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APPENDIX B

APPENDIX B

**SELECT COMMENTS TO SCIENCE ADVISORY BOARD
INCORPORATED BY REFERENCE INTO
INFORMATION QUALITY ACT REQUESTS FOR CORRECTION**

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Comments on the EPA Document, “Draft Toxicological Review of Libby Amphibole Asbestos” (EPA/635/r/002a)

Elizabeth L. Anderson, Ph.D., ATS Fellow

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Introduction

While it was originally intended simply to serve as a central database that would ensure the consistency of EPA health and risk assessments, the IRIS database has become the primary source for information concerning the weight of evidence (hazard identification) and quantitative risk information for known and suspected carcinogens and non-carcinogens for national and international organizations. It is also widely used outside of regulatory settings by companies for product evaluation and stewardship, advocates for changes of environmental policies, and adversaries in litigation.

Because of this expanded role and the impact of the information available from the IRIS database, the IRIS program and many draft toxicological assessments have come under close scrutiny by a broad spectrum of interests, including the scientific community, the U.S. Congress, state and federal agencies, and the Government Accountability Office (GAO). Although the process and its timeliness are issues of concern, the greatest focus has been on the quality of the science, with a recent NAS panel sharply criticizing the program. EPA has made reform of IRIS a major objective (U.S. EPA 2011a).

This draft document under review by the Science Advisory Board needs to be considered in the context of the enormous impact it might have on the national and international communities. Also of importance are the recurring scientific deficiencies that have been noted in recent EPA draft health assessments and the need to restore the public's perception of the scientific quality of IRIS.

Comments from Interested Parties on Previous Health Assessment Documents Intended for IRIS Publication

Because of the problems with the scientific acceptance of the draft EPA risk assessment documents intended for publication in IRIS, increasingly the NAS/NRC has been asked to provide the needed objective scientific review for many of these documents. Recent reviews have included formaldehyde, dioxin, trichloroethylene, and tetrachloroethylene, and now, by Congressional mandate, inorganic arsenic (NRC 2011; NRC 2006a; National Academies 2006a; NRC 2006b; National Academies 2006a; National Academies 2010; NRC 2010; Jacobs 2011).

In each case, the NAS/NRC found fault with the IRIS assessments, which findings have led to further delay in the review and finalization of IRIS Toxicological Reviews of these substances. Concerned with the "persistence of problems encountered with IRIS assessments over the years," and that "future assessments may still have the same general and avoidable problems. . . [i]f the methodologic issues are not addressed," NAS "encourage[d] EPA to address the problems with development of the draft assessments that have been identified" (NRC 2011, p 11).

As noted by other committees, there are many recurring and overlapping themes across these NAS reviews. These scientific concerns are best summarized by the general recommendations made by NAS to EPA in Chapter 7 of the formaldehyde review (NRC 2011) under the banner, "Reframing the Development of the IRIS Assessment":

- Consideration of how to improve each step of the process for better transparency and efficient presentation
- “Evidence Identification: Literature Collection and Collation Phase”
 - Use available evidence and understand the mode of action to select outcomes
 - Use standard protocols.
- “Evidence Evaluation: Hazard Identification and Dose-Response Modeling”
 - Use standardized approaches for study and weight-of-evidence descriptors
 - Establish protocols for reviewing major types of studies.
- “Weight of Evidence Evaluation: Synthesis of Evidence for Hazard Identification”
 - Implement and standardize the approach to using existing weight-of-evidence guidelines
 - Develop uniform language to describe the strength of evidence for non-cancer effects
 - Harmonize the approach for characterizing uncertainty and variability
 - Consolidate the outcomes around common modes of action.
- “Selection of Studies for Derivation of Reference Values and Unit Risks”
 - Establish clear guidelines for study selection
 - Balance strengths and weaknesses
 - Evaluate human vs. experiment evidence
 - Consider combining estimates among studies.
- “Calculation of Reference Values and Unit Risks”
 - Justify assumptions
 - Carefully consider and explain models used
 - Justify statistical and biological models, and describe the fit to the data
 - Determine points of departure
 - Assess analyses that underlie the points of departure
 - Provide the range of estimates and describe the effect of uncertainty factors on the estimates
 - Assess the adequacy of documentation to support conclusions and estimates.

These recommendations were described by NAS as “critical for the development of a scientifically sound IRIS assessment” (NRC 2011, p 121). They are intended to help EPA meet the challenges it faces to ensure the scientific credibility and acceptance of future health risk assessments. Further emphasizing the importance of these recommendations, the Chairman of the formaldehyde committee, Dr. Jonathan Samet, echoed these themes in his testimony before Congress: “The committee’s review of the EPA’s draft IRIS assessment of formaldehyde identified both specific and general problems with the document. The persistence of the problems encountered with the IRIS assessment methods and reports concerned the committee, particularly in light of the continued evolution of risk-assessment methods and the growing societal and legislative needs to evaluate many more chemicals in an expedient manner” (Samet 2011).

Many of these themes also are expressed by individual states and federal agencies in their reviews of these EPA draft health assessment documents, including the subject draft toxicological assessment for Libby Amphibole under current review (U.S. EPA 2011b). The agencies that have provided comments on the Draft Libby Amphibole review include the National Center for Environmental Health (NCEH)/Agency for Toxic Substances and Disease Registry (ATSDR), Centers for Disease Control and Prevention (CDC),

Department of Defense (DOD), National Institute of Environmental Health Sciences (NIEHS), National Institute for Occupational Safety and Health (NIOSH), and Office of Management and Budget (OMB).

Further, the U.S. Government Accountability Office's report on chemical assessments also makes it clear that EPA faces both long-standing and new challenges in implementing the IRIS Program (GAO 2011). The GAO report also reiterates issues raised previously by NAS concerning clarity and transparency, and the other general recommendations by the NAS (summarized above). Therefore, we are seeing a broad consensus emerge that it is a high priority to improve the scientific integrity of risk assessments. This is the context and challenge for this SAB Panel as it comes together to assess the integrity of the Draft Toxicological Review of Libby Amphibole Asbestos ("Draft Toxicological Review").

EPA Charge to the SAB on Libby Amphibole Asbestos

I was asked by WR Grace to assess the current Draft Toxicological Review, specifically to evaluate the context of the assessment, and the recommendations that have already been expressed during the review procedure. Further, given my experience implementing health assessments, I was asked to comment on the practical issues involved in this review process and the potential implication of the proposed IUR and RfC.

The EPA charge to this SAB committee requested that it "consider the accuracy, objectivity and transparency of EPA's analysis and conclusions" (U.S. EPA 2011c). In addition, EPA requested that the SAB committee respond specifically to many of the same issues identified in the recommendations of NAS, GAO, and others. These items include:

Noncancer/inhalation reference concentration (RfC)

- Selection of study population
- Selection of the critical endpoint and mode of action
- Methodology for the exposure reconstruction and development of exposure estimates
- Selection of exposure-response model
- Selection of model for point of departure (POD)
- Appropriateness of uncertainty factors.

Cancer/inhalation unit cancer risk (IUR)

- Selection of study population
- Exposure-response modeling
- Determination of POD
- Justify approaches used for confounding
- Approach for calculating the IUR
- Adequacy of descriptions of uncertainties and limitations.

Comments Specific to the Draft Toxicological Review of Libby Amphibole Asbestos

As mentioned above, EPA has acknowledged the NAS recommendations as being important in furthering its goal to improve IRIS (EPA 2011a). For this draft toxicological review, the scientific issues that have been identified by numerous federal agencies and individual scientists echo the themes summarized by the NAS in its prior recommendations to EPA. In its charge to this SAB committee, EPA clearly requests that these recommendations be taken into consideration. Some of the examples that I have noted, and that are noted by federal agencies as particularly important, are summarized below.

For cancer, the endpoints lung cancer and mesothelioma (hazard identification) are not in question, but the choice of data for characterizing potency and the statistical methods used require careful review. Together with a number of federal agencies and other reviewers, I call your attention to the following concerns that have been identified either in comments to the SAB or in the June 2011 comments to EPA by federal agencies on the Interagency Science Consultation Draft Toxicological Review (U.S. EPA 2011b), which should be made available to this SAB Panel:

- Use of data from a subcohort (unpublished), rather than evaluation of the entire Libby miners cohort [NIEHS, OMB, Moolgavkar, S. H. (2011)]
- Choice of statistical models (e.g., Poisson distribution model used, rather than traditional Peto model previously used by EPA) and methods [ATSDR, Moolgavkar, S.H.]
- Treatment of lag time [DOD, OMB, Moolgavkar, S.H.]
- Consideration of mode of action and possibility of non-linearity [OMB, DOD, NIEHS]
- Treatment of confounding factors such as smoking [OMB, NIEHS]
- Treatment of uncertainties [ATSDR, NIEHS, Moolgavkar, S.H.].

For the non-cancer endpoints, both hazard identification and exposure-response characterization must be critically reviewed. First, basing the hazard identification on human studies, as opposed to animal experiments, presents challenges for choosing a critical endpoint that is clearly associated with the agent in question. Second, the exposures must be characterized adequately. Equally challenging are the choice of modeling approaches and uncertainty factors for derivation of the RfC. Together with a number of federal agencies and other reviewers, I call your attention to the following concerns that have been identified:

- Use of a truncated cohort instead of the full Marysville cohort [NIEHS, OMB, Moolgavkar, S.H.]
- Choice of critical endpoint, pleural thickening, and treatment of confounders [ATSDR, OMB, Moolgavkar, S.H.]
- Characterization of exposure for a selected Marysville cohort (e.g., attributing all disease to Libby amphibole when some workers were exposed to other sources at other locations) [NIOSH]
- Choice of statistical methods for exposure characterization [Moolgavkar, S.H.]
- Justification of magnitude of uncertainty factors (10 and 10) for RfC derivation [DOD, OMB, ATSDR]
- Treatment of uncertainties [ATSDR, NIEHS, Moolgavkar, S.H.].

In addition, many of the reviewers have commented on the implications and practicality of implementing the proposed RfC, particularly ATSDR and OMB. I also note some of the challenges that would be presented if this level were to be adopted by IRIS.

It is important to note that the RfC value derived in the draft assessment, 0.00002 f/cc, is below most estimates of background concentrations in the U.S. (ATSDR 2001). This issue would affect not just Libby but the entire nation, including areas of the country with naturally occurring amphibole in soils, such as Eldorado Hills, California, where the amphibole background level (about 0.0008 f/cc) is about 40 times higher than the proposed RfC (U.S. EPA 2011b).

As a practical matter, future data collection efforts will also be severely affected by the proposed RfC. If the proposed RfC were to be adopted, large amounts of current and historical sampling data from Libby would not meet the required sensitivity level for noncancer hazard evaluation. For example, the current analytical sensitivity for EPA ambient air sampling at Libby exceeds the proposed RfC. Similarly, analytical sensitivities for EPA's activity-based sampling program for Libby, which has been ongoing for several years, are 10 to 100 times above the levels needed to evaluate a hazard quotient of 1 using the proposed RfC. Furthermore, the cost of analyzing samples down to this unprecedented low level would be several thousand to tens of thousands of dollars per sample. The RfC would have significant implications for risk assessment and, in many cases, may drive a risk assessment, especially for exposure durations shorter than about 20 years, for which a hazard quotient of 1 would be reached before a 10^{-6} cancer risk. These issues could extend to any site or residence where risk assessment for amphibole asbestos is necessary and where it is necessary to distinguish contaminant levels from background.

To my knowledge, this is the first effort to establish a safe level of exposure for noncancer endpoints at low levels of exposure for any form of asbestos. EPA has acknowledged that this document is the frontier of amphibole asbestos science (Jackson, 2009). Because of the enormous implications, particular attention needs to be focused on this entire approach.

In summary, the charge to this committee is important, and the committee should give careful consideration to all comments received. A thorough review by this committee, taking into consideration the recommendations from many groups—particularly the National Academy of Sciences / National Research Council—will strongly support EPA's efforts to reestablish the scientific credibility of the IRIS program and further the advancement of science and public health protection in the U.S. It will also prevent the protracted period of review that has characterized recent assessments and caused unnecessary delays for risk assessors in the field who need access to reliable toxicity values.

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Attachment: Background of the Author

For the U.S. Environmental Protection Agency (EPA), Dr. Anderson is a co-author of the first federal policies that adopted risk assessment and risk management as the basis for setting health-protective policies and guidelines for conducting carcinogen risk assessment, published in 1976. She founded and directed the Agency's Carcinogen Assessment Group, the Reproductive Effects Group, the Mutagenicity Group, and the Exposure Assessment Group, which encompassed the Office of Health & Environmental Assessment. Initially, this office conducted all of the Agency's risk assessments or provided review of any risk assessment work done by a regulatory program office. This office was the central EPA risk assessment program for 10 years. As each program office began to conduct some of their own risk assessments, it became necessary to establish the Risk Assessment Forum to provide a mechanism for sharing risk assessment results and methods for use by EPA programs and regions. As Chairperson of the first EPA Risk Assessment Forum, Dr. Anderson was instrumental in establishing the Integrated Risk Information System (IRIS). The original purpose of the IRIS database was to provide a central repository of risk assessment results; where differences were noted, the Forum was the mechanism for resolving inconsistencies. Dr. Anderson has also worked extensively on international risk assessment issues to address human health and ecological consequences of exposure to environmental toxicants, including efforts for private companies, governments, the World Health Organization, and the Pan American Health Organization.

Dr. Anderson is a founder and past-President of the Society for Risk Analysis, regularly serves on peer-review panels for public agencies and institutions, has participated in numerous national and international commissions and organizations concerned with risk-based issues, and has lectured and published widely in the field of risk assessment. She was also Editor-in-Chief of the journal, *Risk Analysis: An International Journal*, from 1998 to 2008.

Dr. Anderson is a Fellow of the Academy of Toxicological Sciences and the recipient of numerous awards, including the Twentieth Century Distinguished Service Award, Ninth Lukacs Symposium (1999), Outstanding Service Award of the Society for Risk Analysis (1997), Jerry F. Stara Memorial Award (1994), SES Bonus for Outstanding Performance (1984), EPA Gold Medal for Exceptional Service (1978), Kappa Kappa Gamma National Achievement Award (1974), and a William Author Mattox Merit Scholarship (1962). She also holds a patent and continues her professional activities through memberships in the American Association for the Advancement of Science, American College of Toxicology, New York Academy of Sciences, Society for Risk Analysis, and Society of Toxicology.

Dr. Anderson is currently Vice President for Health Sciences at Exponent.

APPENDIX B – 2

Additional Comments on the EPA Document, “Draft Toxicological Review of Libby Amphibole Asbestos” (EPA/635/r/002a)

Elizabeth L. Anderson, Ph.D., ATS Fellow
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Summary

I, Dr. Anderson, have previously provided two sets of written comments to the EPA prior to and during the February 6–8, 2012, SAB meeting (Anderson 2012a,b). The additional comments provided herein are provided in response to questions I was asked during that meeting and in light of the new studies and data requested by the SAB. Because of his vast experience on these topics, obtained while at NIEHS and subsequently, I have asked Dr. David Hoel to join me in this submission. A brief biosketch for Dr. Hoel is appended. The main points we would like to make are summarized below, and further discussion is provided in subsequent sections.

Selection of Critical Endpoint

- 1) It appears that the adverse effects that EPA is ultimately endeavoring to prevent are primarily decreased lung volume and decreased measures of lung function. EPA arrives at these endpoints by using pleural plaques, because EPA asserts that the presence of pleural plaques leads to lung function deficits. This relationship is not clearly supported by the literature, particularly for low exposure.
- 2) We agree with members of the SAB who recommended that EPA consider all non-cancer endpoints and the dose-response relationships, including those for pulmonary function deficits. Of special importance, if the Rohs et al. (2008) cohort data are to be used, EPA needs to base its assessment on the full cohort data set and include the pulmonary function data that we understand will be available later this year.
- 3) Pleural plaques are a sensitive endpoint, because they require far less cumulative exposure compared to pleural and interstitial diseases. They are also difficult for differential diagnosis, because other conditions can be mistaken for pleural plaques on x-rays.
- 4) The ILO (2000) guidelines define localized pleural thickening as pleural plaques that are located in the parietal pleura and appear predominantly on the chest wall, diaphragm, or other sites. In contrast, the location of diffuse pleural thickening is on the visceral pleura (the outermost covering of the lung tissue), where it is conceivable that the condition could impair lung function. It is far less biologically plausible that pleural plaques (located on the chest

wall and not in direct contact with lung tissue) would encroach on lung volume and thereby interfere with lung function.

- 5) For this draft assessment, we are in the rare position of deriving the inhalation reference concentration (RfC) from human data rather than from laboratory animal studies. This fact should remove some of the precautionary measures that are often involved when selecting the critical endpoint from experimental studies. If the quantitative relationship between LPT (pleural plaques) is not clearly confirmed to be associated with an adverse effect such as decreased lung function, and the biological mechanism for such a relationship is unknown, then LPT (pleural plaques) can be viewed only as a marker of exposure that is not verifiably causative of an adverse effect or on a biological pathway to cause disease. In this case, using a marker of exposure as a surrogate for an adverse effect and as the critical endpoint for the derivation of the RfC, raises serious questions of appropriateness and public policy. Markers of exposures from human data have not typically formed the bases for RfC and RfD derivation. Further setting this precedent will present challenges for many other substances in the environment where biomonitoring data define markers of exposure for many substances. The NAS has addressed the importance of these data and concluded that our ability to measure these markers far exceeds our ability to assess related risk (NAS 2006). Setting RfCs, RfDs and cancer risk levels of acceptability based on these markers will be highly precautionary and will raise serious challenges of social and economic consequence, reminiscent of the early 1970s when zero risk tolerance was abandoned in favor of risk assessment and risk management policies (Albert et al 1977).

Recommendations:

- Consider all non-cancer endpoints and the dose-response relationships, including for pulmonary function deficits.
- Despite the deficiencies for RfC derivation, if this study is to be used, the reassessment should rely on the full cohort and include the pulmonary function data, which are expected later this year.
- Further consider whether localized pleural thickening, in general and as defined by the ILO (2000), is plausibly linked to impairment of lung function. If not, consider this precautionary policy choice in light of the social and economic consequence of setting RfCs, RfDs, and unit cancer risk based on markers of exposure.

Derivation of the Reference Concentration (RfC)

- 6) EPA's benchmark dose modeling, based on the Rohs et al. (2008) sub-cohort, appears to be a case where the prevalence rates at the highest doses dominate the model fit, whereas the key interest is at lower doses. The available data are extremely limited (only 12 cases) for characterizing effects at lower doses.
- 7) EPA's display of a putative good fit for their dose-response model to the raw data in Figure E-1 is misleading. Other more common ways of summarizing the raw data, such as in the original Rohs publication, are at least as legitimate as EPA's method, do not show a

monotonic response at low doses, and more clearly show that there is little dose-response at low doses.

- 8) Because the cumulative exposure point of departure (POD) was converted to average air concentration over a 70-year lifetime (minus 10 years) to derive the RfC, the RfC will be below an effects threshold for almost all exposure scenarios used in risk assessment (e.g., a 30-year residential scenario).
- 9) The proposed RfC is currently equal to the POD divided by 6000. Although this factor includes both uncertainty factors and an adjustment for lifetime exposure, it essentially provides a margin of exposure on the POD. EPA has placed a cap of 3,000 on the upper end of the safety factors, with the notation that uncertainties exceeding this level make the resulting guidance levels too uncertain to be of use.
- 10) Depending on the inclusion and assessment of the available literature from other asbestos exposures, we agree with several members of the SAB that the database deficiency factor of 10 could be reduced to 3.

Recommendations:

- Consider whether sufficient information currently exists for an RfC derivation.
- Resolve issues with the choice and goodness of fit of the proposed BMD model.
- Evaluate the significance of low-exposure dose-response data limitations.
- Resolve the issue of lifetime averaging and real-world applications of the RfC that would result in erroneous findings of unacceptable non-cancer hazard.

Practical Considerations

- 11) From a practical standpoint, the resulting non-cancer RfC, 0.00002 f/cc, is so low that use of this level will frustrate cleanup efforts and confuse the public. This is because distinguishing the incremental contribution of source contamination over background will be difficult, time consuming, and costly.
- 12) The RfC is below detection limits for years of data collected at Libby, rendering those data either useless or confusing to the public as they try to understand risks. It will not be appropriate, nor will it meet data quality objectives, to use data with inadequate sensitivity that cannot detect at least a non-cancer hazard quotient of 1; simply equating non-detects in the existing data to zero will not be acceptable for this purpose.
- 13) Although the EPA draft assessment is focused on Libby Amphibole Asbestos (LAA), for the novel non-cancer proposed RfC, there is no convincing literature that would preclude application of these results to all types of asbestos exposures.

Recommendations:

- Taking the above considerations into account, outline a plan of action to implement this very low RfC.
- Because of the potentially profound implications of this draft RfC, confirm that it is based on a solid scientific foundation.

Selection of Critical Endpoint for RfC Derivation

Pleural plaques have long been regarded as markers of exposure but not necessarily of risk; pulmonary function deficits and parenchymal interstitial abnormalities are also associated with asbestos exposure. Clearly, diffuse pleural thickening is associated with pulmonary function deficits, and this is biologically plausible because they are defined according to their intimate association with the lung tissue (visceral pleura). The POD needs to rely on a data set that, at a minimum, allows for proper characterization of exposure and provides information on all three endpoints, to determine whether low-level exposure to asbestos leads only to markers of exposure (e.g., pleural plaques) or whether these markers are risk factors for pulmonary function deficits. At present, no data specific to LAA allow for this analysis to be conducted adequately. More data are needed for the Marysville cohort to characterize pulmonary function for the Rohs et al. (2008) full data set. These additional data may be available by the end of 2012. Further, the entire body of available literature to address these non-cancer issues for all asbestos types should be used to further explore the appropriateness of this choice for this critical endpoint and the resulting POD. No final RfC should be issued until all important studies are considered; the full Rohs et al. data set should be used together with the anticipated pulmonary deficit data.

It appears from EPA's Draft Toxicological Review that the adverse effects that they are ultimately endeavoring to prevent are "chronic chest pain, decreased lung volume, and decreased measures of lung function" (p. 5-21). EPA arrives at these endpoints by using pleural plaques as the critical endpoint and assumes an association, both biologically and statistically, with pulmonary function deficits. Thus, it relies on the Rohs et al. (2008) data to characterize a dose-response relationship between pleural plaques and cumulative exposure in the absence of pulmonary function deficit data and relies on other studies as a foundation for linking pleural plaques with this deficit. The challenge is that other studies do not provide a reliable basis for this linkage, either biologically or statistically.

The Rohs et al. team has lung function data, as we are sure was expressed to EPA during the course of communications regarding these data. We know that EPA was informed formally of this in a January 12, 2012, letter from Dr. Lockey to Dr. Wong. In addition, Dr. Lockey's previous study of the Marysville cohort reported on just this subject (Lockey et al. 1984), and he actually did not find a statistically significant relationship between "restrictive lung defect" (defined as FEV1/FVC ratio of equal to or greater than 70% and FVC less than 80% predicted) and cumulative exposure (p. 954). Lockey et al. goes on to state:

"The lack of association between simple spirometric and DLcosb measurements and fiber exposure most likely reflects the low cumulative fiber exposure and

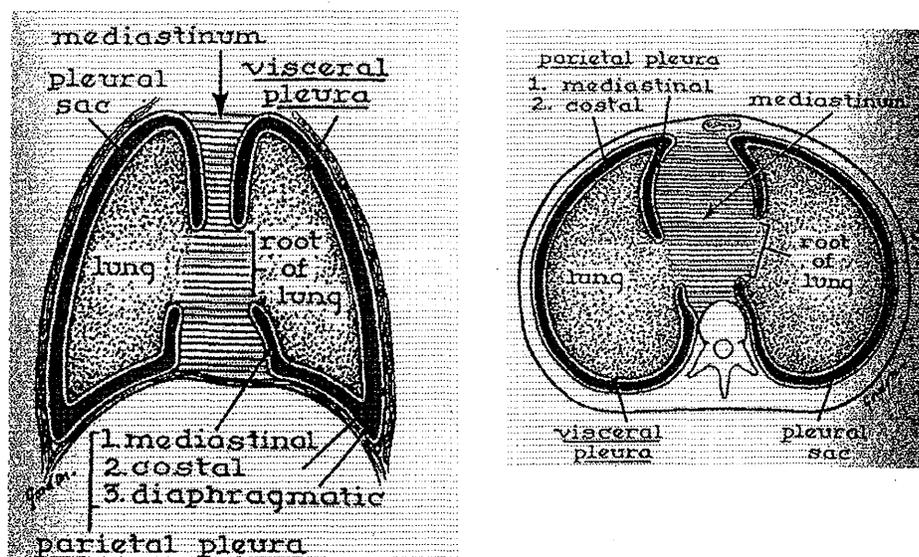
short interval period. Simple spirometric measurements have been shown to be sensitive indicators of the toxic effects of cumulative asbestos exposure... The level of cumulative fiber exposure needed to cause a change in spirometric values is greater than the exposure levels reported in the present study. Weill and colleagues (18) reported decrease in lung function after 100 mppcf-year dust exposure, while Becklake and colleagues (19) showed an effect at a cumulative dust exposure index of 10 to 100 mppcf-year. Berry and Lewinsohn demonstrated a 12.1% reduction for FEV, and 10.6% reduction for FVC per 100 fiber/cc-years (20)" (p. 956).

All of these cumulative exposure values are orders of magnitude greater than those relied upon by EPA in the Rohs et al. study.

Since the Draft Toxicological Review was published, Larson et al. (2012a) evaluated the dose-response relationship between cumulative exposure of Libby mine and mill workers and restrictive spirometry, showing that the odds of restrictive spirometry were significantly elevated at 166 f/cc-yr, similar to the studies summarized by Lockey et al. (1984) above. Comparatively, the cumulative dose at which pleural plaques was significantly elevated in the Larson et al. study was less than 1 f/cc-yr. If there truly was a relationship between pleural plaques and restrictive spirometry, one would not have expected a nearly 200-fold difference between these two values (166 vs. 1 f/cc-yr).

Assuming that EPA will continue to consider using pleural plaques as associated with adverse effects such as decreased lung function, it should more strongly recognize that it is still *highly* debated in the medical/scientific community whether or not discrete pleural thickening (plaque) impairs lung function. This issue is the topic of a multitude of published articles spanning nearly 50 years. Cugell and Kamp (2004) recognize nearly 80 articles published on this topic by 2001. However, EPA discusses only 10 of these studies in the Draft Toxicological Review. Of those, EPA reports that only 5 found a potential association between pleural plaques and decreased lung function, though even some of those results may have been confounded by parenchymal changes.

Further, ILO (2000) defines localized pleural thickening (pleural plaques) as being located in the parietal pleura, which lines the diaphragm, chest wall, and cupula. This definition makes it difficult to understand how lesions at these sites (which are not on the lungs themselves [visceral]) are biologically plausible causes of pulmonary deficits.



At the beginning of the review article that EPA references to support an association between pleural plaques and lung function deficit (Rockoff et al. 2002), the editor of the journal in which the article was published felt the need to place the following disclaimer on the article:

“Whether or not Pleural plaques cause significant pulmonary function impairment and/or clinical symptoms remains controversial. Currently, an international panel of experts is being assembled to reach consensus on a variety of asbestos-related disease issues, including the topic addressed by this report. In spite of the controversial nature of this subject, the editorial board decided to publish this provocative review.”

We suspect that the assembled panel of experts to which this disclaimer refers produced the American Thoracic Society’s “Diagnosis and Initial Management of Nonmalignant Diseases Related to Asbestos” (ATS 2004), which EPA does reference throughout the Draft Toxicological Review. The ATS document itself concludes:

“This [decrements in vital capacity associated with pleural plaques] has not been a consistent finding and longitudinal studies have not shown a more rapid decrement in pulmonary function in subjects with pleural plaques. Decrements, when they occur, are probably related to early subclinical fibrosis... There is a significant but small association between the extent of circumscribed pleural plaques and FVC, which is not seen with diffuse pleural thickening. Even so, most people with pleural plaques alone have well preserved lung function” (p. 705).

This conclusion is reiterated in a more recent article that is co-authored by a member of the SAB (Dr. Kane):

“Plaques may be associated with decreases in lung function and symptoms of dyspnea, but most individuals with pleural plaques alone display no apparent symptoms and no obvious impaired lung function” (Broaddus et al. 2011, p. 164).

The amount of materials that the EPA relied upon to formulate their opinion of an association between pleural plaques and decrements in lung function is limited. In contrast, the recent Toxicological Review on Tetrachloroethylene contains tens of detailed tables containing tens to hundreds of articles reviewed and summarized (U.S. EPA 2012). Given the unprecedented step by EPA to formulate an RfC for an asbestos fiber, a more detailed analysis needs to be performed and documented.

LPT (pleural plaques) are a very sensitive endpoint, requiring far less cumulative exposure to cause them than the other distinct pleural condition, diffuse pleural thickening, and interstitial disease (ATS 2004). They are also difficult for differential diagnosis, because other conditions can be mistaken for pleural plaques on x-rays. These other conditions include subpleural fat in obese individuals, intrathoracic muscles, soft tissue shadows along the ribs, and healed rib fractures (Hillerdal 1997; Cugell and Kamp 2004).

LPT (pleural plaques) are caused not only by exposure to asbestos, but can also be caused by prior tuberculosis, trauma, hemothorax, chronic empyema, and talc instillation (ATS 2004; Broaddus et al. 2011). The other causes typically result in unilateral pleural thickening. As stated in Broaddus et al. (2011), “multiple and bilateral pleural plaques, particularly when calcified, are considered to be pathognomonic for asbestos or erionite exposure.” Also, the ATS (2004) report states that “Pleural plaques are bilateral, but not symmetric, lesions of the parietal pleura.”

The rate of pleural abnormalities in an unexposed population is uncertain and can vary (Gujral et al. 2010). It can differ depending on the population studied, the study’s ability to clearly define the exposure or lack of exposure to asbestos in the population studied, and the definition of the pleural abnormality of interest.

More recently published studies, not referenced in the Draft Assessment, have been noted by the SAB. The Larson et al. (2012b) article addresses pleural plaques and lung function in the Libby community. This article concluded, “Controlling for the presence of these abnormalities as well as age, smoking status and other covariates, restrictive spirometry was also associated with LPT (OR 1.4; 95% CI 1.1 to 1.8).” We note that Larson et al.’s population included those with occupational exposure to non-Libby asbestos. Weill et al. (2011), who analyzed the same initial cohort of 7,307 as Larson et al., excluded 1,327 of the study participants because they had “occupations or activities likely to be associated with exposure to traditional, non-vermiculite asbestos-containing materials” (p. 377). Larson et al. recognized:

“A caveat of this study is the body habitus of participants; 4591 (71%) were classified as overweight or obese (table 1). Obesity is associated with reduced FVC and restrictive changes²⁷ as well as increased perception of circumscribed

pleural thickening.²⁸ Evidence for potential confounding can be seen in the high prevalence of restriction among obese participants (table 1). In addition, some argue that the excess of pleural abnormalities in this cohort may be due in part to obesity with subpleural fat being misclassified as plaque in up to 30% of the cases.²⁹ To offset the confounding effect of obesity, we controlled for BMI in all models.”

However, given the high percentage of overweight or obese persons in the population, it should be considered when interpreting the results.

Larson et al. also recognized: “Thus, although our analysis controlled for the presence of parenchymal abnormalities, our observed association between LPT and restriction may be due to ‘subradiographic’ fibrosis.^{37,}”

It is rare that RfCs are based on human data. If the quantitative relationship between LPT (pleural plaques) is not confirmed to be associated with an adverse effect such as decreased lung function, and the mechanism for such a relationship is unknown, it can be viewed only as a marker of exposure that is not verifiably causative of an adverse effect. If this is the case, the question arises as to whether using a marker of exposure as a surrogate for an adverse effect and as the critical endpoint for the derivation of the RfC is appropriate. The National Academy of Sciences addressed a parallel issue when it reviewed biomonitoring for chemicals detected in humans (NRC 2006):

“The ability to generate new biomonitoring data often exceeds the ability to evaluate whether and how a chemical measured in an individual or population may cause a health risk or to evaluate its sources and pathways for exposure. As CDC states in its National Reports on Human Exposure to Environmental Chemicals, the presence of a chemical in a blood or urine specimen does not mean that the chemical causes a health risk or disease. The challenge for public-health officials is to understand the health implications of the biomonitoring data, to provide the public with appropriate information, and to craft appropriate public-health policy responses.” (p. 2)

Similar to pleural plaques, many of the chemical markers of exposure detected in humans are not reversible, in that they might persist in the body indefinitely—for example, persistent lipophilic organic compounds such as organochlorine pesticides.

Dose-Response Model for RfC

EPA presents its dose-response model compared to the raw results in the restricted Rohs et al. (2008) data set in Figure E-1 (reprinted below as Figure 1). The model estimates a relationship between cumulative exposure and the prevalence of localized pleural thickening (pleural plaques) based on a data set of 108 subjects with 12 cases (7 unilateral, 5 bilateral). EPA determined that the best-fitting model was a Michaelis-Menten form, assuming a 1% background rate. By choosing the sub-cohort for this non-cancer evaluation, large amounts of data are discarded.

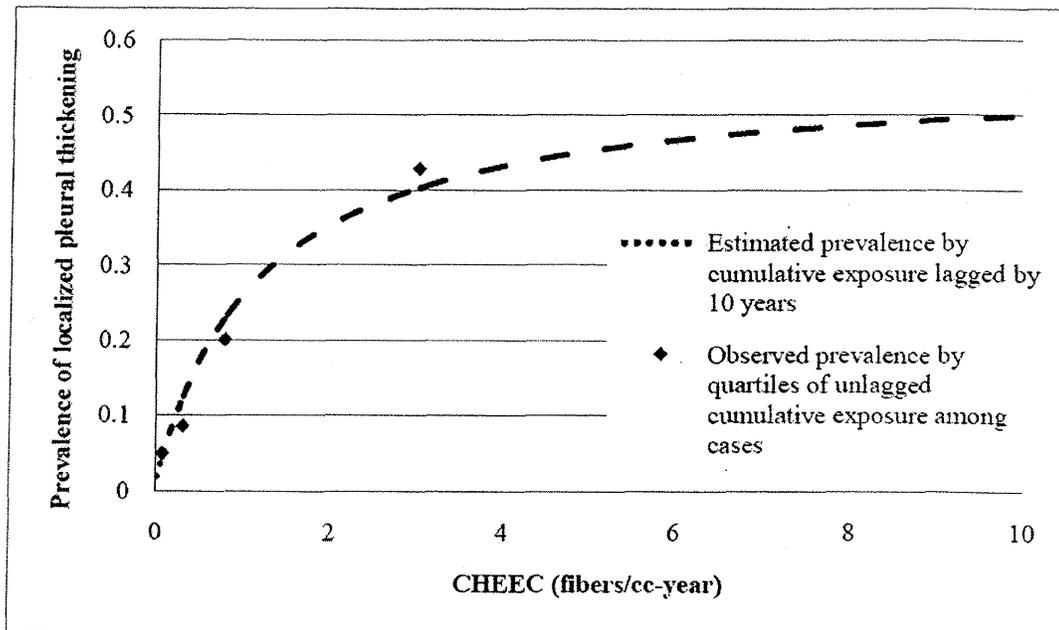


Figure 1. EPA's dose-response model fit for pleural thickening versus raw data in quartiles of cases (Figure E-1 in EPA Draft Toxicological Review)

It is peculiar that a Michaelis-Menten model was even attempted, given that this type of model is based on receptor binding in enzyme kinetics, and the development of plural plaques, while not well understood biologically, probably has little to do with enzyme kinetics. Also, the 1% background rate is an arbitrary selection that may have a significant effect on the model result. Because the background rate is not estimated directly from the data, the AIC value for the Michaelis-Menten model will be artificially lower, which gives it an unfair advantage in competing with the other models. The fitted Michaelis-Menten model limits the maximum prevalence of pleural thickening (56%), which has been exceeded in cohorts of very highly exposed insulation workers.

EPA's model fit shows a maximum slope at zero exposure (characteristic of a Michaelis-Menten model), which results in increasing risks with exposure, even for tiny exposures. EPA's model predicts a doubling of the assumed background rate of 1% at only 0.023 f/cc-yr. However, a review of the raw data shows that the dose-response at the lower doses is far less clear than might be concluded from EPA's figure.

To plot the raw data (and possibly in the dose-response modeling itself), EPA apparently divided the data into quartiles by the cases. In other words, EPA ordered the data by exposure and then divided the data set to make groups with three cases in each of four quartiles. This raises the question of whether or not the "independent x-value" in the regression is dependent on the outcome values. At the least, we can approximately reproduce the quartiles with this method.

The common way to divide the data into quartiles is to order the data by exposure, select an even number of subjects for each quartile, and calculate the prevalence in each quartile, such as was done in the Rohs et al. study. Table 1 shows the result when using this approach. When the quartiles are assembled with an approximately even number of subjects, the dose-response pattern looks very different. There is no discernible effect in the first three quartiles. In fact, the second quartile has no cases, compared to two in the first quartile, and the three cases in the third quartile are not statistically higher than the two cases in the first quartile.

Table 1. Rohs restricted data set divided into quartiles with even numbers of subjects

Quartile	Exposure (f/cc-yr)	Cases	Subjects	Prevalence
1	0.033	2	29	0.069
2	0.092	0	30	0.000
3	0.20	3	29	0.103
4	1.1	7	30	0.233

One can also divide the data into deciles with approximately equal numbers of subjects, as shown in Table 2. In this case, there is no clear effect for 9/10ths of the exposure distribution. There is one case in both the first and ninth deciles where the difference in exposure is 100-fold. Only in the 10th decile is a statistically elevated incidence clear (4 cases for 11 subjects).

Table 2. Rohs restricted data set divided into deciles with even numbers of subjects

Decile	Exposure (f/cc-yr)	Cases	Subjects	Prevalence
1	0.02	1	12	0.08
2	0.04	0	12	0.00
3	0.07	1	12	0.08
4	0.09	0	12	0.00
5	0.11	0	11	0.00
6	0.14	1	12	0.08
7	0.22	2	12	0.17
8	0.32	2	12	0.17
9	0.50	1	12	0.08
10	2.29	4	11	0.36

Given the extremely small number of cases (12) and the fact that 4 of these cases are in the top decile of exposure, reliable conclusions about the dose-response relationship at low doses (far above the reference concentration estimate) cannot be made.

The fit in EPA's model is dominated by the response at the highest dose, which is undesirable in BMD modeling. EPA states in its benchmark dose guidance document (U.S. EPA 2000):

“In the absence of a mechanistic understanding of the biological response to a toxic agent, data from exposures that give responses much more extreme than the BMR do not really tell us very much about the shape of the response in the region of the BMR” (emphasis added).

In summary, EPA's modeling appears to be a case where the prevalence rates at the highest doses dominate the model fit, whereas the key interest is at lower doses. The available data appear to be extremely limited for characterizing effects at lower doses.

Metric for the Derived RfC: Division of POD by 60 years

The real-world use of the proposed RfC in the Draft Toxicological Review, 2×10^{-5} f/cc, can result in a finding of an unacceptable non-cancer hazard for exposures that do not exceed the POD adjusted by uncertainty factors. This dichotomy arises because the RfC has been derived for a lifetime of exposure, and in standard risk assessment practice, the RfC is not prorated for less than lifetime chronic exposure durations.

Asbestos exposures are evaluated in a different way from exposures to other toxic substances. The concentration metric is in fibers per volume of air, rather than the mass-based concentration used for other toxic substances. The use of lifetime cumulative exposure (f/cc-years) as the POD is also uncommon; typically, the POD is expressed in concentration terms.

The Draft Toxicological Review's proposed RfC can be split into three elements: the POD (fibers/cc-year), the combined uncertainty factors (UFs) (unitless), and the lifetime exposure duration (ED) (years). Using the values presented in the Draft Toxicological Review, the calculation of the proposed RfC can be broken down as follows:¹

- $POD = 0.1177 \text{ f/cc-years}$
- $UF = 10 \text{ and } 10 = 100$
- $POD/UF = 0.001177 \text{ f/cc-years}$
- $ED = 70 \text{ years (lifetime)} - 10 \text{ years (lag)} = 60 \text{ years}$
- $RfC = POD/UF/ED = 0.0000196 \text{ f/cc (rounds to } 0.00002 \text{ f/cc)}$.

The RfC is the POD divided by 6000, representing the air concentration that equates to the POD/UF for an exposure scenario that involves a lifetime of exposure. These adjustment factors

¹ The order of these steps is presented slightly differently in the Draft Toxicological Review, in which the POD is initially divided by 60 years and then by the uncertainty factors.

are highly conservative, and the lifetime adjustment factor of 60 presents a dilemma for asbestos risk assessors, as explained below.²

The standard human health risk assessment practice, such as that applied by EPA for Superfund, uses the RfC as a benchmark for deriving the hazard quotient (HQ), the measure of non-cancer risk.³ For any chronic exposure scenario (by convention, an exposure occurring over 7 or more years) the HQ is the ratio of the average daily exposure concentration (EC) to the RfC; accordingly, if the EC exceeds the RfC, the HQ will exceed 1. Although an HQ exceeding 1 does not necessarily indicate there is an actual health risk, typically action is required to reduce the exposure.⁴ Unlike the flexibility of accepting risk for management purposes that span a range of 10^{-6} to 10^{-4} , there are no ranges of acceptability for the non-cancer endpoint around the hazard index of 1. An exceedance of the hazard index of 1 requires risk management.

The EC is defined as the time-weighted concentration over the exposure duration in years; thus, for an exposure lasting 30 years, the EC is the average concentration over those 30 years, not a lifetime.⁵ For example, using the 30-year exposure as an example, the HQ for an EC of 2.1×10^{-5} f/cc (a concentration that is just above the draft RfC value) exceeds 1, which would potentially result in a conclusion that further action is required. However, the cumulative exposure for this example would be approximately 0.0006 f/cc-years (2.1×10^{-5} f/cc \times 30 years), which is only about $\frac{1}{2}$ of the POD/UF (0.001177 f/cc-years). Therefore, an exposure concentration less than the “safe” level would trigger an “unacceptable risk” conclusion. Three approaches are suggested to resolve this contradiction:

1. Require the EC to reflect the lifetime average concentration.
2. Express the RfC in units of cumulative exposure (i.e., f/cc-years, made equivalent to the POD/UF).
3. Base the POD itself on exposure concentrations rather than cumulative exposure. This was done in the Draft Toxicological Review but only as a sensitivity analysis (see Section 5.3.7 of the Draft Toxicological Review). It is unclear whether that analysis was rigorous; for example, it is not clear whether the BMD model selected was based on the best fit to the

² EPA’s IRIS glossary (http://www.epa.gov/iris/help_gloss.htm) defines the RfC as follows: “Chronic Reference Concentration (RfC): An estimate (with uncertainty spanning perhaps an order of magnitude) of a continuous inhalation exposure for a chronic duration (up to a lifetime) to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. It can be derived from a NOAEL, LOAEL, or benchmark concentration, with uncertainty factors generally applied to reflect limitations of the data used. Generally used in EPA’s noncancer health assessments.”

