

**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

Charge to Consultants	B-1
Pre-Meeting Comments	
Bruce Case	B-7
Vincent Castranova	B-43
James Crapo	B-53
David Hoel	B-61
Morton Lippmann	B-71
Roger McClellan	B-83
Bertram Price	B-97
Claire Sherman	B-111
Leslie Thomas Stayner	B-123
Kyle Steenland	B-137
Mary Jane Teta	B-145

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.

Berman DW and Crump K. 1999. Methodology for Conducting Risk Assessments at Asbestos Superfund Sites. Part 1: Protocol, Interim Version. February 15, 1999.

EPA 1986. Airborne Asbestos Health Assessment Update. U.S. Environmental Protection Agency. EPA 600/8-84-003F. 1986.

Bruce Case

Bruce Case

Associate Professor
McGill University
462 Argyle Avenue
Westmount, Quebec H3Y 3B4
CANADA
514-398-7192 #00521
Fax: 514-398-7446
Email: bruce.case@mcgill.ca

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 μm* . 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 ($< 5 \mu\text{m}$) 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 *unreasonable* based on current knowledge to assign any weight at all to fibers of less than $5 \mu\text{m}$ 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 chrysotile 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% (33¹/8009 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 estimates². 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 than 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 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.**

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 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 between 5 and 10 mm. 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)

Bruce W. Case, M.D., M.Sc., Dipl. Occupational Hygiene, F.R.C.P.(C.)

Monday, February 17, 2003

- Abraham JL, Hull, M., Case, B.W. (2002). "Mesothelioma Among Workers and in the Vicinity of Asbestiform Fiber-Bearing Talc Mines in New York State." Ann Occup Hyg 46(S1): 132-135.
- Acheson ED, Gardner MJ, Pippard EC and Grime LP (1982). "Mortality of two groups of women who manufactured gas masks from chrysotile and crocidolite asbestos: a 40-year follow-up." Br J Ind Med 39(4): 344-8.
- Amandus HE and Wheeler R (1987). "The morbidity and mortality of vermiculite miners and millers exposed to tremolite-actinolite: Part II. Mortality." Am J Ind Med 11(1): 15-26.
- Armstrong BK, de Klerk NH, Musk AW and Hobbs MS (1988). "Mortality in miners and millers of crocidolite in Western Australia." Br J Ind Med 45(1): 5-13.
- ATSDR (2002). "Report on the Expert Panel on Health Effects of Asbestos and Synthetic Vitreous Fibers: The Influence of Fiber Length (DRAFT)." IN PREPARATION.
- Berry G (1994). "Mortality and cancer incidence of workers exposed to chrysotile asbestos in the friction-products industry." Ann Occup Hyg 38(4): 539-46, 413.
- Berry G (1999). "Models for Mesothelioma Incidence Following Exposure to Fibers in Terms of Timing and Duration of Exposure and the Biopersistence of the Fibers." Inhal Toxicol 11(2): 111-130.
- Berry G and Newhouse ML (1983). "Mortality of workers manufacturing friction materials using asbestos." Br J Ind Med 40(1): 1-7.
- Case BW (1991). "Health Effects of Tremolite. Now and in the Future." Annals of the New York Academy of Sciences 643: 491-504.
- Case BW (1991). "On talc, tremolite, and tergitersation. Ter-gi-ver-sate: 2: to use subterfuges." Br J Ind Med 48(5): 357-9.
- Case BW (1994). "Biological Indicators of Chrysotile Exposure." Annals of Occupational Hygiene 38(4): 503-518.
- Case BW, Churg, A., Dufresne, A. Sébastien, P. McDonald, A.D. and McDonald, J.C. (1997). "Lung Fiber Content for Mesothelioma in the 1891-1920 Birth Cohort of Quebec Chrysotile Workers: A Descriptive Study." Ann Occup Hyg 41(S1): 231-236.
- Case BW, Richardon L, Parent M-É, Désy M, and Siemiatycki J (2002). "Preliminary findings for pleural mesothelioma among women in the Québec chrysotile mining regions." Ann. Occup. Hyg 46(S1): 128-131.
- Case BW, Dufresne A, McDonald AD, McDonald JC and Sebastien P (2000). "Asbestos fiber type and length in lungs of chrysotile textile and production workers: Fibers longer than 18 μ m." Inhalation Toxicology 12: 411-418.
- Case BW and Sebastien P (1987). "Environmental and Occupational Exposures to Chrysotile Asbestos a Comparative Microanalytic Study." Arch Environ Health 42(4): 185-191.
- Case BW and Sebastien P (1989). "Fiber Levels in Lung and Correlation with Air Samples." Non occupational Exposure to Mineral Fibers. J. Bignon, J. Peto and R. Saracci, Editors 90: 207-218.
- Case BW, Sebastien P and McDonald JC (1987). "Lung Fiber Analysis in Accident Victims a Biological Assessment of General Environment Exposures." Meeting On Epidemiology In Environmental Health Held At The First International Symposium On Environmental Epidemiology, Pittsburgh, Pennsylvania, Usa, June 43(2): 178-179.
- Churg A and Green F (1990). "Re: Mesothelioma in railroad machinists [letter; comment]." Am J Ind Med 17(4): 523-30.
- Churg A and Vedal S (1994). "Fiber burden and patterns of asbestos-related disease in workers with heavy mixed amosite and chrysotile exposure." Am J Respir Crit Care Med 150(3): 663-9.
- Cooper WC, Wong O and Graebner R (1988). "Mortality of workers in two Minnesota taconite mining and milling operations." J Occup Med 30(6): 506-11.

