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July 3, 2008

Ms. Vivian Turner
EPA Science Advisory Board (1400F)
U.S. Environmental Protection Agency
1200 Pennsylvania Ave, NW
Washington, D.C. 20460

RE: Comments on the Proposed Approach for Estimation of Bin-Specific Cancer Potency Factors for Inhalation Exposure to Asbestos

Dear Ms. Turner:

I have completed a detailed review of the indicated proposal and would like to offer the following comments and recommendations for consideration. For convenience, my comments are divided into the following topics: the "general approach" and the "supporting studies (data) being considered". Based on my knowledge of and experience with the topic (see attached biographical sketch), my overall recommendations to the panel are that:

- the general approach of the proposal be endorsed (although several details need to be modified, a few of which are identified in my following comments);
- it be acknowledge that the proposed work is premature and that the supporting database needs first to be improved and substantially expanded;
- focused studies be initiated to develop the needed data; and
- the severe pitfalls of conducting a meta analysis over a set of studies that are insufficiently rich to test the hypotheses of interest be highlighted.

The General Approach

The following are some general comments and suggestions that I hope will prove helpful.

1. When Dr. Kenny Crump and I completed our 2003 document (Berman and Crump 2003, which is a forerunner to the current proposal), it was understood that the document was intended to suggest an *interim* protocol for risk assessment. In fact, it was rushed out so that people would have access to an approach that offered a substantial improvement in health protectiveness over the existing EPA approach (IRIS Current), primarily because it addressed the difference in potency between chrysotile and amphibole asbestos but also because it stressed the need to consider longer fibers than those considered by the existing EPA protocol. Given the expressed EPA desire at the time to rush the document out for this purpose, as indicated in the introduction, it addressed only those comments by the peer-consultation panel that could be readily satisfied, while it was

understood that the remaining comments would be addressed following completion of a more thorough study, that Dr. Crump and I had just initiated.

Importantly, it was also decided at the time that, although the peer panel had recommended evaluation using a variety of approaches for meta analysis (which would be a very good thing to do, at a minimum, to test and validate the robustness of the findings of the 2003 protocol document and any later refinements), such an analysis was in fact premature because a more pressing need was to develop improved data for exposure reconstruction that would overcome the severe limitations of the existing data being used for this purpose. Such limitations, for example, prevent formal testing of exposure metrics with a cut point in width at 1.5 μm (another recommendation of the peer panel) because too few of the critical size distributions contain this particular cut point. In fact, although the current proposal suggests that metrics with this cut point would be evaluated, it is unclear how this would be accomplished without severely restricting the number of epidemiological studies that would be included in the analysis (due to lack of corresponding size data).

A more detailed discussion and evaluation of such limitations and related issues is provided in the attached manuscripts (Berman and Crump 2008a and b), which have been accepted for publication in *Critical Reviews in Toxicology*. The manuscripts represent the latest extension of the work Dr. Crump and I have been conducting for the last 20 years, which until 2005 had been funded almost exclusively by the EPA. The latest work incorporates data from the most recent literature (including relevant studies published since our 2003 document). The manuscripts also present the results of a sensitivity analysis to facilitate judgment of the robustness of our findings.

The follow-on study that Dr. Crump and I had initiated in 2003 was designed to develop data suitable for reconstructing exposures that would allow formal fitting of metrics representing a much broader range of length and width combinations than can currently be supported. This includes explicitly testing metrics with a width cut point at 1.5 μm and, perhaps even more important, evaluating metrics that separately delineate longer lengths than the longest cut point at 10 μm imposed by all but one or two of the published studies currently available for supporting exposure reconstruction. We continue to pursue such data today.

Given the above, therefore, I believe that the proposed study puts the cart before the horse and should be postponed until improved data become available for exposure reconstruction that will support a much richer evaluation of the parameters of interest. This is especially true given that it would be surprising if the proposed analysis generated findings substantially different than what Dr. Crump and I have reported to date *as long as identical hypotheses were being tested using identical input data*. The point is that our findings are unlikely to be artifacts of our statistical approach alone. Moreover, once better data are generated, it should be possible not only to evaluate exposure metrics containing "bins" (categories of structures exhibiting specific sizes and types) that may better predict biological activity than the metrics that can currently be tested, but it would also be possible to formally fit a broader range of risk models and to apply more varied statistical approaches for the meta analysis itself. Effects concerning variation in input data are further addressed below.