³ See Risk Assessment Guidance for Superfund (RAGS), Volume I: Human Health Evaluation Manual (Part F, Supplemental Guidance for Inhalation Risk Assessment). <http://www.epa.gov/oswer/riskassessment/ragsf/>

⁴ See OSWER DIRECTIVE 9355.0-30 at <http://www.epa.gov/oswer/riskassessment/pdf/baseline.pdf> and EPA’s briefing materials slides presented at the February 2012 SAB meeting ([http://yosemite.epa.gov/sab/sabproduct.nsf/125B336CA388F5648525799B0083082A/\\$File/SAB+Libby+Presentation_NCEA_Bussard.pdf](http://yosemite.epa.gov/sab/sabproduct.nsf/125B336CA388F5648525799B0083082A/$File/SAB+Libby+Presentation_NCEA_Bussard.pdf))

⁵ 30 years is selected for this example, because it is the typical assumption for upper-bound residential exposure duration.

concentration data or if it was adopted from the main analysis using cumulative exposure.

Option 1 is problematic, because it redefines the EC. Option 2 is viable, because the conversion of the EC to a cumulative exposure is a trivial matter. Option 3 should be considered further.

In addition, as described above, the proposed RfC is currently equal to the POD divided by 6000. Although this factor includes both uncertainty and adjustment for lifetime exposure, it essentially provides a margin of exposure on the POD. EPA has placed a cap of 3,000 on the upper end of the safety factors, with the notation that uncertainties exceeding this level make the resulting guidance levels too uncertain to be of use (U.S. EPA 2002). We agree with several members of the SAB that the database deficiency factor of 10 could be reduced to 3, based on the available literature regarding other asbestos exposures.

Implications of the Proposed RfC

In my (Dr. Anderson's) initial comments and addendum provided to the SAB, I stressed the wide-ranging implications that the proposed RfC would have on past and future sampling efforts using EPA's activity-based sampling program for Libby as an example. I demonstrated that the proposed RfC, in most cases, would likely drive any risk assessment, because in most cases, the non-cancer hazard would eclipse the cancer risk targets of one in one million to one in ten thousand. I also pointed out the disparity between current analytical targets and those that would be associated with the draft RfC, and the increased time and cost that may be involved with achieving the "new" data quality objectives.

With respect to costs, I noted that per-sample costs would likely range in the low thousands of dollars to tens of thousands of dollars, and I provided some figures based on information provided to me by a single lab. Since then, we have talked with another lab, and although the above ranges still hold true, the second lab's costs were somewhat lower. We therefore have included these additional cost estimates as a low end of the cost range and provide a revised Table 1-2 (originally provided in my addendum comments) below. With respect to time to analyze samples, this will depend on the materials collected on the filters (non-asbestos mineral structures on the filter would significantly increase the time) and the staffing capabilities of the lab. The new sensitivities would require examining on the order of 100 to 500 grid openings. My understanding is that this level of effort will require days or weeks, rather than hours, of a microscopist's time, which is the primary determinant of time and cost (U.S. EPA 2008).

In my (Dr. Anderson's) addendum comments, I provided a graph that shows the tendency of the proposed RfC to drive risk assessment. We have performed a similar analysis for dioxin (2,3,7,8-TCDD) using the new oral reference dose (RfD). The LAA and dioxin figures are compared below. In contrast to LAA, where the non-cancer hazard will drive risk at about the 1-in-1,000,000 level, the new dioxin RfD will drive risk only if the target risk is above 1 in 100,000, approaching 1 in 10,000 for longer exposures. We present this information here to confirm the importance of this RfC decision and the need to meet the challenge to confirm a solid scientific foundation to support this decision.

April 9, 2012

Although the EPA draft assessment is focused on LAA, for the novel non-cancer proposed RfC, there is no convincing literature that would preclude application of these results to all types of asbestos exposures, including past and present exposures that are occupational, indoor residential, or ambient exposures. These forms of asbestos are widespread and well known.

Table 1-1: Calculation of Required Analytical Sensitivity for Noncancer Health Endpoint Based on Draft RFC

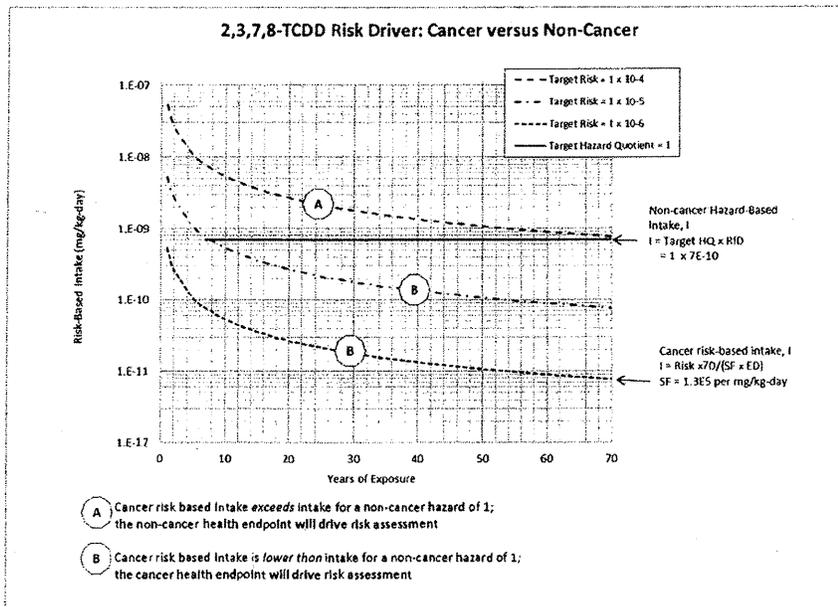
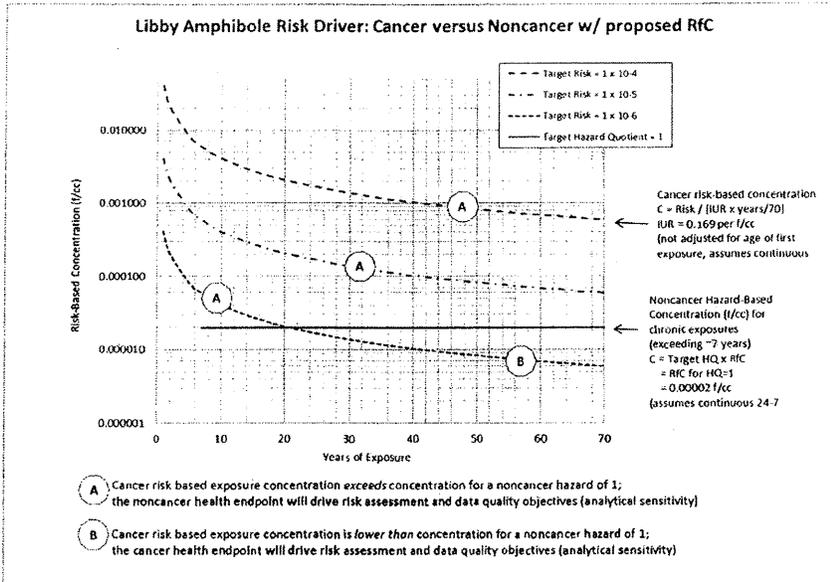
Scenario	Exposure Time (hrs)	Exposure Frequency (days/year)	Target Analytical Sensitivity (f/cc)	note	Draft RFC (f/cc)	Calculated		
						Time Weighting Factor, TWF (3)	Required target noncancer Hazard Quotient (HQ) = 1 (4)	Required target noncancer target Hazard Quotient = 0.2 (1 of 5 scenarios)
Residents in yards	8	60	0.002	(1)	2.0E-05	0.055	0.00012	0.000024
Residents in gardens	4	60	0.003	(1)	2.0E-05	0.027	0.00024	0.000049
Child playing on driveway	2	120	0.004	(1)	2.0E-05	0.027	0.00024	0.000049
Driving on Libby roads	4	180	0.001	(1)	2.0E-05	0.082	0.00008	0.000016
Biking in Libby (adult)	2	90	0.005	(1)	2.0E-05	0.021	0.00032	0.000065
Breathing ambient air			0.0000395	(2)	2.0E-05	1.0	0.00002	

Table 1-2: Calculation of Per Sample Costs of Laboratory Analysis to Meet Draft RFC-Required Analytical Sensitivities

Scenario	Required Sensitivity for noncancer (Target Hazard Quotient = 1) (4)	Assumed Typical Sampling Duration (min)	Assumed flow rate of sampling pump (Liters/min)	Volume of Air Sampled (Liters)	Cost to Analyze Volume to Required Sensitivity for HQ=1 (5)	Cost to Analyze for HQ=0.2 (1 of 5 scenarios)
Residents in yards	1.22E-04	120	5	600	\$ 2,700 - \$ 15,500	\$ 13,500 - \$ 77,500
Residents in gardens	2.43E-04	120	5	600	\$ 1,400 - \$ 7,800	\$ 7,000 - \$ 39,000
Child playing on driveway	2.43E-04	120	5	600	\$ 1,400 - \$ 7,800	\$ 7,000 - \$ 39,000
Driving on Libby roads	8.11E-05	240	10	2400	\$ 1,100 - \$ 5,800	\$ 5,500 - \$ 29,000
Biking in Libby (adult)	3.24E-04	120	5	600	\$ 1,100 - \$ 5,800	\$ 5,500 - \$ 29,000
Breathing ambient air	2.00E-05	7200	2	14400	\$ 800 - \$ 3,900	

Notes:

- Scenario, exposure and target sensitivity values taken from Table 3-3 of EPA Sampling and Analysis Plan (EPA 2010) [Supplemental Activity-based Sampling Libby Asbestos Site, Operable Unit 4, June 2010.](http://www.epa.gov/region8/superfund/libby/OU4_AmbientAirSamplingResults2010-2011.pdf)
http://www.epa.gov/region8/superfund/libby/OU4_SupplementalABS_SAP.pdf
- Typical Sensitivity from EPA Libby sampling "Ambient Air Sampling Results for Operable Unit 4, Libby asbestos Site, Libby, Montana 2010-2011" http://www.epa.gov/region8/superfund/libby/OU4_AmbientAirSamplingResults2010-2011.pdf
- Time Weighting Factor (fraction of time exposed) = exposure duration x exposure frequency / (24 x 365)
- 4 = RFC/TWF/3 for activity based scenarios (EPA 2010) and =RFC for ambient
- High end of range is based on discussions with an analytical asbestos laboratory the cost for TEM analysis can be approximated by the following formula
Cost = (RFC/Required sensitivity) x (5.66 x 10⁷/Volume sampled in Liters)
Low end assumes \$135 per sample including 10 grid openings plus \$5 per grid opening thereafter



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Background and Qualifications: Dr. David G. Hoel

Dr. David G. Hoel is a Distinguished University Professor in the Department of Medicine at the Medical University of South Carolina in Charleston, and is a Principal Scientist at Exponent, Inc. He received an A.B. in mathematics and statistics from the University of California at Berkeley and a PhD in mathematical statistics from University of North Carolina in Chapel Hill, and was a post-doctoral fellow in preventive medicine at Stanford University. Prior to joining the Medical University of South Carolina, Dr. Hoel was Division Director for Risk Assessment at the NIEHS in North Carolina. Dr. Hoel is a Fellow of the AAAS, a member of the Institute of Medicine of the National Academies, and a National Associate of the National Academies. His awards include the Spiegleman Gold Medal in Public Health and the Ramazzini Award in Environmental and Occupational Health. He has served on numerous governmental and National Academy committees, including the EHC and RAC of EPA's Science Advisory Board and the BEIR V committee of the National Academy of Sciences. He was a member of IARC's committee on ionizing radiation (report 100D) and contributed to the United Nations' UNSCEAR report 2006. Dr. Hoel's research has focused on risk assessment methods with particular interest in low-dose radiation exposures and cancer. This work has included stays in Hiroshima as a Director at the Radiation Effects Research Foundation, and he currently is a RERF Scientific Counselor. Until this year, he was a member of National Academies' Board on Nuclear and Radiation Studies. Finally, he has testified several times in both the House and Senate on human health issues.

APPENDIX B – 3

**CLINICAL BACKGROUND INFORMATION AND COMMENTS ON
RECENT SCIENTIFIC PUBLICATIONS AND THE DRAFT EPA REPORT
(AUGUST 2011) PERTAINING TO LIBBY AMPHIBOLE ASBESTOS**

**A Report Submitted to
The Scientific Advisory Board
United States Environmental Protection Agency**

By

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April 8, 2012

EXECUTIVE SUMMARY

This report is submitted to the United States Environmental Protection Agency (EPA) Scientific Advisory Board. Because of my knowledge and extensive experience as an academic pulmonologist, my expertise in occupational and environmental lung disease and my expertise in clinical risk assessment, I was asked by Exponent to prepare and submit this report to provide objective clinical background information, and to comment on recent scientific publications and the DRAFT EPA Toxicological Review (August 2011) pertaining to Libby Amphibole asbestos.

This report focuses on the characteristics of nonmalignant asbestos-related pleural disease, the association between nonmalignant asbestos-related pleural disease and pulmonary function abnormalities and the association of nonmalignant asbestos-related pleural disease with clinical symptoms, particularly as they to individuals exposed to Libby Amphibole asbestos from vermiculite mining and processing in Libby, Montana.

In order to provide sufficient clinical background information for later comments and professional opinions, the clinical characteristics of benign asbestos pleural effusion (BAPE), pleural plaques, diffuse pleural thickening, rounded atelectasis and asbestosis (interstitial lung parenchyma disease) are summarized. These summaries include references medical and scientific publications that are frequently cited and referred to by pulmonologists in clinical practice.

Four recent publications pertaining to Libby Amphibole asbestos exposure were critically reviewed. A critical assessment, professional commentary and professional opinions are provided for each. These are summarized in the paragraphs that are in the appendix.

In the following sections I will provide my opinion and commentary of clinically-related conclusions that appear on page 5-21 of the DRAFT EPA Toxicological Review of Libby Amphibole Asbestosis.

“Parietal plaques are known to induce chronic constricting chest pain that increases in severity as the extent of the plaques increases.”

In my opinion, this statement is poorly worded and does not adequately reflect the typical presentation of patients with asbestos-related pleural plaques. Indeed, there is no conclusive evidence that pleural plaques *induce* clinically-significant chest pain and no conclusive evidence that constricting chest pain increases as the extent of the plaques increases.

“Pleural thickening in general is associated with reduced lung function parameters with increased effect correlating with increased severity of the pleural thickening.”

In my opinion this statement is poorly worded. It is true that a large body of literature has demonstrated that *diffuse pleural thickening* is commonly associated with restrictive ventilatory impairment, that is, with “reduced lung function parameters.” It is also true that, in general, the severity of restrictive ventilatory impairment correlates with the severity of *diffuse pleural thickening*. Therefore, in my opinion, this statement should be reworded to more accurately reflect that it pertains to *diffuse pleural thickening* only. This statement does not reflect the preponderance of a large body of literature pertaining to localized pleural thickening (LPT or pleural plaques) which demonstrates that there is no statistically significant or clinically significant reduction in lung function associated with localized pleural thickening, per se.

“There is clear evidence from HRCT studies that the presence and extent of visceral thickening does impair lung function, although, when evaluated independently, parietal plaques were not statistically correlated with decreased pulmonary function.”

In my opinion, this statement is poorly worded. The two references cited to support this statement (Schwartz et al 1993; Copeley et al, 2001) do not use the term “visceral thickening.” They use the more commonly used term “diffuse pleural thickening.” Diffuse pleural thickening is an abnormality of the visceral pleura (not the parietal pleura) and typically results as a consequence of a previous benign asbestos pleural effusion (BAPE). Thus, by “visceral thickening” I assume that the report authors are referring to diffuse pleural thickening. In my opinion the more commonly used term *diffuse pleural thickening* rather than “visceral thickening” should be used in this statement.

It is true that the publications of Schwartz et al (1993) [42] and Copley et al (2001) [31] do demonstrate that diffuse pleural thickening, as determined by high resolution CT scan of the chest (HRCT), does impair lung function and that the severity of impairment is correlated with the extent of diffuse pleural thickening.

In my opinion, the more commonly used term “pleural plaques” should be used instead of the term “parietal plaques” in the above statement. It is true that the preponderance of a large body of literature demonstrates that there is no statistically significant or clinically significant correlation between pleural plaques and decreased pulmonary function. [28]

“Specifically considering the designation of LPT, lung function impairment has been demonstrated in several studies where pleural thickening without CPA involvement has been studied.”

In my opinion, this statement is poorly worded, is somewhat confusing and is potentially misleading. While it is correct that several studies “where pleural thickening without CPA

involvement has been studied” did demonstrate “lung function impairment,” these studies *do not* demonstrate that the “lung function impairment” was *caused by or directly related to* the “pleural thickening without CPA involvement.” Furthermore, this statement *directly contradicts* the previous statement in this section of the DRAFT EPA report, which [correctly] states that “parietal plaques were not statistically correlated with decreased pulmonary function.”

An American Thoracic Society Document states that “Decrements when they occur [in patients with pleural plaques] are probably related to early, subclinical fibrosis” and “Even so, most people with pleural plaques alone have well preserved lung function.” [7]

Thus, the radiographic classification of localized pleural thickening (LPT) (ILO 2000) includes pleural lesions associated with chronic chest pain, decreased lung volume, and decreased measures of lung function.

Based upon my comments in the above paragraphs, it is my opinion that this statement is poorly worded and does not accurately or completely represent the scientific facts. In summary, LPT (pleural plaques) are usually asymptomatic, there is no scientifically conclusive evidence that LPT (pleural plaques) causes a significant decrease in lung volume (i.e. total lung capacity) and LPT (pleural plaques) does not typically produce significant “decreased measures of lung function,” although mild small airways obstruction may occur from early subradiographic lung parenchyma fibrosis that occurs coincidentally with LPT.

**CLINICAL BACKGROUND INFORMATION AND COMMENTS ON
RECENT SCIENTIFIC PUBLICATIONS AND THE DRAFT EPA REPORT
(AUGUST 2011) PERTAINING TO LIBBY AMPHIBOLE ASBESTOS**

INTRODUCTION

This report is submitted to the United States Environmental Protection Agency (EPA) Scientific Advisory Board. Because of my knowledge and extensive experience as an academic pulmonologist, my expertise in occupational and environmental lung disease and my expertise in clinical risk assessment, I was asked by Exponent to prepare and submit this report to provide objective clinical background information, and to comment on recent scientific publications and the DRAFT EPA Toxicological Review (August 2011) pertaining to Libby Amphibole asbestos.

This report will focus on the characteristics of nonmalignant asbestos-related pleural disease, the association between nonmalignant asbestos-related pleural disease and pulmonary function abnormalities and the association of nonmalignant asbestos-related pleural disease with clinical symptoms, with particular attention to recent studies pertaining to individuals exposed to Libby Amphibole asbestos from vermiculite mining and processing in Libby, Montana. The reviewed publications have been studied in detail and my scientific assessment, professional opinion and commentary are provided.

This report will also provide my scientific assessment, professional opinion and commentary of clinically-related conclusions pertaining to nonmalignant asbestos-related pleural disease contained on page 5-21 of the DRAFT EPA Toxicological Review of Libby Amphibole Asbestosis that was published in August 2011. Malignant pulmonary diseases that may develop as a result of asbestos exposure, such as lung cancer and mesothelioma, are not discussed in this report.

BACKGROUND

There is a large body of scientific and medical literature about relationships and potential relationships between asbestos exposure and the development of nonmalignant pulmonary disease. It is important to understand the basic facts of what is known and what is not known with scientific certainty about the characteristics of various type of nonmalignant pulmonary disease that may develop after exposure to asbestos as a background for the assessments, professional opinions and commentary specifically pertaining to Libby amphibole asbestos exposure. The necessary background information is provided in this section of the report.

Nonmalignant pulmonary disease related to asbestos exposure can be classified into two general categories: pleural disease and lung parenchyma fibrosis (or asbestosis). There are several different types of pleural disease, each with its specific characteristics and potential human health effects. These include benign asbestos pleural effusion (BAPE), pleural plaques (also known as localized pleural thickening or LPT), diffuse pleural thickening and rounded atelectasis. Asbestosis-related lung parenchyma fibrosis, or asbestosis, may occur coincidentally with any type of pleural disease or may occur in the absence of pleural disease. The general characteristics and human health effects of asbestos-related nonmalignant pleural disease and asbestosis are discussed in the background sections that follow.

Nonmalignant Pleural Disease

Nonmalignant pleural disease is the most common category of asbestos-related diseases. [1]. The pleura consists of two components, the parietal pleura and the visceral pleura. The parietal pleura lines the inner wall of the thoracic cavity, including the diaphragm and the mediastinum. The visceral pleura covers the entire surface of the lung, including the interlobar fissures. The parietal pleural and the visceral pleura are separated by a “potential space” that contains a microscopically thin layer of fluid in normal individuals. The two components of the pleura are not typically discernible on chest radiographs in normal individuals; that is, they are typically visualized as one thin lining between the inner wall of the thoracic cavity and the lung. The

pleura is generally thought to be more sensitive to adverse effects of asbestos than the lung parenchyma. [2] Pleural disease can occur as benign asbestos pleural effusion (BAPE), pleural plaques (also called localized pleural thickening), diffuse pleural thickening, and rounded atelectasis. Each of these entities is discussed in the following sections.

Benign Asbestos Pleural Effusion (BAPE)

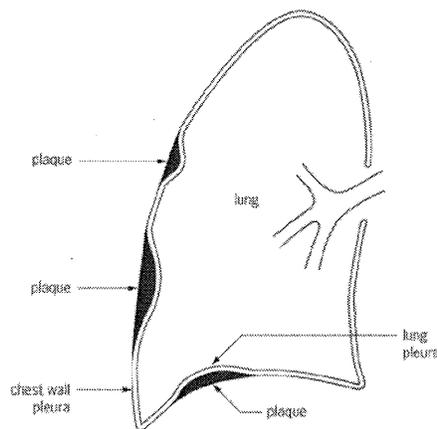
Benign asbestos pleural effusions (BAPE) are thought to be the earliest pleural disorder to occur following asbestosis exposure. [2, 3] Benign pleural effusions were first described in relation to asbestos exposure in the 1960s. [2, 4] Their exact prevalence is unknown, since many cases are subclinical, but one study estimates a prevalence of 3% among 1135 asbestosis-exposed workers. [2, 4, 5] Benign asbestos pleural effusions usually occur within 10 years of exposure [6], but they may develop much later, as well. [3] They are typically hemorrhagic exudates containing mixed cell types and usually do not contain asbestos bodies (so called “ferruginous bodies”). [1, 5] The majority of benign asbestos pleural effusions are unilateral, although bilateral effusions have been reported. [5, 7] Typically, benign asbestos pleural effusions are asymptomatic, but they may be associated with fever and/or pleuritic chest pain. [7] The pleural effusions usually resolve over a few months, but can persist for longer periods or recur after initial resolution. [1, 2] Of importance is the fact that *diffuse pleural thickening* of the *visceral pleura* is commonly seen after resolution of benign asbestosis pleural effusions. [5, 7] There is no evidence that benign asbestos pleural effusions are associated with the development of pleural plaques (localized pleural thickening).

The development of benign asbestosis pleural effusions is generally thought to be exposure-dependent. [5] However, there are reports that they can occur in some individuals following slight asbestos exposure. [5, 8] Pleural effusions are a common entity in clinical practice, and the diagnosis of a benign asbestos pleural effusion largely depends upon the exclusion of other causes of pleural effusions in an asbestos-exposed patient. The differential diagnosis for an exudative pleural effusion includes parapneumonic effusion, tuberculosis, malignancy, pulmonary embolus, pancreatitis, connective tissue disease, trauma, azotemia, and drugs.

Pleural Plaques (Localized Pleural Thickening)

The most common manifestation of asbestos exposure is pleural plaques, which are discrete areas of pleural fibrosis that almost always arise from the parietal pleura but may, rarely, arise from visceral pleura, as well. Pleural plaques are also known as localized pleural thickening (LPT). They tend to occur 20–30 years after exposure to asbestos. [2, 9, 10, 11] Most pleural plaques seen on chest radiographs occur on the posterolateral chest wall between the seventh and tenth ribs, the lateral chest wall between the sixth and ninth ribs, the dome of the diaphragm, and the mediastinal pleura. [1, 12] Pleural plaques on the dome of the diaphragm are generally thought to be diagnostic of previous asbestos exposure. [1] Pleural plaques are typically not seen in the apices of thorax or the costophrenic angles. Approximately two thirds of pleural plaques are bilateral, but they may be unilateral, as well. [1, 13] Some authors report a left-sided predominance of unilateral pleural plaques, whereas others have found no predominance for one side of the chest over the other. [14, 15]

Typical presentations of pleural plaques, in a lateral perspective of the chest, are depicted in the following diagram.



The size and number of pleural plaques are variable from one asbestos-exposed individual to another. Calcification is reported in 10%–15% of cases. [2] On histological examination, the plaques are relatively acellular, with a “basket-weave” appearance of collagen bundles. Asbestos fibers may be seen within the plaques, but asbestos bodies (so called “ferruginous bodies”) are usually not present. [1, 2] The pathogenesis of pleural plaques is uncertain, but it is generally thought that asbestos fibers reach the parietal pleura via lymphatic channels and cause an inflammatory reaction in the parietal pleura tissue. Other possible mechanisms of pleural plaque formation could be the hematogenous carriage of asbestos fibers to the parietal pleura or the direct migration of asbestos fibers through the lung to the parietal pleura, but neither of these possible mechanisms has been proven. [1, 2, 16, 17]

Although the International Labor Organization (ILO) uses posterior-anterior chest radiography to assess and classify pleural disease, conventional and high-resolution CT scans of the chest are more sensitive for the detection of pleural plaques. [2, 18] One study reports that conventional CT scans of the chest revealed pleural plaques in 95% of asbestos-exposed subjects compared with 59% detected on chest radiography. [19] Another study demonstrated that high-resolution CT scans of the chest (HRCT) detected pleural plaques in 100% of asbestos-exposed subjects compared with the detection of pleural plaques 93% of subjects on conventional CT scans of the chest. [20] A third study showed that high-resolution CT scans of the chest (HRCT) had a sensitivity of 97% and a specificity of 100% for the detection of pleural disease as a whole. [21] The authors of this study specifically recommended high resolution chest CT (HRCT) for distinguishing pleural disease from subpleural fat. In my opinion this is a noteworthy recommendation, since multiple studies have shown that subpleural fat can be misinterpreted as pleural plaques on anterior-posterior chest radiography. [1, 7, 22, 23, 24]

The above-cited studies point out the possibility of significant limitations in epidemiological studies that have used chest radiography alone to detect the presence or absence of pleural plaques. *In this regard, it is possible that epidemiological studies which have used chest radiography alone to detect the presence or absence of pleural plaques have significantly*

underestimated the number of subjects that actually have pleural plaques. That is, it is possible that a significant number of individuals who had no pleural plaques detected by chest radiography alone could have pleural plaques demonstrated on conventional CT scans of the chest or high-resolution CT scans of the chest, if either of these imaging modalities had been used to detect their presence or absence.

Pleural plaques are markers of previous asbestos exposure and are often incidental findings on chest radiographs. [1, 7] Pleural plaques are typically asymptomatic, with a British Thoracic Society document stating that they are “nearly always asymptomatic.” [25]. However, two studies have reported an association between pleural plaques, chest pain and chest “tightness” or “pressure” similar to that seen in angina pectoris. [26, 27] There are significant limitations to these studies, and while it may be true that chest pain, chest “tightness” or chest “pressure” may occur in individuals with pleural plaques, there is no conclusive evidence that the pleural plaques per se are the cause of these symptoms; that is, it is possible for these symptoms to be caused by other factors in individuals who have coincidental pleural plaques.

Multiple studies regarding the effect of pleural plaques on lung function have yielded conflicting results. However, the majority of these studies have demonstrated that there is no statistically significant or clinically significant association between pleural plaques and the impairment of lung function. [28] Two studies have demonstrated a small but statistically significant reduction in forced vital capacity (FVC), in the range of 5%, among individuals with pleural plaques compared with matching controls. [29, 30] However, a more recent study that determined the presence of pleural plaques with conventional chest CT scans, measured lung volumes in addition to FVC and controlled for the presence of lung parenchyma fibrosis did not show any reduction in FVC or total lung capacity (TLC) associated with pleural plaques. [31] This raises the distinct possibility that the small decrements in lung function observed in some studies of patients with pleural plaques were not due to the pleural plaques per se, but may be due to subradiographic fibrosis of the lung parenchyma that may occur coincidentally with LPT. A recent large, well-designed study by Clin, et al, assessed the relationship between isolated

pleural plaques and lung function in 2,743 subjects who had isolated pleural plaques and the absence of lung parenchyma abnormalities on high-resolution CT scans (HRCT) of the chest. This study showed a small but statistically significant reduction in total lung capacity (TLC), forced vital capacity (FVC) and the forced expiratory volume in one second (FEV1) among subjects with isolated pleural plaques. However, even though there was a small statistically significant reduction in lung function associated in subjects with isolated pleural plaques, the measured values of TLC, FVC and FEV1 were still *well within the normal range* for these subjects. The authors appropriately concluded that the small decrease in lung function among study subjects with isolated pleural plaques is unlikely to be of clinical relevance for the majority of subjects. [32] Another study has shown that there is no impairment of gas exchange or lung function during exercise in patients with pleural plaques. [33] An American Thoracic Society Document states that “Decrementations when they occur [in patients with pleural plaques] are probably related to early, subclinical fibrosis” and “Even so, most people with pleural plaques alone have well preserved lung function.” [7]

The differential diagnosis for pleural plaques should include subpleural fat, adipose tissue, rib fracture, companion shadows for ribs, early mesothelioma, and other pleural masses and metastases from a primary malignant tumor in the chest or elsewhere.

Diffuse Pleural Thickening

Diffuse pleural thickening is almost always a consequence of one or more previous benign asbestos pleural effusions (BAPE). [2] It is less specific for asbestos exposure than pleural plaques, because other causes of exudative pleural effusions can also lead to the development of diffuse pleural thickening. It results from thickening and fibrosis of the visceral pleura, which leads to fusion with the parietal pleura. [2] This is a consequence of the significant pleural inflammation that accompanies previous benign asbestos pleural effusions. [34] The pathophysiological process of diffuse pleural thickening development is thought to be associated with inflammation and fibrosis of lymphatic vessels. Direct extension of lung fibrosis into the visceral pleura may also contribute to its pathogenesis. [35] The clinical diagnosis of

diffuse pleural thickening on posterior-anterior chest radiographs requires the presence of a smooth uninterrupted pleural opacity that extends over at least one-quarter of the chest wall, with or without obliteration of the costophrenic angle. [2, 36] The CT scan criterion for diffuse pleural thickening is a continuous sheet of pleural thickening more than 5 cm wide, more than 8 cm in craniocaudal extent, and more than 3 mm thick. [37]

In general, conventional chest CT scans of the chest are more sensitive and specific than chest radiography and high resolution chest CT scans (HRCT) for the detection of diffuse pleural thickening. In one study, conventional chest CT scans detected diffuse pleural thickening in 100% of asbestos-exposed subjects, whereas chest radiography detected diffuse pleural thickening in only 70% of asbestosis-exposed subjects. [19] In another study of 100 asbestos-exposed workers, diffuse pleural thickening was detected in seven subjects. The diffuse pleural thickening was detected in two subjects by chest radiography, in four subjects by conventional CT scans of the chest, and in only 1 subject by high-resolution CT scans of the chest (HRCT). [38]

Two prospective studies of asbestos-exposed workers have shown the presence of diffuse pleural thickening in 5-13.5% of asbestos workers that developed between 3 and 34 years following first exposure to asbestos. [18, 39] It has also been shown that the prevalence of diffuse pleural thickening increases from the time of first exposure to asbestos and appears to be dose-related. [7, 18] The time from first asbestos exposure to the development of diffuse pleural thickening varies widely, from as early as 1 year following first exposure up to 20 years following first exposure. [1, 7, 39]

Dyspnea and chest pain are commonly reported among patients with diffuse pleural thickening, although these symptoms are usually mild. [18, 39, 40] Ventilatory failure with carbon dioxide retention, cor pulmonale and death has been reported in 4 patients with bilateral diffuse pleural thickening and one patient with unilateral diffuse pleural thickening. [7]

Multiple studies have shown a statistically significant correlation between chest CT scan findings of diffuse pleural thickening and restrictive ventilatory impairment of lung function. [1, 31, 39, 40, 41] This is in contrast to the findings among individuals with pleural plaques, in which the majority of studies show no statistically or clinically significant impairment in lung function associated with the presence of pleural plaques. One study has shown a statistically significant association between diffuse pleural thickening and lower lung volumes, as well as a dose response relationship between the extent of pleural thickening and the decrement in lung function. [42]

The differential diagnosis of diffuse pleural thickening includes organizing pleural effusion or empyema (“pleural peel”), tuberculosis, connective tissue diseases, talcosis, pleural metastases, and mesothelioma.

Rounded Atelectasis

Rounded atelectasis is defined as “invaginated fibrotic pleura and thickened and fibrotic interlobular septa.” [43] That is, thickened, fibrotic pleura folds onto itself and surrounds (entraps) an area of lung that creates a round, mass-like structure extending into the lung from the pleural surface. When present, rounded atelectasis is usually apparent on both posterior-anterior chest radiographs and CT scans of the chest.

The pathogenesis of rounded atelectasis is not certain, but is thought to be due to inflammation and subsequent fibrosis in the superficial layer of the pleura. As the fibrous pleural tissue matures, it contracts, causing pleura to fold onto itself and into the lung, which in turn, causes atelectasis by entrapping a portion of lung tissue. [44] Asbestosis exposure is the most common cause of rounded atelectasis [7] Asbestos-related rounded atelectasis is also known as asbestos pseudotumor or Blesovsky syndrome. [1, 18] Rounded atelectasis is much less common than asbestos-related pleural plaques or diffuse pleural thickening. [1]

The typical chest radiographic appearance of rounded atelectasis is a rounded, peripheral, pleural-based “mass” with distortion of the surrounding lung parenchyma. Either a pleural plaque or diffuse pleural thickening is usually seen in the vicinity of rounded atelectasis. The CT scan characteristics of rounded atelectasis are a round or oval “mass” adjacent to the pleura, a “comet tail” of bronchovascular structures extending into the “mass,” and thickening of the adjacent pleura. Loss of volume in the affected lung is often, but not always, seen. [45] The chest radiograph and chest CT scan characteristics of rounded atelectasis are similar to those of lung cancer, which is the principal disease in the differential diagnosis. Stability or shrinkage of the “mass” following initial detection strongly suggests rounded atelectasis, but a biopsy may be required to exclude the possibility of lung cancer in some cases. [46]

Rounded atelectasis is almost always asymptomatic. It does not cause significant lung function abnormalities itself, although lung function abnormalities may be associated with coincidental diffuse pleural thickening or lung parenchyma fibrosis. Although rounded atelectasis can mimic lung cancer on chest radiographs and CT scans, there is no evidence that it is a pre-malignant condition. [18]

Asbestosis Related Lung Fibrosis - Asbestosis

Asbestosis is the term given to interstitial fibrosis of the lung parenchyma caused by the inhalation of asbestos fibers. *Asbestosis does not* occur as a consequence of asbestos-related pleural disease. It may or may not be associated with coincidental asbestos-related pleural plaques or diffuse pleural thickening, but it is a *different disease*. [47] There is a dose-response relationship between the extent of asbestos exposure and severity of interstitial fibrosis. [6, 48] The lag-time between exposure and onset of symptoms is usually at least 20 years and may be up to 40 years, but can be as short as 3 years in individuals who have a constant, heavy asbestos exposure. [48]

The pathogenesis of asbestosis is not completely understood. It is generally thought that the chronic inhalation of asbestos fibers and the subsequent deposition of asbestos fibers in the lung parenchyma stimulates the chronic, ongoing release of reactive oxygen species, inflammatory mediators and various “growth factors” from alveolar macrophages and neutrophils, which directly damage lung tissue and promote the proliferation of interstitial fibroblasts. Over time, the lung damage and fibroblast proliferation leads to the development of interstitial fibrosis in the lung parenchyma. [48, 49, 50] Asbestos bodies (so called “ferruginous bodies”) are often seen within and adjacent to areas of interstitial fibrosis.

The interstitial fibrosis of asbestosis is typically more pronounced in the lower lobes and subpleural areas of the lung, but may involve the right middle lobe and the lingula of the left lung. The upper lobes of the lung can be involved in advanced cases, but this is not common. So called “honeycombing” of the lung can also occur in advanced disease, but this is also not common. [20, 38].

The chest radiograph features of asbestosis include areas of “ground-glass” opacities that are typically most prominent in the lower lung zones, small nodular opacities throughout the lung, a “shaggy” cardiac silhouette, and ill-defined diaphragmatic contours. [48] These same characteristics are seen on CT scans of the chest. It has been reported that 80% of patients with asbestosis have coexistent pleural disease on chest radiography, and that the percentage of coexistent pleural disease increases to 100% with on high-resolution CT scans of the chest. [20, 48] Fibrous bands are sometimes seen to extend inward from the pleura into the lung parenchyma. [48]

CT scans of the chest, especially high-resolution CT scans (HRCT), are more sensitive than chest radiography for detecting asbestosis. One study has shown that high-resolution CT scans of the chest (HRCT) detected asbestosis in 80% of asbestos-exposed patients with clinical symptoms but no chest radiographic evidence of asbestosis. This study also showed that high-resolution CT scans of the chest (HRCT) detected changes of asbestosis in one-third of asbestos-exposed

patients with neither clinical nor chest radiographic evidence of asbestosis. [38] Another study showed that 57 of 169 asbestos-exposed patients with normal chest radiographs had high-resolution chest CT scan findings suggestive of asbestosis. [51]

Asbestosis is usually associated with dyspnea, which may become severe if the disease progresses and is typically worse with exercise. [7] Patients with asbestosis typically have lung function abnormalities consisting of restrictive ventilatory impairment (decreased forced vital capacity with a well-preserved FEV1/FVC ratio and decreased total lung capacity), decreased diffusion capacity and arterial hypoxemia. [7, 52] Mixed restrictive and obstructive ventilatory impairment may also be seen. [7, 30]

Both the radiographic findings and the lung function abnormalities of asbestosis may remain static or progress over time [7, 53] The rate and extent of asbestosis progression after cessation of asbestos exposure appears to be associated with the level of exposure and the duration of exposure (i.e. cumulative exposure). [7, 54]

DEFINITIONS – INTERNATIONAL LABOR (ILO) CLASSIFICATION OF PNEUMOCONIOSES

In 1980, the International Labor Office (ILO) published guidelines for the classification of pleural and parenchymal radiographic findings caused by pneumoconioses. This was entitled *Guidelines for the Use of the ILO International Classification of Radiographs of Pneumoconioses*. These guidelines were intended to facilitate the coding of the posterior-anterior chest radiograph abnormalities of individuals with pneumoconioses in a reproducible manner. [18, 55] It is important to emphasize that these guidelines pertain only to abnormalities found on posterior-anterior radiographs of the chest. They do not specifically pertain to conventional or high-resolution CT scans of the chest.

The original 1980 ILO Classification guidelines were revised in 2000 and again in 2011. Since different scientific studies have used different editions of the ILO Classification for assessing posterior-anterior chest radiograph abnormalities associated with asbestos-related pleural and parenchymal lung disease over the years, a brief summary of the 1980 ILO Classification guidelines and changes to the guidelines in 2000 and 2011 are discussed in the sections that follow.

1980 ILO Classification of Pneumoconioses [56]

The 1980 ILO classification provides three types of guidelines for interpreting radiographic abnormalities: verbal descriptions, drawings and diagrams and standard reference films, which are available from the ILO on request.

Lung parenchyma abnormalities are classified according to “profusion scores” that consider the size, shape and location of opacities within the lung. Lung parenchyma abnormalities are classified as small opacities, small irregular opacities and large opacities in each area of the lung where opacities are found.

Pleural abnormalities are classified as diffuse pleural thickening, circumscribed pleural thickening (plaques), blunted costophrenic angle, and pleural calcifications. The classification of each type of abnormality is essentially made from reference drawings and diagrams provided in the publication, or comparison with standard radiographs provided by the ILO. The abnormalities are scored on the basis of thickness, extent, and poor definition of the diaphragm, poor definition of cardiac borders and the location of calcifications.

It should be noted that the term “localized pleural thickening” *is not used* in the 1980 ILO Classification and that the term circumscribed pleural thickening (plaques) is used rather than the commonly used term “pleural plaques.” It should also be noted that costophrenic angle obliteration is not considered in the classification of diffuse pleural thickening.

2000 ILO Classification of Pneumoconioses [57]

The main changes in the 2000 ILO Classification are the definitions used for pleural abnormalities. In this edition, pleural abnormalities are classified as pleural plaques (localized pleural thickening), costophrenic angle obliteration and diffuse pleural thickening.

The classification of pleural plaques (localized pleural thickening) is essentially made from reference drawings and diagrams provided in the publication, or comparison with standard radiographs provided by the ILO. Pleural plaques are reported as present or absent. If present on the chest wall they are recorded as in-profile or face-on, and separately recorded for the right and left sides. A minimum width of "about 3 mm" is required for an in-profile plaque to be recorded as present. Pleural plaques are further classified by the site, the presence or absence of calcification and the extent of plaques along the chest wall.

Costophrenic angle obliteration is recorded as either present or absent, separately for the right and left sides. The lower limit for recording costophrenic angle obliteration is defined by a standard radiograph. If the pleural thickening extends up the chest wall from the obliterated costophrenic angle, the thickening should be classified as diffuse pleural thickening.

Diffuse pleural thickening is reported only if the pleural thickening extends up the lateral chest wall in continuity with an obliterated costophrenic angle. Diffuse pleural thickening is recorded as either present or absent along the chest wall. If present, it is reported as in-profile or face-on, and separately for the right and left side. The extent of the plaque along the chest wall is recorded. A minimum width of "about 3 mm" is required for in-profile diffuse pleural thickening to be recorded as present.

The 2000 ILO classification states that diffuse pleural thickening has historically referred to thickening of the visceral pleura. The report acknowledges, however, that the distinction

between parietal and visceral pleural thickening is not always possible on a posterior-anterior chest radiograph.

2011 ILO Classification of Pneumoconioses [58]

The verbal descriptions, drawings and diagrams in the 2011 edition of the ILO Classification are the same as those in the 2000 ILO Classification.

The principal focus of the 2011 Guidelines is to extend the applicability of the classification scheme to include digital chest images. The 2011 ILO guidelines mandate that “B” readers acquire digital reference images from the ILO and compare them side-by-side with subject images when “B” reading chest radiographs. The intent of this mandate is to improve the accuracy of chest radiograph interpretations and to reduce “B” reader error.