- Davis JM, Addison J, Bolton RE, Donaldson K, Jones AD and Smith T (1986). "The pathogenicity of long versus short fiber samples of amosite asbestos administered to rats by inhalation and intraperitoneal injection." Br J Exp Pathol 67(3): 415-30.
- Davis JM, Addison J, McIntosh C, Miller BG and Niven K (1991). "Variations in the carcinogenicity of tremolite dust samples of differing morphology." Ann N Y Acad Sci 643: 473-90.
- Davis JM and Jones AD (1988). "Comparisons of the pathogenicity of long and short fibers of chrysotile asbestos in rats." Br J Exp Pathol 69(5): 717-37.
- de Klerk NH, Armstrong BK, Musk AW and Hobbs MS (1989). "Cancer mortality in relation to measures of occupational exposure to crocidolite at Wittenoom Gorge in Western Australia." Br J Ind Med 46(8): 529-36.
- de Klerk NH, Armstrong BK, Musk AW and Hobbs MS (1989). "Predictions of future cases of asbestos-related disease among former miners and millers of crocidolite in Western Australia [see comments]." Med J Aust 151(11-12): 616-20.
- de Klerk NH, Musk AW, Cookson WO, Glancy JJ and Hobbs MS (1993). "Radiographic abnormalities and mortality in subjects with exposure to crocidolite." Br J Ind Med 50(10): 902-6.
- Dement JM and Brown DP (1994). "Lung cancer mortality among asbestos textile workers: a review and update." Ann Occup Hyg 38(4): 525-32, 412.
- Dement JM, Brown DP and Okun A (1994). "Follow-up study of chrysotile asbestos textile workers: cohort mortality and case-control analyses." Am J Ind Med 26(4): 431-47.
- Gardner MJ, Winter PD, Pannett B and Powell CA (1986). "Follow up study of workers manufacturing chrysotile asbestos cement products." Br J Ind Med 43(11): 726-32.
- Gillam JD, Dement JM, Lemen RA, Wagoner JK, Archer VE and Blejer HP (1976). "Mortality patterns among hard rock gold miners exposed to an asbestiform mineral." Ann N Y Acad Sci 271: 336-44.
- Hansen J, de Klerk NH, Eccles JL, Musk AW and Hobbs MS (1993). "Malignant mesothelioma after environmental exposure to blue asbestos." Int J Cancer 54(4): 578-81.
- Hansen J, de Klerk NH, Musk AW and Hobbs MS (1998). "Environmental exposure to crocidolite and mesothelioma: exposure- response relationships." Am J Respir Crit Care Med 157(1): 69-75.
- Hodgson JT and Darnton A (2000). "The quantitative risks of mesothelioma and lung cancer in relation to asbestos exposure." Ann Occup Hyg 44(8): 565-601.
- Hughes JM, Weill H and Hammad YY (1987). "Mortality of workers employed in two asbestos cement manufacturing plants." Br J Ind Med 44(3): 161-74.
- IARC (1996). Consensus Statement. Mechanisms of Fiber Carcinogenesis. Kane AB, Boffetta, P., Saracci, R., Wilbourn, J.D. Lyon (and Oxford), International Agency for Research on Cancer; WHO / Oxford University Press. 140: 1-9.
- Knox JF, Holmes S, Doll R and Hill ID (1968). "Mortality from lung cancer and other causes among workers in an asbestos textile factory." Br J Ind Med 25(4): 293-303.
- Liddell FD and Armstrong BG (2002). "The combination of effects on lung cancer of cigarette smoking and exposure in quebec chrysotile miners and millers." Annals of Occupational Hygiene 46(1): 5-13.
- Liddell FD, McDonald AD and McDonald JC (1998). "Dust exposure and lung cancer in Quebec chrysotile miners and millers." Ann Occup Hyg 42(1): 7-20.
- Lippmann M (1990). "Effects of fiber characteristics on lung deposition, retention, and disease." Environ Health Perspect 88: 311-7.
- Luo S, Liu X, Mu S, Tsai SP and Wen CP (2003). "Asbestos related diseases from environmental exposure to crocidolite in Da-yao, China. I. Review of exposure and epidemiological data." Occup Environ Med 60(1): 35-42.

