µm width, to all widths up to 3 µm, was not a great deal of extra costs, and there you would have then the means of comparability with previous work. If you measure the widths, it doesn't mean to say you necessarily have to use all of them in the model, and I would hope that you would retain the concept of either a 0.4 µm or a 0.5 µm—I don't care which—width. And I don't particularly like 10 µm, but I do say that the 20 µm cut-off to the extra toxicity, to the extra potency; a 20 µm number there would, in fact, eliminate pretty well all cleavage fragments. You would just not think of cleavage fragments at that point in one of these counts. But, I became a little bit disturbed; I got the impression that the intention was to be increasing that 0.5 µm width and actually using that in the Berman/Crump model. If that's the case, then I would say that you are going the wrong way; you're going to be bringing all the cleavage fragment arguments over here.

Day 2 (afternoon), Comment 5: Catherine Simmons, Bolter & Yates

My name is Catherine Simmons, and I'm an industrial hygienist. I work for Bolter and Yates in Park Ridge, Illinois. My comments have to do with the importance of the exposure assessments that were conducted originally, that all this work has been based on. Most of that work, or a lot of that work, was done by industrial hygienists, and the determination of appropriate sampling strategies normally is best done by persons trained in the field of industrial hygiene and would best be performed by persons certified in the practice of industrial hygiene. And I guess what I would like to see is that industrial hygienists be included in evaluation of that data and with the factors that are figured into the importance of the information and if there are deficiencies in the data and how they are weighted. That's all I have to say.

Appendix F

Observer Post-Meeting Comments

Appendix F
Observer Post-Meeting Comments

Betty Anderson

The quantitative aspect of carcinogen risk assessment is included here because it may be of use in the regulatory decision-making process, e.g., setting regulatory priorities, evaluating the adequacy of technology-based controls etc. However, it should be recognized that the estimation of cancer risks to humans at low levels of exposure is uncertain. At best, the low-dose linearity extrapolation model used here provides a rough but plausible estimate of the upper limit of risk; i.e., it is not likely that the true risk would be much more than the estimated risk, but it could very well be considerably lower. The risk estimates presented below should not be regarded as accurate representations of the true cancer risks even when the exposures are accurately defined. The estimates presented may, however, be factored into regulatory decisions to the extent that the concept of upper risk limits is found to be useful.

There is no solid scientific basis for any mathematical extrapolation model that relates carcinogen exposure to cancer risks at the extremely low concentrations that must be dealt with in evaluating environmental hazards. For practical reasons such low levels of risk cannot be measured directly either by animal experiments or by epidemiologic studies. We must, therefore, depend on our current understanding of the mechanisms of carcinogenesis for guidance as to which risk model to use. At the present time the dominant view of the carcinogenic process involves the concept that most cancer-causing agents also cause irreversible damage to DNA. This position is reflected by the fact that a very large proportion of agents that cause cancer are also mutagenic. There is reason to expect that the quantal type of biological response, which is characteristic of mutagenesis, is associated with a linear non-threshold dose-response relationship. Indeed, there is substantial evidence from mutagenesis studies with both ionizing radiation and a wide variety of chemicals that this type of dose-response model is the appropriate one to use. This is particularly true at the lower end of the dose-response curve; at higher doses, there can be an upward curvature, probably reflecting the effects of multistage processes on the mutagenic response. The low-dose linearity and nonthreshold dose-response relationship is also consistent with the relatively few epidemiologic studies of cancer responses to specific agents that contain enough information to make the evaluation possible (e.g., radiation-induced leukemia, breast and thyroid cancer, skin cancer induced by arsenic in drinking water, liver cancer induced by aftatoxins in the diet). There is also some evidence from animal experiments that is consistent with the linear nonthreshold model (e.g., the initiation stage of the two-stage carcinogenesis model in rat liver and mouse skin).

Because its scientific basis, although limited, is the beat of any of the current mathematical extrapolation models, the linear nonthreshold model has been adopted as the primary basis for risk extrapolation to low levels of the dose-response relationship.

Suresh Moolgavkar

Comments on Technical Support Document for a Protocol to Assess Asbestos-Related Risk
Suresh H. Moolgavkar, M.D., Ph.D.
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GENERAL COMMENTS

I would like to commend Drs. Berman and Crump for taking on the formidable task of reviewing and synthesizing the vast literature on asbestos. Asbestos is one of the few agents for which extensive epidemiological data are available allowing risk assessments to be based largely on these data, with ancillary and supporting information derived from experimental studies. Drs. Berman and Crump have appropriately chosen to use this approach in their proposed revision of the current EPA approach to assessing the carcinogenic risk posed by exposure to asbestos. I believe, however, that the charge questions that the Expert Panel and the Observers have been asked to address are too narrowly framed. The current EPA approach to risk assessment for asbestos is based on a document that appeared in 1986. Given that almost 20 years have elapsed since that risk assessment, there are clearly important fundamental issues that need to be thoroughly addressed in the current document.