COMMENTS ON CLINICALLY-RELATED CONCLUSIONS IN THE DRAFT EPA TOXICOLOGICAL REVIEW OF LIBBY AMPHIBOLE ASBESTOSIS (AUGUST 2011)

In the following sections I will provide my opinion and commentary of clinically-related conclusions that appear on page 5-21 of the DRAFT EPA Toxicological Review of Libby Amphibole Asbestosis.

“Parietal plaques are known to induce chronic constricting chest pain that increases in severity as the extent of the plaques increases.”

In my opinion, this statement is poorly worded and does not adequately reflect the typical presentation of patients with asbestos-related pleural plaques. Indeed, there is no conclusive evidence that pleural plaques *induce* clinically-significant chest pain and no conclusive evidence that constricting chest pain increases as the extent of the plaques increases.

Asbestosis-related pleural plaques are found on the parietal pleura. The parietal pleura is the most common thoracic structure that causes chest pain. In contrast, the visceral pleura and the lung parenchyma are insensitive to most painful stimuli. Thus, any pathological process that involves the parietal pleura, including pleural plaques, has the potential to cause chest pain. Pain related to parietal pleura pathology can present either as chest wall pain (pleurisy) or as retrosternal chest "tightness" or "pressure" similar to that experienced in angina pectoris due to coronary artery disease. From a clinical perspective, a thorough investigation for other possible etiologies of chest pain should be conducted in any patient with asbestosis-related pleural plaques who presents with chest pain.

The British Thoracic Society and the United States Agency for Toxic Substances and Disease Registry (ATSDR) have taken the position that pleural plaques are usually asymptomatic. [25, 66] A British Thoracic Society monograph states that "A grating sensation in the chest is described in less than 1%." [25] An American Thoracic Society review states that "Chronic, severe pleuritic pain is rare in patients with asbestosis-related pleural disease." [7] This review also states that "Vague discomfort appears to be more frequent," "studies examining the frequency of atypical chest pain in asbestos-exposed patients have not been performed," and "in the few cases that have been described, it was present for many years, disabling and often bilateral." [7]. A study published in 1988 found that there was no difference in thoracic pain between 130 subjects with pleural plaques and 1,103 control subjects without pleural plaques or chest radiograph abnormalities. [68]

A report published in 1990 described four asbestos-exposed patients with pleural disease who had "disabling, persistent and often bilateral pleuritic pain." [26] However, it is not possible to conclude that the persistent chest pain experienced by these patients was caused by pleural disease per se, since each had a history of other abnormalities that could, possibly be the cause or a factor contributing to the chest pain. In fact, the author of this publication states that "No explanation can be offered for the persistence of pleural pain in these four patients" and "Such

pain has not been described in the many patients who have come to medical attention with asbestos induced pleural plaques.”

A 2000 publication reported that among 86 patients with asbestosis exposure and benign pleural disease (both pleural plaques and pleural thickening) 28% had “nonanginal pain,” 20% had “mild angina” and 5% had “severe angina” as self-reported on the Rose chest pain questionnaire. [27] However, 72% of these subjects were current or former smokers, coronary artery disease was not definitively excluded as the etiology of “angina” pain, anxiety may have contributed to the self-reporting of pain on the Rose questionnaire, and that subjects may have confused the sensation of pain with dyspnea, among other limitations.

Thus, the statement that “Parietal plaques are known to induce chronic constricting chest pain that increases in severity as the extent of the plaques increases” cannot be substantiated, in my opinion. After an extensive literature search, I have found no evidence of any publication that conclusively addresses the severity of any type of chest pain and the extent of pleural plaques. In my professional experience, most pulmonologists would concur that pleural plaques are commonly found as an incidental finding on chest radiographs, that pleural plaques usually asymptomatic, that some such patients may present with a relatively mild, vague chest discomfort or “tightness” and that any patient with pleural plaques who presents with chest “tightness” or chest “pain” should have a thorough evaluation for other possible etiologies of these symptoms.

“Pleural thickening in general is associated with reduced lung function parameters with increased effect correlating with increased severity of the pleural thickening.”

In my opinion this statement is poorly worded and an overgeneralization of known facts. It is true that a large body of literature has demonstrated that *diffuse pleural thickening* is commonly associated with restrictive ventilatory impairment, that is, with “reduced lung function parameters.” It is also true that, in general, the severity of restrictive ventilatory

impairment correlates with the severity of *diffuse pleural thickening*. Therefore, in my opinion, this statement should be reworded to more accurately reflect that it pertains to *diffuse pleural thickening* only. This statement does not reflect the preponderance of a large body of literature pertaining to localized pleural thickening (LPT or pleural plaques) which demonstrates that there is no statistically significant or clinically significant reduction in lung function associated with localized pleural thickening, per se.

“There is clear evidence from HRCT studies that the presence and extent of visceral thickening does impair lung function, although, when evaluated independently, parietal plaques were not statistically correlated with decreased pulmonary function.”

In my opinion, this statement is poorly worded. The two references cited to support this statement (Schwartz et al 1993; Copeley et al, 2001) do not use the term “visceral thickening.” They use the more commonly used term “diffuse pleural thickening.” Diffuse pleural thickening is an abnormality of the visceral pleura (not the parietal pleura) and typically results as a consequence of a previous benign asbestos pleural effusion (BAPE). Thus, by “visceral thickening” I assume that that the report authors are referring to diffuse pleural thickening. In my opinion the more commonly used term *diffuse pleural thickening* rather than “visceral thickening” should be used in this statement.

It is true that the publications of Schwartz et al (1993) [42] and Copley et al (2001) [31] do demonstrate that diffuse pleural thickening, as determined by high resolution CT scan of the chest (HRCT), does impair lung function and that the severity of impairment is correlated with the extent of diffuse pleural thickening.

In my opinion, the more commonly used term “pleural plaques” should be used instead of the term “parietal plaques” in the above statement. It is true that the preponderance of a large body of literature demonstrates that there is no statistically significant or clinically significant correlation between pleural plaques and decreased pulmonary function. [28]

“Specifically considering the designation of LPT, lung function impairment has been demonstrated in several studies where pleural thickening without CPA involvement has been studied.”

In my opinion, this statement is poorly worded, is somewhat confusing and is potentially misleading. While it is correct that several studies “where pleural thickening without CPA involvement has been studied” did demonstrate “lung function impairment,” these studies *do not* demonstrate that the “lung function impairment” was *caused by or directly related to* the “pleural thickening without CPA involvement.”

According to the 2000 and 2011 ILO Classifications, “pleural thickening without CPA [costophrenic angle] involvement would be classified as “Pleural Plaques (Localized Pleural Thickening).” That is, Localized Pleural Thickening (LPT) is exactly the same entity as “Pleural Plaques.” Thus, this statement *directly contradicts* the previous statement in this section of the DRAFT EPA report, which [correctly] states that “parietal plaques were not statistically correlated with decreased pulmonary function.” This is confusing; it does not make sense.

In one publication cited to support this statement in the DRAFT EPA Report (Kilburn and Warshaw, 1991), it is stated that “Plaques or diffuse pleural thickening did not reduce or ‘restrict’ total lung capacity, not [nor] did they produce a different pattern of impairment from the orderly continuum of obstruction in small airways proceeding to air trapping and a reduced vital capacity seen in pulmonary asbestosis.” [68] That is, subjects with pleural plaques or diffuse pleural thickening showed a mild degree of small airways obstruction, but did not show restrictive ventilatory impairment. They further state that “We think, therefore, that pleural asbestos disease signifies the presence of pulmonary asbestosis [i.e. lung parenchyma fibrosis] that is beneath the threshold for detection by routine chest radiography” and “The probable lesions are cellular infiltrates and fibrosis around small bronchioles, limiting flow in these airways as measured by spirometry. [68] That is, the authors think that there was no lung

function impairment associated directly with LPT per se. They opine that the mild obstruction in the small airways they observed was most likely not due to the LPT, but was probably due to subradiographic fibrosis of the lung parenchyma surrounding small airways that may occur coincidentally with LPT. Similar findings were reported in another publication cited in this section of the DRAFT EPA report (Garcia-Closas, et al, 1995). [69] An American Thoracic Society Document states that “Decrements when they occur [in patients with pleural plaques] are probably related to early, subclinical fibrosis” and “Even so, most people with pleural plaques alone have well preserved lung function.” [7]

Thus, it is possible for some patients with LPT (pleural plaques) to have small airways obstruction related to coincidental, subradiographic, peribronchiolar lung parenchyma fibrosis, but this abnormality *is not caused by or not directly related to the LPT*. The small airways obstruction could cause mild to moderate dyspnea on exertion in some individuals, but, in my opinion this is unlikely to be clinically significant in the vast majority of affected individuals. In this regard, it is my opinion that the above statement in the DRAFT EPA Report does not accurately or completely reflect the facts.

Thus, the radiographic classification of localized pleural thickening (LPT) (ILO 2000) includes pleural lesions associated with chronic chest pain, decreased lung volume, and decreased measures of lung function.

Based upon my comments in the above paragraphs, it is my opinion that this statement is poorly worded and does not accurately or completely represent the scientific facts. In summary, LPT (pleural plaques) are usually asymptomatic, there is no scientifically conclusive evidence that LPT (pleural plaques) causes a significant decrease in lung volume (i.e. total lung capacity) and LPT (pleural plaques) does not typically produce significant “decreased measures of lung function,” although mild small airways obstruction may occur from early subradiographic lung parenchyma fibrosis that occurs coincidentally with LPT.

NOTES:

The professional opinions and commentary in this report are those of the report author and do not necessarily reflect the opinions of the Medical University of South Carolina or any other member of its faculty.

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APPENDIX

REVIEW OF FOUR RECENT PUBLICATIONS RELATED TO LIBBY VERMICULITE EXPOSURE

Four recent publications related to Libby vermiculate exposure and related to the scope and focus of this report were reviewed in detail. My assessment of these publications and my professional opinions regarding the conclusions of each of these four publications are summarized in the sections that follow.

Larson TC, Lewin M, Gottschall EB, et al. Associations between radiographic findings and spirometry in a community exposed to Libby amphibole. *Occup Environ Med* 2012; Published online, March 1, 2012, doi:10.1136/oemed-2011-1000316. [59]

The objective of this study was to determine if abnormal spirometry is associated with localized pleural thickening (LPT), as defined by the authors, on posterior-anterior chest radiographs, using data from a community-based spirometry screening cohort in Libby, Montana.

In this study authors state that posterior-anterior chest radiographs were evaluated by using the 1980 International Labor Office International Classification of Radiographs of Pneumoconioses [56]. Although the classification of “localized pleural thickening” (LPT) is not used in the 1980 ILO Classification, the authors used this term by defining LPT as “circumscribed pleural plaque on chest wall and/or diaphragmatic pleural thickening detected in the same hemithorax by \geq two “B” readers with DPT [diffuse pleural thickening] not detected.”

The authors conclude that restrictive spirometry is significantly associated with LPT [as defined by the authors themselves], indicating that LPT may result in lung function impairment. They also report that the severity of restriction in this study is correlated with the extent of LPT on posterior-anterior chest radiographs of study subjects.

In my opinion, there are several potentially significant limitations to this study. This is especially true with regard to *limitations of the data that were available and analyzed by the*

authors. Although the methods of data analysis appear to be appropriate, limitations in the data itself introduce considerable uncertainty in the robustness of the above conclusions. Some of limitations were appropriately acknowledged and discussed by the authors in the manuscript. I will provide my opinion regarding potential limitations in the paragraphs that follows.

The authors defined restrictive spirometry as $FEV1/FVC > LLN$ and $FVC < LLN$. Any spirometry study that meets these criteria would clearly be abnormal and, in general, “restrictive spirometry” is an appropriate classification for these criteria. However, a definitive diagnosis of restrictive ventilatory impairment cannot be made from spirometry alone. Furthermore, best clinical practice would include a convex pattern on the flow-volume loop, in addition to FEV1 and FVC measurements, for a determination of possible restriction to be made on the basis of spirometry alone. [60] There is no mention of flow-volume loops being assessed in this study. While “restrictive spirometry”, as defined by the authors, is suggestive of restrictive ventilatory impairment, the definitive diagnosis of restrictive ventilatory impairment requires the measurement of lung volumes, specifically the total lung capacity (TLC). That is, “restrictive spirometry” may not be a totally accurate reflection of restrictive ventilatory impairment in some subjects in the study cohort, in pure physiological terms. Since lung volumes were not measured in the study cohort, “restrictive spirometry” is merely a “best estimate” of the possibility of restrictive ventilatory impairment from the data that were available to the authors, and cannot be considered to be definitive in a pure physiological sense. This is a result of the limited data that was available to the authors. It is not possible to quantify the uncertainty in study results that could result from the use of “restrictive spirometry” rather than measuring lung volumes to accurately determine the presence or absence of restrictive ventilatory impairment. This potentially significant limitation was not specifically discussed by in the manuscript.

The authors report that they fitted a generalized logit model for estimating the risk of functional impairment predicted among participants with restrictive spirometry and a high

degree of LPT. They defined severity of functional impairment as mild, moderate or severe based upon the percent predicted of the FEV1. Although this is a generally accepted method of assessing severity of functional impairment associated with “restrictive spirometry”, it does not allow one to accurately predict symptoms or prognosis for individual patients. [60] It is also true that problems in severity assessment arise when the values of both FEV1 and FVC lie near their upper limits of normal or lower limits of normal. In these situations, a literal interpretation of the functional pattern is considered to be “too simplistic” and could “fail to properly describe” the functional status. [60] Thus, for a variety of physiological reasons, FEV1 and FVC may sometimes fail to properly identify the severity of ventilatory impairment, especially when measured spirometric values are close to the upper and lower limits of normal. The measurement of total lung capacity (TLC) is the only clinically accurate way of assessing the severity of restrictive ventilatory impairment, and this was not performed in this study. It is impossible to quantify the degree of uncertainty that could result from the use of FEV1 to assess the functional severity of “restrictive spirometry” in this study. This potentially significant limitation was not specifically discussed in the manuscript.

The authors report that 71% of subjects were classified as “overweight or obese”. It is well-known from multiple publications in the medical literature that subpleural fat deposits can be easily mistaken from plural plaques (LPT) on plain posterior-anterior radiographs of the lung, even by the most astute and experienced radiologists. A high resolution CT scan of the chest is needed to definitively distinguish subpleural fat from pleural plaques (LPT). Thus, although the authors appropriately controlled for body mass index (BMI) in the logistic regression analysis, it is still possible that, in some cases, areas of LPT (as defined by the authors) are actually subpleural fat deposits and not LPT (pleural plaques), per se. Again, it is not possible to quantify the degree of uncertainty that could result from the possible misinterpretation of subpleural fat deposits as LPT in this study. This potentially significant limitation was not specifically discussed in the manuscript.

Another potentially significant limitation of this study is that chest radiography alone was used to determine the presence, width and extent of pleural plaques. As previously mentioned, *it is possible that epidemiological studies which use chest radiography alone to detect the presence or absence of LPT (pleural plaques) could significantly underestimate the number of subjects that actually have LPT (pleural plaques).* That is, it is possible for a significant number of subjects who had no LPT detected on anterior-posterior chest radiographs to have LPT (pleural plaques) detected on conventional CT scans of the chest or high-resolution CT scans of the chest, if either of these imaging modalities had been used to detect its presence or absence. [20] Thus, it is possible that a significant number of subjects in this study who had no LPT detected by chest radiography and also had normal spirometry actually did have LPT that was simply not detected. It is not possible to quantify the degree of uncertainty in the reported study results that could result from the limitations of anterior-posterior chest radiography to detect the presence or absence of LPT. However, in my opinion, it is possible that the actual number of cohort subjects with LPT and normal spirometry could be significantly greater than the number observed and reported in this study. This, in turn, could decrease the odds that LPT was actually associated with “restrictive spirometry.” It could also decrease the odds that the severity of LPT was actually associated with the presence of “restrictive spirometry.”

It is a well-known fact that overweight and obese individuals may develop restrictive ventilatory impairment as a consequence of their weight alone. The potential effect of body weight on the development of restrictive ventilatory impairment cannot be assessed from spirometry alone; it requires measurement of the expiratory reserve volume (ERV). ERV was not measured on this study. Therefore, it is possible that, in some cases, the observed “restrictive spirometry” could be due to increased body weight alone and not due to the presence of LPT (pleural plaques). Although the authors appropriately attempted to control for body mass index (BMI) in their logistical regression analysis, in the absence of ERV measurements this statistical methodology does not exclude the possibility of “restrictive spirometry” being a consequence of elevated body weight in some subjects. The authors appropriately acknowledge this limitation in the manuscript. From the available data, it is not impossible to quantify the degree of uncertainty

that could result from the effect of elevated body weight on the measurement of “restrictive spirometry” in this study.

In the legend of Table 3, the authors state that “The sum of the participants with an LPT abnormality index score > 0 , $n=1060$, is greater than the number of participants with LPT in table 2 due to counting participants with LPT detected by one reader.” The rationale for this is not explained in the manuscript. Furthermore, this is inconsistent with the methodology described in the Methods section: “Two B readers independently evaluated each radiograph using the 1980 International Labor Organization (ILO) Classification.” “When they disagreed about the presence of pneumoconiosis, a third reader was used.” The result of using the radiographic assessment of one reader (rather than two or three) is that there were 352 more subjects reported to have an LPT abnormality > 0 in Table 3 than the number of participants reported to have LPT in Table 2. The authors do not provide a plausible rationale for this in the manuscript, and this simply does not make sense. This raises the possibility that, in the assessment of some radiographs, the authors did not include assessments from two readers who determined that there was no LPT and only included the assessment from one reader who determined that there was LPT in the Table 3 LPT data. This would be a serious methodological flaw in study execution and, in my opinion, would invalidate the authors’ conclusion that the severity of restriction is correlated with the extent of LPT on posterior-anterior chest radiographs of study subjects. The possibility of this serious methodological flaw in study execution was not discussed in the manuscript.

In the manuscript, the authors cite three publications that also show an association between “restrictive spirometry” and LPT. [30, 52, 61] In general, however, these studies contain some of the same data limitations that are present in this study. They also appropriately state that “the LPT-restriction association has been an inconsistent finding with some studies finding no association with the presence of radiographic LPT or the surface area of LPT on high-resolution CT scans.” [31, 36, 62] In addition they appropriately state that, although they attempted to control for the presence of parenchymal abnormalities, the “observed association between LPT

and restriction may be due to 'subradiographic' fibrosis", as suggested in several other publications. [7]

In summary, it is my opinion that the reported associations are suggestive of the authors' conclusions, but, as a result of potentially significant study limitations, they do not provide a clear-cut scientific basis for determining that the conclusions are correct. In this regard, if high-resolution CT scans of the chest (HRCT) had been used to detect the presence or absence of subpleural fat, the presence or absence of LPT and the extent (severity) of LPT, it is very possible that there would be no statistically significant association between "restrictive spirometry" and LPT or the extent (severity) of LPT. Furthermore, in my opinion, the use of data from only one "B" reader in assessing the effect of LPT extent on the severity of restriction by anterior-posterior chest radiographs alone (Table 3) raises a serious question about the validity of the authors' conclusion that the severity of restriction is correlated with the extent of LPT on posterior-anterior chest radiographs of study subjects.

Larson TC, Antao VC, Bove FJ, Cusack C. Association between cumulative fiber exposure and respiratory outcomes among Libby vermiculite workers. *Journ Occup Environ Med* 2012; 54; 56-62. [63]

The objective of this study was to examine the association between cumulative fiber exposure and health outcomes in workers (n=336) with Libby amphibole exposure. Health outcomes include the presence of radiographic pleural abnormalities (DPT and LPT), radiographic parenchymal abnormalities, normal spirometry, obstructive spirometry, restrictive spirometry, shortness of breath, cough and chronic bronchitis.

In this study, the authors state that the 1980 ILO Classification was used to determine the presence of parenchymal abnormalities, diffuse pleural thickening (DPT) and localized pleural thickening (LPT) on posterior-anterior chest radiographs. Although the term localized pleural

thickening (LPT) is not mentioned in the 1980 ILO Classification, the authors used this term in the manuscript by defining it as “the presence of circumscribed plaque on the chest wall (as indicated on the International Labor Office Form) or diaphragm without the presence of DPT or parenchymal abnormalities”.

The authors classified spirometry findings based upon the lower limits of normal (LLN) for FEV1/FVC, FEV1 and FVC. Normal spirometry was defined as $FEV1/FVC \geq LLN$ and $FVC \geq LLN$. Obstructive spirometry was defined as $FEV1/FVC < LLN$ and $FVC \geq LLN$. Restrictive spirometry was defined as $FEV1/FVC > LLN$ and $FVC < LLN$. Mixed spirometry was defined as $FEV1/FVC < LLN$ and $FVC < LLN$. Lung volumes were not measured in this study.

Exposure estimates were made using “cumulative fiber exposure” (CFE). CFE as defined by the authors has the unit of fibers/cubic centimeter-year (f/cc-y). Historical and personal air sampling data were used to estimate the time-weighted average (TWA) exposure for all fiber types for each work area on the basis of contrast microscopy. CFE for each job held by a worker was estimated by weighting the 8-hour TWA for each job held by a worker by the length of time (in years) that the spent at that job. The total CFE for each worker was determined by summing the CFE from each job that the worker held. The aggregate CFE values were then categorized by quartiles for statistical analysis: < 0.4 ; $0.4-3.5$; $3.6-15.7$; and ≥ 15.7 .

The prevalence of non-cancer health outcomes was determined for each quartile (category) of exposure for the following covariates: DPT, LPT, parenchymal abnormalities, restrictive spirometry, shortness of breath, cough and chronic bronchitis. In addition to this categorical analysis, logistic regression models were developed for the following relationships using restricted cubic spline (RCS) functions to overcome potential disadvantages of converting continuous exposure variables into categorical variables: relationship between CFC and odds of radiographic diffuse pleural thickening (DPT); relationship between CFE and odds of radiographic localized pleural thickening (LPT); relationship between CFE and odds of radiographic parenchymal abnormalities; relationship between CFC and odds of restrictive

spirometry; relationship between CFE and odds of shortness of breath; relationship between CFE and odds of excess cough; and relationship of CFE and odds of chronic bronchitis. The statistical methodology used for the categorical analyses appears to be appropriate; however, it is beyond my level of statistical expertise to comment on the appropriateness of using RCS functions for the logistic regression analyses.

Based upon these analyses, the authors have reached the following four conclusions that are important with respect to the focus and scope of this report:

1. The odds ratio of radiographic LPT occurring on a posterior-anterior chest radiograph in the study cohort is statistically significant at a CFE of less than 1 f/cc-y, which is far below what would be experienced by a typical worker exposed at the current permissible exposure level of 0.1 f/cc-y over a working life of 45 years (i.e. 4.5 f/cc-y).
2. In the categorical analysis, only 13% of study subjects had restrictive spirometry and its risk was only slightly elevated for the highest quartile of exposure. In the RCS logistic regression analysis the odds ratio of restrictive spirometry occurring among cohort subjects in this study were statistically significant at a CFE of 166 f/cc-y.
3. The odds of shortness of breath and excess cough did not reach statistical significance in either the categorical or RCS logistic regression analyses. In the categorical analysis, the odds ratio of chronic bronchitis was statistically elevated in the third exposure quartile (CFE 3.6 – 15.7 f/cc-y) and decreased to a non-significant level in the fourth exposure quartile (CFE \geq 15.7). In the RCS logistic regression analysis, the odds ratio of chronic bronchitis became statistically significant at a CFE of 24 f/cc-y.

4. The shape of the exposure response curves generally correlates with CFE less than 400 f/cc-y for the objective outcomes, providing evidence that Libby amphibole is a causative agent of adverse pulmonary outcomes.

In my opinion, there are potentially significant limitations of this study. This is especially true with regard to *limitations of the data that were available and analyzed by the authors*.

Although the methods of data analysis appear to be appropriate, limitations in the data itself introduce considerable uncertainty in the robustness of the above conclusions. As mentioned previously, it is beyond my level of statistical expertise to assess the appropriateness of using RCS functions for the logistic regression analyses. Some of the study limitations were appropriately acknowledged and discussed by the authors in the manuscript. I will provide my opinion of potential study limitations in the paragraphs that follows.

As discussed in the previously reviewed Larson article [59], while “restrictive spirometry”, as defined by the authors, is clearly abnormal and suggestive of restrictive ventilatory impairment, the definitive diagnosis of restrictive ventilatory impairment requires the measurement of lung volumes, specifically the total lung capacity (TLC). That is, “restrictive spirometry” may not be a totally accurate reflection of the presence of restrictive ventilatory impairment in some subjects, in pure physiological terms. Since lung volumes were not measured in the study cohort, “restrictive spirometry” is merely a “best estimate” of the possibility of restrictive ventilatory impairment from the data that were available to the authors, but cannot be considered definitive in a pure physiological sense. Again, this is a result of the limited data that was available to the authors. It is not possible to quantify the uncertainty in study results that could result from the use of “restrictive spirometry” rather than lung volumes. This potentially significant limitation was not discussed in the manuscript.

As in the previously discussed Larson article [59], a large number of overweight and obese subjects in the study cohort could result in subpleural fat being misinterpreted as LPT on posterior-anterior chest radiographs, even by astute and experienced radiologists. Thus,

although the authors appropriately controlled for body mass index (BMI) in both the categorical and RCS logistic regression analyses, it is still possible that, in some cases, areas of LPT (as defined by the authors) are actually subpleural fat deposits and not LPT (pleural plaques), *per se*. This, in turn, could significantly affect the “accuracy” or “robustness” of the authors’ conclusion that the odds ratio of radiographic LPT occurring on a posterior-anterior chest radiograph in the study cohort is statistically significant at a very low CFE of less than 1 f/cc-y, which is far below what would be experienced by a typical worker exposed at the current permissible exposure level of 0.1 f/cc-y over a working life of 45 years (i.e. 4.5 f/cc-y). Again, it is not possible to quantify the degree of uncertainty that could result from the possible misinterpretation of subpleural fat deposits as LPT in this study. Although the authors controlled for BMI in both the categorical and RCS logistic regression analyses, the possibility of subpleural fat deposits being misinterpreted as LPT was not specifically discussed in the manuscript.

Another potentially significant limitation of this study is that chest radiography alone was used to determine the presence or absence of pleural plaques. As previously mentioned, *it is possible that epidemiological studies which use chest radiography alone to detect the presence or absence of LPT (pleural plaques) could significantly underestimate the number of subjects that actually have LPT (pleural plaques)*. That is, it is possible for a significant number of subjects who had no LPT detected on anterior-posterior chest radiographs to have LPT (pleural plaques) detected on conventional CT scans of the chest or high-resolution CT scans of the chest, if either of these imaging modalities had been used to detect its presence or absence. [20] It is not possible to quantify the degree of uncertainty in the reported study results that could result from the limitations of anterior-posterior chest radiography to detect the presence or absence of LPT in this study. However, it is possible that the odds ratio of LPT occurring on a conventional chest CT or high-resolution chest CT (HRCT) could become statistically significant at a CFE that is significantly higher than 1 f/cc-y, as reported in this study.

As discussed in the assessment of the previous Larson article [59], it is possible that, in some cases, the observed “restrictive spirometry” could be due to increased body weight alone and not due to the presence of LPT (pleural plaques). The authors did not control for body mass index (BMI) in the categorical analysis or the RCS logistic regression analyses of “restrictive spirometry”. Therefore, in the absence of expiratory reserve volume (ERV) measurements the statistical methodology used in this study does not exclude the possibility of “restrictive spirometry” being a direct consequence of elevated body weight in some subjects. From the available data, it is not impossible to quantify the degree of uncertainty that could result from the effect of elevated body weight on the measurement of “restrictive spirometry” in this study. The possibility that elevated body weight could contribute to the “restrictive spirometry” observed in this study was not specifically discussed in the manuscript.

A potentially significant limitation of this study is the possibility of selection bias of participating workers. Only 18% of the eligible worker population participated in this study (336/1832). In this regard, the authors state that, since study subjects self-selected themselves to participate in the study, a variation of the healthy worker survival effect may have resulted in workers with lower exposures remaining healthy enough to participate in the study. The authors specifically acknowledge the potential effects of selection bias on the prevalence of LPT observed in this study. The authors opine that, because the latency period of LPT is typically greater than 20 years after initial exposure, the prevalence of LPT in this study may be lower than expected because participating workers had a lower median time since first exposure than the total eligible worker population. It is also possible that participating workers had a lower CFE than the total eligible worker population, which could bias results toward the presence of LPT at a lower exposure level. Thus, it is possible that the observation of the statistically significant odds ratio for LPT occurring at a very low CFE (less than 1 f/cc-y) may not be representative of the total eligible worker population. This possibility was not specifically discussed in the manuscript.

Another potential limitation is the possibility of exposure misclassification. The authors state that samples taken before 1967 were collected by the use of a midget impinger, whereas later samples were collected with a membrane filter. A conversion factor was used to convert the midget impinger “total respirable dust” results to “fiber exposure” results obtained by a membrane filter. In this regard the authors acknowledge the possibility of errors in the CFE estimates. Since the accuracy of the conversion factor was not assessed or discussed, in my opinion, it is possible for significant inaccuracies to occur in the conversion of midget impinge readings to “fiber exposure” units that are measured by a membrane filter. Neither the derivation nor the accuracy of the conversion factor was specifically discussed in the manuscript.

The authors also point out the possibility of bias in the self-reporting of respiratory symptoms. They state that the “self-reports” may have been biased by a worker’s belief that his or her health was affected by amphibole exposure or by [psychological] hypersensitivity to symptoms that would otherwise be ignored. The possibility of bias in the self-reporting of respiratory symptoms was adequately addressed by the authors in the manuscript.

In summary, it is my opinion that the reported associations are suggestive of the authors’ conclusions, but, as a result of potentially significant study limitations, they do not provide a clear-cut scientific basis for determining that the conclusions are correct. It should be noted that, because of the design and nature of this study, the authors do not demonstrate any correlation between DPT, LPT, or parenchymal abnormalities and ventilatory impairment.

Rhos AM, Lockey JE, Dunning KK, et al. Low-level fiber-induced radiographic changes caused by Libby vermiculite. A 25-year follow-up study. Am J Respir Crit Care Med 2008; 177: 630-637. [64]

This is a follow-up study of a 1980 report that demonstrated a small but significant prevalence of pleural changes on posterior-anterior chest radiographs associated with amphibole fibers in cohort of 513 workers exposed to Libby vermiculite ore. The objective of this study was to evaluate the extent of radiographic changes and cumulative fiber exposure (CFE) in 280 members of the original cohort who completed chest radiographs and interviews 25 years after cessation of exposure.

Posterior-anterior chest radiographs were classified for pleural and interstitial changes by three board-certified radiologists who are "B" readers, using the 2000 International Labor Organization International Classification of Radiographs of Pneumoconioses (2000 ILO Classification). No pleural or interstitial changes were noted by any of the three radiologists on known normal films that were randomly interspersed with study films.

Vermiculaite fiber exposure was assessed by Cumulative Fiber Exposure (CFE) measured in fibers / cubic centimeter-year (f/cc-y). CFE was calculated by multiplying the 8-hour time-weighted average of fiber exposure for each job held by the worker by the number of years worked at each job between 1963 and 1980, then summing the results for each job. The CFE data was then categorized into quartiles by fiber exposure (f/cc-y) as follows: First (0.005 - 0.24); Second (0.25 - 0.74); Third (0.75 - 1.91); and Fourth (1.92 - 19.03).

The authors conclude that industrial exposures to fibers of Libby vermiculite ore *cause* pleural thickening at low lifetime CFE levels of less than 2.21 fiber/cc-y. This is significantly below the lifetime CFE for a worker exposed to the current OSHA permissible exposure limit of 0.1 fiber/cc for regulated asbestosis in general industry, over a 45-year working life (CFE of 4.5 fiber/cc-y). They also conclude that the prevalence of pleural changes in the 280 study participants was 28.7%, with 22.9% having LPT, 3.7% having DPT, and 2.1% having both pleural thickening and interstitial parenchymal changes. In addition they conclude that there is a statistically significant correlation between increasing CFE (exposure quartiles) and the number of cohort

subjects with pleural changes (of all types) on posterior-anterior chest radiographs and that the prevalence of pleural changes increased with age.

In my opinion, there are potentially significant limitations of this study. This is especially true with regard to *limitations of the data that were available and analyzed by the authors*.

Although the methods of data analysis appear to be appropriate, limitations in the data itself introduce considerable uncertainty in the robustness of the above conclusions. Some of the study limitations were appropriately acknowledged and discussed by the authors in the manuscript. I will provide my opinion of potential study limitations in the paragraphs that follows.

As in the previously discussed Larson articles [59, 63], the relatively large number of overweight and obese subjects in the study cohort could result in subpleural fat being misinterpreted as LPT on posterior-anterior chest radiographs, even by astute and experienced radiologists. BMI was measured on 231 of the 280 subjects in the study cohort, with 211 of this 239 being either overweight or obese by BMI criteria. The authors acknowledge that “subpleural fat can mimic pleural thickening”, but state that “This was not a factor in our study because the percentage of distribution of pleural changes was evenly distributed across all BMI categories”. In my opinion, the fact that the observed pleural changes were evenly distributed across all BMI categories does not exclude the possibility that subpleural fat was misinterpreted as LPT on some radiographs or that the number of potential misinterpretations was evenly distributed across all BMI categories. The possibility of subpleural fat being misinterpreted as LPT does, in turn, add uncertainty to the study results and could significantly affect the “accuracy” or “robustness” of the previously stated conclusions of the authors. Again, it is not possible to quantify the degree of uncertainty that could result from the possible misinterpretation of subpleural fat deposits as LPT in this study. The possibility that subpleural fat could be misinterpreted as LPT even though the percentage of distribution of pleural changes was evenly distributed across all BMI categories was not specifically discussed in the manuscript.

As in the previously discussed Larson articles [59, 63], another potentially significant limitation of this study is that chest radiography alone was used to determine the presence or absence of pleural plaques. As previously mentioned, *it is possible that epidemiological studies which use chest radiography alone to detect the presence or absence of LPT (pleural plaques) could significantly underestimate the number of subjects that actually have LPT (pleural plaques).* That is, it is possible for a significant number of subjects who had no LPT detected on anterior-posterior chest radiographs to have LPT (pleural plaques) detected on conventional CT scans of the chest or high-resolution CT scans of the chest, if either of these imaging modalities had been used to detect its presence or absence. [20] It is not possible to quantify the degree of uncertainty in the reported study results that could result from the limitations of anterior-posterior chest radiography to detect the presence or absence of LPT in this study. However, it is possible that industrial exposures to fibers of Libby vermiculite ore are associated with the presence of pleural thickening at a higher lifetime CFE level than 2.21 fiber/cc-y, as reported in this study.

The authors appropriately acknowledge that participation bias is a potential limitation in this study. They correctly state that “Although age was similar between participants and nonparticipants, those hired on or before 1973 were more likely ($P < 0.01$) to participate.” This adds further uncertainty to the reported prevalence of pleural abnormalities by quartile of exposure and, as the authors appropriately state, “there could be less confidence in the prevalence of pleural changes by quartiles of exposure, especially for workers with the lowest exposure.” From the available data, it is not impossible to quantify the degree of uncertainty in the prevalence of pleural changes by quartiles of exposure that could result from the possibility participation bias. However the authors state that “participation bias with respect to disease prevalence is likely negligible” on the basis of assuming that the radiographs of the all living nonparticipants included in this study were normal and this “did not change the finding of a significant trend of increasing pleural changes across increasing exposure quartiles.” In my opinion, this is an insufficient basis for implying that “participation bias with respect to disease prevalence is likely negligible” since it is still true that workers hired on or before 1973 wee

more likely to participate in the study and, given the possibility of a longer latency period for the development of pleural abnormalities, it is possible and plausible for this group to have a higher prevalence of disease than study participants hired in later years. This potentially significant limitation was not discussed in the manuscript.

The authors state that misclassification of exposure is another potential limitation in this study, as a result of limited industrial hygiene data at the facility on which the 1980 study and the follow-up studies were based. They acknowledge that extensive overtime by workers was not taken into consideration in the dose construction, and that this could result in potential underestimation of exposure. This fact alone could have a significant impact on the accuracy of the authors' conclusion that industrial exposures to fibers of Libby vermiculite ore *cause* pleural thickening at low lifetime CFE levels, since it is quite possible for the actual exposures to be significantly higher than those recorded and used in the study. In this regard, it is my opinion that the authors' conclusion that exposure to fibers of Libby vermiculite ore *cause* pleural thickening at low lifetime CFE levels is not a scientifically valid conclusion.

In summary, it is my opinion that the associations reported in this publication are suggestive of the authors' conclusions regarding the prevalence of pleural changes, the correlation between increasing CFE (exposure quartiles) and the number of cohort subjects with pleural changes (of all types), and the prevalence of pleural changes with increased age. However, as a result of potentially significant study limitations, the reported associations do not provide a clear-cut scientific basis for determining that the conclusions are correct. Furthermore, because of the possibility of a significant misclassification of exposure data, it is my opinion that the authors' conclusion that exposure to fibers of Libby vermiculite ore *cause* pleural thickening at low lifetime CFE levels is not scientifically valid.

Weill D, Dhillon G, Freyder L, et al. Lung function, radiological changes and exposure: analysis of ATSDR data from Libby, MT, USA. Eur Respir J 2011; 38: 376-383. [65]

The objective of this study was to investigate the respiratory health of 4,524 participants in the ATSDR Libby Environmental Health Project in terms of their pulmonary function (spirometry) results, radiographic findings and exposure pathways.

The study population consisted of 4,524 participants in the Libby Environmental Health Project who were in the age range of 25 – 90 years and had posterior-anterior chest radiographs and spirometric test results. The study population was selected from the 7,307 Libby Environmental Health Project participants, all of whom were current and former Libby residents who lived in the Libby area for ≥ 6 months prior to December 31, 1990.

Findings on posterior-anterior Radiographs of the chest were classified according the 1980 International Labor Office International Classification of Radiographs of Pneumoconioses (1980 ILO Classification). The reported radiographic classification results were based upon a consensus agreement of two out of three ATSDR “B” readers. The authors report that 4,397 radiographs had a consensus agreement.

Spirometry results were limited to FEV₁, FVC and FEV₁/FVC%. Percent predicted values were computed using the observed values reported by the ATSDR and applying the standard normative equations developed by Knudson et al. The authors reported the analysis of spirometry findings directly in terms of FEV₁ percent predicted, FVC percent predicted and FEV₁/FVC percent predicted. They did not attempt to interpret the possibilities of “restrictive” or “obstructive” abnormalities from the spirometry data; they simply presented the data themselves.

The authors divided the study cohort into seven mutually exclusive exposure groups, based upon specific ATSDR exposure pathway queries. The study population was also divided into age quartiles. Radiographic findings were assessed in each of the seven exposure groups within age quartiles for each exposure group. Spirometry data was analyzed by age and smoking status.

The relationship between radiographic findings and age, body mass index (BMI), gender, ever smokers and FVC percent predicted were analyzed. Unpaired t-tests were used for the comparison of continuous variables and Chi-squared tests were used for comparison of categorical variables. Multiple linear regression analysis was used to assess statistical associations between radiographic findings, spirometric test results and exposure categories.

Based upon the analyses conducted with study data, the authors reached the following five conclusions:

1. The pulmonary function of the screened population as a whole is well within normal limits in all age groups, smoking categories and exposure groups. There was an expected detrimental effect on lung function due to cigarette smoking.
2. In both females and males, and considering smokers and never-smokers, the prevalence of pleural plaques increased with age quartile. As expected, the prevalence of pleural plaques among all age groups was much less in the environmental exposure group (range 0.42–12.74%), as compared with those that worked at the mine (range 20–45.68%), or those who lived with a mine worker (range 1.34–37.67%).
3. With regard to the effect of pleural plaques on FVC in males, there was a small, probably clinically insignificant reduction of < 4.5%. There was no effect attributable to radiographic findings of plaque seen in females.
4. The closing of the old wet and dry mills at the facility appears to be associated with an overall post-1976 reduction in pleural abnormalities in the general population, resulting in prevalence rates < 2% for plaque and < 0.2% for DPT or CAO.
5. DPT is associated with a reduction in FVC, particularly when found to be greater than extent 2 and width a. [1980 ILO Classification]

In general, in my opinion, this is a straight-forward, well-designed study that appears to be well executed. The methods of statistical analysis are straight-forward and appropriate.

As in the three other recent Libby-related studies reviewed in this report, it is possible that, in some cases, subpleural fat could have been misinterpreted as pleural plaques on the posterior-anterior chest radiographs evaluated in this study. The mean body mass index (BMI) of study subjects was above average in all age groups. The mean BMI of subjects with pleural abnormalities exclusive of diffuse pleural thickening (DPT), costophrenic angle obstruction (CAO) or profusion $\geq 1/0$ was in the obese range (30.30 +/- 0.24 kg / m²). Similarly, the mean BMI of subjects with diffuse pleural thickening (DPT) or costophrenic angle obstruction (CAO) excluding profusion $\geq 1/0$ was also in the obese range (30.79 +/- 1.25 kg / m²). Subjects without radiographic evidence of pleural abnormalities and no profusion $\geq 1/0$ had a lower mean BMI, although it was still in the overweight range (28.48 kg / m²). The possibility of subpleural fat being misinterpreted as pleural plaques (LPT) adds uncertainty to the results of data analyses used to reach conclusions (2), (3), (4) and (5). Again, it is not possible to quantify the degree of uncertainty that could result from the possible misinterpretation of subpleural fat deposits as LPT in this study. The authors did indicate that they found no statistically significant effect of BMI on FVC, which decreases the uncertainty related to conclusion (3).

Another potentially significant limitation of this study is that chest radiography alone was used to determine the presence or absence of pleural plaques. As previously mentioned, *it is possible that epidemiological studies which use chest radiography alone to detect the presence or absence of LPT (pleural plaques) could significantly underestimate the number of subjects that actually have LPT (pleural plaques)*. That is, it is possible for a significant number of subjects who had no LPT detected on anterior-posterior chest radiographs to have LPT (pleural plaques) detected on conventional CT scans of the chest or high-resolution CT scans of the chest, if either of these imaging modalities had been used to detect its presence or absence. [20] It is not possible to quantify the degree of uncertainty in the reported study results that could result from the limitations of anterior-posterior chest radiography to detect the presence or absence of LPT in this study. However, in my opinion, it is possible that the actual number

of cohort subjects with pleural plaques (LPT) and normal spirometry could be significantly greater than the number observed and reported in this study. This, in turn, could possibly decrease the percentage of males with a reduced FVC to a statistically insignificant level.