- McConnell EE, Axten C, Hesterberg TW, Chevalier J, Miiller WC, Everitt J, Oberdorster G, Chase GR, Thevenaz P and Kotin P (1999). "Studies on the inhalation toxicology of two fibreglasses and amosite asbestos in the Syrian golden hamster. Part II. Results of chronic exposure." Inhal Toxicol 11(9): 785-835.
- McDonald AD, Case BW, Churg A, Dufresne A, Gibbs GW, Sebastien P and McDonald JC (1997). "Mesothelioma in Quebec chrysotile miners and millers: epidemiology and aetiology." Ann Occup Hyg 41(6): 707-19.
- McDonald AD and Fry JS (1982). "Mesothelioma and the fiber type in three American asbestos factories - preliminary report." Scand J Work Environ Health 8 Suppl 1: 53-8.
- McDonald AD, Fry JS, Woolley AJ and McDonald J (1983). "Dust exposure and mortality in an American chrysotile textile plant." Br J Ind Med 40(4): 361-7.
- McDonald AD, Fry JS, Woolley AJ and McDonald JC (1983). "Dust exposure and mortality in an American factory using chrysotile, amosite, and crocidolite in mainly textile manufacture." Br J Ind Med 40(4): 368-74.
- McDonald AD, Fry JS, Woolley AJ and McDonald JC (1984). "Dust exposure and mortality in an American chrysotile asbestos friction products plant." Br J Ind Med 41(2): 151-7.
- McDonald AD and McDonald JC (1978). "Mesothelioma after crocidolite exposure during gas mask manufacture." Environ Res 17(3): 340-6.
- McDonald AD and McDonald JC (1980). "Malignant mesothelioma in North America." Cancer 46(7): 1650-6.
- McDonald JC (1998). "Unfinished business: the asbestos textiles mystery [editorial]." Ann Occup Hyg 42(1): 3-5.
- McDonald JC, Armstrong B, Case B, Doell D, McCaughey WTE, McDonald AD and Sebastien P (1989). "Mesothelioma and Asbestos Fiber Type. Evidence from Lung Tissue Analyses." Cancer 63(8): 1544-1547.
- McDonald JC, Gibbs GW, Liddell FD and McDonald AD (1978). "Mortality after long exposure to cummingtonite-grunerite." Am Rev Respir Dis 118(2): 271-7.
- McDonald JC, McDonald AD, Armstrong B and Sebastien P (1986). "Cohort study of mortality of vermiculite miners exposed to tremolite." Br J Ind Med 43(7): 436-44.
- Miller BG, Searl A, Davis JM, Donaldson K, Cullen RT, Bolton RE, Buchanan D and Soutar CA (1999). "Influence of fiber length, dissolution and biopersistence on the production of mesothelioma in the rat peritoneal cavity." Ann Occup Hyg 43(3): 155-66.
- Muhle H and Pott F (2000). "Asbestos as reference material for fiber-induced cancer." Int Arch Occup Environ Health 73 Suppl: S53-9.
- Newhouse ML, Berry G and Skidmore JW (1982). "A mortality study of workers manufacturing friction materials with chrysotile asbestos." Ann Occup Hyg 26(1-4): 899-909.
- Newhouse ML, Berry G, Wagner JC and Turok ME (1972). "A study of the mortality of female asbestos workers." Br J Ind Med 29(2): 134-41.
- Newhouse ML and Sullivan KR (1989). "A mortality study of workers manufacturing friction materials: 1941-86." Br J Ind Med 46(3): 176-9.
- Paci E, Buiatti E and Geddes M (1987). "A case-referent study of lung tumors in non-asbestos textile workers." Am J Ind Med 11(3): 267-73.
- Peto J (1980). "Lung cancer mortality in relation to measured dust levels in an asbestos textile factory." IARC Sci Publ(30): 829-36.
- Peto J, Doll R, Howard SV, Kinlen LJ and Lewinsohn HC (1977). "A mortality study among workers in an English asbestos factory." Br J Ind Med 34(3): 169-73.