The first of these issues is reanalyses of the epidemiological data and, particularly, a thorough reassessment of the exposure-response relationships for lung cancer and mesothelioma with the different asbestos types. Such reanalyses would explore various models and functional forms for asbestos-induced lung cancer and mesothelioma. Disappointingly, Drs. Berman and Crump choose to use only minor extensions of the models and methods used in the 1986 EPA document. Although they also attempt to use models based on ideas on multistage carcinogenesis, this section of the document has some technical problems (detailed below). In any case, this attempt is soon abandoned for lack of time. A question of some importance is the differential potencies of the various kinds of asbestos fibers. There is considerable evidence from the experimental literature that for fibers in a given size class carcinogenicity is largely determined by tissue burden which, in turn, is determined by the biopersistence. Analyses of several long-term rat bioassays for many of the man-made fibers are consistent with this hypothesis (Moolgavkar et al., 2000, 2001a,b). This observation could help explain not only the vastly different potencies of amphiboles and chrysotile in causing lung cancer and mesothelioma in humans, but also the different temporal patterns of risk after exposures to these agents end. A careful analysis of the epidemiological data sets currently available could be used to address this issue. I would encourage further more detailed analyses to address this issue because it is clearly important in the understanding of the temporal evolution of risk, particularly after exposure stops. If possible other data sets with individual-level information should be obtained for analyses. Where possible these data sets should be analyzed without collapsing the data into cross tabulations, which can lead to considerable loss of information. Dr. Leslie Stayner suggested that the Quebec and Libby

data sets be obtained and analyzed in addition to the Wittenoom and South Carolina data sets that Drs. Berman and Crump already have.

Although I believe that the main focus of any reassessment of asbestos risk should be reanalyses of epidemiology studies, and a number of pages in this document are devoted to such reanalyses, the *raison d'être* of this assessment appears to be the introduction of a new exposure index for asbestos. This exposure index, which is based on the counting of fibers by TEM, is justified largely on experimental grounds. Clearly, in order to use this new index of exposure there should be a method of establishing congruence between the new index and the old one based on PCM measurements which were used in most of the epidemiological studies. Drs. Berman and Crump attempt to set up such a relationship. While I found their argument virtually impossible to follow in the written report. Their presentation at the workshop was much clearer.

DETAILED COMMENTS

Epidemiology Studies

I believe that any reanalyses of the epidemiology studies should focus on the following issues.

I. A thorough reevaluation of the exposure-response relationships for lung cancer and mesothelioma for the various types of asbestos fibers. Questions of interest include the choice of a suitable metric of exposure (cumulative exposure versus separate consideration of intensity and duration of exposure) and evolution of risk after exposure to asbestos stops. If, as Drs. Berman and Crump point out, asbestos fibers act mainly as 'promoters' in the carcinogenic process, then one would expect (as with cigarette smoke) duration of exposure to be much more important than intensity of exposure in determining risk and cumulative exposure would be a poor metric. There is considerable evidence that after exposure to cigarette smoke or ionizing radiation stops, the risk among the exposed drops and eventually approaches the risk in the non-exposed. A similar phenomenon appears to be observable with chrysotile, but not amphibole, exposure, probably reflecting the long biological half-lives of the amphiboles. Thus, a careful evaluation of temporal evolution of risk is an integral part of any asbestos risk assessment.

II. To the extent possible, an assessment of the joint roles of asbestos and cigarette smoking in determining the risks of lung cancer and mesothelioma.

III. Comparison of the results of these analyses with other recently published syntheses of the epidemiology literature.

I consider each of these issues in more detail below.

Exposure-response relationships

For the most part, for analyses of lung cancer, Drs. Berman and Crump have used the excess relative risk (ERR) model used in the 1986 EPA document or an extension of it that incorporates a baseline multiplicative factor for lung cancer. The outputs of the analyses applied to the various occupational cohorts are presented in tables. When the values of the multiplicative factor (α) are significantly different from 1, these should be presented in the tables. They currently are not. There is little justification for taking the geometric mean of estimates when α is close to significant. These analyses also introduce a number of 'uncertainty factors' that are used to adjust the confidence intervals for the potencies. These 'uncertainty factors' are clearly subjective (as acknowledged by the authors) and no justification or rationale is given for the choice of one number or another for any particular data set. It would be helpful to have at least a qualitative discussion of the considerations that went in to the choices for any specific data. Moreover, there appears to be no justification for using these factors to inflate the confidence intervals. At least some of these uncertainty factors could be replaced by more rigorous approaches to analyses of uncertainties. For example, there is a rich literature on the incorporation of exposure uncertainties in to statistical analyses. Some of these methods could be exploited.