In my opinion, this is an excellent study overall. There are, however, several potentially significant limitations to this study, as a consequence of inherent limitations in the data that were available to be analyzed by the authors. My professional opinions regarding the authors' conclusions are as follows:

- It is my opinion that conclusion (1) is correct: "The pulmonary function of the screened population as a whole is well within normal limits in all age groups, smoking categories and exposure groups. There was an expected detrimental effect on lung function due to cigarette smoking."
- It is my opinion that conclusion (3) is likely to be correct: "With regard to the effect of pleural plaques on FVC in males, there was a small, probably clinically insignificant reduction of < 4.5%. There was no effect attributable to radiographic findings of plaque seen in females."
- It is my opinion that the following statement related to conclusion (3) is likely to be correct: "our review of the ATSDR data does not support the conclusion that pleural changes are associated with clinically significant reduced lung function."
- It is my opinion that the reported associations that provide the basis for conclusions (2), (4) and (5) are suggestive, but, as a result of a potentially significant study limitations related to the use of anterior-posterior radiographs to detect the presence or absence of pleural plaques (LPT) and the possible misinterpretation of subpleural fat for pleural plaques (LPT), they do not provide a clear-cut scientific basis for determining that these conclusions are correct.

BIOGRAPHICAL SKETCH

LAWRENCE C. MOHR, JR., M.D., F.A.C.P., F.C.C.P

Dr. Lawrence C. Mohr, Jr., is Professor of Medicine, Biostatistics and Epidemiology and Director of the Environmental Biosciences Program at the Medical University of South Carolina.

Dr. Mohr earned A.B. and M.D. degrees from the University of North Carolina, where he was elected to Phi Beta Kappa and was presented the Merck Award for Excellence in Chemistry. His postdoctoral training includes a medical internship, a residency in internal medicine and fellowship training in pulmonary medicine, all at Walter Reed Army Medical Center, Washington, D.C.

Dr. Mohr has directed the Environmental Biosciences Program since 1995. This is a university-wide program that coordinates and manages multidisciplinary research projects related to the risks of environmental exposures to human health. He is also actively involved in medical education and patient care. In addition to his administrative and research responsibilities, Dr. Mohr has an outpatient medical practice and regularly serves as the attending physician on the inpatient Pulmonary Medicine Consult Service. He is a Fellow of the American College of Physicians and a Fellow of the American College of Chest Physicians. He has special interests and expertise in environmental and occupational lung disease, clinical risk assessment, biomarker applications, international health and the medical response to natural, nuclear, chemical and biological disasters.

Dr. Mohr has served on numerous government, scientific and professional boards and committees. These include the Board of Regents of the Uniformed Services University of the Health Sciences, the Board of Regents of the American College of Chest Physicians (ACCP), Chair of the ACCP Government Relations and Ethics Committees, the Editorial Board of the medical journal *CHEST*, the Board of Trustees of the Chest Foundation and the Peer Review Committee of the U.S. Department of Energy Office of Science and Technology. Dr. Mohr has been an ACCP delegate to the Council of Subspecialty Societies and the National Congress on Public Health Preparedness. He currently serves as a member of the ACCP Occupational and Environmental Health Steering Committee. He was Founding Chair of the ACCP Disaster Response Network and has participated in both domestic and international disaster response activities. From 1987 to 1993, Dr. Mohr served as White House Physician on the staffs of President Ronald Reagan and President George H.W. Bush.

Dr. Mohr has authored multiple medical and scientific publications. He was an editor of the book, *Biomarkers: Medical and Workplace Applications*, published by the Joseph Henry Press of the National Academy of Sciences. He is a Section Editor of *Intensive Care Medicine*, published by Lippincott Williams and Wilkins. He lectures nationally and internationally on topics related to occupational and environmental lung disease. Dr. Mohr has received a number of professional awards and is listed in *Who's Who in the World*, *Who's Who in America*, *Who's Who in Science and Engineering*, *Who's Who in Medicine and Healthcare*, *Outstanding People of the Twentieth Century*, *Best Doctors in America* and *America's Top Physicians*. He has been awarded an honorary Doctor of Science degree by Nebraska Wesleyan University.

Prior to his medical career, Dr. Mohr served as a U.S. Army officer. He is a graduate of the U.S. Marine Corps Command and Staff College. His military decorations include the Defense Distinguished Service Medal; the Silver Star Medal; four awards of the Bronze Star Medal, with two "V" devices for heroism in ground combat; the Purple Heart; two awards of the Meritorious Service Medal; the Air Medal; two Awards of the Army Commendation Medal; the National Defense Service Medal; the Vietnam Service Medal; and the Republic of Vietnam Campaign Medal.

APPENDIX B – 4

Via Email
Dr. Angela Nugent
Designated Federal Officer
EPA Science Advisory Board (1400R)
1200 Pennsylvania Avenue, N.W.
Mail Code: 1400R
Washington, DC 20460

Re: Draft Libby Amphibole Asbestos IRIS Assessment

Dear Dr. Nugent:

With respect to the EPA Libby Amphibole Asbestos (LAA) assessment, I understand that the chartered SAB requested revision to certain portions of the SAB Panel draft report to better address whether localized pleural thickening is an appropriate endpoint. I further understand that the SAB has asked for a more complete discussion of the SAB Panel's conclusions with respect to the studies that the SAB Panel cited on page 18 of its August 30, 2012 DRAFT Quality Review Report of the EPA DRAFT Assessment entitled Toxicological Review of Libby Amphibole Asbestos (August 2011).

I have just completed my own critical assessment of those same studies and have concluded that there are conflicting results, inconclusive evidence, and considerable scientific uncertainty regarding a causal relationship between localized pleural thickening and pulmonary function deficits. Furthermore, there are other excellent studies, which were not considered by the SAB Panel, that show no statistically significant or clinically significant correlation association between pleural plaques and decreased pulmonary function. Because the work of the SAB continues on this issue, I am respectfully providing the SAB with the attached summary of my critical assessment of the literature cited by the panel, for the purpose of aiding the SAB in achieving a balanced and scientifically rigorous final report.

I recommend that the SAB advise the EPA to conduct a formal, systematic and scientifically rigorous weight of evidence evaluation to assess the strength of any EPA assertion that pulmonary deficits (or any other functional impairments) are due to localized pleural thickening. The strengths and limitations of the full body of relevant scientific and medical literature should be taken into consideration and evaluated by scientifically rigorous weight of evidence guidelines. In the absence of a scientifically rigorous weight of evidence evaluation which assesses the full range of literature on this topic, I recommend that the SAB avoid implying that localized pleural thickening, per se, typically or universally causes pulmonary function impairment, or is on the pathway to impairment. I further recommend that the SAB withhold final publication of its Quality Review Report until after the recommended weight of evidence evaluation has been completed.

In its peer review report on the draft IRIS assessment, the National Academy of Sciences stressed the importance of EPA conducting a robust weight of evidence (WOE) evaluation as part of the IRIS process. In light of the National Academy of Sciences recommendation, and consistent with the information contained in my attached report, it would be especially appropriate for the SAB to develop scientifically rigorous weight of evidence guidelines and conduct a formal weight of evidence evaluation of the association between localized pleural thickening (pleural plaques) and pulmonary function. I strongly recommend that the EPA conduct this weight of evidence evaluation as soon as possible.

I would appreciate your forwarding this recommendation and my attached report to Dr. Agnes Kane, to the SAB Panel that considered the referenced assessment, and to the full chartered SAB. Thank you. Please feel free to contact me if you have any questions.

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**SCIENTIFIC REVIEW AND PROFESSIONAL COMMENTARY
PERTAINING TO THE ASSOCIATION BETWEEN ASBESTOS-RELATED
LOCALIZED PLEURAL THICKENING (PLEURAL PLAQUES) AND LUNG FUNCTION**

**A Report Submitted to
The Scientific Advisory Board
United States Environmental Protection Agency**

By

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November 2, 2012

EXECUTIVE SUMMARY

This report is respectfully submitted to the United States Environmental Protection Agency (EPA) Scientific Advisory Board (SAB) for the purpose of providing objective clinical and scientific background information, as well as professional comments and recommendations, pertaining to statements regarding the relationship between asbestos-related localized pleural thickening [LPT] (also known as pleural plaques) and lung function which are contained in the DRAFT Report of the *EPA Scientific Advisory Board Quality Review of the EPA DRAFT Assessment entitled Toxicological Review of Libby Amphibole Asbestos (August 2011), dated August 30, 2011* (DRAFT Quality Review Report).

The sole purpose of this report is to provide the EPA Scientific Advisory Board with objective evidence, expert professional commentary, conclusions and recommendations regarding the conflicting scientific literature, inconclusive evidence, considerable scientific uncertainty and doubtful clinical significance pertaining to the relationship between isolated asbestos-related LPT (pleural plaques) and lung function at the present time.

I focused this detailed review on the DRAFT Quality Review Report and the literature it cites on page 18 to determine to what extent the cited literature supports proposed conclusions regarding the association between isolated asbestos-related LPT (pleural plaques) and lung function. I have determined that the cited literature does not provide strong, unequivocal scientific evidence to support the broad conclusions of the DRAFT Quality Review Report. The following conclusions and recommendations are submitted to the EPA Scientific Advisory Board:

CONCLUSIONS

1. There is a large body of conflicting and inconclusive peer-reviewed scientific literature regarding the relationship between asbestos-related localized pleural thickening and lung function. In this regard, there is considerable uncertainty about the scientific

validity of any assertion that “LPT is associated with reduced lung function.” Further rigorous scientific evaluation is necessary before the EPA Scientific Advisory Board can make this assertion with any acceptable degree of scientific certainty.

2. There is no *weight of evidence* study, based upon scientifically rigorous *weight of evidence guidelines*, to support the assertion of the EPA Scientific Advisory Board that “LPT is associated with reduced lung function.” Thus, it is not clear exactly what scientific criteria the EPA Scientific Advisory Board used to support this statement.
3. The body of literature cited in the DRAFT Quality Review Report to support the assertion that “LPT is associated with reduced lung function” does not provide a definitive, scientifically rigorous basis for making such an assertion. Indeed, one cited publication does not even address the relationship between LPT and lung function and one cited publication is a letter to the editor regarding another cited publication without consideration of the scientifically robust response from the authors.
4. In its DRAFT Quality Review Report, the EPA Scientific Advisory Board did not consider, or even mention, the results of a robust, peer-reviewed Delphi Study that was published as the *American College of Chest Physicians Consensus Statement on the Respiratory Health Effects of Asbestos* in the journal *CHEST* [4] in which there was *strong disagreement* by a panel of 71 experts in the respiratory health effects of asbestos with the statement “pleural plaques alter lung function to a clinically significant degree.”
5. In its DRAFT Quality Review Report, the EPA Scientific Advisory Board did not consider, or even mention, the findings of the *Public Health Assessment of the Libby Asbestos Site* that was prepared by the Division of Health Assessment and Consultation of the United States Agency for Toxic Substances and Disease Registry (ATSDR), dated April 22, 2010. [5] In this report the ATSDR reports a very small 1.8% incidence of moderate to severe restriction in breathing capacity and does not include LPT (pleural plaques) among the strongest risk factors for restrictive changes in pulmonary function in *Libby Community Environmental Health Project* participants. The ATSDR position appears to be

inconsistent with the EPA Scientific Advisory Board statement that “LPT is associated with reduced lung function.”

RECOMMENDATIONS

1. The EPA Scientific Advisory Board should modify the statement that “*Pleural thickening is associated with restrictive lung function*” in Question 2 of its DRAFT Report to reflect the fact that this clearly pertains to *diffuse pleural thickening*, but does not necessarily pertain to localized pleural thickening [LPT]. The EPA Scientific Advisory Board should make it clear that, although *some* reports suggest a small, restrictive decrement in lung function associated with LPT, there are a number of other excellent reports that show no statistically or clinically significant decrement in lung function associated with asbestos-related LPT, especially after controlling for parenchymal changes indicative of interstitial fibrosis. The EPA Scientific Advisory Board should also make it clear that there is considerable scientific uncertainty about whether or not any significant relationship between asbestos-related LPT and a decrement in lung function typically or universally exists at this time.
2. The EPA Scientific Advisory Board should delete the statement that “LPT is associated with reduced lung function” and replace it with a statement that takes into account the fact that a large body of scientific literature shows that there is no statistically or clinically significant decrement in lung function associated with asbestos-related LPT, especially after controlling for parenchymal changes indicative of interstitial fibrosis. Once again, the EPA Scientific Advisory Board should make it clear that there is considerable scientific uncertainty about whether or not any significant relationship between asbestos-related LPT and a decrement in lung function typically or universally exists at the present time.
3. Do not support the assertion that “LPT is associated with reduced lung function” as a reason for using localized pleural thickening [LPT] as the critical endpoint for deriving

the inhalation reference concentration (RfC) in the IRIS assessment pertaining to Libby Amphibole Asbestos at this time. In view of numerous conflicting reports in the scientific and medical literature, as well as the considerable scientific uncertainty regarding whether or not any significant relationship between asbestos-related LPT and a decrement in lung function typically or universally exists, there is no clear-cut, scientifically rigorous basis for using the statement “LPT is associated with reduced lung function” as a reason for using LPT as the critical endpoint for deriving the RfC at the present time.

4. That the EPA Scientific Advisory Board convene an independent, objective panel of experts in asbestos-related respiratory health effects to develop scientifically rigorous *weight of evidence guidelines* for investigating any association between asbestos-related LPT and lung function. [24, 25, 26]
5. That the EPA Scientific Advisory Board subsequently convene an independent, objective panel of experts in asbestos-related respiratory health effects to perform a formal *weight of evidence evaluation* of the association between asbestos-related LPT and lung function, based upon previously determined, scientifically *rigorous weight of evidence guidelines*, for the purpose of providing a clear-cut, robust, scientifically valid assessment of this association. [24, 25, 26]
6. Revisit the appropriateness of using the statement “LPT is associated with reduced lung function” as a reason for using localized pleural thickening [LPT] as the critical endpoint for deriving the inhalation reference concentration (RfC) in the IRIS assessment pertaining to Libby Amphibole Asbestos after the previously recommended *weight of evidence evaluation* has been completed.
7. Withhold publication of the final version of the final EPA Scientific Advisory Board Quality Review Report of the EPA DRAFT Assessment entitled Toxicological Review of Libby Amphibole Asbestos (August 2011) until after the previously recommended *weight of evidence evaluation* has been completed. The final version of this report should address the scientific appropriateness of using the statement “LPT is associated

with reduced lung function” as a reason for using localized pleural thickening [LPT] as the critical endpoint for deriving the inhalation reference concentration (RfC) in the IRIS assessment pertaining to Libby Amphibole Asbestos based upon the *weight of evidence* contained in the recommended evaluation.

8. Consider, address and reference the *American College of Chest Physicians Consensus Statement on the Respiratory Health Effects of Asbestos* [4] with respect to any statements regarding the association of LPT and lung function in the final EPA Scientific Advisory Board Quality Review Report of the EPA DRAFT Assessment entitled *Toxicological Review of Libby Amphibole Asbestos* (August 2011).
9. Consider, address and reference the *Public Health Assessment of the Libby Asbestos Site* that was published by the Division of Health Assessment and Consultation of the United States Agency for Toxic Substances and Disease Registry (ATSDR) [5] with respect to any statements regarding the association of LPT and lung function in the final EPA Scientific Advisory Board Quality Review Report of the EPA DRAFT Assessment entitled *Toxicological Review of Libby Amphibole Asbestos* (August 2011).

INTRODUCTION

This report is respectfully submitted to the United States Environmental Protection Agency (EPA) Scientific Advisory Board (SAB). Because of my knowledge and extensive experience as an academic pulmonologist, my expertise in occupational and environmental lung disease and my expertise in clinical risk assessment, I was asked by Exponent to prepare and submit this report for the purpose of providing objective clinical and scientific background information, as well as professional comments and recommendations, pertaining to statements regarding the relationship between asbestos-related localized pleural thickening [LPT] (also known as pleural plaques) and lung function which are contained in the DRAFT Report of the *EPA Scientific Advisory Board Quality Review of the EPA DRAFT Assessment entitled Toxicological Review of Libby Amphibole Asbestos (August 2011), dated August 30, 2011* (DRAFT Quality Review Report).

The assessments and comments in this report are provided in response to Question 2 on page 18 of the DRAFT Quality Review Report:

Question 2. Radiographic evidence of localized pleural thickening in humans was concluded by the EPA to be an adverse effect and was selected as the critical effect for the derivation of the RfC. Pleural thickening is associated with restrictive lung function, breathlessness during exercise and, for some individuals, chronic chest pain. Please comment on whether the selection of this critical effect and its characterization is scientifically supported and clearly described. If a different health endpoint is recommended as the critical effect for deriving RfC, please identify this effect and provide scientific support for this choice.

This report is submitted for the purpose of addressing the language in Question 2 which states that “Pleural thickening is associated with restrictive lung function.” In that regard, this report will more specifically focus on the relationship between localized pleural thickening [LPT] and lung function, since this is a particularly important area of concern.

Localized pleural thickening (LPT) is defined as discrete areas of non-malignant pleural fibrosis that almost always arise from the parietal pleura. On histological examination, LPT is relatively *acellular*, with a “basket-weave” appearance of collagen bundles. Asbestos fibers may occasionally be seen within area of LPT, but asbestos bodies (so called “ferruginous bodies”) are usually not present. [1, 2] The pathogenesis LPT is uncertain, but it is generally thought that asbestos fibers reach the parietal pleura via lymphatic channels and cause an inflammatory reaction in the parietal pleura tissue. Calcification is reported in 10%–15% of cases. [2]

It is clear that *diffuse* pleural thickening related to asbestos exposure is typically associated with significant restrictive ventilatory impairment. However, diffuse pleural thickening is a distinct entity that is very different from LPT. In contrast to diffuse pleural thickening, for LPT there are multiple conflicting reports, as well as considerable scientific uncertainty, about whether or not there is a significant association between LPT and the development of restrictive lung function in asbestos-exposed individuals. In this regard, there is no clear-cut, definitive scientific evidence that isolated LPT, in and of itself, is typically or universally associated with a statistically significant, or clinically significant, reduction in lung function.

The DRAFT Quality Review Report states that “LPT is associated with reduced lung function.” In my opinion this statement is an oversimplification and overstatement of currently available scientific evidence, and does not accurately reflect full body of scientific evidence pertaining to the relationship between LPT and lung function in asbestos-exposed individuals. While *some* reports do suggest a small statistically significant reduction in lung function among individuals with asbestos-related LPT, there are a number of other excellent reports that show no statistically or clinically significant decrement in lung function associated with asbestos-related LPT, especially after controlling for parenchymal changes indicative of interstitial fibrosis. This is the stated position of the esteemed British Thoracic Society. [3] In view of these conflicting reports and significant scientific limitations of some reports that suggest a relationship between LPT and reduced lung function, there is considerable scientific uncertainty about whether or not such a relationship typically or universally exists.

Furthermore, in my professional experience, at the present time the vast majority of pulmonologists *do not believe* that there is a direct, *clinically significant* relationship between LPT and a reduction in lung function. This professional viewpoint is supported by published reports that show no reduction in lung function associated with LPT, as well as published reports that suggest a small reduction in lung function associated with LPT in which the lung function parameters remain well within the normal range and are not *clinically significant*. The lack of clinical significance is reflected in the results of a robust Delphi Study that was published as the *American College of Chest Physicians Consensus Statement on the Respiratory Health Effects of Asbestos* in the journal *CHEST* in 2009. [4] In this report there was *strong disagreement* by a panel of 71 experts in the respiratory health effects of asbestos with the statement “pleural plaques alter lung function to a clinically significant degree.” That is, among prominent experts in the respiratory health effects of asbestos, there is *strong disagreement* with the assertion that there is a clinically significant relationship between pleural plaques and reduced lung function. In this regard, the language in the DRAFT Quality Review Report seems to be in direct conflict with the *American College of Chest Physicians Consensus Statement on the Respiratory Health Effects of Asbestos*. In this regard, I believe it is important for the EPA Scientific Advisory Board to carefully consider the strongly held view of a large number of experts in the respiratory health effects of asbestos that there is no clinically significant association between pleural plaques [LPT] and reduced lung function. While this view is fundamentally important in its own right, as part of the large body of medical literature pertaining to the relationship between pleural [LPT] and lung function, it is also important for the EPA Scientific Advisory Board to address this matter with an appropriate clinical perspective. While clinical issues are typically beyond the purview of the EPA and its Scientific Advisory Board, an official statement that “LPT is associated with reduced lung function” could, possibly, have the unintended consequence of being construed by some clinical practitioners as a new “federal health care standard” and subject some asbestos-exposed individuals to an increased number of diagnostic studies and increased health care costs, even though the preponderance of scientific evidence, medical evidence and expert opinion indicates that any such relationship is *not clinically significant* at the present time. As a strong proponent of

evidence-based medicine, it is my opinion that it is very important for the EPA Scientific Advisory Board to consider and address the matter of *clinical significance* in its report.

During my review of the DRAFT Quality Review Report, I could find no indication that The Scientific Advisory Board considered the findings of the *Public Health Assessment of the Libby Asbestos Site* that was prepared by the Division of Health Assessment and Consultation of the United States Agency for Toxic Substances and Disease Registry (ATSDR), dated April 22, 2010.

[5] In this report the ATSDR states that among asbestos-exposed participants in the *Libby Community Environmental Health Project*, only “1.8% of the participants had moderate to severe restriction in breathing capacity.” The ATSDR also states that “the strongest risk factors for restrictive changes in pulmonary function included current cigarette smoking, being a former mine worker, chest surgery, having a high body mass index, and age.” That is, the ATSDR *does not* mention LPT as being among the strongest risk factors for restrictive changes in pulmonary function in *Libby Community Environmental Health Project* participants. Thus, the EPA Scientific Advisory Board statement that “LPT is associated with reduced lung function” appears to be inconsistent with the position of the ATSDR, which is another agency of the United States federal government. This requires clarification. The EPA Scientific Advisory Board statement is also inconsistent with the results of an excellent, well-designed, detailed, scientifically robust study by Copley, et al, which concludes that there is no independent association between pleural plaques [LPT] and a decrement in lung function. [6] In fact, there is no indication that the EPA Scientific Advisory Board even considered this excellent and important peer-reviewed publication in its DRAFT Quality Review Report. This also requires clarification, in my opinion.

During my review of the DRAFT Quality Review Report, I could find no indication that a scientifically rigorous, *weight of evidence approach* was used to arrive at the Scientific Advisory Board conclusion that “LPT is associated with reduced lung function.” Nor can I find any indication that the EPA, or its Scientific Advisory Board, has ever issued *weight of evidence guidelines* for the rigorous scientific evaluation of the large body of conflicting medical and

scientific literature pertaining to this issue. In the absence of a *weight of evidence approach* that is based upon scientifically rigorous *weight of evidence guidelines*, it is not at all clear what criteria were used to evaluate the relationship between LPT and lung function. In my opinion, this is a significant scientific deficiency in the DRAFT Quality Review Report report and needs clarification by the EPA Scientific Advisory Board.

The sole purpose of this report is to provide the EPA Scientific Advisory Board with objective evidence, expert professional commentary and recommendations regarding the conflicting scientific literature, considerable scientific uncertainty and doubtful clinical significance pertaining to the relationship between isolated asbestos-related LPT (pleural plaques) and lung function at the present time. In this regard, I have no personal, professional, or financial conflicts of interest in this matter. My sole intent is to help insure that the *full body* of currently available scientific and medical evidence is carefully considered in addressing this issue, consistent with my passionate belief that all public policy related to environmental health effects should be based upon sound and rigorous science. In my opinion the EPA Scientific Advisory Board has a responsibility to avoid overstating the relationship between asbestos-related LPT (pleural plaques) and lung function, and instead should take the current state of confusing uncertainty as a “golden opportunity” to bring scientific clarity to the issue through an independent, scientifically rigorous *weight of evidence* assessment. I strongly recommend that it do so prior to issuing a final report on its *Quality Review of the EPA Draft Assessment entitled Toxicological Review of Libby Amphibole Asbestos (August 2011)*.

CRITICAL ASSESSMENT OF THE LITERATURE CITED IN THE SAB REPORT

The Scientific Advisory Board cites seventeen published reports to support its assertion that “LPT is associated with reduced lung function”. In my professional opinion, this body of cited literature does not provide a sufficient degree of definitive, scientifically rigorous evidence to support this broadly-stated conclusion. My critical assessment of these reports, and reasons why I believe they do not sufficiently support this conclusion, are provided below.

Lilis, et al (1991). [7] This report shows a dose-related relationship with a decrease in FVC alone and the extent of both circumscribed pleural fibrosis and diffuse pleural fibrosis on chest radiographs. It is assumed that the term circumscribed pleural fibrosis pertains to the older term for LPT as defined in the 1980 ILO classification. While the methodology of this report is sound considering the data that was available to the investigators, there are multiple limitations to this study. First of all, a pleural index score for circumscribed pleural fibrosis was determined from chest radiographs, which are less accurate than high resolution CT scans in estimating the extent of pleural thickening and less accurate in distinguishing pleural fibrosis from pleural fat. Secondly, FVC alone is the only lung function parameter reported. In the absence of the FEV1, the FEV1/FVC ratio and lung volumes, the reduced FVC could suggest either restrictive or obstructive ventilatory impairment. Furthermore, smoking was not controlled by pleural index score. This is important, since it is possible that the reported reduction in FVC with increasing pleural index score could, possibly, be related to chronic obstructive lung disease from smoking and not be related to circumscribed pleural fibrosis. Furthermore, the study was not controlled for body mass index (BMI). Therefore, it is also possible the reported reduction in FVC could, possibly, be related to increased body mass. *Thus, while the results of this study are suggestive of a relationship between the pleural index score and a reduction in FVC, they are by no means definitive of a direct relationship and do not establish circumscribed pleural fibrosis as the cause of the FVC reduction.*

Paris et al (2009). [8] The stated objective of this study was to describe the relationships between asbestos exposure and pleural plaques [LPT] and asbestosis in a large cohort of formerly exposed asbestos workers, and to assess asbestos exposure parameters linked to the presence of HCRT [high resolution computed tomography] of these two diseases by means of multivariate analysis. This study demonstrated “strong relationships between asbestos exposure and the presences of pleural plaques [LPT] and, to a lesser extent, between asbestos exposure and asbestosis.” The presence of pleural plaques [LPT] was associated with time since first exposure and cumulative exposure index. The presence of asbestosis was associated with cumulative exposure index. The duration of exposure was not associated with either pleural

plaques [LPT] or asbestosis. Although the methodology used in this study was sound, the authors themselves properly state that this study has a number of limitations. Most importantly, however, the SAB Report cites this publication as supporting the assertion that there is a “relationship between LPT and lung function.” However, *lung function was not, in any way, investigated in this study. It is purely an imaging assessment and has nothing to do with lung function. Therefore, in no way does this study support the SAB assertion that there is a “relationship between LPT and lung function.”* Indeed, it is very puzzling why the SAB would cite this publication in support of that assertion.

Clin, et al (2011). [9] The objective of this study was to analyze the relationship between isolated pleural plaques [LPT] confirmed by CT scanning and lung function in subjects with occupational exposure to asbestos. This is a well-designed and well executed study. The results show that isolated parietal and/or diaphragmatic pleural plaques [LPT] are associated with a *slight reduction* in total lung capacity (TLC) among subjects with pleural plaques [LPT], with these subjects having a TLC of 98.1% predicted in comparison to a TLC of 101.2% predicted in subjects free of pleural plaques [LPT] at a p-value that barely meets statistical significance ($p = 0.0494$). The authors also report a forced vital capacity of 96.6% predicted among subjects with pleural plaques [LPT] in comparison to 100.4% in subjects free of pleural plaques [LPT] ($p < 0.001$) and a forced expiratory volume in one second (FEV1) of 97.9% predicted among subjects with pleural plaques [LPT] in comparison to 101.9% predicted in subjects free of pleural plaques [LPT] ($p = 0.0032$). The authors conclude that there is a *trend* toward a “restrictive pattern” among individuals with isolated and/or diaphragmatic pleural plaques [LPT], although “*the observed decrease in FVC and TLC is unlikely to be of real clinical significance for the majority of subjects studied.*” *Indeed, from a clinical perspective, both the TLC and FVC of subjects with pleural plaques are not abnormal – they are both well within the normal range.* It is also important to point out that the proportional decrease in FVC is greater than the proportional decrease in the TLC among subjects with pleural plaques [LPT]. Since TLC is the “gold standard” for assessing restrictive ventilatory impairment, this suggests the possibility that FVC alone, as used in the Lilis study, may not be a reliable parameter for assessing restrictive ventilatory

impairment in subjects with pleural plaques [LPT]. Although the methodology used in this study is sound, the authors acknowledge several limitations, such as the subjects not being representative of the general population exposed to asbestos, possible selection bias with respect to subjects that had been previously diagnosed with asbestos exposure-related diseases and the possibility of a “healthy worker effect.” It is certainly possible that any or all of these limitations could account for the very slight decrease of TLC observed among subjects with pleural plaques [LPT]. *Thus, not only is it unlikely that the observed results are of real clinical significance, it is also possible that the very slight difference in the TLC between subjects with and without pleural plaques [LPT] is the result of inherent statistical errors related to the limitations acknowledged by the authors.*

ATS Official Statement (2004). [10] The American Thoracic Society (ATS) Official Statement on the Diagnosis and Initial Management of Nonmalignant Diseases Related to Asbestos states that “studies of large cohorts have shown that a significant reduction in lung function attributable to the plaques, averaging about 5% reduction in FVC, even when interstitial fibrosis (asbestosis) is absent radiographically. Three references are cited in support of this statement; all three references use FVC alone (not TLC) as the measurement of lung function and chest radiographs (not CT scans) for the determination of pleural plaques [LPT]. However, the ATS Official Statement also states that *“This has not been a consistent finding and longitudinal studies have not shown a more rapid decrement in pulmonary function in subjects with pleural plaques.”* Three references are also provided in support of this statement. In this regard, the report also states that *“Decrements, when they occur, are probably related to early subclinical fibrosis”* - that is, early subclinical *lung parenchyma fibrosis* and not LPT. In addition, while the report cites two references that show a significant but small association between the extent of circumscribed pleural plaques and FVC, the authors conclude with the statement that *“most people with pleural plaques have well preserved lung function.”* They cite one reference that used CT scans to determine the presence of pleural plaques [LPT] which showed no effect on lung function related to pleural plaques [LPT]. *Thus, this comprehensive report objectively cites some of the conflicting study results that have appeared in the medical literature and, in my*

opinion, does not provide a sufficient weight of evidence to unequivocally assert that pleural plaques [LPT] in and of themselves are universally or typically associated with a decrement in lung function. Indeed, it is the expert opinion of the report authors that decrements, when they do occur, are probably related to early subclinical lung parenchyma fibrosis and not to LPT, per se.

Ohlson, et al (1984). [11] The stated objectives of this study were compare the lung function of long-term asbestos cement workers without asbestosis to a reference group and to elucidate the possible impact of pleural plaques on lung function. The presence of pleural plaques [LPT] was determined by chest radiography. This study, which was well-controlled for smoking, showed that there was a statistically, but probably not clinically, significant decrease in both FEV1 and FVC among workers exposed to asbestos cement dust after adjustment for age, height, tracheal area and smoking history. *There were no significant differences in lung function between those with and without pleural plaques [LPT].* The authors conclude that that the group exposed to asbestos cement dust had a minor impairment in lung function, that this was mainly due to obstructive changes [not restrictive changes], that the lung function changes were probably not clinically significant and that there were no significant differences in lung function between asbestos-exposed workers with and without pleural plaques [LPT]. Thus, the results of this study do not support an assertion that pleural plaques, in and of themselves, are associated with a decrement of lung function. *The results of this study also raise the possibility that studies which have used FVC as the only lung function parameter in investigating the effect of pleural plaques (such as the previously cited Lilis study), could have shown a decrement in FVC that was due to obstructive changes (due to dust, smoking or some other exposure), with the decrement in FVC being unrelated to the presence of pleural plaques [LPT].*

Ohlson, et al (1985). [12] This was a four year follow-up study of ventilatory function in former asbestos cement workers to determine whether there was any decline in lung function in the four year period, to assess the relationship between pleural plaques [LPT] and ventilatory function and to examine the comparability of cross-sectionally predicted versus longitudinally

determined changes after four years. The presence of pleural plaques [LPT] was determined by chest radiography. The main result of this study was a progressive decrease in FEV1 and FVC during four years, with the group that had the highest exposure losing 8% of the FEV1 and 9% of the FVC and the group with the lowest exposure losing 5% of the FEV1 and 5% of the FVC. Thus, there was a progression of *obstructive ventilatory impairment* during the four year follow-up period, with the greatest decline in FEV1 and FVC occurring among former workers who had the highest asbestos exposure. Consistent with the results of the previously reported Ohlson, et al study, *this study showed that pleural plaques [LPT] had no effect on the decline in lung function*. Since this was a longitudinal study, it shows that the presence of pleural plaques [LPT] had no effect on the decline in lung function over a four year time period. The authors opine that the observed obstructive pattern could be explained by the aerodynamic properties of the dust generated from the handling and trimming of asbestos cement products. *Again, however, the longitudinal obstructive decline lung function was unrelated to the presence of pleural plaques [LPT]*.

Jarvolm and Sanden (1986). [13] The objective of this study was to determine whether individuals with pleural plaques [LPT] have impaired respiratory function, compared with individuals with similar asbestos exposure but without pleural plaques [LPT]. The study cohort consisted of non-smoking, male, asbestos-exposed shipyard workers. The presence of pleural plaques [LPT] was determined by chest radiography. The study results showed that subjects with pleural plaques [LPT] had lower FEV1 and lower FVC than subjects without pleural plaques [LPT] and that these differences were statistically significant. The decrease in FEV1 appeared to be less than the FVC, suggesting a mild restrictive process. In general the FVC was about 5% lower in subjects with pleural plaques [LPT] than in subjects without pleural plaques [LPT]. The study also showed that the average differences in FVC between subjects with and without pleural plaques [LPT] were 3.4% for men with low asbestos exposure and 8.2% for men with high asbestos exposure. The FVC difference for men with low asbestos exposure was not statistically significant; the FVC difference for men with high asbestos exposure was statistically significant. The majority of FVC values for all subjects were within the normal range, however

3% of men without pleural plaques [LPT] and 16% of men with pleural plaques [LPT] had an FVC below the lower limit of normal. Based upon these results the authors conclude that *“pleural plaques are associated with slightly impaired lung function.”* However, the authors do not assert that pleural plaques [LPT] are the cause of the slightly impaired lung function. They state that the low sensitivity of chest radiographs to detect pleural plaques [LPT] makes it probable that several cases of plaques were undetected and that *“This would also mean that it was difficult to detect an effect associated with plaques.”* Furthermore, the authors carefully point out that *“it is improbable that pleural plaques themselves decrease lung volume merely by their size”* and *“a few small pleural plaques cannot reduce chest mobility by 5-10%.”* They go on to state that *“another possible hypothesis the existence of subradiographic fibrosis associated with the plaques.”* They also state that *“This hypothesis is supported by the finding that the difference in FVC between men with and without pleural plaques is only significant for the heavily exposed men.”* This implies that it is that it is unlikely that pleural plaques [LPT] in and of themselves are the cause of the lower FVC observed in subjects with pleural plaques, rather it seems more likely that the lower FVC in these subjects is caused by lung parenchyma fibrosis that is not detectable by chest radiograph.

Hjortsberg, et al (1988). [14] The objective of this study was to investigate the pattern of changes in lung function caused by asbestos and the additive effect of smoking in asbestos-exposed subjects with pleural plaques. This study was not designed to assess the effect of pleural plaques [LPT] on lung function in asbestos-exposed individuals. *Since the reference group (control group) in this study consisted of healthy non-smoking men without a history of asbestos exposure, the results of this study cannot be used to make any inference about the effect of asbestos-related pleural plaques [LPT] on lung function.* Chest radiographs were used to determine the presence of pleural plaques in asbestos-exposed subjects. Stepwise logistic regression analysis was used to assess pulmonary function data for the ability to predict whether subjects belong to the asbestos-exposed group. The results of this study do suggest that vital capacity (VC) is the most sensitive lung function parameter for discriminating between asbestos-exposed subjects and non-exposed subjects and that smoking does not have any

influence on the VC. The authors also demonstrate that there is no statistically significant difference in diffusion capacity among smokers, ex-smokers and non-smokers in the asbestos-exposed group. Once again, however, *the results of this study cannot be used to conclude that there is any reduction in lung function between asbestos-exposed subjects with and without pleural plaques.*

Oliver, et al (1988). [15] The objective of this study was to investigate the association between asbestos-related pleural plaques [LPT] and lung function in a group of workers occupationally exposed to asbestos. Chest radiographs were used to determine the presence of pleural plaques [LPT]. The study results show a statistically significant inverse relationship between FVC% predicted and the level of diagnostic certainty (none, suspect, definite) among subjects with pleural plaques [LPT], however in all cases the reported FVC% predicted was in the normal range (> 80% predicted). There was no such relationship between FEV1 and the diagnostic certainty of pleural plaques [LPT]. In this regard, pleural plaques [LPT] were associated with a restrictive pattern, however this association, although statistically significant, was relatively small (4.3 percentage points) and was not very strong ($p = 0.0431$). In this regard, it is important to note that when age and height were taken into account, there was a statistically significant difference in both FVC and FEV1 between groups with and without pleural plaques, suggesting that obstruction could, possibly, be contributing to the observed difference in FVC. In a univariate logistic regression analysis, the prevalence of dyspnea was higher in the group with pleural plaques (39.5% vs 26.6%, $p = 0.025$), however in a multivariate analysis there was no correlation between dyspnea and pleural plaques [LPT] or the extent of pleural plaques [LPT] by level of certainty, when controlling for asbestos exposure and smoking. Also of importance is the finding that there was no association between single breath carbon monoxide diffusing capacity (DLCO) and either pleural plaques or the suggestion of a restrictive ventilatory phenomenon by FVC. However, there was a statistically significant difference in DLCO among subjects who had both pleural plaques and an FVC suggestive of restriction. The authors state that this finding suggests that the DLCO reduction in this group was related to the presence of interstitial fibrosis that was not present on chest radiograph and not necessarily to

the presence of pleural plaques [LPT] per se. *They further state that the clinical significance of the observed 4.3 % decrement in FVC among subjects with pleural plaques is uncertain and that “the presence of both pleural plaques and restriction may be a marker of radiographically occult interstitial fibrosis in asbestos-exposed populations.” The authors make no assertion that the observed decrement in FVC is caused by pleural plaques [LPT], per se.*

Borbeau, et al (1990). [16] The objective of this study was to investigate whether asbestos-related pleural abnormality and isolated pleural plaques [LPT] are associated with respiratory impairment independently of parenchymal abnormality. Chest radiographs were used to detect the presence of pleural abnormalities and pleural plaques [LPT]. Lung parenchymal abnormality was determined by gallium-67 uptake measured 48 hours after a 4 microcurie injection. Results showed that subjects with isolated pleural plaques had a 200 ml decrease in FEV1 and a 350 ml decrease in FVC in comparison with subjects without pleural plaques, after adjusting for age, height, smoking, and parenchymal disease by quantitative gallium-67 uptake, and that these differences were statistically significant ($p < 0.05$). However, there was no demonstrable difference in most cardiorespiratory measurements on sub-maximal and maximal exercise between subjects with and without pleural plaques [LPT]. Based upon these results the authors conclude that it *is possible* that isolated pleural plaques [LPT] are associated with significant reductions in spirometric lung volumes independently of radiographic or subradiographic asbestos-related parenchymal lung disease. However, they do not state that there is a direct causal relationship between pleural plaques [LPT] and a reduction in spirometric lung volumes. *Indeed, in view of the relatively small differences in FEV1 and FVC between subjects with and without pleural plaques and the absence of significant differences in cardiorespiratory measurements on exercise, the authors are careful to state that “This supports the clinical opinion that pleural plaques are little more than a sign of asbestos exposure.”*

Schwartz, et al (1990). [17] The objective of this study was to determine whether pleural fibrosis is associated with diminished lung volumes and, if so, whether the two of pleural fibrosis (circumscribed pleural plaques versus diffuse pleural thickening) is a determinant of the

extent of pulmonary impairment. The presence of circumscribed pleural plaques [LPT], diffuse pleural thickening and interstitial fibrosis were determined by chest radiographs. The results of this study showed that subjects with circumscribed pleural plaques [LPT] had a mean decline in FVC of 140 ml (90.3% predicted) and those with diffuse pleural thickening had a mean decline of 270 ml (almost twice as great as subjects with circumscribed pleural plaques [LPT]) (85.7% predicted) in comparison to asbestos-exposed subjects without circumscribed pleural plaques [LPT] or pleural thickening (94.7% predicted); these differences were statistically significant. In all cases the FVC values remained in the normal range. For each category of pleural fibrosis (none, circumscribed pleural plaques [LPT] and diffuse pleural thickening) the observed FVC was lower for those with radiographically apparent interstitial fibrosis than for those without radiographically apparent interstitial fibrosis. Among subjects with concurrent interstitial fibrosis, there was a consistent decline in the FVC% predicted that was significantly associated with the type of pleural fibrosis: none = 83.3% predicted, circumscribed pleural plaques = 80.1% predicted, and diffuse pleural thickening = 73.6% predicted. Thus, asbestos-exposed workers with radiographically normal parenchyma as well as those with radiographically-apparent interstitial fibrosis were found to have a similar, independent relationship between the presence and type of pleural fibrosis and decrements in FVC. However, *the authors state that, because asbestos-exposed workers with pleural fibrosis have more extensive exposure histories than those with normal pleura, it is quite possible that they are also more likely to have parenchymal fibrosis.* It is also well known that chest radiographs are not particularly accurate in quantitating the extent of parenchymal fibrosis. In this regard, *the authors state that it is possible that for each ILO grade of radiologically-apparent parenchymal fibrosis, those with pleural fibrosis have more parenchymal fibrosis than those with normal pleura.* They also state that *“it is difficult to conceive that pleural plaques, in and of themselves, result in the abnormal chest wall motion that accounts for the observed decrements in FVC.”* Finally, the authors state that *“We are therefore led to speculate that subclinical alveolitis or interstitial fibrosis not detected by routine chest radiograms is responsible for the development of restrictive lung function among those with asbestos-induced pleural fibrosis.”* That is, they do

not directly attribute the observed lung function abnormalities to the presence of pleural plaques [LPT], per se.