- Rodelsperger K, Woitowitz HJ, Bruckel B, Arhelger R, Pohlabein H and Jockel KH (1999). "Dose-response relationship between amphibole fiber lung burden and mesothelioma." Cancer Detect Prev 23(3): 183-93.
- Rogers AJ, Leigh J, Berry G, Ferguson DA, Mulder HB and Ackad M (1991). "Relationship between lung asbestos fiber type and concentration and relative risk of mesothelioma. A case-control study." Cancer 67(7): 1912-20.
- Roggli VL, Pratt PC and Brody AR (1993). "Asbestos fiber type in malignant mesothelioma: an analytical scanning electron microscopic study of 94 cases [see comments]." Am J Ind Med 23(4): 605-14.
- Sébastien P, Armstrong, B., Case, B.W. (1988). " Estimation of amphibole exposure from asbestos body and macrophage counts in sputum: a survey in vermiculite miners." Ann Occup Hyg 32: 195-201.
- Sebastien P, McDonald JC, McDonald AD, Case B and Harley R (1989). "Respiratory cancer in chrysotile textile and mining industries: exposure inferences from lung analysis." Br J Ind Med 46(3): 180-7.
- Selikoff IJ, Hammond EC and Seidman H (1979). "Mortality experience of insulation workers in the United States and Canada, 1943--1976." Ann N Y Acad Sci 330: 91-116.
- Sluis-Cremer GK (1991). "Asbestos disease at low exposure after long residence time in amphibole miners." Toxicol Ind Health 7(1-2): 89-95.
- Sluis-Cremer GK (1991). "Asbestos disease at low exposures after long residence times." Ann N Y Acad Sci 643: 182-93.
- Sluis-Cremer GK, Liddell FD, Logan WP and Bezuidenhout BN (1992). "The mortality of amphibole miners in South Africa, 1946-80." Br J Ind Med 49(8): 566-75.
- Spirtas R, Heineman EF, Bernstein L, Beebe GW, Keehn RJ, Stark A, Harlow BL and Benichou J (1994). "Malignant mesothelioma: attributable risk of asbestos exposure." Occup Environ Med 51(12): 804-11.
- Stanton MF (1974). "Editorial: Fiber carcinogenesis: is asbestos the only hazard?" J Natl Cancer Inst 52(3): 633-4.
- Stanton MF, Layard M, Tegeris A, Miller E, May M, Morgan E and Smith A (1981). "Relation of particle dimension to carcinogenicity in amphibole asbestos and other fibrous minerals." J Natl Cancer Inst 67(5): 965-75.
- Stanton MF, Laynard M, Tegeris A, Miller E, May M and Kent E (1977). "Carcinogenicity of fibrous glass: pleural response in the rat in relation to fiber dimension." J Natl Cancer Inst 58(3): 587-603.
- Stanton MF and Wrench C (1972). "Mechanisms of mesothelioma induction with asbestos and fibrous glass." J Natl Cancer Inst 48(3): 797-821.
- Stayner LT, Dankovic DA and Lemen RA (1996). "Occupational exposure to chrysotile asbestos and cancer risk: a review of the amphibole hypothesis [see comments]." Am J Public Health 86(2): 179-86.
- Takahashi K, Case BW, Dufresne A, Fraser R, Higashi T and Siemiatycki J (1994). "Relation between Lung Asbestos Fiber Burden and Exposure Indices Based on Job History." Occupational and Environmental Medicine 51(7): 461-469.
- Teschke K, Morgan MS, Checkoway H, Franklin G, Spinelli JJ, van Belle G and Weiss NS (1997). "Mesothelioma surveillance to locate sources of exposure to asbestos." Can J Public Health 88(3): 163-8.

- Teta MJ, Lewinsohn HC, Meigs JW, Vidone RA, Mowad LZ and Flannery JT (1983). "Mesothelioma in Connecticut, 1955-1977. Occupational and geographic associations." J Occup Med 25(10): 749-56.
- Ulvestad B, Kjaerheim K, Martinsen JI, Damberg G, Wannag A, Mowe G and Andersen A (2002). "Cancer incidence among workers in the asbestos-cement producing industry in Norway." Scand J Work Environ Health 28(6): 411-7.
- Wagner JC, Sleggs CA and Marchand P (1960). "Diffuse pleural mesothelioma and asbestos exposure in the North Western Cape Province." Brit J Industr Med 17: 260-71.
- Weill HW AJ, Balmes J, Case BW, Churg AM, Hughes J, Schenker M and Sébastien P (1990). "Health effects of tremolite. This official statement of the American Thoracic Society was adopted by the ATS Board of Directors, June 1990." Am Rev Respir Dis 142(6 Pt 1): 1453-8.
- Woitowitz HJ and Rodelsperger K (1994). "Mesothelioma among car mechanics?" Ann Occup Hyg 38(4): 635-8.
- Wong O (2001). "Malignant mesothelioma and asbestos exposure among auto mechanics: appraisal of scientific evidence." Regul Toxicol Pharmacol 34(2): 170-7.
- Wright RS, Abraham JL, Harber P, Burnett BR, Morris P and West P (2002). "Fatal asbestosis 50 years after brief high intensity exposure in a vermiculite expansion plant." Am J Respir Crit Care Med 165(8): 1145-9.
- Yeung P and Rogers A (2001). "An occupation-industry matrix analysis of mesothelioma cases in Australia 1980-1985." Appl Occup Environ Hyg 16(1): 40-4.