2. I would also like to suggest that, while the proposed statistical approach may mitigate some of the potential limitations of the approach used to date by Dr. Crump and me, it

also introduces new limitations. Perhaps the best illustration of such tradeoffs is that the proposed attempt to avoid use of our equation expressing the effects of uncertainty as log normally distributed comes at the expense of assuming the shape and spread of the variability of a substantial number of additional inputs supported by very little data. Of course, all such considerations can be properly evaluated as part of a detailed sensitivity analysis, which will need to be completed once any future meta analysis is performed.

3. With regard to the 8 criticisms of our work that are presented in the proposal (P. 48), we agree with many of them and have previously acknowledged them, have addressed two of them in our recent publications (Berman and Crump 2008a,b), and have previously suggested (in concurrence with the recommendations of the peer consultation panel) that alternate methods of analysis should be performed (once better data become available that allow more robust testing of relevant hypotheses). This should also be accompanied by a comprehensive sensitivity analysis to identify the best approach and most robust of findings that can ultimately be relied upon for constructing an effective protocol to assess asbestos-related risks. At the same time, other than incorporating different approaches for conducting the meta analysis (which are themselves subject to a similar range of criticisms), such criticisms cannot be effectively addressed until better data are developed for improved exposure reconstruction.

I should also note that it was not necessary to formally test the goodness of fit of the metric evaluated in our 2003 document. As we have pointed out in our 2008 papers, it is clear by visual inspection that none of the metrics we were able to evaluate with existing data entirely reconcile all of the observed variation across studies.

4. As one final note, it is not entirely clear to me why it would be of interest to produce yet another *interim* protocol (as proposed) when what is really needed is to develop the data required for improved exposure reconstruction and then to conduct the detailed analysis that can ultimately be used to support modification of EPA's asbestos policy.

The Studies Being Considered (Input Data)

Perhaps the most critical issue associated with a meta-analysis (no matter what statistical procedures are employed) is its dependence on the input data. If a data set is insufficiently rich to provide adequate power to test hypotheses of interest, this may not be readily apparent, but its use may result in findings that do not adequately reflect reality. Moreover, such a limitation is unlikely to be uncovered in a sensitivity analysis because it would require adding additional data not used in the original analysis. At the same time, however, it would not make sense to not use all of the available data for the original analysis. That is why Dr. Crump and I endeavored to incorporate as broad a range of studies as reasonably possible and why we are looking to incorporate an even broader range of studies, once we obtain the exposure-reconstruction data that will allow us to do so. This again is why I believe the proposed analysis is premature; it should be conducted only after a richer data set becomes available.

Keeping the above in mind, I would like to note several potential issues that I believe should be addressed regarding the data proposed for consideration.

1. It is not entirely clear why several of the studies that Dr. Crump and I incorporated into our analysis have been eliminated from the proposed analysis. Even if there is a desire

to avoid use of "unpublished" data, summaries of all of the studies that we employed have been published. Thus, for example, Quebec miners and millers (Liddell et al. 1997, which contains estimated mesothelioma rates as well as the number of cases in specific exposure groups so that sufficient data are available for use of these data), the New Orleans plants studied by Hughes et al. (1987), the Wittenoom crocidolite miners (Berry et al. 2004), the newer study of the South Carolina textile plant (Hein et al. 2007) and the companion size data (Dement et al. 2007), and insulation applicators (Selikoff and Seidman 1991) can all be incorporated into the proposed mesothelioma analysis. Interestingly, by eliminating these studies, one is left with a database containing only a single study (the Seidman et al. 1986 study of insulation manufacturers) in which the primary exposure is to amphibole (in this case, it is amosite). Thus, it is not clear at all what potential biases might be introduced by such truncation of data.