Miller, et al (1992). [18] The objective of this study was to assess the relationship between pulmonary function to radiographic interstitial fibrosis in a large cohort of 2,611 asbestos-exposed insulators, with and without pleural abnormalities. This is a comprehensive, well-designed study of a large number of asbestos-exposed individuals. The results showed a statistically significant inverse relationship between FVC and the ILO profusion score on chest radiographs (as a measure of interstitial fibrosis), with a stepwise decrease in FVC with increasing score, except for the intermediate scores of 1/2 and 2/1, which were no different from each other. Of note is the fact that workers with a profusion score of 0/0 (i.e. no radiographic evidence of interstitial fibrosis) had an FVC that was lower than expected (88.0% predicted). The authors indicate that the lower than expected FVC was most likely the result of interstitial fibrosis that was not detectable on chest radiographs, citing a previous study which showed that 18% of patients with histological evidence of interstitial fibrosis had no interstitial fibrosis detectable on chest radiographs. Study results also showed that that 56% of study subjects had pleural thickening, with 83% of these subjects having circumscribed pleural thickening [LPT] and 17% of these subjects having diffuse pleural thickening. Subjects with circumscribed pleural thickening [LPT] had a mean FVC of 82.4% predicted and subjects with diffuse pleural thickening had a mean FVC of 69.0% predicted in comparison to subjects with no pleural thickening, who had a mean FVC of 88.9% predicted. Thus, this study demonstrates that diffuse pleural thickening is associated with a greater diminution of FVC than circumscribed pleural thickening. It also demonstrates that the FVC in subjects with circumscribed pleural thickening [LPT] is significantly lower than the FVC in subjects without circumscribed pleural thickening at all profusion scores for radiographic interstitial fibrosis, including a profusion score of 0/0 in which there is no radiographic evidence of interstitial fibrosis. As noted in previously cited publications, it is highly unlikely that the decrement in FVC observed in subjects with circumscribed pleural thickening [LPT] is related to restrictive movement of the chest wall. However, *the observed decrement FVC in subjects with circumscribed pleural thickening [LPT]*

and a profusion score of 0/0 (i.e. the absence of radiographically detectable interstitial fibrosis) is consistent with the possibility that the observed FVC decrement is related to subradiographic interstitial fibrosis, as suggested in several previously cited studies, and not to the circumscribed pleural thickening [LPT], per se.

Van Cleemput, et al (2001). [19] The objectives of this study were to investigate the relationship of the measured size of pleural plaques to estimated asbestos exposure and to investigate the possible relationship of plaque size and pulmonary function. High resolution CT scans of the chest were used to detect the presence of pleural plaques [LPT] and to measure the size of the pleural plaques. This was a well-designed study that has the advantage of using high resolution CT scans for the assessment of pleural plaques [LPT], which enabled the investigators to exclude potential confounding factors, such as diffuse pleural thickening and subradiographic interstitial fibrosis, which may not have been apparent in studies that used chest radiographs alone for the assessment of pleural plaques [LPT]. Thus, they were able to better isolate any effects of pleural plaques themselves more accurately than studies that used chest radiographs. In my opinion, this is the best and most definitive study on the relationship of pleural plaques [LPT] to lung function that has been published to date. Pleural plaques were detected in 70% of asbestos-exposed subjects and none were detected in control subjects who were not exposed to asbestos. Neither interstitial fibrosis nor diffuse pleural thickening was evident on high resolution CT scans of asbestos-exposed subjects. Study results showed that there was no relationship between pleural plaque [LPT] surface area and cumulative asbestos exposure, time since first exposure, or smoking history. Furthermore, *neither the presence nor the extent of pleural plaques was correlated with lung function parameters. Specifically, there was no statistically significant difference in vital capacity (VC), FEV1, the FEV1/FVC ratio, measurements of airflow, or diffusion capacity between asbestos-exposed subjects with pleural plaques [LPT] and asbestos-exposed subjects without pleural plaques determined by high resolution chest CT scans.*

Miller (2002). [20] This is a short *letter to the editor* submitted to the *American Journal of Respiratory and Critical Care Medicine*, in response to the study of Van Cleemput, et al, which was discussed above. In this letter, the author congratulates Van Cleemput, et al, for using high resolution CT scans to quantitate the extent of asbestos-related pleural plaques and to estimate associations with asbestos exposure with lung function. However, he appears to be critical of the Van Cleemput, et al, study, by stating that it is difficult to relate one variable, such as pleural plaques, to another, such as pulmonary function, when the spectrum of each variable is limited. In this regard, he is confirming a well-known, inherent difficulty in conducting such studies. He indicates that not reporting the “degree of pleural plaques” on chest radiographs, in accordance with the criteria of the 1980 International Labour Office Classification of Radiographs (1980 ILO Classification) is a matter of concern. He briefly reports the main results of three other studies that did use the 1980 ILO Classification that showed conflicting results. He then offers the opinion that “It must be concluded that when sufficient numbers of workers with a sufficient extent of PP [pleural plaques] are analyzed, there is a significant effect on pulmonary function attributed to PP [pleural plaques].” *The opinion of the author is respected, although it does not in any way effect the scientific rigor of the Van Cleemput, et al, study or the validity of the results obtained.* First of all, it should be noted that at the time of the Van Cleemput publication in 2001, the 1980 ILO Classification was obsolete, having been replaced by the 2000 ILO Classification. Secondly, the methodology used by Van Cleemput, et al, to determine the surface area (extent) of pleural plaques [LPT] on high resolution CT scans of the chest is significantly more accurate than determining the extent of pleural plaques [LPT] on chest radiographs using the 1980 ILO Classification. Thirdly, the number of subjects in the Van Cleemput study provides more than enough statistical power to achieve a high degree of statistical significance in study results. Fourthly, as pointed out in the response to this letter from the article authors, their study included pleural plaques whose size (surface area) was representative of the average case, and that very large pleural plaques are neither common nor representative. *Thus, I concur with the response from the article authors in concluding that the comments in this letter do not invalidate their observation that there was no effect of pleural plaques [LPT] on pulmonary function, not even a trend.*

Whitehouse (2004). [21] The objective of this study was to assess the incidence and extent of pleural-related changes and the longitudinal loss of lung function associated with tremolite exposure from the vermiculite mining and processing activity in Libby, Montana. Initial chest radiographs were used to assess the presence and extent of pleural changes. Repeated measures of covariance were used to statistically assess pulmonary function over time, with time-modeled linearity. This is an *excellent, straight-forward study* that is well-designed to investigate the stated objectives. It specifically pertains to tremolite exposure from vermiculite mining and processing in Libby, Montana, and takes into account smoking history and body mass index (BMI). Of 123 subjects studied, 67 (55%) had pleural changes only, consisting of either pleural plaques [LPT] or diffuse pleural thickening. That is, *both pleural plaques and diffuse pleural thickening were included in determining whether or not pleural changes were present on initial chest radiographs*. The remaining 56 subjects (45%) had both pleural changes and minimal radiographic evidence of interstitial changes. Study results show that the total group of 123 subjects showed an average, statistically significant, yearly loss of 2.2% in FVC, 2.3% in TLC and 3.0% in DLCO over a period of 35 months. For the 67 subjects with pleural changes alone on initial chest radiographs, there was an average, statistically significant, yearly loss of 2.2% in FVC, 2.9% in TLC and 2.9% in DLCO over a period of 35 months. In this regard, the authors opine that “it would appear that tremolite-actinolite-richierite-winchite amphibole found in Libby vermiculite has a propensity for causing pleural changes that result in a progressive restrictive pattern on pulmonary function testing,” implying that Libby vermiculite could have lung function effects that are different from other forms of asbestos. *However, this study showed no statistically significant correlation between the extent of pleural changes on chest radiograph and the loss of pulmonary function*. Furthermore, this study was not designed to specifically investigate the effect of pleural plaques [LPT] on the loss of lung function, and *does not demonstrate that pleural plaques [LPT], per se, are associated with a loss of lung function*. In this regard, the authors demonstrated that “*the only clearly discernible event leading to accelerated loss of pulmonary function in the entire group was benign asbestos related pleural effusions.*” They also state that “*Pleural changes alone are unlikely to cause a*

decrease in DLCO" and that "DLCO decreases are likely to be associated with interstitial disease not apparent clinically on either plain chest radiograph or HRCT."

Sichletidis, et al (2006). [22] The objective of this study was to evaluate the progression of radiologic findings as well as the progression in respiratory function among asbestos-exposed individuals in Northern Greece, 15 years after initial evaluation. Chest radiographs were used to assess the presence, extent and progression of radiologic findings. The results of this study showed that, during the 15 year period between 1988 and 2003, the mean surface area of pleural plaques among 126 subjects increased from $8.52 \pm 11.4 \text{ cm}^2$ to $17.18 \pm 19.24 \text{ cm}^2$. However, the authors do not report the statistical significance of this difference in plaque surface area and, in view of the large standard deviations in plaques surface area, statistical significance is doubtful. This is a major limitation. Furthermore, the authors provide no explicit information on exposure cessation. That is, we do not know if, or when, exposure cessation occurred during the 15 year interval period. This is another major limitation. The authors report a statistically significant decrease in both TLC and FVC during the 15 year interval. However, only 18 out of the 126 subjects (14%) had pulmonary function tests performed. Thus, it is questionable whether this small sample is representative of the group of 126 as a whole. This is another major limitation. Finally, among the 18 subjects who had pulmonary function tests, the authors report a statistically significant, but weak, negative correlation between expansion in plaque surface area and TLC ($r = -0.486$, $p = 0.041$). Again, it is questionable whether this change in TLC among 18 subjects is representative of the group of 126 subjects as a whole. Furthermore, the coefficient of determination is very weak ($r^2 = 0.236$), indicating that the observed decrease in TLC is primarily due to factors other than the expansion in plaque surface area. *In general, in my opinion, this is a poorly designed, very weak study with multiple significant scientific limitations. In this regard, cannot be used to make any scientifically valid or acceptable inference about the relationship between pleural plaques [LPT] and lung function.*

Wilken, et al (2011). [23] This study is a systematic review and meta-analysis of the results of 30 peer-reviewed publications, consisting of 9,921 asbestos-exposed workers. The objectives

of this study were to identify and quantify alterations of lung function parameters in subjects occupationally exposed to asbestos, as well as to assess whether or not occupational exposure to asbestos leads to impairment in lung function independently from the non-malignant radiological findings of pleural fibrosis and asbestosis (interstitial fibrosis). Of significance is the fact that *both* pleural plaques [LPT] and diffuse pleural thickening were considered together as a *single entity* in the assessment of pleural fibrosis; *that is pleural plaques [LPT] was not considered as a separate entity in the assessment of pleural fibrosis*. This study systematically collected detailed information from the studies reviewed and used robust methods of statistical analysis to assess relationships between lung function and non-malignant radiographic findings reported in the reviewed studies. Based upon a meta-analytical analysis of FVC, FEV1 and the FEV1/FVC ratio, the results of this study showed that asbestos exposure is associated with both restrictive and obstructive ventilatory impairment and that, even in the absence of radiological parenchymal or pleural fibrosis there is a trend for functional impairment. That is, impairment in lung function clearly exists among asbestos-exposed subjects, however lung function impairment occurs *“either with or without asbestos-related radiographic abnormalities.”* With respect to forced vital capacity (FVC), study results show that FVC impairment occurred in workers without radiographic evidence of either asbestos-related parenchymal or pleural abnormalities, that the impairment in FVC was most pronounced in subjects with radiographic evidence of asbestosis (86.5% predicted, 95% CI = 83.7 - 89.4% predicted), that subjects with pleural fibrosis had a significantly less degree of FVC impairment (89.0% predicted, 95% CI = 86.5 – 91.5% predicted), that subjects with normal radiographic imaging had the least amount of FVC impairment (95.7% predicted, 95% CI = 93.9 – 97.3% predicted), that FVC was significantly lower in all three radiological sub-groups among studies using chest radiographs compared with those using high resolution chest CT scans, and that FVC was significantly lower in the normal imaging and pleural fibrosis radiographic sub-groups in which more than 25% of the subjects were never smokers. The study did not take into account differences in body mass index (BMI) among subjects in different subgroups. In view of study results that show that functional impairment occurs either with or without radiographic abnormalities and the fact that both pleural plaques [LPT] and diffuse pleural thickening were both included in the pleural

fibrosis radiographic subgroup, *no inference can be made about the lung function effects of pleural plaques [LPT], per se. That is, this study does not demonstrate any direct effect of asbestos-related pleural plaques [LPT] on a reduction in lung function.*

CONCLUSIONS

Based upon my extensive, objective review of the medical and scientific literature that addresses the relationship between asbestos-related localized pleural thickening and lung function, as well my objective critical review of the literature cited by the EPA Scientific Advisory Board to support its assertion that “LPT is associated with reduced lung function” in its DRAFT Quality Review Report, I have reached the following conclusions:

1. There is a large body of conflicting and inconclusive peer-reviewed scientific literature regarding the relationship between asbestos-related localized pleural thickening and lung function. In this regard, there is considerable uncertainty about the scientific validity of any assertion that “LPT is associated with reduced lung function.” Further rigorous scientific evaluation is necessary before the EPA Scientific Advisory Board can make this assertion with any acceptable degree of scientific certainty.
2. There is no *weight of evidence* study, based upon scientifically rigorous *weight of evidence guidelines*, to support the assertion of the EPA Scientific Advisory Board that “LPT is associated with reduced lung function.” Thus, it is not clear exactly what scientific criteria the EPA Scientific Advisory Board used to support this statement.
3. The body of literature cited in the DRAFT Quality Review Report to support the assertion that “LPT is associated with reduced lung function” does not provide a definitive, scientifically rigorous basis for making such an assertion. Indeed, one cited publication does not even address the relationship between LPT and lung function and one cited publication is a letter to the editor regarding another cited publication without consideration of the scientifically robust response from the authors.

4. In its DRAFT Quality Review Report, the EPA Scientific Advisory Board did not consider, or even mention, the results of a robust, peer-reviewed Delphi Study that was published as the *American College of Chest Physicians Consensus Statement on the Respiratory Health Effects of Asbestos* in the journal *CHEST* [4] in which there was *strong disagreement* by a panel of 71 experts in the respiratory health effects of asbestos with the statement “pleural plaques alter lung function to a clinically significant degree.”
5. In its DRAFT Quality Review Report, the EPA Scientific Advisory Board did not consider, or even mention, the findings of the *Public Health Assessment of the Libby Asbestos Site* that was prepared by the Division of Health Assessment and Consultation of the United States Agency for Toxic Substances and Disease Registry (ATSDR), dated April 22, 2010. [5] In this report the ATSDR reports a very small 1.8% incidence of moderate to severe restriction in breathing capacity and does not include LPT (pleural plaques) among the strongest risk factors for restrictive changes in pulmonary function in *Libby Community Environmental Health Project* participants. The ATSDR position appears to be inconsistent with the EPA Scientific Advisory Board statement that “LPT is associated with reduced lung function.”

RECOMMENDATIONS

1. The EPA Scientific Advisory Board should modify the statement that “*Pleural thickening is associated with restrictive lung function*” in Question 2 of its DRAFT Report to reflect the fact that this clearly pertains to *diffuse pleural thickening*, but does not necessarily pertain to localized pleural thickening [LPT]. The EPA Scientific Advisory Board should make it clear that, although *some* reports suggest a small, restrictive decrement in lung function associated with LPT, there are a number of other excellent reports that show no statistically or clinically significant decrement in lung function associated with asbestos-related LPT, especially after controlling for parenchymal changes indicative of interstitial fibrosis. The EPA Scientific Advisory Board should also make it clear that there is considerable scientific uncertainty about whether or not any significant

relationship between asbestos-related LPT and a decrement in lung function typically or universally exists at this time.

2. The EPA Scientific Advisory Board should delete the statement that “LPT is associated with reduced lung function” and replace it with a statement that takes into account the fact that a large body of scientific literature shows that there is no statistically or clinically significant decrement in lung function associated with asbestos-related LPT, especially after controlling for parenchymal changes indicative of interstitial fibrosis. Once again, the EPA Scientific Advisory Board should make it clear that there is considerable scientific uncertainty about whether or not any significant relationship between asbestos-related LPT and a decrement in lung function typically or universally exists at the present time.
3. Do not support the assertion that “LPT is associated with reduced lung function” as a reason for using localized pleural thickening [LPT] as the critical endpoint for deriving the inhalation reference concentration (RfC) in the IRIS assessment pertaining to Libby Amphibole Asbestos at this time. In view of numerous conflicting reports in the scientific and medical literature, as well as the considerable scientific uncertainty regarding whether or not any significant relationship between asbestos-related LPT and a decrement in lung function typically or universally exists, there is no clear-cut, scientifically rigorous basis for using the statement “LPT is associated with reduced lung function” as a reason for using LPT as the critical endpoint for deriving the RfC at the present time.
4. That the EPA Scientific Advisory Board convene an independent, objective panel of experts in asbestos-related respiratory health effects to develop scientifically rigorous *weight of evidence guidelines* for investigating any association between asbestos-related LPT and lung function. [24, 25, 26]
5. That the EPA Scientific Advisory Board subsequently convene an independent, objective panel of experts in asbestos-related respiratory health effects to perform a formal *weight of evidence evaluation* of the association between asbestos-related LPT and lung

function, based upon previously determined, scientifically *rigorous weight of evidence guidelines*, for the purpose of providing a clear-cut, robust, scientifically valid assessment of this association. [24, 25, 26]

6. Revisit the appropriateness of using the statement “LPT is associated with reduced lung function” as a reason for using localized pleural thickening [LPT] as the critical endpoint for deriving the inhalation reference concentration (RfC) in the IRIS assessment pertaining to Libby Amphibole Asbestos after the previously recommended *weight of evidence evaluation* has been completed.
7. Withhold publication of the final version of the final EPA Scientific Advisory Board Quality Review Report of the EPA DRAFT Assessment entitled Toxicological Review of Libby Amphibole Asbestos (August 2011) until after the previously recommended *weight of evidence evaluation* has been completed. The final version of this report should address the scientific appropriateness of using the statement “LPT is associated with reduced lung function” as a reason for using localized pleural thickening [LPT] as the critical endpoint for deriving the inhalation reference concentration (RfC) in the IRIS assessment pertaining to Libby Amphibole Asbestos based upon the *weight of evidence* contained in the recommended evaluation.
8. Consider, address and reference the *American College of Chest Physicians Consensus Statement on the Respiratory Health Effects of Asbestos* [4] with respect to any statements regarding the association of LPT and lung function in the final EPA Scientific Advisory Board Quality Review Report of the EPA DRAFT Assessment entitled Toxicological Review of Libby Amphibole Asbestos (August 2011).
9. Consider, address and reference the *Public Health Assessment of the Libby Asbestos Site* that was published by the Division of Health Assessment and Consultation of the United States Agency for Toxic Substances and Disease Registry (ATSDR) [5] with respect to any statements regarding the association of LPT and lung function in the final EPA Scientific Advisory Board Quality Review Report of the EPA DRAFT Assessment entitled Toxicological Review of Libby Amphibole Asbestos (August 2011).

NOTES:

The professional opinions and commentary in this report are those of the report author and do not necessarily reflect the opinions of the Medical University of South Carolina or any other member of its faculty.

The report author has no personal, professional or financial conflicts of interest with respect to the literature reviews, assessments, professional opinions or professional commentary contained in this report.

The report author was retained by Exponent to objectively review the DRAFT Report of the EPA Scientific Advisory Board Quality Review of the EPA DRAFT Assessment entitled Toxicological Review of Libby Amphibole Asbestos (August 2011), dated August 30, 2012 and provide comments to the EPA and its Scientific Advisory Board. The author understands that the work was funded by W R Grace.

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APPENDIX B – 5

**Comments to the SAB on the EPA document EPA/635/R-002A, "Draft
Toxicological Review of Libby Amphibole Asbestos"**

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Attachments

Appendix A: Moolgavkar Slides for presentation at the SAB meeting, Feb 6-8, 2012.

Appendix B: Moolgavkar October Report on the EPA document EPA/635/R-002A, "Draft Toxicological Review of Libby Amphibole Asbestos" together with slides shown at the listening session in October, 2011.

EXECUTIVE SUMMARY

This Executive Summary identifies my principal scientific concerns set forth more fully in the following report regarding the U.S. EPA's proposed quantitative risk assessment for cancer and non-cancer endpoints for Libby amphibole asbestos.

The EPA draft risk assessment for Libby amphibole ("2011 Draft") uses data on lung cancer and mesothelioma from a sub-cohort of the full cohort of Libby miners to estimate an Inhalation Unit Risk (IUR) for Libby amphibole. The 2011 Draft also uses data on localized pleural thickening from a sub-cohort of a cohort of workers at a vermiculite processing plant to estimate a Reference Concentration (RfC) for non-cancer adverse impacts on human health. While the current draft represents an enormous amount of effort, it has a number of significant scientific deficiencies.

1. Instead of using the full Libby cohort with follow-up through 2006, the 2011 Draft uses a greatly truncated sub-cohort of workers employed after 1959. This selection reduces the number of lung cancers from 111 in the full cohort to 32 in the sub-cohort and the number of mesotheliomas from 19 in the full cohort to 7 in the sub-cohort. The reduction in cohort size biases estimates of risk because older individuals are selectively eliminated from the sub-cohort.
2. The reduction in cohort size also leads to diminished power to detect departures from proportionality (effect modification by age) in the Cox model analyses of lung cancer and precludes the use of the Peto-Nicholson model for mesothelioma. The use of the Peto-Nicholson model is important because it recognizes the significant role of temporal factors, such as duration of exposure and time since exposure stopped, in determining mesothelioma risk following asbestos exposure.
3. For lung cancer, I recommend that a revised draft report analyze the entire Libby cohort and investigate carefully the effect modification of lung cancer risk by age. Since the lung cancer risk assessment is based on a life-table analysis, it is imperative to estimate age-specific relative risks.

4. For mesothelioma, I recommend that a revised draft report use the full cohort with 19 mesotheliomas and perform a full likelihood based time-to-tumor analysis using the Peto-Nicholson model as described in the body of my report, instead of the inadequately-justified Poisson regression that is used in this draft.
5. For the non-cancer risk assessment the 2011 Draft uses a small sub-cohort of workers employed at a vermiculite processing plant at Marysville, Ohio. While the full cohort investigated in Rohs et al. (2008) consists of 280 individuals with 80 cases of localized pleural thickening, the sub-cohort chosen in the 2011 Draft consists of 119 individuals with 12 cases of localized pleural thickening. Thus, the 2011 Draft discards without justification much of the available data.
6. The 2011 Draft does not provide adequate evidence to support the selection of localized pleural thickening as an adverse health impact for asbestos exposure. In previous Agency documents, no attempts have been made to derive an RfC for non-cancer adverse impacts on human health because the choice of an appropriate end-point was not clear. Therefore, the 2011 Draft sets a new precedent and it is imperative that a revised draft make clear why localized pleural thickening should be considered an adverse health impact rather than just a marker of asbestos exposure.
7. I recommend that a revised draft reevaluate the choice of localized pleural thickening as an adverse health impact and analyze the entire Rohs cohort data using appropriate statistical methods as described in the body of this report.
8. I recommend that a revised draft discuss the carcinogenic potency of Libby amphibole in context. Our understanding of the differential carcinogenic potencies of the different types of asbestos fibers has advanced considerably over the last decade. It is incumbent upon a revised draft to describe the contemporary literature on this topic and discuss the carcinogenic potency of Libby amphibole in relation to that of other asbestos fibers.

Background and Qualifications

I am a physician with a Ph.D. in Mathematics and post-doctoral training in Pharmacology, Biophysics, Epidemiology and Biostatistics. In April 2007, I became a Corporate Vice President and the Director of the Center for Epidemiology, Biostatistics and Computational Biology at Exponent, Inc., an international scientific consulting company. I retired from my position as a Full Member of the Fred Hutchinson Cancer Research Center in August 2008. I continue to be an Affiliate Investigator at the Center and Professor of Epidemiology and Adjunct Professor of Applied Mathematics at the University of Washington in Seattle. I am a cancer epidemiologist and research scientist. My main research interest is cancer epidemiology. I was instrumental in developing a biologically-based mathematical model, the two-stage clonal expansion (TSCE) model, often called the Moolgavkar-Venzon-Knudson (MVK) model, for the quantitative estimation and prediction of cancer risk. This model is recognized and used by cancer researchers worldwide.

I have served on the faculties of the Johns Hopkins University, Indiana University, the Fox Chase Cancer Center and the University of Pennsylvania. I have been a visiting scientist at the Radiation Effects Research Foundation in Hiroshima, the International Agency for Research on Cancer (IARC) in Lyon, and the German Cancer Research Center in Heidelberg.

I have served on numerous review panels and as a consultant to the National Cancer Institute (NCI); the Environmental Protection Agency (EPA); the California Air Resources Board; Health and Welfare, Canada; IARC; the CIIT Centers for Health Research; and the Health Effects Institute. I am the author or co-author of more than 160 papers in the areas of Epidemiology, Biostatistics, and Quantitative Risk Assessment, and have edited three books in these areas. Among these is a monograph, "Quantitative Estimation and Prediction of Human Cancer Risk," published by IARC, the agency that conducts cancer research under the auspices of the World Health Organization. I have served on the editorial board of *Genetic Epidemiology* and *Inhalation Toxicology* and am currently one of the editors of *Risk Analysis – An International Journal*. I am an elected member of the American

Epidemiological Society. I was given the Founders' Award by the CIIT Centers for Health Research in 1990 and the Distinguished Achievement Award by the Society for Risk Analysis in 2001. I am a Fellow of the Society for Risk Analysis, the pre-eminent international scientific society for risk assessment.

Among my publications are several papers on carcinogenesis following exposure to fibers. I was an Invited Expert at a workshop, "Mechanisms of Fiber Carcinogenesis," held at IARC in Lyon, France, in early November, 2005. I was the lead panelist for a symposium on fiber carcinogenesis held in Brussels in 2005.

Purpose of this Report

I have been retained by W.R. Grace to review and comment on the scientific issues in the draft risk assessment of Libby amphibole asbestos, which is a mixture of tremolite, winchite and richterite. The purpose of my review and comment is to assist the SAB and the EPA in ensuring that the final assessment of Libby amphibole is based on the best available science. I am intimately familiar with the Libby cohort data. I have analyzed these data with follow-up through 2002 (Moolgavkar et al., 2010) and many of my comments reflect the results of these analyses. I also had access to the Rohs database on a subset of which the 2011 Draft bases its estimate of the RfC for Libby amphibole. I have analyzed these data as well, but have not published the results.

I had previously made oral comments on the 2011 Draft at a "listening session" organized by the EPA in October, 2011. At that time, I also provided written comments to address more fully the technical details that could not be covered in a short verbal presentation. I attach my previous written comments to this document as appendix B. The slides of my October presentation at the listening session are appended to those written comments.

In these comments to the SAB, I summarize the main scientific issues raised by the 2011 Draft risk assessment. I do not discuss the specific toxicity values derived in the 2011 Draft because such numbers can be meaningfully discussed only after the scientific issues have been properly addressed.

The main goals of the 2011 Draft risk assessment are to develop an inhalation unit risk (IUR) for cancer (lung cancer and mesothelioma) and a reference concentration (RfC) for non-cancer endpoints associated with exposure to Libby amphibole.

Cancer Risk Assessment

The current IRIS Inhalation Unit Risk (IUR) for asbestos-associated cancer is based on combining separate slope factors for lung cancer and mesothelioma using a life-table analysis. The general framework for developing an IUR in the 2011 Draft is similar to that used by the Agency for the development of an asbestos cancer slope factor for the IRIS database in 1993, which was based on the risks estimated in an earlier Agency report by Nicholson (1986). The models and methods used in the 2011 Draft to derive individual slope factors for lung cancer and mesothelioma are different, however.

In the 2011 Draft, the EPA develops an IUR for cancer in the following three steps. The procedure is similar, but not identical, to the procedure used in the 1993 IRIS document.

1. Estimate potency for lung cancer (K_L) from the occupational cohort data using a relative risk (RR) model. The RR is assumed to be a function of cumulative exposure. Whereas the 1986 Nicholson analysis was based on regressions through standardized mortality ratios (SMRs), the current 2011 Draft document uses the Cox proportional hazards model applied to a (truncated) Libby worker cohort.
2. Estimate potency for mesothelioma from the occupational cohort data using an absolute risk model. The 1986 analysis was based on a model originally developed by Peto et al. (1982) and then adopted by Nicholson, and which I call the Peto-Nicholson model. In this model, which is based on ideas of multistage carcinogenesis, the hazard function for mesothelioma is a function of exposure concentration, duration of exposure, and time since exposure stopped. The model is

linear in exposure concentration, but non-linear in the time variables. Therefore, this model recognizes explicitly the role of pattern of exposure in determining risk. In this model, risk cannot be expressed as a function of cumulative exposure. The 2011 Draft bases its estimate of potency instead on a Poisson regression analysis of mesothelioma deaths in the same truncated data set used for the lung cancer potency estimate, using cumulative exposure as the measure of exposure. In a giant step backwards, the 2011 Draft does not recognize the important role of the time variables in determining risk.

3. In the final step, risk estimates for mesothelioma and lung cancer are combined using a life-table analysis for lung cancer to arrive at the IUR for cancer.

For its current analyses of lung cancer and mesothelioma, the 2011 Draft uses the sub-cohort of workers employed after 1959 and followed up through 2006. The Draft give two reasons for the choice of this dataset rather than the full Libby cohort. First, it argues that exposure is better characterized¹ in this sub-cohort and second, proportionality of hazards for lung cancer holds in this sub-cohort, and therefore the issue of effect modification by age does not have to be addressed. There is some merit to the first reason, but the second reason does not stand up to scrutiny. In fact, as explained below, effect modification by age is an important feature of many epidemiologic cohort data sets that span several decades and should, in fact, be explicitly addressed in any risk assessments, particularly ones that rely on life table analyses as does the Agency assessment for lung cancer.

¹ The 2011 Draft repeats the old canard (page 5-78 of the report) about non-differential covariate measurement errors leading to risk estimates biased towards the null. This statement, although widely repeated by epidemiologists, is incorrect. First, not only must the misclassification be non-differential, it must satisfy other conditions (e.g., Jurek et al., 2005) for the result to hold. Second, the statement applies to the expectation of the risk estimate, not to the value of the estimate from any single study. Thus, it is possible to have non-differential misclassification that satisfies all the required conditions but the result of a single study may actually overestimate the risk. As Jurek et al. (2005) state, "...exposure misclassification can spuriously increase the observed strength of an association even when the misclassification process is non-differential and the bias it produced is towards the null." Similar discussion is provided by Thomas (1995) and Weinberg et al. (1995).

Lung Cancer

The Libby workers' cohort is the logical choice of dataset on which to base risk estimates for lung cancer and mesothelioma. Over the years there have been numerous publications based on analyses of this cohort (Amandus et al., 1987; McDonald et al., 1986, 2002, 2004; Sullivan, 2007; Moolgavkar et al., 2010; Larson et al., 2010). As the most contemporaneous studies with the longest follow-up, the studies by Sullivan, Moolgavkar, and Larson are the most relevant to this risk assessment. Both Moolgavkar et al. (2010) and Larson et al. (2010) used the Cox proportional hazards model, as does the 2011 Draft, and arrived at similar estimates of RR (~1.1 for 100f/cc-y cumulative exposure). I note here that this RR is quite a bit smaller than that estimated in other asbestos occupational cohorts. The RR associated with exposure to asbestos in the South Carolina Textile Workers' cohort, for example, is substantially larger² (Hein et al., 2007; Richardson, 2009).

The estimation of a single RR for all ages should be interpreted as an averaging of risks over all ages and is appropriate only as a summary measure of risk in the entire cohort. However, a life-table analysis as conducted by the Agency in the 2011 Draft and previous risk assessments, involves the use of age-specific lung cancer mortality rates from a standard population multiplied by the RR to estimate the number of excess lung cancer deaths as a consequence of exposure to asbestos. Therefore, when a life-table analysis is performed, it becomes important to investigate RR as a function of age, i.e., to investigate effect modification by age. The 2011 Draft had a great opportunity here to investigate effect modification by age but appears to have gone to great lengths not to do so. In fact, the 2011 Draft chose a sub-cohort for analyses in which effect-modification by age had been eliminated. As a result, the Draft fails to evaluate the critical importance of effect modification thus biasing the IUR for lung cancer.

There are compelling reasons to use the entire Libby cohort rather than the sub-cohort that the Agency chooses to use.

² Hein et al. (2007) report an RR of about 3 associated with 100 f/cc-yr cumulative exposure as compared to an RR of about 1.11 in Libby for the same cumulative exposure.

1. By discarding more than two-thirds of the lung cancers (111 in the full cohort followed up until 2006 (Larson et al., 2010) as opposed to 32 in the sub-cohort used by the Agency), the power to detect effect-modification by age is greatly diminished. Effect modification by age is an important feature of many epidemiologic data sets (Moolgavkar, 2012), as discussed in more detail in my comments at the October listening session (see Appendix B of this report) and age-specific relative risks should be applied in a life-table analysis. In particular, there is strong evidence of effect modification of lung cancer risk by age in the Libby cohort as can be seen in figure 1 below. The 2011 Draft recognizes that effect modification by age is important in the entire cohort (page 5-76), but then effectively ignores it by choosing a sub-cohort in which it is no longer statistically significant. The single estimate of RR used in the 2011 Draft under-estimates risk at the younger ages and over-estimates it at the older ages (see figure 1 below).
2. The sub-cohort consists of workers who entered the work force after 1959. With follow-up until 2006, there are probably few sub-cohort members over the age of 65 by the end of the study, the age at which the incidence of lung cancer begins to increase rapidly. Therefore, the Agency potency estimates for lung cancer are based primarily on individuals below the age of 65. In particular, with the life-table analysis going out to age 85, it is important that lung cancer at the older ages make some contribution to the estimate of RR. As stated above age-specific RRs should be used in the life-table analyses. If the Agency insists on using a single estimate of RR, it should clearly be estimated from a dataset that spans the entire range of ages. At the very least, a comprehensive uncertainty analysis should be undertaken to investigate how the choice of sub-cohort and the assumption of no effect modification affects the IUR for lung cancer.

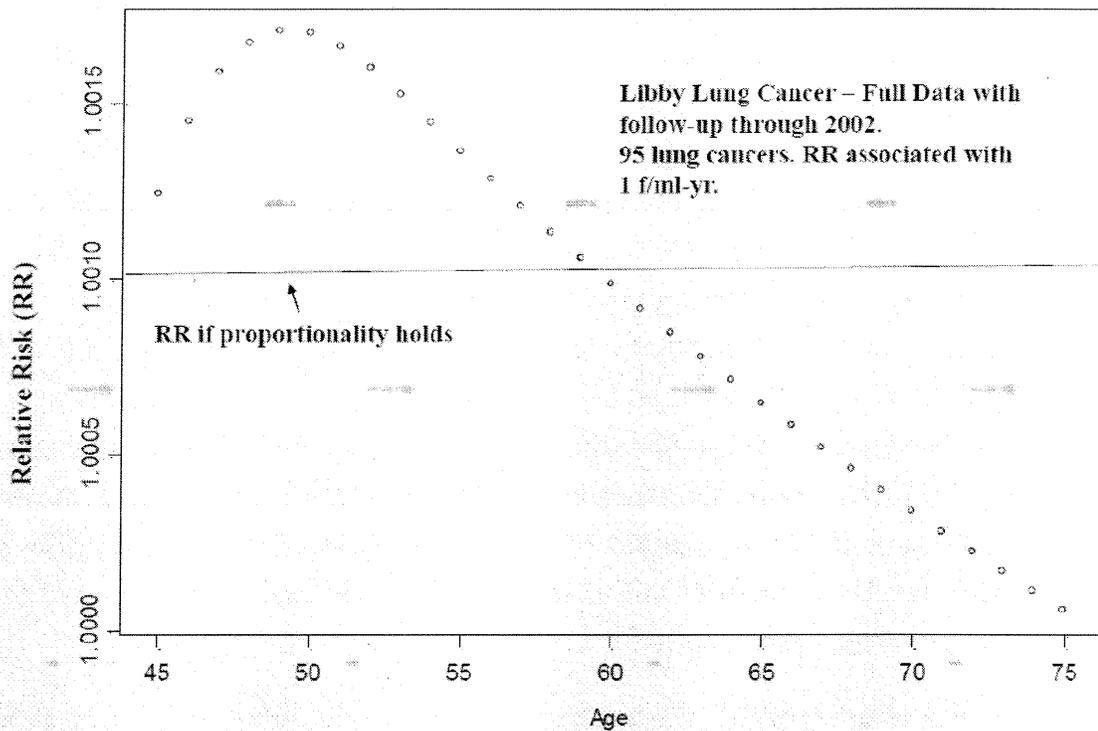


Figure 1. Analysis of lung cancer in the full Libby cohort followed up through 2002 (Sullivan, 2007; Moolgavkar et al., 2010) using natural splines to model RR as a function of age. RR on the y-axis is associated with a cumulative exposure of 1f/cc-yr. Note the strong effect modification by age, which can also be seen in figure 2 below and in slides 8 and 9 in my presentation at the listening session. These slides are appended to my October written comments (Appendix B). A test for effect modification by age is statistically significant. More details are in my October report (Appendix B).

Figure 2 below is taken from a publication by Richardson (2009) analyzing the lung cancer risk associated with asbestos exposure in that cohort. The figure shows the strong effect modification by age in this cohort. Richardson uses the biologically-based two-stage clonal expansion (TSCE) model also known as the Moolgavkar-Venzon-Knudson (MVK) model and shows not only strong effect modification by age, but also that cumulative exposure to asbestos is a poor measure of exposure

for lung cancer risk assessment. In fact, as is the case of mesothelioma, temporal pattern of exposure is important in determining risk. We have conducted similar analyses for lung cancer in the Libby cohort using the TSCC model and can confirm Richardson's findings in the South Carolina cohort, although the magnitude of the lung cancer risk associated with exposure to Libby amphibole asbestos is much smaller.

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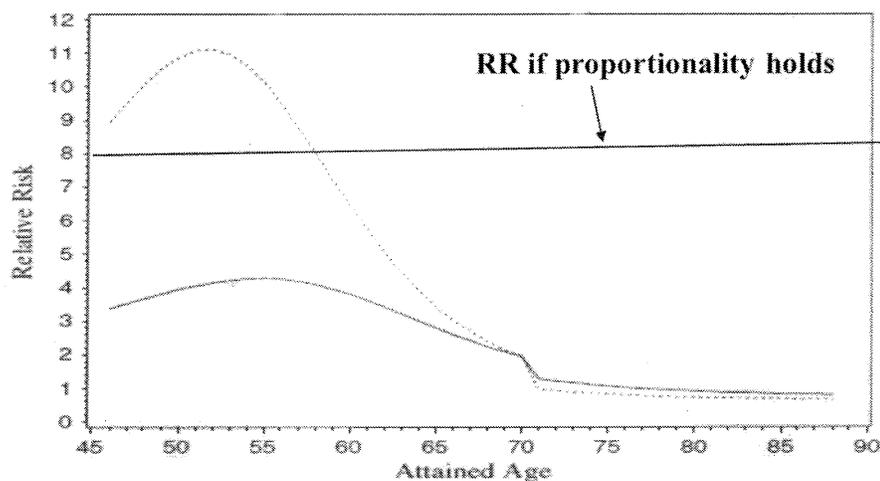


Fig. 2 Lung cancer relative risk by attained age. Predicted impact of asbestos exposure at intensities of 5 (dashed line) and 2.5 fiber/ml (solid line) based upon fitting of the two-stage clonal expansion model (predicted relative risks based on the model parameters shown in Table 2 and allowing for asbestos exposure effect as shown in Table 3, Model 2). Exposure commences at age 20 years and terminates at age 60 years. Ten-year lag assumption

Thus, there is strong evidence that 1) effect modification by age is an important feature of asbestos-associated lung cancer risk, and 2) lung cancer risk after asbestos exposure is a function of the entire exposure history, not just cumulative exposure. In my oral and written comments for the October listening session, I provided other examples showing that effect modification by age, i.e. non-proportionality of hazards is ubiquitous in epidemiologic data sets that span a wide range of ages. Please see the Appendix B for details.

Recommendations for lung cancer risk assessment

1. Utilize the entire Libby data set of Larson et al. (2010) for risk assessment using the proportional hazards model.
2. Use flexible statistical methods, such as spline smoothers, to explore carefully effect modification by age in the data.
3. Explore the role of patterns of exposure in determining risk by using biologically-based models, such as the multistage model and the TSCE (MVK) model.
4. Explore approaches other than the life-table approach for estimating IUR. For example, robust estimation of excess risk may be directly possible from analyses using approaches based on ideas of multistage carcinogenesis, such as the TSCE model.
5. If a life-table approach is necessary, use age-dependent RRs to account for effect modification by age.

Mesothelioma

Analyses of mesothelioma in the Agency report is based on the same sub-cohort as the lung cancer analyses. Whereas there are 19 mesotheliomas in the full cohort, there are only 7 in the sub-cohort used by the Agency. The risk estimate obtained by analysis of these 7 cases is adjusted upward to address under-ascertainment of mesothelioma cases using a method proposed by Kopylev (2011). As discussed below, this adjustment is poorly justified and ill-advised.

It is well known from the work of Peto and Nicholson that temporal factors, such as duration of asbestos exposure and time since exposure stopped, play an important role in determining mesothelioma risk from exposure to asbestos. The 2011 Draft has chosen to ignore this fundamental fact in abandoning the Peto-Nicholson model, which was used in its 1986 risk assessment and which has been shown to describe the data well in multiple occupational cohorts (Berman & Crump, 2008), in favor of a poorly-justified Poisson regression model.

The Peto-Nicholson hazard function for mesothelioma mortality is of the form $h(t) = K_M * g(t)$, where $g(t)$ is a power of time since exposure started and depends also on fiber concentration, and K_M is a constant that depends on fiber type. I

recommend that a revised draft use a generalization (Berman & Crump, 2008) of the original formula to accommodate time-varying exposure concentrations:

$$g(t) = 3 \int_0^{t-10} E(u)(t-u-10)^2 du,$$

where $g(t)$ is the mortality rate (per year) at year t after start of exposure and $E(u)$ at time u is the concentration of asbestos fiber expressed as fibers/ml.

The 2011 Draft states that the Peto-Nicholson model was tried, but did not describe the data as well as the Poisson model that it ultimately used. It is not at all clear, however, that the Peto-Nicholson model was tested appropriately. The version of the model used by Berman and Crump (2008), which accommodates time-varying exposure concentrations, should have been used and a full likelihood time-to-tumor analyses performed to estimate not only K_M , but also the exponent of the duration of exposure. With only 7 cases, such an analysis is probably not feasible. In my opinion, the full Larson data set should be analyzed using the Peto-Nicholson model. With the Poisson regression adopted in the 2011 Draft, all information about time-to-tumor is lost. It is also not clear from the description provided in the report how the Poisson regression was performed. For example, the report should state clearly what contribution each individual in the cohort made to the expectation of the Poisson model. Even if Poisson regression is used for these analyses, it is not clear why it is necessary to use Bayesian MCMC methods. Likelihood-based analyses using generalized linear models appear to be straightforward. The numerous analyses performed and reported on this small dataset are unjustified. How can one discriminate among the many models used with only 7 cases of mesothelioma in the dataset? Small differences in the deviance information criterion (DIC), or whatever criterion is used to measure relative fits, are hardly informative with this small dataset.