Vincent Castranova

Vincent Castranova

Chief, Pathology & Physiology Research Branch
National Institute for Occupational
Safety & Health
1095 Willowdale Road (L 2015)
Morgantown, WV 26505
304-285-6056
Fax: 304-285-5938
Email: vic1@cdc.gov

Dr. Castranova received his B.S. in biology from Mount Saint Mary's College (magna cum laude) and his Ph.D. in physiology and biophysics from West Virginia University School of Medicine. He served as a NIH fellow and research faculty member in the Department of Physiology at Yale University before he took a research position at NIOSH. He is a CDC Distinguished Fellow and Distinguished Consultant. He is a professor in the Department of Physiology and Pharmacology at the West Virginia University's Robert C. Byrd Health Science Center and also was a professor of occupational and environmental medicine at University of Pittsburgh's School of Public Health in 2002. His research interests include the isolation and characterization of the physiological properties of lung cells, in particular, alveolar macrophages, polymorphonuclear leukocytes and alveolar type II epithelial cells; and determining mechanisms involved in disease initiation and progression after exposure to silica, coal mine dust, diesel exhaust particulate, fibers, cotton dust, organic dusts, and microbial products such as endotoxin. His research has resulted in the publication of two books as co-editor and over 280 manuscripts in peer-reviewed journals and chapters in books. He is a member of the American Physiological Society and the Society of Toxicology. He is on the editorial board of the Annals of Agricultural and Environmental Medicine and Toxicology and Applied Pharmacology.

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 find chrysotile 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 $> 10 \mu\text{m}$ vs those between $5\text{-}10 \mu\text{m}$ in length by a factor of greater than 300:1. The equation dismisses particles $< 5 \mu\text{m}$ 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 from 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 $10 \mu\text{m}$ 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 $>10 \mu\text{m}$ 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 where 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, dysregulation 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.

James Crapo

James Crapo

Chairman, Department of Medicine
National Jewish Medical Research Center
1400 Jackson Street
Denver, CO 80206
303-398-1436
Fax: 303-270-2243
Email: crapoj@njc.org

Dr. Crapo is a professor of medicine at the University of Colorado Health Sciences Center, Director of the Ph.D. Program for Graduate Health Care Professionals, and Associate Dean of the School of Medicine, as well as serving as the Chairman of the Department of Medicine of the National Jewish Center. Previous to his appointments in Colorado, he was a professor of medicine and professor of pathology, and director of extrapolation modeling at Duke University. He is a member of the American Thoracic Society, American Federation of Clinical Research, Society of Toxicology, and the American Physiological Society, as well as a fellow of the American College of Physicians. He received his B.S. magna cum laude from Brigham Young University and his M.D. from the University of Rochester. His certified medical specialty is internal medicine, with a subspecialty in pulmonary disease. He is a member of the editorial boards for Inhalation Toxicology, Environmental Health Perspectives, and the American Journal of Physiology: Lung Cellular and Molecular Physiology. He has published several textbooks including Toxicology of the Lung, "Extrapolation of Dosimetric Relationships for Inhaled Particles and Gases," and Textbook of Pulmonary Diseases." He has published numerous reviews, editorials, and book chapters including "Aspects of respiratory tract structure and function important for dosimetry modeling: interspecies comparison," Fate and translocation of Fibers," "Models for Studying airways Response to Environmental Injury," "Application of Morphometric Methods to Study Diffuse and Focal Injury in the Lung Caused by Toxic Agents," and Morphologic, Morphometric, and X-ray Microanalytical Studies on Lung Tissue of Rats Exposed to Chrysotile Asbestos in Inhalation Chambers." He has published many papers related to asbestos including "Pulmonary macrophage accumulation and asbestos-induced lesions at sites of fiber deposition," Characterization of three types of chrysotile asbestos after aerolization," Airway Branching Patterns Influence Asbestos Fiber Location and The Extent of Tissue Injury in the Pulmonary Parenchyma."

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: crocidolite > 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 crocidolite, 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.

David Hoel

David Hoel

Professor
Medical University of South Carolina
36 South Battery
Charleston, SC 29401
843-723-1155
Fax: 843-723-7405
Email: whitepoint@aol.com