Even with the simple linear ERR model chosen for analyses of these data, several choices of approach are possible that could quite significantly affect the parameter estimates. First, the approach evidently used in the 1986 EPA document could be used, i.e., the potency K_L could be estimated by a linear regression of ERR against cumulative asbestos exposure. A slight modification of this procedure would use a weighted linear regression. This procedure, while having the virtue of simplicity, ignores the Poisson nature of the observed data. A better approach would be to acknowledge explicitly that the data are Poisson, as Drs. Berman and Crump do, and use the linear form for ERR. This procedure is tantamount to doing a general linear model (GLM) analysis with Poisson variance, the identity link function and offset given by the expected numbers in each bin. However, the natural link for Poisson regression is not the identity but the log. Hence a third approach would be to use the log link, which would make the ERR log linear. It is possible that the extra parameter α may not be required with this form of the ERR. Other functional forms for exposure-response, such as a linear-quadratic model, could be used as well for analyses of these data.

Drs. Berman and Crump report the results of their analyses in a series of tables. Some of these results are puzzling. For example, tables 14 and 15 in Appendix A (labeled figures 14 and 15) report the results of reanalyses of the cohorts of Amandus and McDonald. Both cohorts are drawn from vermiculite miners in Libby, Montana and there is considerable overlap among the cohorts. Despite this, the potencies (with $\alpha = 1$) differ by a factor of 2. Amandus and Wheeler do not report either average or median cumulative exposures in any of their exposure bins. So clearly, Drs. Berman and Crump had to make a choice of a summary exposure metric in each

exposure bin. Their choices may or may not be reasonable, but they can clearly affect the results, particularly when the bins are broad, as is the case here. For example, in the exposure bin 25-200 (f/ml).yr McDonald et al. report an average cumulative exposure of 77.3 (f/ml).yr. In (virtually) the same cohort the authors use a cumulative exposure of 75 (f/ml).yr in the bin 50-99 (f/ml).yr, which would appear to be too high to be either the mean or the median. When such choices have been made this should be clearly indicated in the table.

With respect to exposure-response analyses for mesothelioma, the authors use a functional form that is virtually identical to that used in the original EPA 1986 document. It is not clear whether other functional relationships were tried. I would like to direct the attention of Drs. Berman and Crump to a recent paper by Berry (1999) that proposes various functional forms for an exposure-response relationship for asbestos-induced mesothelioma. Berry also considers elimination kinetics in this paper and the incidence of mesothelioma after exposure to asbestos stops. He applies the model to the Wittenoom data, which is one of the data sets examined in detail by the authors of this report.

When individual level, rather than grouped, data are available other methods of analyses than the ones described above can be used. Evidently the authors had individual level data from cohorts in South Carolina (exposed mainly to chrysotile) and Wittenoom (exposed to crocidolite). In this case, proportional hazards regression (Cox regression) and methods based on hazard functions derived from considerations of multistage carcinogenesis can be used. Drs. Berman and Crump do not use Cox regression, but they do attempt to analyze the data using hazard functions derived from the two-stage clonal expansion (TSCE) model. In my view this is probably the best approach to understanding the distinct roles of intensity and duration of exposure and the temporal evolution of risk, particularly the behavior of risk after exposure ends. Although Drs. Berman and Crump present some analyses of South Carolina and Wittenoom cohorts using the TSCE model, these analyses appear to be technically flawed and were abandoned for lack of time.

I detail my concerns here regarding the analyses based on the TSCE model. As Drs. Berman and Crump assert, not all parameters of the TSCE model are mathematically identifiable from the hazard function alone. However, identifiable combinations of biological parameters can be readily constructed. These parameters, and not the biological parameters, should be used in the construction of the hazard function and the likelihood. Thus, I would not express the exposure-response relationships as presented by Drs. Berman and Crump on page 6-19 in terms of the biological parameters. Rather, these should be expressed in terms of a set of identifiable parameters. Second, for each individual in the cohort, the hazard function depends explicitly on at least four distinct time intervals, the time between birth and beginning of employment (age at first exposure), the time period after beginning of exposure over which asbestos concentrations in the tissues reach equilibrium, the period of time during which asbestos concentrations remain constant, and the period after exposure stops when tissue concentrations may decline. While in epidemiology studies such information may not be directly available, approximations can be made based on deposition and clearance rates for specific types of asbestos. For example, a

recent paper (Finkelstein and Murray, 1999) reports that the half-life of chrysotile fibers longer than 10 microns is about 8 years. While the authors appear to have taken account of the time-dependent decrease in asbestos concentrations after exposure stops, it is not clear to me that they have explicitly considered some of the other time intervals. The authors also attempt to estimate the half-lives of chrysotile and crocidolite from the incidence data in some of their analyses. I believe this is misguided. On the other hand, the authors assume a constant lag (or latency) period of 4 years. I believe that this period should actually be estimated from the data, either as a constant or as a distribution of lags (gamma distribution, for example).