Finally, the Agency used a method proposed by Kopylev (2011) to adjust risk upward by a factor 1.39 to compensate for under-ascertainment of mesothelioma deaths in the sub-cohort. I believe this adjustment is ill-advised for the following reasons. First, the under-ascertainment of total asbestos exposure because of

exposure to asbestos from other sources should be considered before any adjustment is made for under-ascertainment of mesothelioma (or any other) deaths. Many of the workers at the Libby mines worked there only for short periods of time. A substantial number in the full Libby cohort was employed there for less than one year. It is clear from the data in Peipins et al. (2003) that residents of Libby were employed in other jobs that could have exposed them to asbestos. It is therefore highly likely that exposure to asbestos is under-estimated in the cohort, particularly among short-term workers. This is not a problem peculiar to Libby. It is ubiquitous with occupational cohort studies and the only way to get around it is to perform a case-control study nested within the cohort. Second, I do not believe that the data on under-ascertainment used for estimating the adjustment factor is reliable because standards for the reporting of mesothelioma as a cause death varied from place to place. Third, the adjustment factor is based on a Poisson regression analysis and it is not clear that the same Poisson models were used in the report and in Kopylev et al. (2011). The adjustment factor using a proper likelihood based analysis using the Peto-Nicholson model would likely be different. Fourth, the adjustment factor applied in the Agency report is the one derived by Kopylev et al. (2011) based on the full dataset. It is not clear that the same adjustment factor would be obtained if the method were applied directly to the sub-cohort. Finally, with the amount of scrutiny received by the Libby population it is hardly likely that under-ascertainment is a problem. A revised draft should not apply any adjustment factor for under-ascertainment.

Recommendations for mesothelioma risk assessment

1. Use the entire Libby data (follow-up through 2006) used by Larson et al. (2010) with 19 cases of mesothelioma.
2. Use a likelihood-based time-to-tumor analysis with the Peto-Nicholson model and attempt to estimate both K_M and the exponent in the hazard function so that the dependence of risk on pattern of exposure is explicitly recognized. Moolgavkar et al. (2010) estimated $K_M = 0.5$, half the estimate used in the 1986 EPA asbestos risk assessment. Moolgavkar et al. (2010) could not estimate the exponent because they had information only on the

number (15) of mesothelioma deaths in the cohort followed through 2002, but not on which specific individuals died of the disease. With this information, only K_M can be estimated. Another option would be to use the TSCE model. Both the Peto-Nicholson and the TSCE model recognize and explicitly incorporate pattern of exposure in the hazard function.

3. Abandon the attempt to adjust for under-ascertainment of mesothelioma deaths for reasons set forth above.
4. Abandon the attempt to estimate half-life of Libby asbestos in the pleura. The simple formulation used has no biological interpretation as discussed in my report for the October listening session (Appendix B).

Non-Cancer Risk Assessment

The previous Agency IRIS document for asbestos provides no estimate of an RfC for non-cancer endpoints because of the absence of suitable data for. Thus, the 2011 Draft sets a new precedent in estimating an RfC for non-cancer endpoints. It is therefore of critical importance that the health endpoint on which the RfC is based be carefully evaluated, the appropriate datasets for analyses be identified, and the proper statistical methods be used. The 2011 Draft bases its risk assessment for non-cancer endpoints on a cohort of workers involved in the processing of vermiculite at a plant in Marysville, Ohio, and analyzed by Lockey et al. (1984) and Rohs et al. (2008). The Agency risk assessment is based on a sub-cohort of the cohort analyzed by Rohs et al. (2008). The end-point of interest for the analyses is localized pleural thickening. The Rohs et al. cohort consists of 280 individuals with 80 cases of pleural thickening. The sub-cohort chosen by the Agency includes 119 participants with 12 cases of pleural thickening. Therefore, as is the case for lung cancer and mesothelioma, the 2011 Draft discards much of the data for the analyses in this report.

A fundamental question that is not adequately addressed in the 2011 Draft is whether localized pleural thickening is an adverse health impact or simply a marker of asbestos exposure. While the 2011 Draft cites literature to suggest that localized pleural thickening is associated with various clinical endpoints, such as chest pain, it provides no evidence that these associations are causal. For

example, urinary cotinine, because it is a marker of cigarette smoking, is undoubtedly associated with lung cancer but it clearly does not cause lung cancer.

The 2011 Draft says, "...more accurate exposure data are considered to be those from 1972 and later, as these data were based on analytical measurements."

Based on these considerations, the Agency chose from the Rohs cohort the sub-cohort consisting of workers who began work in 1972 or later. The radiographic examination of these workers was conducted over the period 2002-2005.

However, in their paper, Rohs et al. identified 1973, not 1971, as the year after which "...more comprehensive environmental exposures were available..." The sub-cohort of workers hired after 1973 consists of 94 individuals with 10 cases of pleural abnormalities. I had access to the original Rohs database³ and it includes an identifier for workers hired after 1973 but not for those hired after 1971. The report does not explain this discrepancy.

I have analyzed the full Rohs dataset using logistic regression and spline smoothers to explore exposure-response relationships. The results are shown in figure 3 below. This figure shows that most of the exposure data (the thickness of the rug at the bottom of the figure reflects the number of data points) lies in the range of 0-3 f/cc-yr. In this range of exposure, the flexible exposure-response model does not support a monotonic increasing exposure-response relationship. While the exposure-response relationship is consistent with linearity above 3 f/cc-yr, it is statistically insignificant in this range, possibly because of the paucity of data. There also is evidence of confounding by age (see figure 3).

One of the important criteria enunciated by the Agency for study selection for non-cancer risk assessment is that the exposure-response relationship be robust to adjustment for potential confounders. Thus, on page 5-11, the report states, "Amandus et al. (1987b) report that although cumulative exposure and age are both significant predictors of small opacities, cumulative exposure was not significantly related to pleural abnormalities when age is included in the model, thus limiting the usefulness of these data for RfC derivation based on pleural

³ As the 2011 Draft describes in appendix F, the exposure estimates in the original Rohs database have been revised for the current risk assessment. I do not have access to the revised estimates of exposure.

abnormalities.” In listing the advantages of the Rohs sub-cohort the Agency used, the report on page 5-14 (number 6) clearly states that it considers the absence of any evidence of confounding in this dataset a distinct advantage. I do not have access to the exact data used by the Agency, but I have analyzed full Rohs dataset as described above and there is strong evidence of confounding by age. By its own criteria, the Agency should not be using this dataset for derivation of an RfC.

Finally, the 2011 Draft uses various lags in the analyses of the sub-cohort. The use of lags for the analyses of pleural abnormalities makes no sense. Lags can be used in analyses of hazard or incidence functions when the diagnosis of an end-point, such as cancer, is made at a well-defined point in time. It is unscientific to use lags in the analyses of prevalent conditions, which could have occurred many years before the condition was noted. In the Rohs database all radiography was performed between 2002 and 2005, when pleural abnormalities were noted. These could have occurred many years before the radiography was done. What is the interpretation of a lag in this situation?

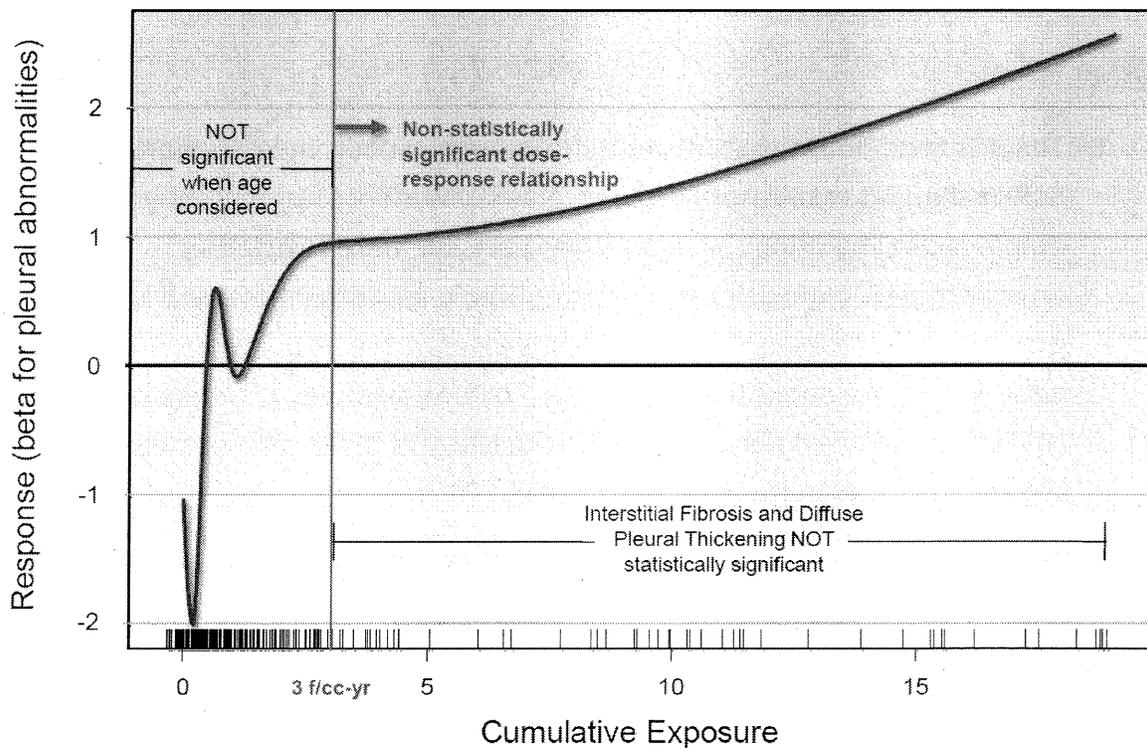


Figure 3 Exposure-response for localized pleural thickening as a function of cumulative exposure in the Rohs dataset.

Recommendations for Non-Cancer Risk Assessment

1. If localized pleural thickening is retained as the endpoint of interest, the full dataset should be used.
2. However, the Agency should acknowledge that the Rohs data does not satisfy its own criteria for use as a dataset for derivation of an RfC.
3. Although I am not a pulmonologist, I am concerned about calling localized pleural thickening an adverse event of clinical significance. The 2011 Draft does not provide adequate evidence to support this position.
4. Fat in the pleura is often mistaken for localized thickening on plain X-ray. Therefore, there may be considerable misclassification of the end-point in the data.
5. The Agency should recognize, as it did in the 1986 risk assessment, that there may not be an appropriate dataset for the derivation of an RfC for non-cancer end-points.

Other Issues

1. There is little doubt that mortality from lung cancer, mesothelioma and non-malignant respiratory disease (NMRD) was increased among workers employed at the mines in Libby. The real issue here is whether environmental exposure to Libby amphibole asbestos increased the risk of mortality from asbestos-associated diseases in the population of Libby. To address this question, the Agency for Toxic Substances and Disease Registry (ATSDR) conducted a mortality study in Libby in 2000. The Agency report should discuss this study in more detail.

The ATSDR undertook a study of mortality from specific causes in the Libby area over the 20-year period 1978-1998. Numbers of deaths from specific causes were compared with numbers that would be expected under national and Montana death rates. Standard epidemiological and statistical techniques were used to compute SMRs and their confidence intervals.

Given the asbestos exposure in this population the main cancers of interest were lung cancer and mesothelioma. Mortality over the period of this study would be expected to reflect the impact of environmental exposure to high levels of Libby amphibole.

The ATSDR reports a small non-significant increase in lung cancer deaths within Libby City and the extended Libby area using Montana death rates as the standard. With US death rates as the standard, no increase in lung cancer deaths is reported. Thus, the number of lung cancer deaths over the period of the study offers no evidence that environmental exposures contributed to the lung cancer mortality over the period 1978-1998.

The ATSDR reports four cases of mesothelioma over the period of the study. Since the background rate of mesothelioma is close to zero, this number points to a significant elevation of risk in the Libby area. However, four cases of mesothelioma are identified in the McDonald (2002, 2004) occupational cohort, and it seems highly likely that these are the cases identified by ATSDR. Thus, the cases in the ATSDR study can, in all likelihood, be explained on the basis of occupational exposure. As in the case of lung cancer, this study offers no evidence that environmental exposure contributed to mesothelioma deaths in the Libby area.

Among the causes of death other than cancer, of most interest are the non-malignant respiratory diseases (NMRD), particularly asbestosis. Eleven deaths from pneumoconioses are reported over the period of the study. All of these are labeled asbestosis in the ATSDR report, although it is not clear how this diagnosis was verified. In any case, the SMR is reported to range between 36 and 47 (depending on the geographic area of analysis) using the Montana rates as the standard, and between 60 and 75 using the US rates as the standard. It is clear that deaths from asbestosis were significantly elevated. Of note, however, is the fact that 10 of the 11 deaths were among males suggesting strongly that occupational exposures were involved in these deaths. There is little evidence that environmental

exposures were involved in the deaths from asbestosis, which is known to be associated with high levels of exposure to asbestos.

In conclusion, there is little evidence that environmental exposure to asbestos contributed to the deaths from respiratory cancer, mesothelioma and asbestosis in the Libby area over the period 1978-1998.

2. A serious deficiency of the 2011 Draft is that it fails to provide context for the carcinogenicity of Libby amphibole. In the last decade, our understanding of the differential carcinogenic potencies of the different types of asbestos fibers has advanced considerably (Hodgson & Darnton, 2000; Berman & Crump, 2008). It is important that the Agency put the carcinogenicity of Libby amphibole in perspective by discussing where in the range of potencies of the various asbestos fibers, the potency of Libby amphibole lies. The paper by Hodgson & Darnton (2000) is not even referenced in this Agency draft and the paper by Berman & Crump (2008) is only mentioned in passing.

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APPENDIX B – 6

COMMENTS ON THE EPA DRAFT RISK ASSESSMENT FOR LIBBY
AMPHIBOLE

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March 27, 2012

As a member of the interested public and a consultant to W. R. Grace, I was given a limited amount of time to testify before the SAB in February, 2012. During that meeting, members of the SAB requested that the Agency provide more support for its risk assessments asking for substantive sensitivity analyses of both the IUR for the cancer endpoints and the RfC for the non-cancer endpoint. Members of the SAB also suggested that numerous additional papers be reviewed and requested access to some datasets. Members of the SAB have now posted updated comments, and the EPA has made a limited dataset available to the general public. My comments here are in response to the posted comments by the SAB, and are based, in part, on reviews of the additional papers that the SAB thought should be considered and on analyses of the limited dataset on pleural plaques made available to the public.

A. Reference Concentration (RfC) for non-cancer adverse effects using discrete pleural thickening (pleural plaques) as the relevant endpoint.

Two fundamental issues arise. Are pleural plaques simply a marker of asbestos exposure, or do they represent an adverse clinical condition? Second, if plaques do represent an adverse clinical condition, are the data and methods used by the Agency valid? I address the second question first.

The data used by the Agency for the derivation of an RfC are inappropriate.

This opinion is based on the following facts.

- The RfC is based on a small subcohort of the cohort of vermiculite workers analyzed by Rohs et al. (2008). The Rohs dataset reports 68 pleural plaques among 280 individuals. The Agency subcohort consists of 118 individuals with 12 cases of pleural plaques. The power to detect any confounding in this small dataset is greatly diminished. It is inappropriate to base a risk assessment on such a small dataset, particularly when the Agency is setting a precedent by proposing for the first time an RfC for non-cancer endpoints for asbestos exposure.
- My previous analysis of the full Rohs dataset indicates **strong confounding by age with the parameter estimate for exposure to Libby amphibole becoming greatly attenuated in joint analyses with age**. When both age and BMI are included in the analysis, the coefficient for Libby amphibole becomes borderline insignificant.
- By the Agency's own criteria when rejecting the Amandus study as a basis for the RfC, the Rohs dataset cannot be used for the estimation of an RfC. Selecting a small subcohort to get around the issue of confounding by age and BMI is not the appropriate way to address this issue.
- **Conclusion:** The Rohs dataset and subsets of it are not suitable for the derivation of an RfC.

The model used by the Agency for the derivation of an RfC is inappropriate.

Even if the data chosen by the Agency for developing an RfC were appropriate, the model used is not. This opinion is based on the following facts.

- Despite a choice of a large number of exposure-response models available in the standard benchmark dose software (BMDS) developed and distributed by the Agency, in this risk assessment, the Agency chose to use a model, the Michaelis-Menten model, which is not among

the models in the BMDS. The Michaelis-Menten model is widely used for enzyme kinetics and receptor binding and its properties make it unsuitable for a dose-response analysis for the estimation of an RfC. The model requires the estimation of a plateau, which is biologically unrealistic. Even in the dose-response modeling for cancer, a relatively rare condition even with high exposures, models with a plateau, implying that a certain fraction of the population is immune, are not used.

- The Agency forced the model through a background prevalence for pleural plaques of 1%, even though the model allows the estimation of a background. There is little support in the literature for any specific background prevalence of pleural plaques. Fixing the background at 1% probably increased the slope of the exposure-response relationship at low exposures. The Agency probably chose to fix the background prevalence because the small data set does not permit the estimation of the background, slope and plateau simultaneously. **As it is both estimated parameters were statistically insignificant (table 4 of the supplemental material provided by the Agency), thus suggesting that the data are consistent with no impact of exposure to Libby amphibole on pleural plaques in these data. Ironically, however, statistical insignificance of the parameters implies a wider confidence interval and consequently a lower estimate of the BMCL¹. The greater the uncertainty, the lower the BMCL.**
- Many of the models tried by the Agency fit the data (by the AIC criterion used by the Agency) almost as well as the Michaelis-Menten model, but exhibit rather different exposure-response relationships. The small dataset simply does not allow discrimination among models. Even as measured by the AIC, however, the Michaelis-Menten model is NOT the best fitting model as I discuss in the next bullet.
- Since the objective is to estimate a reference **concentration**, why does the Agency estimate an exposure-response relationship for **cumulative exposure**? An alternative approach would be to use concentration directly in the statistical analysis. Using the raw data provided by the Agency, I estimated the average concentration for each individual by dividing the cumulative exposure by duration of exposure and then fit a logistic regression model to the data with concentration as the measure of exposure. **This model (AIC = 73) fit the data equally well, or better than the Michaelis-Menten model (AIC = 74). The BMC and BMCL (using the BMDS software package distributed by the Agency) for this model were 0.06 and 0.04, respectively. Since the BMCL is obtained directly in terms of the concentration, it can be used as the point of departure (POD) for an RfC calculation without dividing by 60 (tantamount to adding a third uncertainty factor). With two uncertainty factors of 10 each, this procedure leads to an RfC of 0.0004, about 20 times larger than the RfC estimated by the Agency.**
- **Conclusion:** The data are too sparse to discriminate among models. A model based on concentration yields a better fit than the Agency preferred model and yields an RfC which is more than an order of magnitude lower than that estimated by the Agency. No matter which model is chosen, the sub-cohort used by the Agency should not be used for estimation of an RfC.

¹ BMCL is the lower 95% confidence limit on the benchmark concentration.

The evidence that pleural plaques represent an adverse clinical condition is tenuous at best

Over the years there has been considerable controversy regarding whether pleural plaques are simply a marker of asbestos exposure or whether they are associated with pulmonary deficiencies. Since asbestos exposure is associated with both pleural plaques and decreases in pulmonary function, any study that does not adjust adequately for asbestos exposure is likely to show an association between pleural plaques and decreases in pulmonary function. The SAB Panel identified for its and the Agency's consideration three recent papers on the association between pleural plaques and decreases in pulmonary function, two based on studies in the Libby population (Weill et al., 2011; Larson et al., 2012a) and one based on a study in France (Clin et al., 2011). These papers have attempted to adjust for exposure to asbestos, albeit with modest success. I review these studies here and conclude that any causal association between pleural plaques and decreases in pulmonary function is tenuous at best.

- Studies based on the population of Libby The Weill (2011) and Larson (2012a) studies were both based on the same data, which was collected by the ATSDR. Serious limitations of both studies are the facts that the readers of the X-rays were aware of the exposure status of the subject and no normal X-rays were randomly mixed in with the test X-rays, a practice that is common in studies of this type. Furthermore, precise exposure information was not available. Subjects were classified according to how many 'exposure pathways' they were exposed. Weill reports a small but statistically significant decrease in forced vital capacity (FVC) associated with pleural plaques among men but not among women. This analysis did not control for level of exposure, but Weill reports that he obtains similar results with Grace Workers excluded. A serious problem with this study is the inconsistency of the reported results. For example, Weill reports that his study cohort consisted of 4,524 individuals, but the numbers reported in various tables do not add to this total. In table 6, for example, in which the most important results are reported, there appears to be no consistency in the numbers of men and women in each of the smoking categories.
- Larson (2012a) reports results similar to those reported by Weill. However, Larson's study included a significant number of individuals exposed to non-Libby asbestos. He had no quantitative information on this exposure, which could have been substantial. Therefore, his control for level of exposure was even less precise than that of Weill who excluded subjects with other asbestos exposure. Moreover, his pleural plaque analysis includes individuals with parenchymal abnormalities, although he reports controlling for this in the statistical analysis. It would have been better to repeat the analyses with these individuals excluded. Larson notes also that over 70% of the participants in the study were either overweight or obese. With such a high prevalence of overweight individuals, a number of reported pleural plaques could actually have been pleural fat leading to misclassification of exposure. In a second study, Larson et al. (2012b) examined the association between exposure to Libby amphibole and decreases in pulmonary function among Libby miners and reported that although pleural plaques were significantly increased at cumulative exposures of 1 f/cc-y, restrictive lung disease (a hallmark of which is a decrease in FVC) was observed only at very high exposures (166 f/cc-y). The results of this Larson study would appear to be inconsistent with the study on pleural plaques and

pulmonary function. In summary, in view of the deficiencies in study design (readers not blinded, no normal X-rays mixed in), the very small effect estimates, the ability to adjust for level of exposure only crudely, and the very large exposures associated with loss of pulmonary function in the other Larson (2012b) study, I conclude that these studies provide at best weak evidence of a causal association between pleural plaques and decreases in pulmonary function.

- The Clin et al. (2011) French study This was a study based on high resolution CT (HRCT) scanning, not X-ray, and reported a small but statistically significant decrease in FVC associated with pleural plaques. However, exposures to asbestos could only be estimated and the group with pleural plaques included individuals with 'other abnormalities' not further defined.
- **Conclusion:** Taken together these studies provide only weak evidence of a causal association between pleural plaques and decreases in pulmonary function. Moreover, Weill et al. (2011) and Clin et al. (2011) consider the small reported decreases in pulmonary function to be clinically insignificant.

B. Inhalation Unit Risk (IUR) for Cancer (lung cancer and mesothelioma).

There are two fundamental questions regarding the derivation of the IUR by the Agency. First, is the IUR based on analysis of an appropriate dataset? Second, are the models and methods of analyses appropriate? The answer is no to both questions.

The dataset used by the Agency for estimation of the IUR for cancer is inappropriate.

There is an obvious dataset that should be used for the derivation of an IUR. This is the cohort of vermiculite miners at Libby analyzed by Larson et al. (2010). The Agency chose instead to analyze a greatly truncated sub-cohort of this cohort on the grounds that better exposure assessments were available in the sub-cohort. This is a poor choice for the following reasons.

- The full cohort has 111 deaths from lung cancer and 19 deaths from mesothelioma. The sub-cohort that the Agency analyzed has only 32 lung cancer deaths and 7 mesothelioma deaths. Issues of confounding and effect modification cannot be examined in this small sub-cohort. As Dr. Wayne Berman points out in his recently submitted comments to the SAB, there is much to be gained from analyses of the entire data. SAB Panel preliminary comments strongly advised the Agency to consider the entire data set and address exposure uncertainties using Monte Carlo techniques. I strongly endorse this advice.
- The sub-cohort selectively eliminates older individuals in the full cohort and thus the estimates of risk are based on younger individuals. As discussed below, there is evidence of strong effect modification of the lung cancer risk by age in this cohort, with relative risk (RR) reaching a peak and then dramatically declining. This phenomenon is discussed in some detail in my previous reports. Selectively eliminating older individuals in the cohort has the effect of biasing estimates of the lung cancer risk upwards.
- By drastically reducing the size of the dataset and selectively eliminating older individuals, the Agency has lost the statistical power to detect effect modification of lung cancer risk by age. Dr.

Peto has made the equivalent comment that the Agency has ignored the departure from proportionality of hazards in the data.

- The SAB Panel identified for its and the Agency's consideration the recent paper by Lenters et al. (2011), which, at first glance, might appear to support the Agency's contention that exposure measurement error always biases estimates of risk downward. However, the Lenters paper does not support this conclusion for the following reasons. First, the Lenters analysis uses cumulative exposure as the measure of exposure to asbestos. Cumulative exposure is generally a poor measure because both intensity of exposure and duration of exposure are important for both lung cancer and mesothelioma. Second, the Lenters paper ignores the strong effect modification of lung cancer RR by age, with the RR being substantially lower in older individuals. In fact, if the cohorts with better exposure measurement in the Lenters study are younger, then effect modification could explain the higher RRs in these cohorts. Finally, the theorem about non-differential covariate measurement errors leading to risk estimates biased towards the null is often misinterpreted. This statement, although widely repeated by epidemiologists, is incorrect. First, not only must the misclassification be non-differential, it must satisfy other conditions (e.g., Jurek et al., 2005) for the result to hold. Second, the statement applies to the expectation of the risk estimate, not to the value of the estimate from any single study. Thus, it is possible to have non-differential misclassification that satisfies all the required conditions but the result of a single study may actually overestimate the risk. As Jurek et al. (2005) state, "...exposure misclassification can spuriously increase the observed strength of an association even when the misclassification process is non-differential and the bias it produced is towards the null." Similar discussion is provided by Thomas (1995) and Weinberg et al. (1995).
- **Conclusion:** There is not a single good reason for the selection of the sub-cohort for estimation of the IUR. There are many good reasons for using the entire cohort.

The models used by the Agency for analyses of lung cancer and mesothelioma deaths are inappropriate.

- I know of no lung carcinogen for which cumulative exposure is a reliable determinant of risk. For cigarette smoking, exposure to asbestos, and exposure to radiation, lung cancer risk is determined by intensity of exposure, duration of exposure, and time since exposure stopped. Yet, the Agency has made no attempt to investigate and use models that would have allowed the explicit incorporation of these factors for the estimation of lung cancer risk in the Libby cohort. One approach, which I strongly recommend, is to use methods based on ideas of multistage carcinogenesis, such as the two-stage clonal expansion (TSCE) model, an approach endorsed by Dr. Kreibel². The risk of mesothelioma is well-known to depend on intensity of exposure, duration of exposure, and time since exposure stopped. The Agency recognized this fact in 1986 when it adopted the Peto-Nicholson model. Yet, in this risk assessment the Agency has dropped this model in favor of a model that makes no biological sense. Clearly, the decision

² I am mystified by Dr. Kreibel's recommendation that the Agency adopt the Richardson rather than the Moolgavkar approach since Richardson got his software code from my group. Furthermore, the code used by Richardson is dated and we now have more efficient ways of fitting the model with time-dependent exposures.

to jettison a large part of the data makes it impossible to fit the Peto-Nicholson model, which provides further justification for using the full cohort.

- The model used for analyses of lung cancer deaths completely ignores the strong effect-modification by age. Particularly because ultimately the IUR is based on a life-table analysis it is important to estimate and use age-specific RRs.
- **Conclusion:** For both lung cancer and mesothelioma, the Agency needs to use the entire Larson cohort, and investigate explicitly intensity and duration of exposure in determining risk. In addition, for lung cancer, the Agency should explore effect modification by age and use age-specific RRs for estimation of IUR.

RECOMMENDATIONS TO THE AGENCY

1. Abandon the attempt to derive an RfC for Libby amphibole. A suitable dataset does not appear to be currently available. If the Agency feels obligated to estimate an RfC, this estimate should be based on the full Rohs dataset and a realistic biological model should be used.
2. The IUR for cancer should be based on the entire Larson cohort, the roles of intensity of exposure and duration should be explored using models based on ideas of multistage carcinogenesis, and, for lung cancer, the strong effect modification by age should be recognized and incorporated in the estimation of IUR.
3. It is incumbent upon the Agency to discuss the carcinogenic potency of Libby amphibole in relation to the potencies of other asbestos fibers. The Agency argument that such a discussion could be highly controversial is not convincing. This is not like the 'amphibole hypothesis', which has been hotly debated. In fact, analyses of the Libby miners' data have provided us with solid estimates of the potencies of Libby amphibole for lung cancer and mesothelioma. The analyses by Hodgson & Darnton (2000) and Berman & Crump (2008a, b) provide us with a range of estimates for other asbestos fibers. It is clear that the potency of Libby amphibole for mesothelioma lies somewhere in the middle of the range and is approximately half the potency assumed by the Agency in its 1986 asbestos risk assessment. For lung cancer, the potency of Libby amphibole is rather low compared to other asbestos fibers, considerably lower than the potency assumed by the Agency for its 1986 risk assessment. As it is, the general perception is that Libby amphibole is much more toxic than other asbestos fibers. It is time for the Agency to dispel this myth, at least for cancer risks.

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APPENDIX B – 7

ADDITIONAL COMMENTS ON THE DRAFT RISK ASSESSMENT
FOR LIBBY AMPHIBOLE WITH EMPHASIS ON RE-ANALYSES OF
THE RESTRICTED ROHS COHORT FOR DERIVATION OF A
REFERENCE CONCENTRATION

SURESH H. MOOLGAVKAR, M.D., Ph.D.

April 23, 2012

These comments constitute an addendum to the comments I posted on the Science Advisory Board (SAB) website in March, 2012, and are based on extensive re-analyses of the sub-cohort used by the U.S. Environmental Protection Agency (the Agency) for the estimation of an RfC for Libby amphibole. The focus of these comments is a discussion of my re-analyses of this dataset. In addition, I respond in these comments to some of the recommendations made by the SAB to Administrator Jackson in a draft letter dated April 4, 2012.

I have done extensive re-analyses of the dataset used by the Agency for the estimation of an RfC for Libby amphibole. This dataset is a subset of the data analyzed by Rohs et al. (2008) and includes 118 workers with 12 cases of pleural plaque. These re-analyses show that the dataset is far too small for reliable estimation of an RfC. I believe also that the Agency used an inappropriate model, the Michaelis-Menten model, for estimation of the RfC.

The Michaelis-Menten Model

This model has been widely used to study receptor binding and enzyme kinetics. In its original form, used for the analyses of enzyme kinetics, the model has only two parameters. The model has been extended by the Agency to include a third parameter. In the Agency formulation, the three parameters that can be estimated from the data are a background, a plateau, and a parameter, which I will call the 'slope'.

- The background parameter is an estimate of the fraction of the general (unexposed) population that has pleural plaques.
- The plateau estimates the fraction of 'susceptible' individuals in the population. If the plateau is below 100%, it implies that a certain fraction of the population will never develop pleural plaques no matter how large the exposure to asbestos, a dubious biological construct.
- Finally, the 'slope'¹ determines how steep the exposure-response relationship is, i.e., how quickly the exposure-response curve rises from the background to the plateau.
- **It is clear that if the plateau is equal to the background, then there is no evidence of an exposure-response relationship in the data.**

Estimating the RfC using the Michaelis-Menten and other models

I have re-analyzed the dataset provided by the Agency using both Michaelis-Menten models and logistic regression models, which are more traditional in benchmark dose analyses. For the Michaelis-Menten analyses, I used the approach described by the Agency in its draft risk

¹ The third parameter influences the speed with which the exposure-response curve approaches the plateau, but is not actually the slope in the strict mathematical sense. The slope of the exposure-response curve is not a constant and is a complicated function of all three parameters.

assessment for Libby amphibole, including the use of profile-likelihood-based lower confidence intervals for estimation of the BMCL². I used the BMD software (BMDS) available from the Agency website for the logistic regression analyses. This software also uses profile likelihoods to estimate the BMCL. I confirmed that my model results were identical to those reported by the Agency for the same models. Here are my observations:

1. Although it is possible to estimate all three parameters even in this sparse dataset, the Agency fixed the background rate of pleural plaques at 1% with little justification, and estimated only the plateau and the slope. When all three parameters are estimated from the data, the estimate of background rates varies between 3 and 4.5% depending upon the lag structure chosen for the exposure³.
2. Although I did not test directly the hypothesis of equality of background and plateau in the three-parameter models, the large standard errors I found for each of these parameters suggest that equality of these two parameters cannot be rejected indicating that these data provide little evidence of an exposure-response relationship between cumulative exposure and prevalence of pleural plaques.
3. I tried a number of two-parameter Michaelis-Menten models (background rates fixed) with different lags for exposure and with various assumptions regarding the background rates of pleural plaques. With a ten-year lag and with the assumption that the background rate is 1% (this is the Agency's chosen model), I estimated a BMCL of 0.1178, identical to the BMCL reported by the Agency. As expected, however, the estimate of BMCL depends both on the chosen lag structure and the assumed background rate. These results are shown graphically in figure 1 below.
4. In every one of the Michaelis-Menten models I used to analyze the data, the estimated standard error for the plateau is so large that the hypothesis that the plateau is equal to the background cannot be ruled out by the standard Wald test⁴. **If the Agency insists on using the Michaelis-Menten model, it is incumbent upon the Agency to show that the plateau is statistically significantly different from the background. If the hypothesis of equality of background and plateau cannot be rejected, then the Agency should recognize that the model fails to find an increase in response (pleural plaques) with increasing exposure.**
5. In addition to the Michaelis-Menten model, I have analyzed the data using logistic regression models with both cumulative exposure and average concentration⁵ (cumulative exposure divided by duration of employment) as the measure of exposure.

² This is the lower 95% confidence limit on the benchmark dose or benchmark concentration.

³ By the AIC criterion, the fit of the Michaelis-Menten model is worse when all three parameters are estimated in the data used by the Agency.

⁴ The Agency should develop a likelihood-based test for this hypothesis.

⁵ I use the terms concentration and intensity interchangeably in this document.

The concentration-response models, in particular, fit the data as well as, or better than, the Michaelis-Menten models as judged by the AIC. However, these two classes of model (Michaelis-Menten and logistic) predict very different shapes for the exposure-response curves. This finding suggests very strongly that this sparse dataset does not allow discrimination among models and is, therefore, unsuitable for the estimation of an RfC. Figure 2 shows the exposure-response relationships for some Michaelis-Menten and logistic regression models. As judged by the AICs shown in that figure, the logistic regression concentration-response models describe the data best. SAB member Dr. Sheppard suggests that a supra-linear exposure-response relationship is biologically plausible and has been observed in other contexts, such as the impact of particulate matter on cardiovascular mortality. Be that as it may, the data at issue here are too sparse to distinguish between supra-linear and sub-linear models.

6. An examination of the raw data by deciles of exposure (Table 1) also indicates that there is little evidence of a supra-linear relationship between cumulative exposure and pleural plaques. This table makes it very clear that exposure-response relationships are driven largely by the number of pleural plaques in the highest decile of cumulative exposure.
7. Because the Agency uses cumulative exposure in its analyses of the data, it divides the estimated BMCL by 60 to derive a concentration adjusted for a 70-year lifetime. The Agency then uses two safety factors of 10 each to arrive at an estimate of the RfC. In my opinion, this procedure is tantamount to using three safety factors. If the BMCL is derived for the concentration directly, then two safety factors of 10 each can be applied directly to this BMCL. For example, with lag zero, the logistic concentration-response model (see figure 1) has an AIC of 73.0 (and therefore describes the data better than the Agency preferred Michaelis-Menten model with an AIC of 74.0) with BMCL = 0.04. Using this BMCL as the point of departure and using two safety factors of 10 each yields an RfC = 0.0004, which is 20 times the RfC estimated by the Agency.

Decile	Exposure (f/cc-yr)	Cases	Subjects	Prevalence
1	0.02	1	12	0.08
2	0.04	0	12	0.00
3	0.07	1	12	0.08
4	0.09	0	12	0.00
5	0.11	0	11	0.00
6	0.14	1	12	0.08
7	0.22	2	12	0.17
8	0.32	2	12	0.17
9	0.50	1	12	0.08
10	2.29	4	11	0.36

Table 1: Rohs restricted data set divided into deciles with even numbers of exposed subjects. The second column labeled "Exposure" is the average cumulative exposure lagged 10 years in each decile. It is absolutely clear that there is no evidence of an increase in the prevalence of pleural plaques with increasing cumulative exposure except in the highest decile.

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Comments on SAB recommendations regarding the RfC

With respect to the RfC, “[t]he SAB recommends that EPA include any X-ray abnormalities (localized pleural thickening, diffuse pleural thickening, or asbestosis) as the health outcome.” There are no reported cases of asbestosis in the database used by the Agency for derivation of the RfC. The definition of asbestosis requires demonstration of substantial exposure to asbestos. The SAB appears to be suggesting that all cases of interstitial fibrosis in the data be called “asbestosis” and included in the analyses. In my view this would be totally inappropriate. Pleural plaques are at least considered to be markers of asbestos exposure. In contrast, it is well known that there are many causes of interstitial fibrosis other than exposure to asbestos, a significant fraction of cases of interstitial fibrosis is idiopathic, and age is a strong risk factor for the development of this condition. Control of confounding would be particularly problematic if interstitial fibrosis were included in the analyses. Accordingly, this recommendation is inappropriate and should be withdrawn.

I take issue also with the SAB conclusion that use of the full cohort of 434 workers for confirmatory analyses is reasonable. Rohs et al. (2008) gave excellent reasons for including only a subset of 280 individuals from the original cohort of 434 workers for their analyses. I believe that, if pleural plaques are to be used for the derivation of an RfC, then the sub-cohort analyzed by Rohs et al. (2008) is the most appropriate dataset to use.

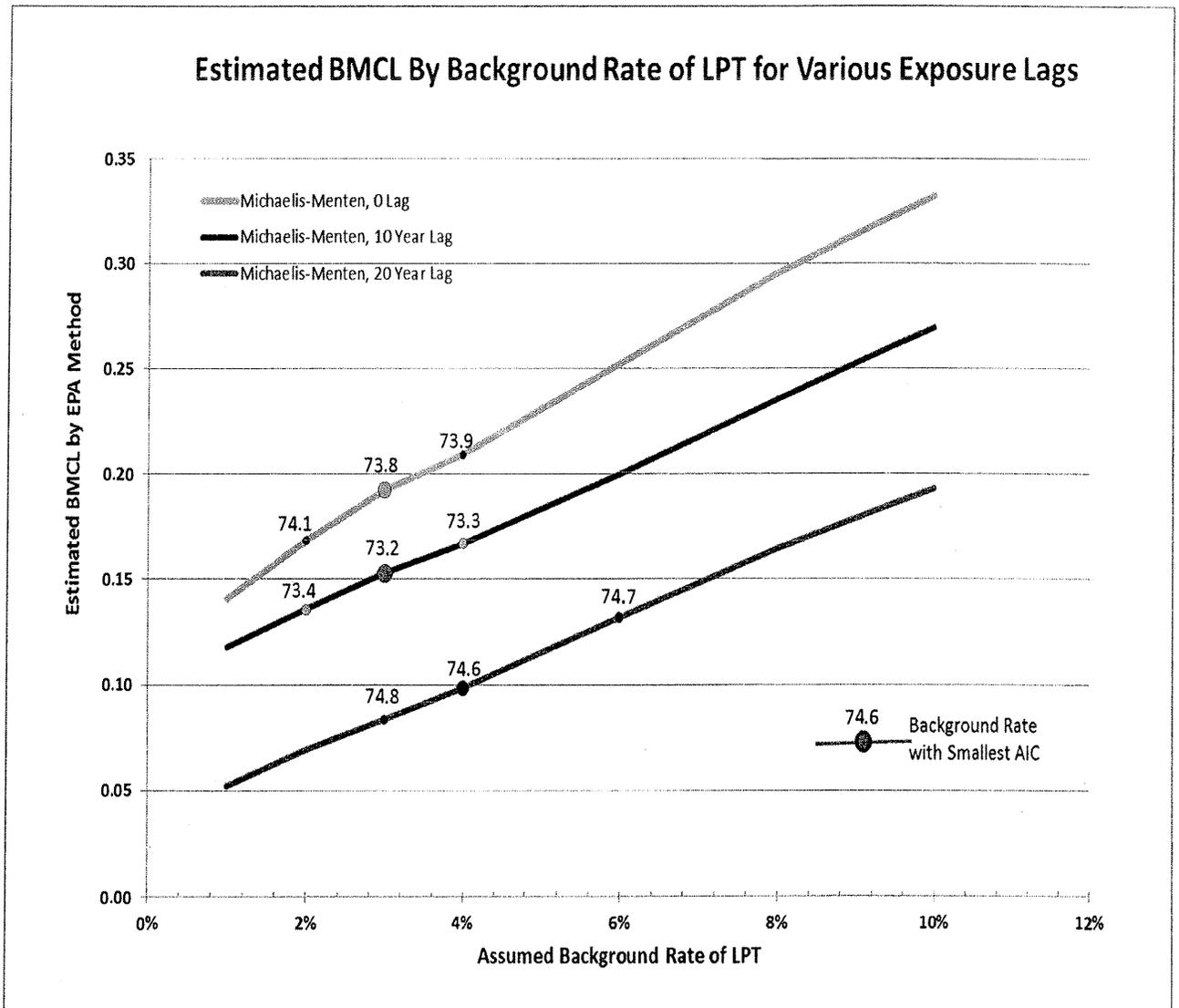


FIGURE 1: Estimated BMCLs using the Michaelis-Menten models. Estimated BMCL depends on both the lag structure for cumulative exposure and on the assumption regarding background rates of pleural plaques. For each lag (0, 10 and 20 years), the AICs are shown for various assumed background rates, with the lowest AIC highlighted. Note that all models describe the data about equally well.