Dr. Hoel received his A.B. (Mathematics and Statistics) with highest honors from the University of California at Berkeley, and his Ph.D. in Statistics from the University of North Carolina at Chapel Hill. He is Distinguished University Professor at the Medical University of South Carolina, Clinical Professor, Department of Radiology at the University of South Carolina School of Medicine, where he also served as Professor and Chairman, Department of Biometry and Epidemiology and Associate Director for Epidemiology at the Hollings Cancer Center. For twelve years he served as the Director of the Division of Biometry and Risk Assessment, National Institute of Environmental Health Sciences in Research Triangle Park, North Carolina. He is a member of International Statistical Institute and a Fellow of the American Statistical Association. He served as the co-editor of Biostatistics in Cancer Risk Assessment, Scientist, Inc., Tokyo, 1991 and Multimedia Modeling and Risk Assessment, (co-editor with J Regens and C Travis), The Medical University of South Carolina Press, 1999. He is the Section Editor, Journal of Environmental Pathology, Toxicology and Oncology,; Contributing Editor, American Journal of Industrial Medicine; Member, International Agency for Research on Cancer Working Group on the Use of Mechanistic Data to Evaluate the Carcinogenicity of Chemicals to Humans, 1991; Member, U.S. Consumer Product Safety Commission's Chronic Hazard Advisory Panel (CHAP), 1999. He is a member of the American Statistical Association, the Royal Statistical Society, the Biometric Society, the International Statistical Institute, and the Society for Risk Analysis, among others. He is a member of EPA's Science Advisory Board's Environmental Health Committee (1997-) and a member of the U.S. Consumer Product Safety Commission's Chronic Hazard Advisory Panel (CHAP),(1999-). He has published over 150 papers, including "Perspective and Overview of the Concepts and Value of Hazard Identification as the Initial Phase of Risk Assessment for Cancer and Human Health," Scandinavian Journal of Work Environmental Health 18(1):83-89, 1992, Huff J and Hoel DG; "Concordance of Carcinogenic Response between Rodent Species: Potency Dependence and Potential Underestimation," Risk Analysis 12:115-121, 1992, Piegorsch WW, Carr GJ, Portier CJ and Hoel DG; and "Multistage Models of Carcinogenesis and Their Implications for Dose-Response Models and Risk Projections," Conference Proceedings: International Conference on Radiation Effects and Protection. Mito, Japan, March 18-20, pp 123-126, 1992, Hoel DG.

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 do. 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 4th to 5th power of duration of smoking.

For mesothelioma, the model assumes that risk is proportional to cumulative exposure. Further, the effect is proportional to the 3rd 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 (Chrysotile) 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 5 μm . 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 4th to 5th power of duration of smoking.

For mesothelioma, the model assumes that risk is proportional to cumulative exposure. Further, the effect is proportional to the 3rd 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

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.

Morton Lippmann

Morton Lippmann

Professor

New York University School of Medicine

57 Old Forge Road

Tuxedo, NY 10987

845-731-3558

Fax: 845-351-5472

Email: lippmann@env.med.nyu.edu

Dr. Lippmann is a professor of environmental medicine at the New York University (NYU) School of Medicine. He holds a Ph.D. (NYU, 1967) in environmental health science, an S.M. (Harvard University, 1955) in industrial hygiene, and a B.Ch.E. (The Cooper Union, 1954) in chemical engineering. At NYU, he directs a research program on human exposure and health effects and the EPA-supported Particulate Matter Health Effects Research Center. He has been the recipient of numerous awards for his research and contributions in aerosol science and pulmonary physiology, human exposure assessment and dosimetry, chemical transformations in the atmosphere, population studies of exposure-response relationships in occupational and community cohorts, and factors affecting the toxicity of airborne fibers. Much of this research has been focused on specific chemical agents, notably ozone, sulfuric acid, and asbestos. Dr. Lippmann is a past president of the International Society of Exposure Analysis (1994–1995), past chairman of the ACGIH (1982–1983), of the EPA Science Advisory Board's Executive Committee (2000–2001), EPA's Advisory Committee on Indoor Air Quality and Total Human Exposure (1987–1993), and EPA's Clean Air Scientific Advisory Committee (1983–1987). He has also chaired and been a member of numerous National Research Council committees, including committees on synthetic vitreous fibers, measurement and control of respirable dust in mines, indoor pollutants, toxicity data elements, and in-vivo toxicity testing of complex mixtures. His publications include 260 research and review papers in the scientific literature and reference texts on environmental health science.

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 $> 5 \mu\text{m}$.

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 controlled 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 $< 5 \mu\text{m}$ 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 ($\sim 5 \mu\text{m}$ in aerodynamic diameter) in a risk analysis for lung cancer. Such fibers can penetrate to small lung airways, and some 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.

References

Baris YI, Simonato L, Artvinli M, Pooley F, Saracci R, Skidmore J, and Wagner JC. 1987. Epidemiological and environmental evidence of the health effects of exposure to erionite fibres: A four-year study in the Cappadocian region of Turkey. *Int. J. Cancer* 39:10-17.

Davis JMG, Addison J, Bolton R, Donaldson K, Jones AD, and Smith T. 1986. The pathogenicity of long versus short fibre samples of amosite asbestos administered to rats by inhalation and intraperitoneal injection. *Brit. J. Exper. Pathol.* 67:415-430.

Davis JMG, Addison J, McIntosh C, Miller BG, and Niven K. 1991. Variations in the carcinogenicity of tremolite dust samples of differing morphology. *Ann. NY Acad. Sci.* 643:473-490.