2. Ironically, although a stated policy of the proposed approach is to use only data from sources published in refereed journals, the size distribution proposed for pairing with the epidemiological study of vermiculite miners from Libby, Montana (McDonald et al. 2004) comes from a letter report from a consultant to a W.R. Grace official (Sebastien 1983). Clearly this report has neither been published nor refereed. It is also labeled as a "preliminary study". Moreover, it appears that the distribution suggested in this study contains structures that are substantially thicker than the data that we used to support our 2003 analysis, which came from EPA (although the available data from that source was too sparse to support the further analyses presented in our 2008 publications). It is also unclear what is meant by "static" sampling in the letter report. If this means that the samples were left out to collect settled dust, it would not be surprising that the distribution contains largely thicker structures because thicker structures (for the same length) settle substantially faster than thinner ones. I also note that only a total of 100 fibers were sized in this study and that there is no indication that any kind of stratified selection was employed. Thus, I am not sure what kind of confidence can be placed in this distribution.

Given all of the above, I suggest that more research seems to be in order to better understand the true nature of the distribution of fibrous structures in the dusts at Libby before a particular distribution is selected to represent these dusts. Further, given all the interest generated by and the work that has been conducted at Libby in recent years, it is a little surprising that better distributions are not readily available and these should be published. I should also note that there is no reason not to include the even more recent epidemiological study of Libby miners (Sullivan 2007).

3. Although the study of Chinese factory workers (Yano et al. 2001) has been proposed for inclusion and, to the extent it can be matched with an appropriate size distribution (see below), this is a step in the right direction, the proposal to treat this study as a "pure chrysotile" study appears misguided (see attached email exchange with Yano, which was produced as evidence at a recent trial). The potential impact of incorporating an incorrect assumption of this type is discussed as part of our sensitivity analysis in Berman and Crump (2008b). I would also like to suggest that selecting an appropriate size distribution to pair with this study may be quite difficult as the factory appears to have manufactured a broad range of asbestos products (requiring a range of milled fiber grades as raw material).
4. I am somewhat concerned about the procedures proposed for matching size distributions to the epidemiological studies. In our studies, I was careful to pair

distributions, at a minimum, by industry and product using a similar range of asbestos mineral types because I believe it is reasonable to assume that the specifications in a particular industry, which tend to call for use of a particular grade of milled fiber for manufacturing a particular product, result in dusts with similar characteristics. This is because I believe that (1) the particular grades of milled fiber likely produce dusts with particular characteristics and (2) the material is all being handled in the same manner when producing the same product. For this reason, however, I was hesitant to pair particular size distributions to cohorts in factories in which varied products and/or with varied mineral types were being manufactured (unless I had access to a size distribution from a factory in which a very similar mix of products was being produced). That is why, for example, I ultimately eliminated the mixed-exposure, mixed-product factory in Asbestos Quebec from consideration in the size study because I did not feel confident I could reasonably match it to a size distribution from a sufficiently similar environment. I am currently working on a manuscript that addresses some of these issues.

Note, in principle, I like the idea of pairing separate size distributions for chrysotile and amphibole asbestos with epidemiological studies involving mixed exposures. In practice, however, this needs to be done only with great care. This may work reasonably well when addressing studies in which all fiber types involve exposure to commercial asbestos (so that the character of the exposure is somewhat controlled by the grade of milled asbestos employed in the particular industry). I am less sure that this can be done for chrysotile mining environments. In such environments, the chrysotile and amphibole are formed in different components of the host matrix under different conditions (William-Jones et al. 2001). Given this situation, it is not clear how to reasonably match the amphibole with amphibole size distributions from other environments because we do not know the effects of the conditions under which it formed. At the same time, if one at least assumes the same distribution for both chrysotile and amphibole, one is acknowledging that the milling of ore (by air classification) is size selective and that both the chrysotile and amphibole are being subjected to the same processing. Similarly, in factory environments using commercial chrysotile fiber with amphibole contamination, it is more likely that the size distribution of such contamination mimics that of the chrysotile (than any other guess one might make) simply because at least both minerals will have survived the same, size-selective milling (by air classification).

I hope that the SAB Panel members find these comments and suggestions helpful. Please note that I have attached a list of references for the indicated citations (in addition to the other attachments previously mentioned).

Please let me know if anyone has any questions about any of the above as I will be happy to respond.

Sincerely,

D. Wayne Berman, Ph.D.
President



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Berman, D.W. and Crump, K.S. (2008). A Meta-analysis of asbestos-related cancer risk that addresses fiber size and mineral type. *Critical Reviews in Toxicology*. Accepted.