There are other serious problems with the procedures used for data analyses using the TSCE model. The authors state on page 6-20 that "either α or β was fixed at zero, because, when the mortality rate is low, h(t) is practically a function of the difference between the two parameters." This is simply not true. First, setting $\alpha = 0$ leads to a nonsensical result because it makes β the rate of apoptosis negative, which is absurd. Second, in particular when the agent under consideration is a promoter as Drs. Berman and Crump believe to be the case with asbestos, both α and β are independently important in determining the hazard. Furthermore, these two parameters are independently important in determining the temporal evolution of risk after exposure stops. If identifiable parameters are used to construct the hazard function it is unnecessary to use simplifying assumptions setting one of the biological parameters to zero. Finally, the authors report results that are patently absurd. They report on page 6.26 that each of the 'mutation rates' from the South Carolina cohort are 250 times larger than the rates estimated from the Wittenoom cohort. This would imply, other parameters being approximately equal, that the background lung cancer rates in South Carolina are 62,500 times higher than the rates in Wittenoom! I have had considerable experience over many years fitting the TSCE model to large and complex occupational cohort data, and I have never encountered results of this type.

The analyses of data with individual-level information offers the best potential for understanding the temporal evolution of risk and the relative roles of intensity of exposure and duration of exposure in asbestos-induced carcinogenesis. Therefore, the Wittenoom and South Carolina data sets should be carefully analyzed. If other data sets, such as Libby and Quebec, can be obtained these should be analyzed in detail as well.

Clearly, the TSCE model analyses need to be redone with proper account taken of the considerations outlined above. In fact, I would be happy to help with such reanalyses.

Consideration of other Carcinogens

To the extent possible it would be of interest to reassess the joint roles of cigarette smoking and asbestos in lung cancer and mesothelioma. Conventional wisdom, going back to Hammond in the seventies, has it that relative risk for lung cancer with joint exposure is multiplicative. There are more recent analyses, by Little and Armstrong for example, that suggest that the risk may be closer to additive. Thus, clearly this issue needs to be addressed, if possible. Current risk projection methods are based on the assumption that the risk of asbestos exposure

multiplies the risk of smoking. Such projections could be quite misleading if this assumption does not hold. There might be information on cigarette smoking in some of the cohorts that would allow this issue to be addressed. For example, if smoking information is available on a subcohort it may be possible to conduct case-cohort analyses to explore this issue. Similarly, a number of the cohorts might have been exposed to other potential lung carcinogens. For example, the mining cohorts might have been exposed to radon and/or diesel exhaust. This is a long shot, but, if possible, these exposures should be investigated.

Comparison with other Recent Studies

A recent comprehensive review of the epidemiology literature by Hodgson and Darnton, referenced by Drs. Berman and Crump, presents detailed tables of the carcinogenic risk posed by various forms of asbestos. It would be useful to have a comparison of the risks presented in that review with those derived by Drs. Berman and Crump in this document.

New Exposure Index for Asbestos

The main goal of this document appears to be to propose a new index or metric of exposure to asbestos fibers. This exposure index would count asbestos fibers using TEM and give appropriate weight to the longer fibers, which are believed to be more toxic. The weights were apparently estimated on the basis of an analysis of experimental data by Berman and Crump in 1995. While the general principle that the longer fibers are more toxic appears to be generally accepted and sound, the cut-off at 10 microns proposed in this document is arbitrary. The experimental data suggest a cut-off at 40 microns. However, because of differences in airway anatomy, which affects deposition of fibers, and in clearance of fibers from the lung, it is difficult to infer from these experiments where the cut-off in humans should be. While any new index, whether or not based on TEM, should be risk-neutral on the existing epidemiological data sets, it is not clear what structures should be actually counted in any practical use of the new method. For example, there is considerable debate as to whether cleavage fragments of similar dimensions as fibers pose the same, or any, carcinogenic risk. Clearly this issue needs to be addressed before the new index can be used for risk assessment.

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