Lippmann M. 1988. Asbestos exposure indices. *Environ. Res.* 46:86-106.

Lippmann M. 1994. Deposition and retention of fibres: Effects on incidence of lung cancer and mesothelioma. *Occup. Environ. Med.* 51:793-798.

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).

Roger McClellan

Roger McClellan
Advisor, Toxicology & Human Health
Risk Analysis
13701 Quaking Aspen Place, NE
Albuquerque, NM 87111
505-296-7083
Fax: 505-296-9573
Email: roger.o.mcclellan@att.net

Roger O. McClellan is currently an advisor to public and private organizations on issues concerned with human health risk analysis, inhalation toxicology, and strategic business analysis for science-based organizations. He is President Emeritus of the Chemical Industry Institute of Toxicology, having served as Chief Executive Officer and President of the Institute from September 1988 through July 1999. During his tenure, the organization achieved international recognition for the development of science undergirding important environmental and occupational health regulations. Prior to his appointment as President of CIIT, Dr. McClellan was Director of the Inhalation Toxicology Research Institute, and President and Chief Executive Officer of the Lovelace Biomedical and Environmental Research Institute, Albuquerque, New Mexico. He began his career with Lovelace in 1966. During his 22 years with the Lovelace organization, he provided leadership for development of one of the world's leading research programs concerned with the toxic effects of airborne materials.

Prior to joining the Lovelace organization, he was a scientist with the Division of Biology and Medicine, U.S. Atomic Energy Commission, Washington, DC (1965-1966), and Hanford Laboratories, General Electric Company, Richland, WA (1959-1964). He received his Doctor of Veterinary Medicine degree from Washington State University in 1960 and a Master of Management Science degree from the University of New Mexico in 1980. Dr. McClellan has served in an advisory role to numerous public and private organizations. He is past Chairman of the Clean Air Scientific Advisory Committee, Environmental Health Committee, and Member of the Executive Committee, Science Advisory Board, U. S. Environmental Protection Agency; Member, Advisory Council for Center for Risk Management, Resources for the Future; a former Member, Health Research Committee, Health Effects Institute; and service on National Academy of Sciences/National Research Council Committees on Toxicology (Past Chairman), Risk Assessment for Hazardous Air Pollutants, and Research Priorities for Airborne Particulate Matter.

Dr. McClellan serves or has served as Adjunct Professor at Duke University, University of North Carolina at Chapel Hill, North Carolina State University, University of New Mexico, University of California-Los Angeles, and Washington State University. He is active in the affairs of a number of professional organizations, including past service as President of the Society of Toxicology and the American Association for Aerosol Research. He currently serves as Chair of the Board of Trustees, Toxicology Excellence in Risk Assessment. He serves in an editorial role for a number of journals, including service as Editor of CRC Critical Reviews in Toxicology. He is a diplomate of the American Board of Toxicology and the American Board of Veterinary Toxicology.

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 amphiboles have the potential to induce mesothelioma. The available literature is not persuasive that pure chrysotile induces 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?

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.

Roger O. McClellan

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.

Bertram Price

Bertram Price

Price Associates, Inc.
1 North Broadway - #406
White Plains, NY 10601
914-686-7975
Fax: 914-686-7977

Email: bprice@priceassociatesinc.com

Dr. Price is the president and founder of Price Associates Inc., where he designs and conducts statistical studies and regulatory reviews, as well as conducting studies concerning risk and risk management including environmental and occupational health regulatory issues. He develops and evaluates study designs, measurement methods, and data quality criteria. Previous to founding Price Associates, Dr. Price was a Vice President, Risk Assessment Consulting Group, at Marsh & McLennan Companies, and was the manager of the Program Office for Statistical Studies at Battelle Memorial Institute where he managed and directed studies conducted for EPA related to TSCA. He received his B.A. in Mathematics from Wittenberg University, his M.S. and Ph.D. in Mathematical Statistics from Ohio State University. He is a Member of the ASTM committee D22 on Sampling and analysis of Atmospheres, and the ASTM subcommittee D22.07 on Asbestos Measurement. He served as a peer review panel member for the report by the World Trade Center Indoor Air Task force Working Group on selecting chemicals of potential concern and setting health-based benchmarks, he is a member of the American Statistical Association, the American Association for the Advancement of Science, and the Society of Risk Analysis. He has authored numerous technical reports, articles, and presentations including "Standard Practice for Determining a Detection Limit for Asbestos Measurements Based on Counts," Trends in Incidence of Mesothelioma and Evaluation of Exposure to Asbestos," "Risk Assessment for Asbestos and management of Low Levels of Exposure to Chrysotile Asbestos," "Cumulative Asbestos Exposure in Epidemiologic Studies of Lung Cancer and Mesothelioma," and "Transmission Electron Microscopy and Its Application to EPA's Proposed Asbestos Worker Protection Rule." He has served as an expert witness in several court cases related to asbestos on the behalf of W. R. Grace, Armstrong World Industries, and Flintkote Company. Dr. Price has prepared several technical reports for the U.S. EPA on Airborne Asbestos Level in Schools, Analysis of Variability Associated with the Measurement of Fiber concentration by Phase Microscopy and Transmission Electron Microscopy for the Office of Toxic Substances.