Berman, D. W. and Crump, K. S. (2003). *Final Draft: Technical Support Document for a Protocol to Assess Asbestos-Related Risk*. Prepared for Mark Follensbee, Syracuse Research Corporation, Syracuse, New York and the Office of Solid Waste and Emergency Response, U.S. Environmental Protection Agency, Washington, D.C. EPA #9345.4-06. Limited revision draft.

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Hein, M. J., Stayner, L. T., Leyman, E., and Dement, J. M. (2007). Follow-up study of chrysotile textile workers: cohort mortality and exposure-response. *Occupational and Environmental Medicine* 64:616–625.

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Sebastien, P. (1983). Analysis by analytical transmission electron microscopy of fibrous particles in Libby's air samples. Preliminary results. Letter report from P Sebastien (McGill University) to H. A. Eschenbach (W.R. Grace and Co.), June 10, 1983.

Seidman, H., Selikoff, I. J., and Gelb, S. K. (1986). Mortality experience of amosite asbestos factory workers: Dose-response relationships 5 to 40 years after onset of short-term work exposure." *American Journal of Industrial Medicine*. 10(5/6):479-514.

Selikoff, I. J., and Seidman, H. (1991). Asbestos-associated deaths among insulation workers in the United States and Canada, 1967-1987. *Annals of the New York Academy of Sciences*. 643:1-14.

Sullivan, P. (2007). Vermiculite, respiratory disease, and asbestos exposure in Libby, Montana: Update of a cohort mortality study. *Environmental Health Perspectives*. 115(4): 579-585.

William-Jones, A.E., Normand, C., Clark, J.R., Vali, H., Martin, R.F., Dufresne, A., and Nayebzadeh, A. (2001). Controls of amphibole formation in chrysotile deposits: evidence from the Jeffrey mine, Asbestos, Quebec. In: *The Health Effects of Chrysotile Asbestos, Can Mineral., Spec Publ.* 5, 89-104.

Yano E, Wang Z-M, Wang X-R, Wang M-Z, Lan Y-J. (2001). Cancer mortality among workers exposed to amphibole-free chrysotile asbestos. *American Journal of Epidemiology* 154: 538-543.

D. Wayne Berman, Ph.D.
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July 3, 2008

Dr. D. Wayne Berman holds a Ph.D. physical chemist from the California Institute of Technology and has more than 25 years experience providing innovative solutions to complex environmental problems for a variety of government and private institutions. He began his career in the environmental field as a member of the group at Clement Associates who pioneered procedures used to perform site risk assessments under the Federal Superfund Program. Many of these procedures are in common use today. In addition to exposure and risk assessment, Dr. Berman has amassed extensive experience in strategic planning, chemical fate and transport, statistics, site investigation, investigation planning and design, feasibility study, chemical process analysis, sampling and analytical method development, data quality analysis, data quality objectives development, regulatory compliance, quality assurance program development, and risk communication.

Dr. Berman is also a recognized expert in the measurement of asbestos in environmental media, the environmental fate and transport of asbestos, and the assessment of asbestos-related risks. He has published and presented extensively on these topics. Dr. Berman managed and served as the principal investigator on a \$1.2 million project for the EPA to develop a mutually consistent set of sampling and analysis methods for the determination of asbestos in environmental media and a companion protocol for assessing asbestos-related risks. Results from this study include the development and publication of an air method, companion technical background document, and a soil-bulk method.

The bulk method is unique because, unlike traditional methods, it provides results that can be used to predict exposure and, therefore, risk. In a published study, Dr. Berman demonstrated that bulk measurements derived using the method could be combined with published dust emission and dispersion models to predict risk with reasonable accuracy.

The risk-assessment protocol was considered in an EPA-sponsored peer-review consultation in February, 2003. The expert panel generally endorsed the overall approach and recommended additional research to refine some of the details. The current version of the protocol (intended as an interim approach while data needed to finalize the protocol were developed) was submitted in 2003 and published by the EPA. The comments of the peer-consultation panel are available on the EPA website. A recent update of this work has also been accepted for publication in *Critical Reviews in Toxicology*.