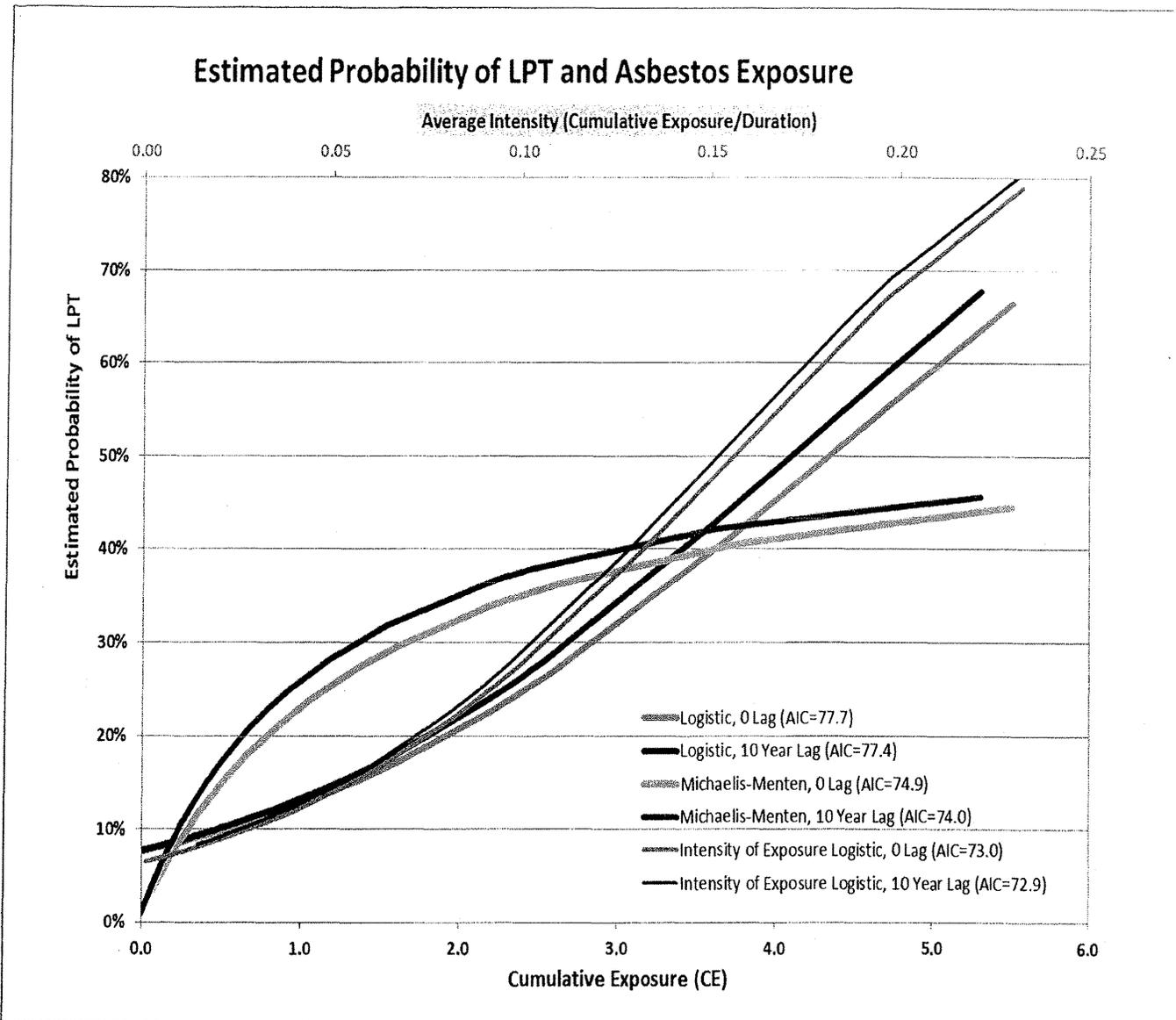


FIGURE 2: Dose-response relationships using Michaelis-Menten and logistic regression models. The two (supra-linear) curves to the left are outputs of Michaelis-Menten models with zero (AIC = 74.9) and 10 year (AIC = 74.0) lags for exposure. The four sub-linear curves to the right are outputs of logistic regression models, two with cumulative exposure as the measure of exposure, and two with average concentration (intensity) as the measure of exposure. Note that by the AIC, the sub-linear concentration-response models describe the as well as, or better than, the EPA chosen model (Michaelis-Menten with 10 year lag). Note also that when all three parameters for the Michaelis-Menten model are estimated from the data, the fit as judged by the AIC becomes worse. Therefore, the logistic concentration-response models are clearly superior.

Recommendations to the Agency

1. Much better justification is required before pleural plaques can be used as an end-point for derivation of an RfC. The inclusion of all X-ray abnormalities as an end-point makes little biological sense because the potential confounders for pleural plaques are different from those for interstitial fibrosis.
2. The dataset used by the Agency for the estimation of an RfC is too small to distinguish among models with very different exposure-response relationships. If the Agency insists on using pleural plaques for the derivation of an RfC, then a more appropriate and larger dataset should be used. The data used by Rohs et al. (2008) is a possible candidate.
3. The use of the Michaelis-Menten model needs to be better justified. What is the interpretation of the plateau? Why should a fraction of the population be immune to the effects of exposure?
4. The Michaelis-Menten model is a three-parameter model. In the absence of reliable information on the background rate of pleural plaques, all three parameters should be estimated from the data. The Agency needs to provide the appropriate analyses to show that in their preferred Michaelis-Menten model, the plateau is statistically significantly different from the background.
5. I endorse the recommendation made by the SAB Panel that the Agency analyses used for the derivation of the Inhalation Unit Risk (IUR) for cancer be extended by using models based on ideas of multistage carcinogenesis. I recommend that these extended analyses be done for both lung cancer and mesothelioma. These analyses will allow the exploration of the temporal aspects of risk following exposure to Libby amphibole. In addition to the analyses based on multistage carcinogenesis, I recommend also that the temporal aspects of risk in lung cancer be explored using conventional statistical approaches, such as the Cox model with flexible spline smoothers to investigate effect modification by age.
6. I do not agree with the SAB Panel that the Agency has chosen the appropriate dataset for the analyses. In fact, the dataset was expressly chosen to eliminate effect modification by age. Therefore, I believe that the entire Libby cohort with follow-up through 2006 should be used for estimation of the IUR. Uncertainties in exposure estimates should be addressed via monte-carlo simulations.
7. The SAB Panel appears to recommend that the algorithms used by Richardson (2008) and Zeka et al. (2011) be used to fit the data using the two-stage clonal expansion (TSCE) model. I would like to inform the Agency that better algorithms and software than those used in these publications have been developed. I would recommend using

APPENDIX B – 8

**COMMENTS ON PANEL RECOMMENDATIONS TO EPA REGARDING THE
DRAFT RISK ASSESSMENT OF LIBBY AMPHIBOLE ASBESTOS – JULY
2012**

Suresh H. Moolgavkar, M.D., Ph.D.

Exponent, Inc.

I have reviewed carefully the most recent version of the draft SAB panel report on EPA's draft Libby Amphibole Asbestos IRIS assessment. Although appreciative of the panel's ongoing efforts, I am once again disappointed that the panel has not seen fit to respond to many of the fundamental scientific issues and concerns raised in earlier public comments. The latest revised report of the panel continues to support EPA positions of dubious scientific validity, and makes assertions that are simply incorrect. The panel should discuss and rectify these errors before sending its report to the full SAB for further review.

Issues arising in the derivation of the RfC

- The panel continues to support the use of pleural plaques or localized pleural thickening ("LPT") as the appropriate non-cancer endpoint for the derivation of an RfC, asserting that this condition is predictive of "risk for other asbestos-related diseases, including asbestosis, mesothelioma and lung cancer." The panel needs to clarify what exactly it means by this assertion. Adenomatous polyps of the colon are predictive of the risk of colon cancer because they lie on the pathway to disease, i.e., they represent an intermediate stage on the pathway to colon cancer. Urinary cotinine levels are predictive of lung cancer because they reflect smoking habits, but elevated cotinine levels are not on the pathway to lung cancer. Similarly, dicentrics in lymphocyte chromosomes from radiation exposures are clearly specific indicators of radiation exposure and thus measures of increased cancer risk but are in themselves not biological cancer risk factors since cells with unstable chromosome aberrations such as dicentrics will not divide. Is the panel asserting that pleural plaques are on the biological pathway to more serious pulmonary disease? Or is the panel saying, as some panel members have appeared to state during the panel's deliberations, that pleural plaques are simply markers of asbestos exposure and therefore correlated with more serious pulmonary disease? If the former, what is the evidence that, *conditional on asbestos exposure*, pleural plaques are associated with serious pulmonary disease? There is very little evidence of which I am aware to support the conclusion that pleural plaques lie on the biological pathway to serious pulmonary disease and the revised draft report does not appear to cite to any. If the panel has concluded that LPT is on the biological pathway to pulmonary disease, it is incumbent upon the panel to cite to the scientific literature supporting that conclusion. If, on the other hand, pleural plaques are simply markers for asbestos exposure, then their use for derivation of the RfC is highly questionable.
- The panel continues to assert that pleural plaques are associated with decreases in pulmonary function without a thorough evaluation of the literature. As noted in my previous comments, none of the papers cited in support of this proposition provides convincing evidence that pleural plaques are associated with decreases in pulmonary function *conditional on asbestos exposure*.
- The panel continues to make the ill-advised recommendation that all X-ray abnormalities be included for the derivation of the RfC. Employing endpoints that may have different sets of confounders is scientifically unsound. There is general agreement that small opacities are

associated with cigarette smoking. Suggesting that asbestosis be included is even more unsound because asbestosis is not a radiographic diagnosis. The X-ray may suggest the existence of pneumoconiosis, which can be caused by many exposures in addition to asbestos. Suggesting that these disparate X-ray abnormalities be combined into a single endpoint for analyses is akin to suggesting that lung cancer and mesothelioma be analyzed together as a single cancer endpoint.

- Despite the panel's clear concern for the paucity of data upon which EPA has based its proposed RfC, the draft report continues to support the use of a small subset of the original Marysville cohort for derivation of the RfC. The panel has completely ignored the analyses I presented in my previous comments that this data set has no power to discriminate among models. Furthermore, the panel recommends that the entire Marysville dataset be used for sensitivity analyses despite considerable missing information. Instead, the subset used in Rohs et al. (2008) should be utilized for this purpose. As Rohs et al. (2008) point out, of the original members of the cohort, only 280 had both readable chest X-rays and complete interviews. Since evaluation of possible confounders should be an important objective of sensitivity analyses, it is more scientifically sound to use the Rohs sub-cohort for the sensitivity analyses than the entire original cohort.
- On page 27, the panel recommends "a thoughtful approach to model selection..." I endorse this recommendation, but am at a loss to understand exactly what the panel is recommending. How does the panel expect EPA to develop a model based on "...considerations of biological/epidemiologic plausibility.." when it is relying on a miniscule dataset? How does the panel expect EPA to examine "local smoother estimates from the data" in this small dataset? To enhance the clarity of its recommendations, the panel should address these questions. Ultimately, the panel recommends use of the dichotomous Hill model. This model is no more "biologically plausible" than the Michaelis-Menten model. These models were first developed for quantitative descriptions of enzyme kinetics and receptor binding and have no foundation in epidemiology. The feature that distinguishes them from the more conventional logistic regression models is that the exposure-response relationship with these models is supra-linear in the low-dose region, rather than sub-linear as with logistic regression. Use of the dichotomous Hill model is no more scientifically justified in this context than use of the Michaelis-Menten model. In fact, the dichotomous Hill model requires the estimation of 4 parameters, one more than the Michaelis-Menten model. In order to fit this model to the small data set, the panel is recommending that EPA fix the values of the background probability of pleural plaques at 1% (as it does for the Michaelis-Menten model) and, in addition, fix the plateau at 85%. Thus, in a giant step backwards, the panel is recommending that the Agency fix two parameters at highly uncertain values.

Issues arising in the derivation of the IUR

- The panel continues to support use of the sub-cohort of workers employed after 1959 as the primary dataset for the derivation of the IUR, but fails to note the limitations of this dataset. While it is true that exposure information was missing on many of the workers hired before

1959, exclusion of these workers excludes many of the older individuals in the cohort when lung cancer, in particular, is most common. As I have pointed out in my previous comments, there is strong evidence of effect-modification by age in the Libby lung cancer data. This finding is consistent with that reported by Richardson in the North Carolina Textile Workers cohort. By eliminating many of the older individuals, the post-1959 dataset does not allow the investigation of effect-modification by age at Libby. Since the estimated IUR is based on a life-table analysis, it is particularly important that effect-modification by age be investigated and age-specific relative risks be used if at all possible. Although various members of the panel appear to have concurred that additional pre-1959 data can and should be used, the revised draft report makes no clear recommendation to that effect. For the above-stated reasons, it should. For mesothelioma, use of the post-1959 dataset leads to a drastic reduction in the number of mesotheliomas used in the analyses. The small number (7) of mesotheliomas in the post-1959 data precludes a proper analysis. In a giant step backwards, the Agency analyzes these data using Poisson regression with cumulative exposure as the measure of exposure. This model for exposure-response flies in the face of all we know about the epidemiology of mesothelioma. The Peto-Nicholson model shows that mesothelioma risk depends independently on intensity and duration of exposure with the incidence being a linear function of concentration and a power function of duration of exposure. This model has been shown to be a good description of mesothelioma incidence in many occupational cohorts (Berman and Crump, 2008). The current asbestos IUR in IRIS recognizes that mesothelioma risk is NOT a function of cumulative exposure. Not to do so in this risk assessment would be a travesty.

- The panel recommendation for investigating the temporal aspects of disease risk is one that I heartily endorse. I would recommend that the panel request EPA go further and explore the temporal aspects of both exposure and risk. The best approach to doing so is to use exposure-response models based on ideas of multistage carcinogenesis. The panel recommends using the TSC model. I concur. It is important, however, that the exact stochastic solution to the model be used, not deterministic approximations. The panel should make that clear in its report.
- In several locations in its revised draft, the panel refers to linearity of exposure-response relationships for amphibole-associated carcinogenesis, suggesting that there is limited evidence to support said linearity. Such statements are, at best, totally misleading and, at worst, completely wrong. The panel needs to be much more explicit as to what it means. What is the 'response' under consideration? What is the measure of exposure? There are currently two widely recognized exposure-response models for mesothelioma, the Peto-Nicholson model (for incidence) and the Hodgson-Darnton model (for life-time risk). Neither is linear with cumulative exposure as a measure of exposure. As noted above, the Peto-Nicholson model cannot even be expressed in terms of cumulative exposure. The Hodgson-Darnton model is couched in terms of cumulative exposure, but is not linear. For lung cancer, the Cox model is log-linear, not linear. Often a linear ERR (excess relative risk) model, in which the ERR is expressed as a linear function of cumulative exposure, is used to analyze the data. However it provides a poorer description of the data than models like the TSC model, in which the entire history of exposure is used rather than summary measures, such as cumulative exposure. The panel should either remove or revise loose statements regarding linearity from its report.

Recommendations

- The panel should recommend that EPA abandon for now the attempt to derive an RfC for Libby amphibole. In the absence of a suitable dataset, derivation of an RfC is unsupportable as a matter of sound science. If the panel continues to endorse the use of pleural plaques as the appropriate endpoint, it should provide stronger support for its assertion that pleural plaques are predictive of more serious pulmonary disease and decrements in pulmonary function.
- The IUR for cancer should be based on the entire Larson dataset or, at the very least, detailed sensitivity analyses based on the full cohort should be undertaken. I endorse the use of the TSCE model for lung cancer analyses providing the exact stochastic solution is used and temporal aspects of exposure and risk, including effect-modification by age, are carefully investigated. For mesothelioma, the Peto-Nicholson model, or some variant of it should be used, at least in the sensitivity analyses. These are fundamental substantive issues. The panel should not get hung up on issues of little or no importance, such as possible correlations between lung cancer and mesothelioma in the data. There is no evidence that, conditional on exposure, there is any correlation between these two outcomes. The panel should revise ill-advised, general statements in the draft report regarding linearity of risk associated with amphibole asbestos, as outlined above.
- As I recommended in my earlier comments, the risk associated with exposure to Libby amphibole should be discussed in the context of risks associated with other amphiboles. There is sufficient information to do so for the carcinogenic potency. This task is relatively straightforward given the publications of Hodgson and Darnton (2000) and Berman and Crump (2008a,b), and can be done without getting into controversial issues. Doing so would enhance the public's understanding of the relative risks of various amphiboles.
- To enhance the transparency of its conclusions and further assist EPA, the panel should ensure that the cover letter to the EPA Administrator is revised to reflect all the central recommendations that the panel's report ultimately makes.

ONE FURTHER COMMENT FOLLOWING THE CONFERENCE CALL ON JULY 25, 2012

SURESH H. MOOLGAVKAR

I would like to point out to the Panel that it is logically inconsistent to say that the Michaelis-Menten and dichotomous Hill models are simply mathematical descriptions of the pleural plaque data without any biological and epidemiological interpretation and then to use the probabilities for background and plateau from epidemiological data. You cannot have it both ways.

APPENDIX B – 9

Statement for Public Teleconference for the SAB review of "Draft Toxicological Review of Libby Amphibole Asbestos" (EPA/635/r/002a)

David G. Hoel, Ph.D.
Exponent, Inc.

May 1, 2012

Prior Comments

1. Additional Comments from Elizabeth Anderson and David Hoel, Exponent, Inc., (04/09/2012)
 - Selection of critical endpoint
 - Derivation of draft RFC
 - Practical considerations

Exposure Response Models for Pleural Plaque Prevalence: Michaelis-Menten:

- Michaelis-Menten models the rate of an enzyme-catalyzed reaction of a single substrate, which is a function of the substrate concentration.
- This is a saturable process and thus is unlikely to have anything to do with the prevalence of pleural plaques resulting from asbestos exposures.
- The model has been changed to add a background prevalence term. Since without any substrate the model then will still have a reaction. Since this makes little sense the modified Michaelis-Menten model should be considered to simply be a non-linear function that is used in a curve fitting exercise.
- The background parameter is set at 1% instead of being estimated from the data. This artificially reduces the AIC value. It would be increased by 2 if the background value was indeed estimated to be 1 from the data. This then gives the modified model an unfair advantage over the other competing models from an AIC standpoint.

Exposure Response Models for Pleural Plaque Prevalence: Hill Model:

- Hill Model models the fraction of occupied sites on a macromolecule by a ligand as a function of the ligand concentration. It estimates the degree of cooperation in the reaction either positive or negative by occupied sites.
- It should be noted that the logit of the fraction of occupied sites is linear in the concentration of the ligand and the log of the dissociation constant (which equals the ligand concentration at ½ occupancy raised to the nth power where n is the Hill parameter). Therefore a simple logistic regression is equivalent to using the Hill model.
- As with the Michaelis-Menten model the Hill model is converted in the analysis into something else by adding a saturation parameter as well as a non-estimated background parameter. The same argument applies to using AIC for model comparisons with other functions which do not include a non-data estimated parameter.

Exposure Response for Pleural Plaques Prevalence:

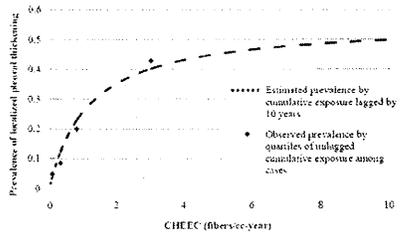


Figure 1. EPA's dose-response model fit for pleural thickening versus raw data in quartiles of cases (Figure E-1 in EPA Draft Toxicological Review)

Exposure Response for Pleural Plaques Prevalence:

- The data used for the curve fitting consists of only 4 data points with some of the models having 3 parameters needing to be estimated. This does seem to approach over-parameterization.
- In determining the 4 data points the exposure intervals are defined by the outcome variable i.e. 3 pleural plaques per exposure interval. The independent variable being the average exposure in the interval is thus also a dependent variable which makes for an interesting error structure in using typical regression methods. This should be discussed.

Exposure Response for Pleural Plaques Prevalence:

- The previously given Figure 1 illustrates the limited nature of the data using intervals based on the number of subjects which is usual instead of defining the intervals by outcome. This also illustrates the very limited nature of model fitting with only 12 outcomes. Also known modifying factors such as BMI and age will not be able to be included because of the limited data.

Table 1. Rohs restricted data set divided into quartiles with even numbers of subjects

Quartile	Exposure (f/cc-yr)	Cases	Subjects	Prevalence
1	0.033	2	29	0.069
2	0.092	0	30	0.000
3	0.20	3	29	0.103
4	1.1	7	30	0.233

Exposure Response for Pleural Plaques Prevalence:

- The background rate that is assumed to be equal to 1% is an interesting modeling assumption. Pleural plaque prevalence appears to increase with age and has been estimated in the U.S. using NHANES II by Rogan et al. (2000) (see EPA section 5.3.2.2.). The reported prevalence for males 45-74 was 7.8% which is quite high for the U.S. considering the 1% assumption. When the preferred modified Michaelis-Menten model was run allowing for background prevalence estimation (estimated at 3.12%) the resulting AIC value was not reported.

Exposure Response for Pleural Plaque Prevalence:

- Using the full Rohs data set restricted to employment beginning at least 20 years prior to screening there are 293 workers. The screening reported 73 workers with pleural plaques and 11 with diffuse pleural thickening.

- None of the cases of pleural thickening had pleural plaques indicating the concept that the plaques are not in the disease pathway of pleural thickening.

- Recommendation:

Apply simple and well understood dose-response models such as logistic regression instead of using biochemical models that are scientifically misleading by being unrelated to the prevalence of pleural plaque formation from asbestos exposures and having been modified in such a way that they are no longer biochemical models.

APPENDIX B – 10

Comments from Dr. David Hoel, 7/23/2012

The SAB has not in my opinion given an adequate review of the proposed RfC methods given in the EPA document. Dr. Suresh Moolgavkar has clearly expressed the failings of the review on a number of important issues and for which I totally concur with his conclusions. To reiterate several points that I had offered previously the following should be considered by the SAB.

- The most scientific questionable position taken by the SAB is that pleural plaques (localized pleural thickening) are “predictive of risk for other asbestos-related diseases, including asbestosis, mesothelioma, and lung cancer.” Arguably, plaques are biomarkers of asbestos exposure but is there any evidence that they are biologically involved with lung cancer? Other well known markers of exposure such as the presence of dicentric chromosomes in lymphocytes from radiation exposures are clearly specific indicators of radiation exposure and thus measures of increased cancer risk but are in themselves not biological cancer risk factors since cells with unstable chromosome aberrations such as dicentric chromosomes will not divide.
- The reference to biochemical models such as Michaelis-Menten and the Hill model is most inappropriate in that it gives a false sense of scientific credibility to a simple curve fitting activity. The formation of pleural plaques has nothing to do with these two biochemical reaction models and as such the impression that they do should not be given. A less deceptive approach would be to use simple polynomial regression or logistic regression which is the same statistically as the Hill model.
- The EPA model assumed a plateau of pleural plaque formation of 56% in a population while data has shown 85% among some worker groups. Using a value less than 100% requires some biological explanation since it is not clear that there is a percentage of individuals who will never have a pleural plaque no matter what are their exposure rate and duration of exposure. In other words they are somehow genetically or otherwise immune. The SAB should justify biologically why they recommend that a value less than 100% be used by EPA and that the value is to be obtained from some study found in the open literature.
- The SAB discusses that cigarette smoking is not an issue with respect to pleural plaques. No mention is however given to BMI and its association with false positive radiograph findings. Further BMI is also associated with pulmonary function deficits which in turn relates to the SAB's conclusion that pleural plaques cause pulmonary function effects.
- Using a single small data set to derive an RfC or RfD is generally inappropriate. Estimated values should be obtained from many other data sets and compared.

APPENDIX B – 11

**COMMENTS TO THE SAB ON THE PANEL RECOMMENDATIONS ON THE
EPA DRAFT RISK ASSESSMENT FOR LIBBY AMPHIBOLE ASBESTOS**

David Hoel

Suresh Moolgavkar

September 18, 2012

We have been following the EPA risk assessment process for Libby amphibole asbestos (LAA) and have made detailed comments to the special SAB panel set up to review the first EPA draft of the risk assessment. We have a number of concerns that were laid out in our previous comments to the panel and to the Agency, and we refer the SAB to those comments. One of us (SM) reviewed the draft in detail when it first appeared in 2011 and provided detailed written and oral comments to the Agency. In the comments below, we would like to raise two fundamental issues with the risk assessment as it stands, one procedural, and the other scientific. The procedural issue relates to the extremely limited manner in which public participation in the risk assessment process has been conducted to date. The scientific issue relates to an analysis of relevant data that EPA failed to provide to the public. The EPA was unwilling to release for analyses the full dataset with all covariates on which its risk assessment for non-cancer endpoints was based. The data were originally collected by the University of Cincinnati (Rohs et al., 2008). Under a FOIA request to the University of Cincinnati, we recently acquired and analyzed the data that forms the basis of the Agency's non-cancer risk assessment. We summarize the results here.

Procedural Issue

1. There was little opportunity for meaningful scientific dialogue with the panel during public meetings. We can understand that when a substantial number of individuals signs up to make comments, it is necessary to enforce a strict time limit on individual comments. However, this was not the situation at these panel meetings. At the discretion of the Chair and the Agency, it should have been possible for members of the public to engage in a meaningful scientific dialogue with the panel. We were denied that opportunity.
2. We understand that it is necessary to have multiple disciplines represented on the panel. However, the most controversial issues usually revolve around the interpretation of the analyses of dose-response data, particularly when these are epidemiologic data. This was clearly the case with this risk assessment for both the cancer and non-cancer endpoints. There were only two panel members who appeared to be comfortable with the more arcane statistical issues, and they were sharply divided in their scientific opinions. Clearly, the panelist who had serious problems with the Agency analyses chose not to submit a minority report. However, the panel report that the full committee is reviewing today purports to present a consensus that was never evident during the public discussions.

Scientific Issue

In a precedent-setting move, the Agency is proposing a reference concentration (RfC) for LAA based on a non-cancer endpoint. The proposed RfC for LAA, which will likely be applied to all forms of asbestos, is 0.00002 fibers/cc, which is below background levels of asbestos in many parts of the country. The Agency uses pleural plaques as the endpoint for derivation of the RfC, contending that pleural plaques are not just markers of asbestos exposure, but are adverse health effects associated with decrements in pulmonary function and other more serious conditions. We believe that this position has little scientific support as we have pointed out to the panel in our previous comments. We do not wish to re-argue this

issue here. We simply point out that the panel recommendations to the Agency on this matter contain serious factual inaccuracies that should be corrected. For example, for pulmonary function, the panel report refers to the American Thoracic Society 2004 report and recommends the addition of 3 additional references (Lilis 1991, Paris 2009, Clin 2011). Paris 2009 does not even discuss pulmonary function and Lilis 1991 is the ATS 2004 reference (112) in the following quote concerning plaques and FVC: "This has not been a consistent finding (110, 111) and longitudinal studies have not shown a more rapid decrement in pulmonary function in subjects with pleural plaques (112). Decrements, when they occur, are probably related to early subclinical fibrosis." The SAB panel specifically lists references used by the ATS 2004 report some of which are incorrect including some that were clearly published several years after the ATS report.

The derivation of this RfC is based on the prevalence of pleural plaques in a small sub-cohort of the full Rohs cohort. Whereas the full Rohs cohort consists of 280 subjects with 68 cases of pleural plaque, the sub-cohort on which EPA bases its RfC consists of 118 individuals with 12 pleural plaques. The table below shows the distribution of cases of pleural plaque in this sub-cohort by deciles of cumulative exposure. It is clear that there is little information in this sub-cohort for a proper dose-response analysis.

Decile	Exposure (f/cc-yr)	Cases	Subjects	Prevalence
1	0.02	1	12	0.08
2	0.04	0	12	0.00
3	0.07	1	12	0.08
4	0.09	0	12	0.00
5	0.11	0	11	0.00
6	0.14	1	12	0.08
7	0.22	2	12	0.17
8	0.32	2	12	0.17
9	0.50	1	12	0.08
10	2.29	4	11	0.36

Table 1: The sub-cohort used by the EPA for derivation of the RfC by deciles of exposure. The second column labeled “Exposure” is the average cumulative exposure in each decile. It is clear that any dose-response relationship is driven by the cases (number of individuals with plaque) in the highest decile.

We have analyzed both the sub-cohort used by the Agency and the full Rohs cohort. We present a brief summary of our findings here. These indicate clearly that the results in the sub-cohort are highly inconsistent with the results in the full cohort. These results indicate also that these data cannot be used for estimation of an RfC using the simplistic approach the Agency has adopted.

In both the full Rohs cohort and the sub-cohort, it is possible to perform dose-response analyses with three distinct measures of ‘dose’, cumulative exposure (ce), concentration, and duration of exposure.

1. The sub-cohort is too small to distinguish among models, with many models yielding virtually identical fits as judged by the Akaike Information Criterion (AIC). Nonetheless, the logistic regression model with concentration as the measure of ‘dose’ describes the data best as judged by the AIC, i.e., has the lowest AIC. Furthermore, concentration is the only measure of ‘dose’ that is statistically significant in these data. Despite this fact, the Agency has based its RfC on the Michaelis-Menten model with ce as the measure of ‘dose’. With only 12 pleural plaques, the dataset is not large enough to test the impact of confounders, such as age and body mass index (BMI). The panel recommended that the EPA use the dichotomous Hill model with ce as the measure of exposure and with two parameters (the background and the plateau) fixed at highly uncertain values derived from epidemiologic studies. We have implemented this model and find that the logistic regression model with concentration as the measure of ‘dose’ describes the data as well as the constrained dichotomous Hill model. Thus, these data are too small to distinguish between the logistic regression model with concentration as a measure of ‘dose’ and the constrained dichotomous Hill model with ce as the measure of ‘dose’. Clearly, these data should not be used for the estimation of an RfC. As noted below, however, when we analyzed the original Rohs data, which has far more pleural plaques than the sub-cohort (68 versus 12), the constrained dichotomous Hill model is resoundingly rejected.
2. In the full Rohs dataset, duration of exposure is by far the best measure of ‘dose’. In fact, it is clear that the probability of pleural plaque is a function of both concentration and duration of exposure and, therefore, ce is a poor measure of ‘dose’. Age is a strong confounder, with the coefficients for any of the measures of ‘dose’ becoming substantially attenuated when age is included in the regression model. Furthermore, the probability of plaque is a non-linear function of duration. The median duration of exposure in this cohort is about 25 years. With the data stratified on duration, there is no evidence of an association of any measure of ‘dose’ with probability of pleural plaques for durations of exposure less than 25 years. It is clear from these

analyses that there is no straight-forward way to estimate an RfC from these data. In fact, if there is no evidence of an association of exposure with probability of plaques for durations of less than 25 years, then the whole concept of a reference concentration needs to be reconsidered.

3. The constrained dichotomous Hill model recommended by the panel does a very poor job of fitting the full Rohs dataset.
4. Both the Agency and the panel appear to have lost sight of a fundamental fact. Since the point of departure (POD) is the lower 95% confidence limit on the benchmark dose (BMD), the greater the uncertainty in the data, the lower the POD. Therefore, in general, small data sets will lead to lower PODs than large datasets because the confidence interval on the BMD is inversely related to the size of the dataset. This is another important reason not to base RfCs on small datasets, such as the one used by the Agency in this risk assessment.

Recommendation

The full SAB should return this risk assessment for reconsideration by the panel.

APPENDIX B – 12

Statement for Public Teleconference for the SAB review of "Draft Toxicological Review of Libby Amphibole Asbestos" (EPA/635/r/002a)

Anatomical Considerations of Localized Pleural Thickenings (Pleural Plaques)

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May 1, 2012

ILO (2000) Definitions Incorrectly Used

EPA's draft Toxicological Review (August 2011) states that either of two conditions are recognized as LPT:

"Pleural thickening: The pleural lining around the lungs (visceral pleura) and along the chest wall and diaphragm (parietal pleura) may thicken due to fibrosis and collagen deposits. Pleural thickening (all sites) is reported as either localized pleural thickening (LPT) or diffuse pleural thickening (DPT). DPT of the chest wall may be reported as in-profile or face on, and is recorded on the lateral chest wall "only in the presence of and in continuity with, an obliterated costophrenic angle" (ILO, 2000). Localized pleural thickening may also be viewed in-profile or face-on and is generally a pleural plaque (parietal). Calcification is noted where present (ILO, 2000)." (p. 5-15)

"Localized pleural thickening (LPT) viewed on a standard radiograph may include both pleural plaques and pleural thickening that does not involve blunting of the costophrenic angle (ILO, 2000). Thus, both parietal plaques and localized thickening of the visceral pleura may be designated as LPT." (p. 5-17)

"In summary, the radiographic classification of localized pleural thickening (LPT) under current ILO guidelines may include both parietal plaques (in the pleura lining the interior of the ribcage) and diffuse visceral thickening (without CPA obliteration) (ILO, 2000)." (p. 5-21)

ILO (2000) Definitions Incorrectly Used (Cont.)

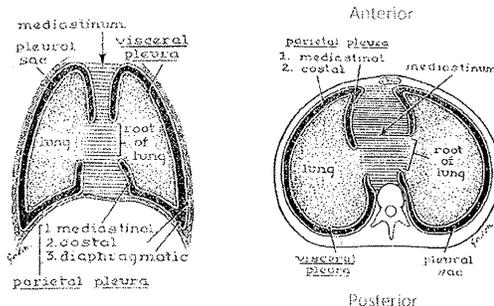
- ILO (2000) classifies as LPT as pleural plaques located in parietal pleura
- ILO states that the category of diffuse pleural thickening (DPT) requires 2 conditions:
 - (visceral) pleural thickening and costophrenic angle blunting.

"For the purpose of the ILO (2000) Classification, diffuse pleura thickening extending up the lateral chest wall is recorded *only* in the presence of, and in continuity with, an obliterated costophrenic angle." from ILO (2000)

ILO (2000) does not have a category of observations for diffuse pleural thickening without CPA obliteration.

Pleural Plaques (LPT) Do Not Displace Lung Tissue

- Pleural plaques (LPT) occur in the parietal pleura
- Parietal pleura does not touch lung tissue
- Pleural plaques (LPT) have small volumes



Pleural Plaques (LPT) Are Not a Critical Effect of Asbestos Exposure

* EPA defines Critical Effect as:

- * The first adverse effect, or its known precursor, that occurs as the dose rate of an agent increases

(http://www.epa.gov/iris/help_gloss.htm#c viewed 4/17/12)

Pleural Plaques (LPT) are Not an Intermediate Stage in Progression to Neoplastic Disease

Pleural Plaques (LPT)

- Well-organized histologically
- Connective tissue covered by epithelium
- Oligocellular
- Nonconfluent cells
- Minimal rate of mitosis
- Normal nuclei
- Extensive extracellular matrix
- Abundant collagen
- Essentially avascular

Tumors

- Lack of organization: chaotic
- Composed of *either* epithelium (carcinomas) or connective tissues (sarcomas)
- High cellularity
- Contiguous mass of cells
- High rate of mitosis
- Dysplastic or anaplastic nuclei
- Small amount of extracellular material
- Scarce collagen
- Vascularity increased beyond typical amount for the tissue

APPENDIX B – 13

Libby Amphibole Asbestos Science Advisory Board Panel Comments

1. Introduction

I have been the Medical Director of the Libby Medical Program (LMP) since January 2001 and as of March 2002 this has been my full time position up to the present time. Attached is a short summary of my professional background.

One of my primary responsibilities as the Medical Director of the LMP is to obtain peer review of chest x-rays and chest CT scans on people in Libby, Montana with asbestos exposure. This peer review process is done by board certified, academic chest radiologists, most of whom are members of the American College of Radiology Pneumoconiosis Committee.

In addition, medical records, pulmonary function tests, chest x-rays and CT scans are sent to pulmonologists for peer review in order to verify the existing diagnosis of previous asbestos exposure in LMP members. These pulmonologists are either practicing Montana or academic pulmonologists. These peer review processes have given me a clear insight and sound foundation as to the types of illness diagnosed in Libby, Montana.

As a physician, I am concerned that the risks associated with Libby Amphibole Asbestos (LAA) are accurately conveyed to the exposed population. I am most concerned that the draft report avoid either overstating or understating those risks, as both can have a potential adverse effect on patients, the health care system, and the broader community, especially with regard to the EPA clean-ups in Libby. I urge the SAB Panel to take this review very seriously with the understanding that many individuals will be living with the results and trying to assess how to apply them to their health care decisions.

2. Non-cancer endpoint: chest pain caused by pleural plaques

EPA's determination that chest pain caused by pleural plaques is an appropriate non-cancer endpoint is without support in the scientific literature.

EPA's chemical-specific charge question II.A.2 to the Science Advisory Board (SAB) requests that the SAB evaluate whether selection of localized pleural thickening (LPT), pleural plaques, as the non-cancer endpoint, on the basis that that condition is associated with restrictive pulmonary function and chronic chest pain, is scientifically supported. My review of the relevant scientific and medical evidence convinces me that it is not.

The draft report concludes that LPT should be used as "an adverse effect and an appropriate endpoint for RfC derivation" P. 5-21. As a physician and based upon my experience with the Libby community and health records subject to peer review at the LMP, I perceived this conclusion as both novel and unsupported.

The draft report summary paragraph, page 5 -21, avoids using the term pleural plaques and instead uses localized pleural thickening (LPT) whereas in fact they both mean the same thing. See ILO 2000 Revised guidelines. In addition, the term pleural lesions is

substituted for pleural plaques without any explanation, justification or reference. Because the draft goes on to state that pleural plaques are not statistically associated with decreased pulmonary function (see draft report at page 2, line 26 and 27), there is no sound scientific basis to conclude that LPT causes decreased lung function.

After review of the discussion in the draft report and cited literature, I want to share the following additional findings with the SAB Panel because the discussion contains a number of fundamental scientific flaws and goes directly to the charge question referenced above that this panel has been asked to address. Overall, the report's basis for using pleural plaques as a non-cancer end point is not supported by the references used in the draft. Moreover, these references do not support – and may even contradict - the statements for which they are cited. This error in the use of scientific literature is particularly disturbing where, as here, the authors are using the literature to support an important unprecedented principle that can have broad influence and wide-ranging policy implications.

a. *The draft report provides no scientific support for its unwarranted assertion that pleural plaques have ragged irregular edges inducing irritation.*

First, the draft report inaccurately describes pleural plaques as having ragged and irregular edges instead of a smooth surface with sharply circumscribed borders. This statement is pertinent because of an inference that the ragged edges cause pain in sensitive lung issue.

As discussed below, the report lacks medical evidence for the hypotheses that pleural plaques have ragged and irregular edges that can irritate the pleura, which in turn, could cause constricting chest pain and loss of pulmonary function. Overall, the use of localized pleural plaques as an endpoint for RfC derivation would be contrary to the medical literature and a significant error. It is important to correct this error because of the potential health care implications for the Libby community. For example, it would be confusing and potentially harmful for angina or other constrictive chest pain to be misdiagnosed as pleural pain from previous asbestos exposure.

The draft at pages 5-18 and 5-21 addresses the unsupported premise that pleural plaques induce constricting chest pain. The discussion on pages 5-18 begins as follows:

"Costal parietal plaques occur between the thoracic cage and parietal pleura, which is normally adherent to the thoracic cage (ATS, 2004; Jones, 2002). Costal parietal plaques have been described as collagen deposits with ragged irregular edges and up to 1 cm in depth and may be calcified."

Moreover, the statement is contrary to the scientific literature. In his lung pathology book, Dr. Andrew Churg describes parietal pleural plaques as follows: "Individual lesions may be completely smooth surfaced and flat, or they may be composed of small rounded knobs or both".

In another pathology book, Dr. Donald Greenberg states: "Grossly, the parietal plaques are elevated, firm, and glistening and have shapely circumscribed borders". He continues: "These ivory-colored structures may have either a smooth surface or a knobby appearance, consisting of multiple 5 mm nodules that create a candle wax dripping appearance".

Neither lung pathologist states pleural plaques have "ragged irregular edges." In fact, the pathology literature states the opposite. References supporting this conclusion include the following:

- Pathology of Occupational Lung Disease: Andrew Churg, M.D. and Francis H. Y. Green, M.D. 1988, page 241
- Pathology of Asbestos — Associated Diseases: Victor L. Roggli, S. Donald Greenberg and Phillip C. Pratt 1992, page 169

b. *There is no scientific support for the assertion that pleural plaques induce chest pain.*

The draft report also lacks any scientific support for the assertion that pleural plaques are associated with chest pain. In support of that alleged association, page 5 – 18 of the draft report states that "These parietal plaques have been associated with constricting pain in the thoracic cavity (Mukherjee et al., 2000; Bourbeau et al., 1990)." However, the cited references (Mukherjee and Bourbeau) do not support the proposition for which they are cited.

The first reference, Mukherjee et al., 2000, is a study of 1280 subjects from Wittenoom, Western Australia who were exposed to crocidolite asbestos. The subjects completed the Rose questionnaire on chest pain and 556 subjects (43%) experienced some chest pain. The type of pain was separated into non-anginal pain and anginal pain. The non-anginal pain was associated with parenchymal disease only. In other words, pleural plaques were not associated with non-anginal pain. Anginal pain was associated with pleural and parenchymal abnormalities. However, the source of anginal pain is the heart, not the pleura. This reference indicates non-cardiac pain is not caused by pleural plaques. Therefore, the Mukherjee study results not only fail to support the assertion in the draft report, but actually conflict with the text of the report. It is worth noting as well that the Mukherjee study is not included in the "References" (Section 7 of the draft report).

In addition, a paragraph on page 5-18 of the report states as follows:

"The parietal pleura is well innervated by the intercostal and phrenic nerves and is considered very sensitive to painful stimuli (Jones, 2002). With respect to parietal plaques, pain during exertion or exercise could result in restrained chest wall motion during exertion or exercise (Bourbeau et al., 1990). Thus, Bourbeau et al., (1990) hypothesized that the dyspnea and changes in pulmonary function noted in individuals with pleural plaques may be due to physical irritation and perhaps a constricting action where parietal plaques are well progressed or numerous and impact a large proportion of the parietal surface."

In Bourbeau et al., 1990, there is no mention of physical irritation (pain) during exertion or exercise resulting in restrained chest wall motion and a constricting action leading to dyspnea and changes in pulmonary function. Thus, this hypothesis regarding physical pain is also unsupported by the cited scientific literature.

In summary, neither cited reference supports the contention that pleural plaques cause chest pain. In fact, one of the references suggests the opposite: that pleural plaques do not cause chest pain.

c. *The ILO Revised 2000 Guidelines are incorrectly interpreted and mis-quoted in support of the proposition that “localized visceral thickening” causes chest pain*

The summary paragraph on page 5-21 of the draft report begins as follows:

"In summary, the radiographic classification of localized pleural thickening (LPT) under current ILO guidelines may include both parietal plaques (in the pleura lining the interior of the ribcage) and diffuse visceral thickening (without CPA obliteration) (ILO, 2000). The two lesions (parietal plaques and localized visceral thickening) are distinct and may contribute independently to observed health effects. Parietal plaques are known to induce chronic constricting chest pain that increases in severity as the extent of the plaques increases."

The ILO guidelines indicate that diagnosing visceral pleural thickening (VPT) on a single PA chest x-ray is unreliable. In addition, the guidelines do not separate VPT into diffuse visceral thickening and localized visceral thickening as the draft report does. The attempt of the report to do so is unfounded science which does not follow the ILO guidelines and only serves to mislead and confuse the reader. No scientific basis exists to conclude that localized visceral thickening contributes to untoward health effects.

The Revised ILO 2000 Guidelines state the following at page7:

- ✓ "Diffuse pleural thickening historically has referred to thickening of the visceral pleura. The radiological distinction between parietal and visceral pleural thickening is not always possible on a postero-anterior radiograph."
- ✓ "For the purpose of the ILO (2000) Classification, diffuse pleural thickening extending up the lateral chest wall is recorded *only* in the presence of, and in continuity with, an obliterated costophrenic angle."

Except for the above passing reference to “visceral pleural thickening”, the ILO 2000 guidelines have no discussion or mention of diffuse visceral thickening. No scientific basis exists for the draft report to conclude or imply that visceral pleural thickening is a separate condition from pleural plaques and a cause of morbidity.