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 (1×10^{-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 1×10^{-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.

Claire Sherman

Claire Sherman

Biostatistician

California Environmental Protection Agency

1515 Clay Street, 16th Floor

Oakland, CA 94612

510-622-3214

Fax: 510-622-3211

Email: csherman@oehha.ca.gov

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 $> 3 \mu\text{m}$ 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 $> 20 \mu\text{m}$ in length, and very few were $> 10 \mu\text{m}$ 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		
	$\leq 4.99 \mu\text{m}$	5 – 7.99 μm	$\geq 8 \mu\text{m}$
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 different (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.

Leslie Thomas Stayner

Leslie Thomas Stayner
Chief, Risk Evaluation Branch
National Institute for Occupational
Safety & Health
Robert Taft Laboratories, C15
4676 Columbia Parkway
Cincinnati, OH 45226
513-533-8365
Fax:513-533-8224
Email: lts2@cdc.gov

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 these risks. He was the 2000 recipient of the NIOSH Special Act Award for organizing a workshop on "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 Crystalline 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_L s 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 carcinogenicity 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 $> 30 \mu\text{m}$ 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_m s 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_m s) was generally not available in these studies, and the K_m s 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_m s (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 implantation 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_f .

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 indicate 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 $1/4^{\text{th}}$ less than 10-20, $1/10^{\text{th}}$ less than 20-40, and 900 times less than $>40 \mu\text{m}$. Based on this model it would seem that assuming a factor of 300 in potency between fiber 5 and 10 μm , and $> 10 \mu\text{m}$ would only make sense if a very larger percentage of the fibers $> 10 \mu\text{m}$ were $> 40 \mu\text{m}$. 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 tumorigenicity 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?

Kyle Steenland

Kyle Steenland

Professor
Rollins School of Public Health
Emory University
1518 Clifton Road
Atlanta, GA 30322
404-712-8277
Email: nsteenl@sph.emory.edu

Dr. Steenland is a Professor in the Department of Environmental and Occupational Health at the Rollins School of Public Health at Emory University. He has a Ph.D. in Epidemiology from the University of Pennsylvania and a Masters in Mathematics (statistics) from the University of Cincinnati. Prior to going to Emory last August, Dr. Steenland spent 20 years at National Institute of Occupational Safety and Health (NIOSH). At NIOSH he worked primarily in occupational cancer epidemiology, as well as the development of epidemiologic methods. He has edited 2 textbooks, one on occupational and the other on environmental epidemiology.

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 cancer. 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.

Mary Jane Teta

Mary Jane Teta
Principal Epidemiologist
Exponent, Inc.
234 Old Woodbury Road
Southbury, CT 06488
203-262-6441
Fax: 203-262-6443
Email: jteta@exponent.com

Dr. Teta specializes in chronic disease epidemiology, particularly occupational and environmental epidemiology studies; regulatory risk assessment, particularly for cancer endpoints; and risk communication to the media and public. She has served on numerous scientific advisory boards including those of ATSDR, EPA, The Mickey Leland Center and the Harvard Center for Risk Analysis. She is an Adjunct Associate Professor of Epidemiology in the Department of Biostatistics and Epidemiology at the University of Massachusetts. She received her Doctorate of Public Health from Yale University and her MPH in Biostatistics from Yale University. She is a Fellow of the American College of Epidemiology; a consultant to EPA's Science Advisory Board; a consultant to several task groups at the American Chemistry Council; former Chair of the Scientific Committee of the American Industrial Health Council; a member of NIOSH's Risk Assessment Task Group; and an NIH consultant for the National Children's Study. Her publications include, "The Influence of Occupational and Environmental Asbestos Exposure on the Incidence of Mesothelioma in Connecticut" and "Mesothelioma in Connecticut 1955-1977: Occupational and Environmental Associations."

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 tumorigenicity. 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 μm) are cleared much more quickly than long (>20 μm) 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 > 10 μm . 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 too 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 5 μm 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 μm clear readily

and the small proportion that do not clear are sequestered in alveolar macrophages. Fibers shorter than 10-20 μm 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 $< 5 \mu\text{m}$. 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 μm are readily handled by macrophages. In addition, the optimum exposure index indicates little impact of exposures as high as 40 μm 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 μm 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 μm 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 μm 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 μm and longer than a minimum of 10 μm that likely contribute to disease. Timbrell (1982) reported complete clearance of short (< 4 μm) 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.