Dr. Berman served as an invited expert on the following panels:

- The Southdown Study Expert Group (N.J. Department of Environmental Protection/U.S. Environmental Protection Agency) 1999 - 2002

- The State of California Asbestos Task Force, 1998-1999
- The National Asbestos Task Force (U.S. Environmental Protection Agency) 1989-1995

Dr. Berman has also been applying his methods and protocol to assist government and private clients across the country in addressing sites contaminated with asbestos. Such sites include the marble quarry in Sparta, NJ, the former Johns-Manville manufacturing facility in Waukegan, IL, the Northridge Estates Site in Klamath Falls, OR, and the Lowry Air Force Base Site in Denver, CO. Risk assessments have been completed for several of these sites and are now available in the public domain.

Berger, Bruce J.

From: E Yano
Sent: Monday, April 05, 2004 4:42 AM
To: Berger, Bruce J.
Subject: Re: Question about study "Cancer Mortality among Workers Exposed to Amphibole-free Chrysotile Asbestos"

Dear Esq. Bruce J. Berger,

At 10:52 04/04/03 -0500, you wrote:

First, does the publication of Tossavainen, et al., "Amphibole Fibers in Chinese Chrysotile Asbestos" cast some doubt on your premise that there is no tremolite in the Chinese chrysotile mines? I understand that your information came from Dr. Kohyama, but I have not seen him publish his results for peer review. Is this perhaps a situation in which he simply did not take enough samples?

Yes, I am also waiting for Dr. Kohyama's publication which he promised but I also have my own measurement in the plant. I tell you that the vast majority of the fiber found in the lung of a biopsy sample was tremolite, however, the proportion of tremolite detected in the work environment was two digit less than that of chrysotile.

We assume three possibilities to explain this discrepancy between the workplace measurement and the lung content:

1. Tremolite can penetrate into lung far better than chrysotile. About 20 years ago, Timbrel UK suggested me that curly shape of chrysotile fiber prevents its penetration into lung due to aerodynamic mechanism.
2. Even the chrysotile fiber which could somehow managed to penetrate into lung may be easily cleared away by its solubility (JC Wagner's idea) or its potency to trigger inflammatory reaction.
3. The remaining chrysotile fiber left in the lung tissue may be cleared away chemically by the acidity of formaline bath.

Second, you commented on p. 542 that cumulative exposures of 25 fiber-years/ml were far below the levels determined in your study. What was your estimate of the cumulative exposures in your study?

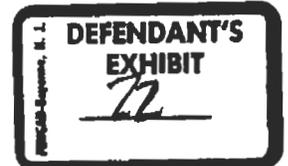
You can make rough estimation by multiplying the fiber concentration in Table 1 (p539) by average number of years in Table 2 or Table 4.

Also, could you estimate what asbestos levels were at the plant in 1972, the date by which workers had to have been working to be included in your study?

We do not have valid information regarding the fiber concentration in 1972. We certainly assume that it was higher than current level. We did have mass concentration in 1972 but our simultaneous measurements for both fiber and mass indicated that conversion of mass concentration into fiber concentration is of little value. Most of the previous studies used the conversion method to estimate the fiber concentration and so did our study in 1970s and 80s.

Third, concerning your pleural mesothelioma case, do you know what the duration of his work history was at the plant?

One of them worked only 4 years between 31 and 34 of his age and developed



Berger, Bruce J.

From: Berger, Bruce J.
Sent: Saturday, April 03, 2004 9:53 AM
To:
Subject: Question about study "Cancer Mortality among Workers Exposed to Amphibole-free Chrysotile Asbestos"

Dear Dr. Yano,

I very much appreciate your study, but I do have some questions.

First, does the publication of Tossavainen, et al., "Amphibole Fibers in Chinese Chrysotile Asbestos" cast some doubt on your premise that there is no tremolite in the Chinese chrysotile mines? I understand that your information came from Dr. Kohyama, but I have not seen him publish his results for peer review. Is this perhaps a situation in which he simply did not take enough samples?

Second, you commented on p. 542 that cumulative exposures of 25 fiber-years/ml were far below the levels determined in your study. What was your estimate of the cumulative exposures in your study? Also, could you estimate what asbestos levels were at the plant in 1972, the date by which workers had to have been working to be included in your study?

Third, concerning your pleural mesothelioma case, do you know what the duration of his work history was at the plant?

Thank you for any information you can provide.

Bruce J. Berger, Esq.