In sum, the statement that “Parietal plaques are known to induce chronic constricting chest pain that increases in severity as the extent of the plaques increases” (p. 5-21) is not supported by any cited scientific reference. Instead of demonstrating that localized pleural plaques cause chest pain, the scientific literature supports the opposite hypothesis: that pleural plaques do not cause chest pain. The following references support this view point:

- "Broderick A, Fuortes LI Merchant JA, Galvin JR, Schwartz DA. Pleural determinants of restrictive lung function and respiratory symptoms in an asbestos-exposed population, Chest 1992; 101: 684-691.
- Jarvholm B, Larsson S. Do pleural plaques produce symptoms? A brief report. J Occup Med 1988; 30: 345-347
- Sutapa Mukherjee, Nicholas de Klerk, Lyle J. Palmer, N. J. Olsen, S. C. Pang, and A. William Musk. Chest Pain in Asbestos-exposed Individuals with Benign

To my knowledge, this draft proposes, for the first time, that a non-cancer endpoint be established for asbestos exposure on the basis that pleural plaques cause chest pain. This is a significant new endeavor with potentially broad ramifications. If undertaken, it should be supported by generally accepted medical principles and findings, as well as sound science. That support is not present in the draft report. As a result, the SAB should recommend to EPA, in response to charge question II.A.2, that EPA remove from the draft report chest pain caused by pleural plaques as a non-cancer end point.

3. Tremolite asbestos compared to LAA

The draft report inappropriately attributes to LAA the toxicity associated with tremolite asbestos. The draft report presents studies which deal with a single form of amphibole asbestos (tremolite) and inappropriately implies that those studies reflect the toxicity of LAA. This comparison inaccurately applies those data.

Tremolite asbestos should not be confused with LAA. Since the composition and characteristics of the two are different, literature regarding tremolite asbestos cannot be applied directly to LAA.

In section 4.2 (**sub-chronic and chronic studies and cancer bioassays in animals oral inhalation and other routes of exposure**), the hypothesis is made that studies using pure tremolite will help "to potentially increase understanding of the effects and mechanisms of Libby amphibole asbestos". This statement is based on the following assumptions:

- "Tremolite is an amphibole asbestos fiber that is a component of Libby Amphibole asbestos (-6%)"
- "In early studies Libby Amphibole asbestos was defined as tremolite."

According to Meeker's publication in 2003, the Libby Amphiboles are composed primarily of winchite 84% and richterite 11%, with only approximately 6% tremolite. (see External Review draft, page 2-14). As a result, studies assessing the toxic effects of tremolite asbestos can not properly be employed, as a matter of sound science, to evaluate the effects of LAA. For example, Table 4-16 (at pages 4-52 and 4-53 of the draft report), "In vivo data following exposure to tremolite asbestos," summarizes nine animal studies (7 rats, 1 mouse and 1 hamster) in which pure tremolite is administered. The toxic effects in these studies should not be compared to LAA, which is only 6% tremolite. None of the studies themselves directly compares tremolite to LAA.

The SAB should advise EPA to make clear that the toxic effects of pure tremolite are not the same as the toxic effects of LAA, and can not properly be used to evaluate the toxic effects of LAA.

4. In vitro comparison studies

The risk assessment should recognize and accurately interpret comparative studies that correlate LAA with other amphiboles and apply the information that these studies yield.

Table 4-18, at page 4-63 of the draft report, summarizes six published studies that directly compare LAA with other amphibole asbestos, either crocidolite or amosite. In all these studies, the LAA is less reactive or causes less DNA and gene damage when compared to crocidolite or amosite. The significance of this table is obscured because of the misleading title of the Table: "In vitro data following exposure to Libby Amphibole asbestos." To avoid confusion and enhance transparency, the report should acknowledge that all available scientific studies that compare LAA to other amphibole asbestos conclude that LAA is less toxic and reactive than other amphibole asbestos.

The SAB should recommend to EPA the following:

- Change the title of Table 4-18 to "In vitro data comparing LAA with other amphibole asbestos."
- Conclude this section by stating: "In all studies that compare the reactivity and toxicity of LAA with other amphibole asbestos, the LAA is less reactive and less toxic."

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Attachment 1

Professional Background

- Board certified in internal medicine and nephrology
- 1970 — 1972 Major United States Army
 - 1970 — 1971 Physician, Brooke Army Medical Center, San Antonio, Texas
 - 1971 — 1972 Commanding Officer, US Army Hemodialysis Unit Saigon, Vietnam
- 1972 — 1996 Practiced internal medicine and nephrology at Monmouth Medical Center (MMC), Long Branch, New Jersey. MMC is a 450 bed hospital with a medical school affiliation and residency programs
- 1997 --1998 Medical Director of VRG International, a contract research organization (CRO), which conducted clinical trials for major pharmaceutical companies
- 1999 — 2000 Medical Director of Wellspring Pharmaceutical Company
- 2001 to present Medical Director of the Libby Medical Program

Attachment 2

References Cited

1. Sutapa Mukherjee, Nicholas de Klerk, Lyle J. Palmer, N. J. Olsen, S. C. Pang, and A. William Musk. Chest Pain in Asbestos-exposed Individuals with Benign Pleural and Parenchymal Disease. *Am. J. Respir. Crit. Care Med.*, Volume 162, Number 5, November 2000, 1807-1811
2. Bourbeau, J. Ernst, P. Chrome, J. Armstrong B. and Becklake, M (1990) The relationship between respiratory impairment and asbestos-related pleural abnormalities in an active work force. *AM Rev Respir Dis* 142:837-842
3. Broderick A, Fuortes LJ Merchant JA, Galvin JR, Schwartz DA. Pleural determinants of restrictive lung function and respiratory symptoms in an asbestos-exposed population. *Chest* 1992; 101: 684-691.
4. Jarvholm B, Larsson S. Do pleural plaques produce symptoms? A brief report. *J Occup Med* 1988; 30: 345-347

APPENDIX B – 14

Comments for EPA and SAB Regarding Libby Amphibole Asbestos

Submitted by Dr. Jay Flynn
April 17th, 2012

Thank you for making available the SAB Panels' deliberative draft report, dated April 11, 2012 (Panel's Draft Report). While I reiterate my previously presented comments and concerns, I wanted to take this opportunity to address a new issue reflected in the Panel's draft report. I concur with the SAB Panels' observation that "additional analyses/cohorts are needed to strengthen and support the RfC." However, I suggest that the SAB Panel reconsider and remove any suggestion that the EPA use a recent Larson paper that uses the ATSDR data from Libby, Montana, 2000 and 2001, for assessing pleural abnormalities among the Libby participants.

At issue is the scientific validity of the following paper: **Associations between radiographic findings and spirometry in a community exposed to Libby amphibole**; Theodore C Larson,¹ Michael Lewin,¹ E. Brigitte Gottschall,² Vinicius C Antao,¹ Vikas Kapil,³ Cecile S Rose² which was published online March 1st, 2012 in the Journal of Occupational and Environmental Medicine. This paper has not yet been published in the Journal itself and will be referenced in this report as the Larson paper.

Due to the following significant problems with this paper and underlying data deficiencies as discussed below, the paper should not assist the EPA in deriving the non-cancer endpoint. In addition, as pointed out in my comments herein, there are significant questions as to whether radiographic evidence of localized pleural thickening (LPT) in humans is scientifically sufficient for derivation of the RfC. I recommend that the SAB Panel reconsider its preliminary assessment of that issue as reflected in the Panel's Draft Report, in light of the limited reliability of this radiographic evidence.

1. Larson's Study Used Data that Failed to Distinguish Between Pleural Abnormalities and Other Innocuous Observations.

Larson used the ATSDR data that grouped together in one category all readings from < 1 to 5 mm in width, but only those that are greater than 2 mm in width are defined under the Larson's methodology as pleural abnormalities. Thus the use of readings of less than 2 mm in width biases the data.

As background, the ATSDR B readers in 2000 and 2001 followed the 1980 ILO Guidelines when interpreting Posterior / Anterior PA Chest X-Rays. Under these 1980 guidelines, the threshold required to identify the thickness of any pleural abnormality was not specified. Thus the B reader had discretion to determine whether a pleural abnormality existed. The 1980 ILO guidelines used by the ATSDR B readers do not have a minimal thickness for reading a pleural abnormality so that the B readers could read any minimal pleural thickening, including pleural fat, as an abnormality.

In the ATSDR data, category "A" reflects all observations that fell within a range of 0 to 5 mm. There is no way to determine which of the X-Rays reflected observations of less than 2 mm. The

Larson paper adapts this ATSDR data, including the determinations from the ATSDR B Readers for use in their 2012 analysis.

In 1990 Bourbeau et al realized a minimal thickness for reading pleural plaques on a chest x-ray by B readers needed to be established. The 1980 ILO Guidelines used by the ATSDR B readers were flawed and outdated. To address this, the Bourbeau model established a minimal threshold of 2mm for pleural abnormalities. Later, further addressing this deficiency in 2000 the ILO established the minimal thickness for reading a pleural plaque at about 3mm in the Revised Edition 2000 of the ILO guidelines, published in 2002.

Simply put: the model and the data are incompatible. The Larson paper uses the Bourbeau model to develop index scores of pleural thickening and the Bourbeau model is incompatible with the ATSDR data. The Bourbeau model establishes a minimal threshold of 2mm for pleural abnormalities. As described above, the ATSDR data applied the 1980 guidelines, so it had no minimal threshold. The Larson paper used the Category A readings from the ATSDR data (encompassing readings within a range of 0 to 5 mm) and applied a scoring system designed only for readings of at least 2 mm. Since these two systems are mis-matched they never should have been used together, making the data flawed and the paper invalid.

Bear in mind, Larson's results were in the very low range of the scoring system 0-24. Modest was a score of <2.5 for LPT and high = or >2.5. The median value for all subjects with LPT was only 2.5. At this low range, minimal degrees of thickness become important especially with the B readers having no minimal threshold to read an abnormality.

- The Bourbeau et al paper uses only one B reader because “one reader was selected prior because a previous study indicated that he achieved better reproducibility for reading of pleural abnormality.” The Larson paper had to depend on two or three B readers to detect a pleural abnormality because this was how the ATSDR medical testing study for Libby, Montana was designed. Bourbeau et al do not specify how the pleural abnormalities identified by multiple B readers should be tabulated. Larson states 708 had circumscribed pleural plaques identified by at least 2 B readers, but does not state how the index scores were derived or what the range of the index scores was. Were the individual scores averaged for only those with positive reads or were the negative B reader reports also included in the averaging?. Including the negative reports when tabulating the index scores could result in a significant lowering of the mean score of 2.5.
- The methodology designed by Bourbeau et al was developed for their research and publications. This has never been validated and accepted by the world wide scientific community.

The Bourbeau et al Assessment of Pleural Abnormality scoring system for chest wall pleural thickening is not recognized by:

- The American College of Radiology Pneumoconiosis Committee
- The American Thoracic Society
- The American College of Chest Physicians

- The National Institute for Occupational Safety and Health (NOISH)

2. Larson's Study Counted Single B Reader Reports, and This Error Caused the Data to be Biased, as Shown in Larson's Table 3.

The Larson paper states in Table 2 that 708 have LPT "as seen by at least two B readers". In Table 3 the numbers are increased to 1,060 because of the Larson study's use of unreliable single B reader reports, for which there may have been conflicting readings by one or two other B readers.

In Table 2, the following should have been provided:

- The breakdown of the 708 with LPT as to their Bourbeau et al index scores. How many had "modest" with an index < median score 2.5 and how many had "high" with an index $\geq 2/5$ median score?
- How was the median index score determined?
- What is the range and breakdown of the high index scores for LPT?
- Of the 708 with LPT how many had 2 B readers and how many had 3 B readers reporting especially since 1,118 of the x-rays were read by B Reader 3?

In Table 3, for the analysis, 561 have LPT less than or equal to the median of 2.5 and 499 greater than the median 2.5. This makes a total of 1,060 for the analysis. This is an increase of 352 (50%) of the ATSDR Libby participants over the 708 with LPT. The breakdown of the index scores for this group is also missing, so that one is unable to determine the contribution of this group to each of the modest and high groups. We are further informed the 352 "add-ons" had "LPT detected by only one reader". Since all x-rays were read by 2 or 3 B readers, this implies each of the 352 "add-ons" had one or two B readers that did not identify LPT. If Larson had provided this data indicating the number of B readers for each ATSDR Libby participant, one would be able to determine how many of the 352 "add-ons" had 2 B readers indicating LPT was not present. By omitting all of the above data and methodology, this paper becomes very unscientific.

The Larson paper changed from using 2 or 3 B readers to identify a pleural plaque (LPT) to a single B reader. This change was announced in fine print under Table 3 and never mentioned in the **Methods, Results, or Discussion** in the paper. This critical change in methodology makes the paper flawed and unscientific.

3. The Study Fails to Consider B Reader's Significant Findings of Pleural Fat as Required to Be Noted Under ATSDR B Reader Report Form Box "4D.Fat?" and Therefore the Larson Paper is Unscientific and Seriously Flawed

On a PA chest x-ray pleural fat can mimic pleural plaques and one cannot be distinguished from the other, CT scanning is necessary to do this. The adult population of Libby, Montana has an

incidence of obesity of 49%.³ This obesity compounds the problems of distinguishing pleural plaques from pleural fat on a PA chest x-ray. ATSDR attempted to try to identify pleural fat by putting box "4D.FAT?" on the B reader reporting forms.⁴ This portion of the ATSDR form asks B Readers to note observations of pleural fat.

Larson relied upon the ATSDR reporting forms to obtain the index scores reported in their paper. However, the Larson paper fails to consider the B Reader observations of pleural fat, as documented in box "4D.FAT?" because this data from the B reader report forms is not discussed in the paper. The Larson paper fails to consider documenting pleural fat and its influence on the interpretation of the PA chest x-rays by the ATSDR B readers.

- If a B reader identified a pleural plaque(s) on the PA x-ray and checked box "4D.FAT?" was the result considered to be pleural fat and the report omitted from the paper by the authors?
- If the report was counted, then pleural fat was construed in Larson's paper as pleural plaque. This is not accurate.
- Box "4D.FAT?" was not restricted to the oblique x-rays. The Libby Medical Program has examples where a B reader identifies a plaque(s) in 3A, 3B, or 3C, checks no in Box 4C, and then checks box "4D.FAT?" as positive^{5,6}. The Larson paper omitted box "4D.FAT?" from the analysis of the B reader reporting forms that determined the index scores. By ignoring box "4D.Fat?" pleural fat was never identified before being incorporated into the Methods and Results of the paper.

The fact that pleural fat was not accounted for in the B reader reports is unscientific and a serious flaw of the paper. In their paper Larson acknowledge "no negative radiographs were deliberately included as controls." This was a significant mistake in the ATSDR study design. The 2000 – 2001 study should have had control chest x-rays from an unexposed population with BMI's that match those in the Libby study. The inclusion of control chest x-rays would clearly show the impact of pleural fat when attempting to identify pleural plaques in this population.

A significant flaw in the methodology employed by the Larson paper is that it failed to distinguish between pleural plaques and pleural fat, such that observed incidences of pleural plaques may well have been nothing other than irrelevant pleural fat. Obesity not only affects the accuracy of distinguishing between pleural plaques and pleural fat but it also has an impact on pulmonary functions testing, causing restrictive changes. The associations between radiographic findings and spirometry in the Larson paper may be nothing more than the effects of obesity in the Libby population and be unrelated to pleural plaques.

For all of these reasons, in conclusion, in view of the scientifically unsound methodology employed by the Larson paper, the SAB should recommend that EPA not rely on this Larson study, in whole or in part, to reach a determination that pleural plaques cause a loss of pulmonary function.

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Attachments

1. Bourbeau et al 1990; Assessment of Pleural Abnormality
2. Larson et al 2012; Table 3
3. Libby Medical Program BMI data 12/31/2010
4. Standard B Reader Forms for Panel Radiologists (BR1, BR2, BR3) from ATSDR study in Libby, Montana, 2000 – 2001
5. ATSDR Libby participant #10774002, B Reader 1 identifies a face on plaque in 3C., 4C. is checked no and 4D.Fat? is checked positive.
6. ATSDR Libby participant #10548802, B Reader 3 identifies an in profile plaque in 3C., 4C. is checked no and 4D.Fat? is checked positive.

Assessment of Pleural Abnormality

High kilovoltage PA chest radiographs were taken in each subject and read into the ILO 1980 International Classification of Radiographs of Pneumoconioses (24) by two NIOSH-certified B readers. For the present study, one reader was selected a priori because a previous study (25) indicated that he achieved better reproducibility for readings of pleural abnormality. The pleura had to be thickened by 2 mm or more for abnormality to be read. Semiquantitative scores were computed for each of three sites: chest wall, costophrenic angle, and diaphragm. The score for chest wall pleural thickening was computed by summing the reading in profile for each site, using the product of the width category a, b, or c (converted to a numerical score of 1, 2, or 3) and the extent category 1, 2, or 3 plus the reading *en face* (using the extent category 1, 2, or 3). Right and left sides were then added together giving a score ranging from zero to 24. Scores of 1 or 2 were given for obliteration of one or both costophrenic angles and of 1 or 2 for thickening of one or both diaphragms. Because a previous study from our laboratory using the same readers suggested that confluent pleural plaques and diffuse thickening could not be reliably distinguished using the criteria stated in the ILO 1980 instructions (25), our readers were instructed to consider diffuse thickening to be present *only* when there was blunting of the costophrenic angle.

Environment

Table 3 Odds of restrictive and obstructive spirometry by degree of radiographic pleural abnormality and covariates* (ORs (95% CI))

	Row n	Restriction	Obstruction
DPT†			
Index=0	6341	1	1
0<index ≤ median (3.0)	78	2.1 (1.1 to 3.8)	1.9 (0.9 to 3.8)
Index > median	57	5.6 (2.7 to 11.6)	1.7 (0.6 to 4.9)
LPT‡			
Index=0	5416	1	1
0<index ≤ median (2.5)	561	1.3 (1.0 to 1.7)	1.0 (0.7 to 1.4)
Index > median	499	1.9 (1.5 to 2.5)	0.9 (0.6 to 1.3)

Statistically significant associations are in bold.

*All models control for parenchymal abnormality, age, sex, smoking history, body mass index, exposure group, number of exposure pathways, duration of residence in Libby and shortness of breath.

†Pleural abnormality index calculated by converting in-profile diffuse thickening widths from 'a', 'b' and 'c' to 1, 2 and 3, then multiplying in-profile widths by in-profile extents and adding face-on extents, and summing the result for each hemithorax. Average severity from two or three B readers used. Possible range of severity index: 0–24. The sum of participants with a DPT abnormality index score >0, n=135, is greater than number of participants with DPT presented in table 2 due to counting participants with DPT detected by only one reader.

‡Pleural abnormality index calculated by converting in-profile localised thickening widths from 'a', 'b' and 'c' to 1, 2 and 3, then multiplying in-profile widths by in-profile extents and adding face-on extents, and summing the result for each hemithorax. Average severity from two or three B readers used. Possible range of severity index: 0–24. The sum of participants with an LPT abnormality index score >0, n=1060, is greater than number of participants with LPT presented in table 2 due to counting participants with LPT detected by only one reader.

DPT, diffuse pleural thickening; LPT, localised pleural thickening.

BMI

Calculations of Body Mass Index on Applicants and Members of the Libby Medical Program Updated December 31st, 2010

As of December 31st, 2010, 1581 applicants and members of the LMP have had BMI's calculated. The results are as follows:

BMI 40 or >	93	6%
BMI 30 to 39.9	678	43%
BMI 25 to 29.9	564	36%
BMI < 25	246	15%
Total	1581	100%

A. OUTCOME FORM FOR CHEST X-RAYS

BR 1

CASE ID

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1A. DATE OF X-RAY <table border="1" style="display: inline-table; vertical-align: middle;"><tr><td> </td><td> </td><td> </td></tr></table> / <table border="1" style="display: inline-table; vertical-align: middle;"><tr><td> </td><td> </td><td> </td></tr></table> / <table border="1" style="display: inline-table; vertical-align: middle;"><tr><td> </td><td> </td><td> </td></tr></table> <small>MONTH DAY YEAR</small>										1B. FILM QUALITY If not Grade 1 give reason: <table border="1" style="display: inline-table; vertical-align: middle;"><tr><td>1</td><td>2</td><td>3</td><td>U/R</td></tr></table>	1	2	3	U/R	1C. IS PA FILM COMPLETELY NEGATIVE? Yes <input type="checkbox"/> PROCEED TO SECTION 4C No <input type="checkbox"/> PROCEED TO SECTION 2																																																																			
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4A. ANY OTHER ABNORMALITIES? Yes <input type="checkbox"/> COMPLETE 4B, 4C AND 4D No <input type="checkbox"/> PROCEED TO SECTION 4C																																																																																		
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SHOULD PARTICIPANT SEE A PHYSICIAN BECAUSE OF COMMENTS IN SECTION 4D? Yes <input type="checkbox"/> No <input type="checkbox"/>																																																																																		

LIBBY COMMUNITY ENVIRONMENTAL HEALTH PROJECT

BR 3

CASE ID

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Film Reader: JEP

Date of Reading

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MONTH DAY YEAR

LIBBY COMMUNITY ENVIRONMENTAL HEALTH PROJECT

BR 1

CASE ID: 10774002

5877

<p>1A. DATE OF X-RAY 10 30 00 MONTH DAY YEAR</p>	<p>1B. FILM QUALITY If not Grade 1 give reason: 2 3 UR</p>	<p>1C. IS PA FILM COMPLETELY NEGATIVE? Yes <input type="checkbox"/> PROCEED TO SECTION 4C No <input checked="" type="checkbox"/> PROCEED TO SECTION 2</p>																													
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<p>SHOULD PARTICIPANT SEE A PHYSICIAN BECAUSE OF COMMENTS IN SECTION 4D? Yes <input checked="" type="checkbox"/> No <input type="checkbox"/></p>																															

CASE ID 10548802

2557

<p>1A. DATE OF X-RAY 081500 MONTH DAY YEAR</p>	<p>1B. FILM QUALITY If not Grade 1 give reason: 23 UR</p>	<p>1C. IS PA FILM COMPLETELY NEGATIVE? Yes <input type="checkbox"/> PROCEED TO SECTION 4C No <input checked="" type="checkbox"/> PROCEED TO SECTION 2</p>																																																																								
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APPENDIX B – 15



**Department of Environmental Health
Occupational and Environmental Medicine Division**

University of Cincinnati
Academic Health Center
PO Box 670056
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January 31, 2012

Diana Wong, Ph.D
Designated Federal Officer
Scientific Advisory Board
U.S. EPA

RE: Material for SAB review related to the Draft Toxicological Review of Libby Amphibole
Asbestos

Dear Dr. Wong,

Attached please find material for review by the Scientific Advisory Board (SAB) related to the Draft Toxicological Review of Libby Amphibole Asbestos. The file contains information about upcoming analyses/publications related to the Marysville, Ohio cohort. This cohort is instrumental in understanding the health risks associated with Libby amphibole exposure. The SAB may find it useful to be aware of the upcoming availability of this additional research related to this cohort.

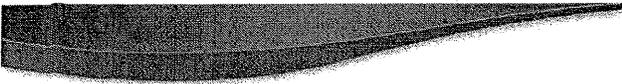
Sincerely,

James E. Lockey, MD, MS
Professor-Department of Environmental Medicine
Division of Occupational and Environmental Medicine
Department of Internal Medicine, Pulmonary Division
University of Cincinnati College of Medicine

Status of data collected in 2010-2011 related to the University of Cincinnati pulmonary health study of 513 Marysville, Ohio workers exposed to Libby amphibole

Title/Topic	Content	Status
Exposure estimates for workers in a facility expanding Libby vermiculite: Updated values and comparison to original 1980 values	Methodology utilized to refine the Marysville, Ohio workers exposure matrix and comparison to the exposure matrix used in the 1980 and 2004 epidemiologic studies	Submitted for publication December 2011
Mesothelioma associated with commercial use of vermiculite containing Libby amphibole	SMRs and SRRs used to investigate potential asbestos-related mortality among 136 deceased workers from the Marysville cohort	Submitted for publication December 2011
Chest X-ray and HRCT findings associated with low levels of exposure to Libby amphibole (tentative title)	Cross-sectional analyses evaluating association between cumulative fiber exposure and chest X-rays/HRCTs of 191 Marysville workers as related to pleural and parenchymal changes	In preparation; target to submit Spring 2012
Spirometry, Diffusion, Lung Volume studies	Cross-sectional and longitudinal analyses regarding the potential association between cumulative fiber exposure and spirometry collected in 1980 (n=512), 2004 (n=231), 2010 (n=154), diffusion and lung volume studies from 2010 (n=154) and chest HRCT (n=191)/X-ray (n=305) findings.	Data analysis pending; target to submit Summer/Fall 2012
Autoimmune disease/biomarkers (grant submitted)	Evaluate the potential association between cumulative fiber exposure and autoimmune disease and/or autoimmune biomarkers via serum samples and health questionnaires from 151 members of the Marysville cohort.	Biological sample analyses pending; target to submit Winter 2013

APPENDIX B – 16



U.S. EPA's External Review Draft Toxicological Review of Libby Amphibole Asbestos

Presentation for the
Science Advisory Board
6 Feb, 2012

David Bussard,
Director, Washington Division
National Center for Environmental Assessment
Office of Research and Development
U.S. Environmental Protection Agency

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Overview

- Noncancer Assessment
- Cancer Assessment
- New Publications

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Why Assess Libby Amphibole Asbestos Specifically?

- Clear awareness of noncancer effects in those exposed to Libby amphibole and no IRIS value explicitly for noncancer effects of asbestos.
- Opportunity with epidemiology data to study exposures to the material as mined at Libby and processed rather than estimate its risk from its component minerals.

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Toxicological Review

- Review of the available scientific literature most relevant to evaluating the potential health hazard posed from exposures to Libby amphibole asbestos (LAA).
- Aware of the broader literature on asbestos generally, but not trying to publish a review of the entire asbestos literature.

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Elements of Toxicological Review

- Hazard description.
- Reference Concentration (RfC): "An estimate *(with uncertainty spanning perhaps an order of magnitude)* of a continuous inhalation exposure to the human population *(including sensitive subgroups)* that is likely to be without an appreciable risk of deleterious effects during a lifetime."
- Inhalation Unit Risk (IUR): "An inhalation unit risk (IUR) is typically defined as a plausible upper bound on the estimate of cancer risk per $\mu\text{g}/\text{m}^3$ air breathed for 70 years." [fibers/cc in this case]



Literature Search in Support of the Libby Amphibole Assessment

- Used search terms for relevant mineral forms:
 - Libby amphibole ("Libby", "Libby asbestos," etc.)
 - Tremolite
 - Winchite
 - Richterite
- Focused additional search on some related **ISSUES** (e.g. fiber toxicokinetics, susceptible populations, MOA for asbestos in general).
- Drew from a range of literature sources
 - Peer-reviewed journals
 - Government reports
 - Materials submitted to the EPA docket



Section 4: Noncancer Hazard Identification

- Weight of evidence is adequate for:
 - Localized pleural thickening / pleural plaques
 - Diffuse pleural thickening
 - Asbestosis
- Data were insufficient for hazard determination:
 - Other systemic effects



Study Selection Criteria for RfC Quantification (Table 5-2, Section 5.2.1.1)

- Exposure estimates are available for the study group
- Good study design characteristics
 - Sufficient follow-up
 - Study size / participation rates and no indication of bias
 - Design/analytic approach to address relevant sources of potential confounding
- Relevant exposures
 - Chronic studies versus subchronic or acute
 - Exposure intensity (inform environmental scenarios)
- Good measurements of exposure
 - Measured data (site/task specific)
 - Sample collection / analysis
 - Availability of individual-level exposure data
 - Quality of exposure reconstruction
- Good ascertainment of effects (health outcomes)
 - Severity of effect (precursor, minimal effect, more severe effect)
 - Measurement techniques adequate and sensitive
 - Measurement of effects independent of knowledge of exposure level/group



Two occupational cohorts for RfC Derivation (Section 5.1)

- Miners in Libby, Montana
[Amandus et al. (1987 a,b); McDonald et al. (1986b)]
- O. M. Scott workers in Marysville, Ohio
(vermiculite from Libby, MT)
[Lockey et al. (1984); Rohs et al. (2008)]

Advantages of O.M. Scott Cohort: (Section 5.2.1.3.2)

- Adequate follow-up
- Minimal exposure outside of the workplace
- Better quality radiographs (ILO 2000, for some)
- Lower exposures – closer to POD
- Ability to consider more covariates



EPA decided to conduct its own exposure-response modeling with individual data

- Published data only presented by exposure quartiles.
- New analysis would allow for explicit evaluation of important covariates.
- ...allow use of the higher quality data (sub-cohort); increasing confidence in the resulting exposure-response relationship.
- ...allow sensitivity analyses



Several Radiological Endpoints Considered (Section 5.2.1.4)

- Available data for exposure-response modeling was limited to effects as viewed using standard radiographs:
 - Small opacities – asbestosis
 - Costophrenic angle (blunting/obliteration)
 - Pleural thickening
 - Localized pleural thickening (LPT)
 - Diffuse pleural thickening (DPT)



Criteria for Selecting Critical Effect (applied in Section 5.2.2)

- Adverse itself, a precursor to an adverse effect or a biologic marker for a relevant health effect.
- Confounding can be adequately accounted for.
- Measured with adequate sensitivity for the results to be biologically relevant.
- Adequate data to define an exposure-response relationship (BMDL or LOAEL/NOAEL).

EPA selected localized pleural thickening (LPT)

EPA Has Requested Review of the Exposure Reconstruction (Section 5.2.3.1, Appendix F)

- O.M. Scott workers**
- Original Job Exposure Matrix (Lockey 1985)
 - No exposure measurements prior to 1972;
 - Engineering controls implemented from 1968 on
 - 235 air samples
 - Additional information available for exposure reconstruction
 - 589 new air samples
 - Focus groups
 - Seasonal work schedules

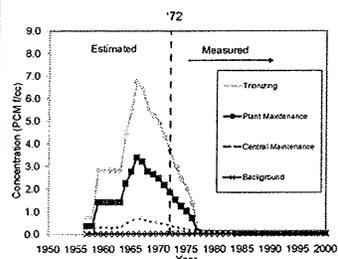


Figure 5.1. Estimated and measured exposure concentrations in Marysville, OH facility

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Criteria for selection of the Sub-cohort from O.M. Scott (Marysville, Ohio) (Section 5.2.3.2)

Criteria	Full Cohort	Sub-cohort (Limit to those hired after 1971)
Type and Quality of Outcome Assessment (i.e. Radiographs)	Merge 1980 and 2000-2005 exam data	2002-2005 exam data
Quality of exposure data (measured, reconstructed, quality of information for reconstruction)	Missing measured data for pre-1972 exposures. Pre-1972 exposures were reconstructed (Appendix F).	Post-1971 exposure estimates based on measured data
Sample size (statistical power)	N=434, 61 LPT cases	N=118, 12 LPT cases
Data available to address covariates (age, DOB, sex, BMI, smoking, hire date etc.)	Not available for the 1980 cohort (e.g. smoking and BMI)	Lower proportion of missing data (i.e. BMI)
Available endpoints for consideration as the critical effect	LPT, OPT and asbestosis	LPT (only 1 case OPT)
Time to x-ray, from first exposure	Range: (6 mo. to 47 years)	Range: (23.2 to 32.6 years)

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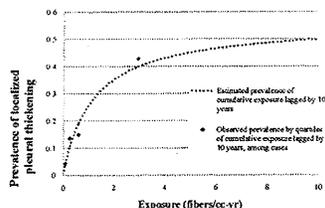
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RfC Exposure-Response Modeling (Section 5.2.3.3, Appendix E)

Best-fitting model was a Michaelis-Menten model
 $P(LPT) = \text{background} + \frac{(\text{Plateau} - \text{background}) \times CE}{\text{exp}(-a) + CE}$

Benchmark dose software suite of models evaluated.



Graph of observed and estimated prevalence of localized pleural thickening calculated using the Michaelis-Menten model with 10-year lagged exposure.

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Reference Concentration (Section 5.2.4)

- Point of Departure: $0.1177 \text{ (fibers/cc)} \times \text{year}$
The lower 95th confident interval on exposure causing a 10% LPT response
- Converted to lifetime exposure concentration:
 $0.1177 \div (70-10) \text{ yrs} = 1.96 \times 10^{-3} \text{ fibers/cc}$
- Uncertainty Factors Applied: Total of 100
 $1.96 \times 10^{-3} \text{ fibers/cc} \div 100$

$$\text{RfC} = 2 \times 10^{-5} \text{ fibers/cc; lifetime exposure}$$

Note: The alternative full cohort model provided a POD of 0.0136 (fibers/cc) \times year, where T=40 years. If UF total of 100 were applied that would yield an RfC of 4×10^{-6} fibers/cc for lifetime exposure.

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Sensitivity Analyses (Section 5.3.1)

- Limited Quantitative impact:
 - Sensitivity to background rate of LPT (15%)
 - Sensitivity to lag (50%)
- Smoking status
 - Statistical power is limited, but analysis suggests a POD for smokers might be lower
- Extrapolation to full-lifetime exposures
 - Two alternatives presented
 - PODs vary by a factor of 4
- Choice of critical effect (Table 5-5)
 - As expected, POD for LPT was lower than PODs for DPT and small opacities
 - Limitation of critical effect to bilateral LPT would result in similar POD: 0.1337 vs. 0.1177 (fibers/cc) yrs

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Charge asks your advice on key decision points:

Data on which the RfC is based:

- Exposure reconstruction
- Choice of sub-cohort
- Endpoint selection

Quantitative assessment:

- Exposure-response modeling
 - Evaluation of covariates
 - Selection of best-fit model
- Extrapolation to full-lifetime exposures
- Application of uncertainty factors

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Section 4: Evaluation of Carcinogenicity

"Carcinogenic to Humans"

- Associated with increased mortality
 - Lung cancer
 - Mesothelioma

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Criteria for Study/Dataset Selection

- 1) All studies of cancer incidence or mortality in people exposed to Libby Amphibole asbestos
- 2) Excluded studies without quantitative exposure data (community studies)
- 3) Excluded studies without well-defined populations (case studies)

Libby workers cohort (Sullivan, 2007)

- Cohort study of inhalation exposures of chronic duration
- Well-documented design, methods, and population characteristics
- Could (with researcher, Dr. Sullivan) extend mortality follow-up and conduct individual-level data analysis

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Original analysis

Individual-level data allow for more detailed cancer analysis than from using only summary results in the literature.

- Better understanding of important aspects of the job exposure matrix (5.4.3.5)
- Allows explicit control of important covariates (5.4.3.6)
- Allows investigation of various parameterizations of exposure (5.4.2.4)
- Allows accounting for time-varying aspects of exposure (5.4.3.6.2)
- Allows sensitivity analysis of influence of early high exposure intensities (5.4.3.6.4)
- Allows sensitivity analysis of potential confounding by smoking (5.4.3.6.5)

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Prior published analyses have sometimes used the full cohort and sometimes sub-cohorts.

Reference	Cohort definition	Employment Requirement	Mortality Follow-up	Study size (N)
McDonald et al. (1986a and 2004)	Males hired prior to 1963 Exposures 1935-1982	1 year or more	1999	406
Amandus and Wheeler (1987)	Males hired prior to 1970 Exposures 1935-1982	1 year or more	1982	575
Sullivan (2007)	White males still alive post-1959 Exposures 1935-1982	1 day or more	2001	1,672
Berman and Crump (2008)	White males still alive post-1959 Exposures 1935-1982	1 day or more	2001	1,672
Larson et al. (2010a)	Full cohort Exposures 1935-1993	1 day or more	2006	1,882
Moolgavkar et al. (2010)	White males still alive post-1959 Exposures 1935-1982	1 day or more 1 year or more	2001 2001	1,662 801

* Re-analysis of Sullivan (2007)

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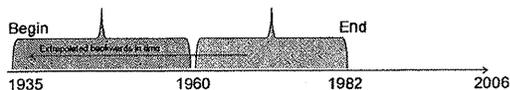
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NIOSH Job Exposure Matrix: important information is missing regarding pre-1960 exposures.

Exposure data extrapolated back in time from late 1960s

Job-specific exposure information with range 1-188 fibers/cc



71% of workers had missing department and job title (706/991) during this time.

Only 1% of workers had missing department and job title (9/880)

EPA identified the sub-cohort hired after 1959 as most appropriate study population.

- Reduces measurement error
- Reduces bias

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Variety of Exposure Metrics Evaluated

(Section 5.4.2.5)

➢ Responsive to SAB's review of OSWER asbestos modeling.

➢ Allows exploration of the influence of early versus late exposures

- CE metric gives equal weight to all exposures
- Residence-time weighted CE gives relatively greater weight to early exposures
- Decay (half-lives) gives relatively greater weight to late exposures

➢ When also considering lags and decay rates, a suite of 40 different parameterizations of exposure metrics considered:

- Lag time to account for cancer latency (0, 5, 10, 15, or 20 years)
- Decay of exposure metric (half-life of 5, 10, 15, or 20 years)

➢ For mesothelioma, the metric proposed by Peto and used by Nicholson in IRIS assessment of asbestos (EPA, 1986a) was also evaluated.

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Cancer Exposure-Response Modeling

(Section 5.4.3.6)

> For each kind of cancer modeled, EPA used a model form similar to those in the literature for this cohort.

- o Mesothelioma:
 - Absolute risk model [EPA, 1986a; Moolgavkar et al., 2010]
 - Specifically, a Poisson regression absolute risk model used for rare events (McDonald et al., 2004)
- o Lung cancer:
 - Relative risk model [EPA, 1986a; Sullivan, 2007]
 - Specifically, Cox regression relative risk models used for analysis of time-varying exposures [Larson et al., 2010a; Moolgavkar et al., 2010]

> Model / exposure metric selection criteria based on relative model fit; then selected health-protective when similar fit.

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Cancer Exposure-Response Results

(Section 5.4.4)

> Model / exposure-metric results

- o Mesothelioma:
 - The best-fitting approach had lagged CE with decay (Table 5-11)
 - The metrics that gave more weight to early exposures, such as the Peto model used by Nicholson used in the 1986 IRIS assessment of asbestos (EPA, 1986a) and RTW models, did not fit this data well.
- o Lung cancer:
 - Adequate model fit with multiple exposure metrics (Table 5-12)
 - The best-fitting approach had lagged CE with or without decay

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Derivation of the Cancer IUR (Section 5.4.5)

- 1) Point of Departure (POD): (Appendix G)
 - Exposure-response models for each cancer were used to calculate lifetime cancer risk
 - Response: 1% extra risk of mortality for continuous lifetime exposure (central estimate and 95% lower bound)
- 2) Cancer-specific unit risks were obtained by dividing the extra risk (1%) by the POD (lower bound on risk-specific exposure).
 - Mode of action not established.
 - Linear extrapolation default.

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Derivation of the Cancer IUR (Section 5.4.5)

- 3) Mesothelioma unit risk adjusted to compensate for underascertainment of deaths (Kopylev et al., 2011)
 - Adjustment factor of 1.39 times (39% increase)
- 4) The cancer-specific unit risk estimates for mortality from mesothelioma and lung cancer separately were then statistically combined to derive the proposed IUR=0.17 per fibers/cc (see Section 5.4.5.3 for combined cancer)

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- Comparison with other result shows a very similar estimate of mesothelioma cancer unit risks.
- EPA's central estimate of lung cancer unit risk is higher than that of others using this cohort.

Study	Mesothelioma		Lung Cancer	
	Cases/N	Estimated lifetime risk (per fibers/cc)	Cases/N	Estimated Lifetime risk (per fibers/cc)
EPA (this assessment)	7/880	Upper Bound = 0.12 Central = 0.08	32/880	Upper Bound = 0.068 Central = 0.040
Sullivan, 2007	15/1,672	(No estimates of absolute risk)	99/1,672	Upper Bound = 0.037 Central = 0.023
Berman and Crump, 2008	19/1,672	(No estimates provided)	93/1,672	Upper Bound = 0.079 Central = 0.027
Moolgavkar et al., 2010	15/1,662	Upper Bound = 0.13 Central = 0.08	95/1,662	Upper Bound = 0.011 Central = 0.009
Larson et al., 2010	19/1,862	(No estimates of absolute risk)	98/1,862	Upper Bound = 0.010 Central = 0.007

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Smoking and Lung Cancer (Section 5.4.6)

- Looked at potential confounding of lung cancer results (Section 5.4.6.1.6).
 - Restriction to sub-cohort partially limits confounding by smoking
 - Modeling of birth date partially addresses changes in smoking patterns
 - Proportional hazard test did not show changes over time when smoking rates were changing after Surgeon General's report (1964)
- Method of Richardson (2010) to evaluate confounding by smoking in the absence of data on smoking did not suggest any confounding. (Section 5.4.3.6.5)
- Lung cancer results may reflect effect modification (Section 5.4.6.1.7)
 - Possible that the estimated effect for lung cancer is actually the risk for an interaction between Libby Amphibole asbestos and smoking
 - Would overestimate risk in populations with lower smoking rates

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Charge asks your advice on key decision points:

Data on which the IUR is based:

- Choice of sub-cohort
- Missing data (employment)

Quantitative assessment:

- Exposure-Response Modeling
 - Exposure metric
 - Model selection
- Adjustment for mesothelioma under ascertainment
- Derivation of combined unit risk for lung cancer and mesothelioma mortality
- Smoking as a potential confounder

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Additional Literature

- Supports EPA's finding that pleural thickening is observed in the low exposure range.

Association Between Cumulative Fiber Exposure and Respiratory Outcomes Among Libby Vermiculite Workers (Larson et al., JOEM, 2012)

Radiographic Evidence of Non-occupational Asbestos Exposure from Processing Libby Vermiculite in Minneapolis Minnesota (Alexander, et al., EHP, 2011)

Modeling community asbestos exposure near a vermiculite processing facility: Impact of human activities on cumulative exposure (Adgate et al., Journal of Exposure Science and Environmental Epidemiology (2011) 21, 529-535)

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Additional Literature

- Supports EPA's finding that pleural plaques may contribute to observations of restrictive lung function deficits.

Do asbestos-related pleural plaques on HRCT scans cause restrictive impairment in the absence of pulmonary fibrosis? {Clin et al., 2011, Thorax 2011 Nov;66(11):985-91}

Radiographic Abnormalities and Spirometry Results in a Cohort Exposed to Libby Amphibole. Larson et al., 2009-abstract Am J Respir Crit Care Med 179;2009:A5894. [Full publication upcoming]

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Additional Literature

- Supports EPA's focus sub-cohort that minimizes exposure measurement error.

A meta-analysis of asbestos and lung cancer: Is better quality exposure assessment associated with steeper slopes of the exposure-response relationships? {Lenters et al. 2011, Env. Health Perspectives, Nov;119(11):1547-55.}

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Thank You

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Water, Office of Children's Health
Protection and Regions 2, 7, 8, and 10*
Interagency Science Consultation:
Department of Defense
Department of Health and Human Services
(ATSDR, NIEHS and NIOSH)
Office of Management and Budget
Council on Environmental Quality