APPENDIX B

APPENDIX B

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

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APPENDIX B – 1

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":

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- 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),

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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.

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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.].

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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.

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APPENDIX B – 2

April 9, 2012

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

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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

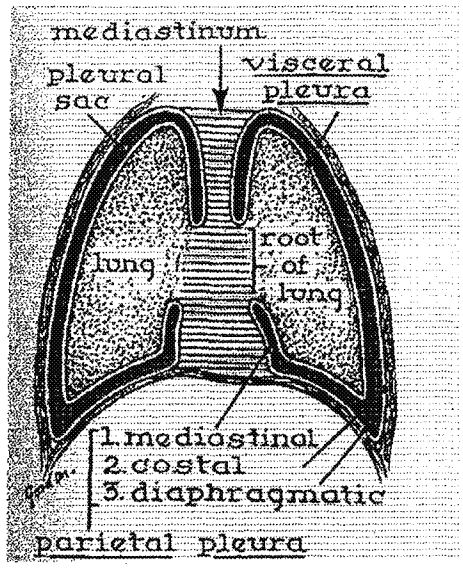
> short interval period. Simple spirometric measurements have been shown to be sensitive indicators of the toxic effects of cumulative asbestos exposure... The level of cumulative fiber exposure needed to cause a change in spirometric values is greater than the exposure levels reported in the present 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).

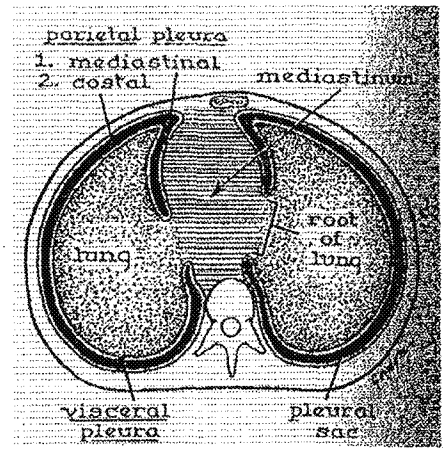
All of these cumulative exposure values are orders of magnitude greater than those relied upon by EPA in the Rohs et al. study.

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 changes[27] 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.

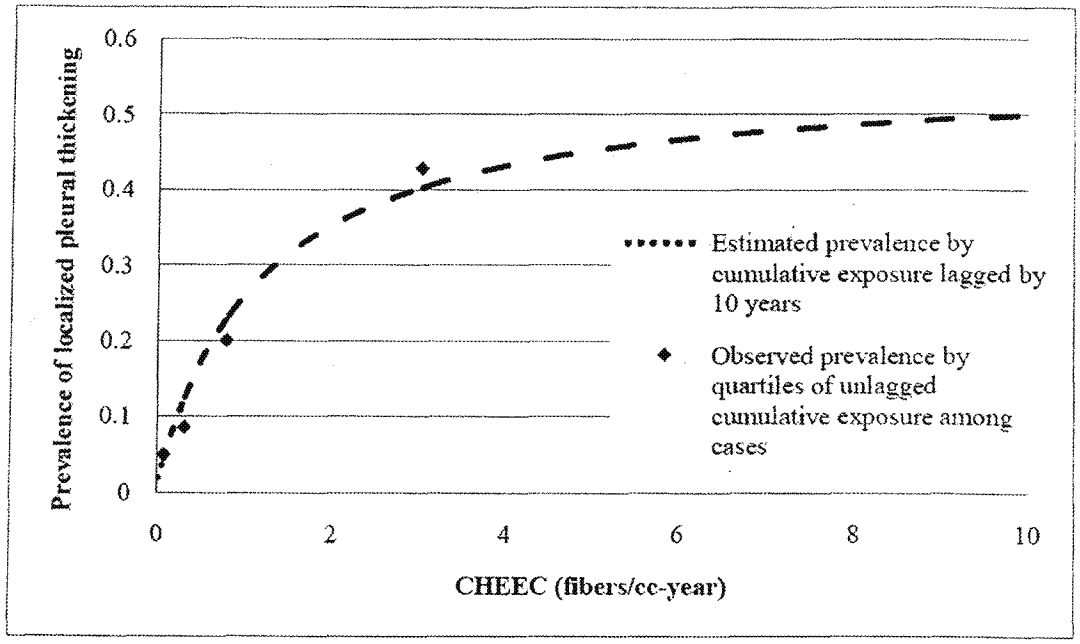


Figure 1. EPA's dose-response model fit for pleural thickening versus raw data in quartiles of cases (Figure E-1 in EPA Draft Toxicological Review)

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 f/cc-years
- UF = 10 and 10 = 100
- POD/UF = 0.001177 f/cc-years
- ED = 70 years (lifetime) – 10 years (lag) = 60 years
- RfC = POD/UF/ED = 0.0000196 f/cc (rounds to 0.00002 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 × 30 years), which is only about ½ 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

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[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+Presntation_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.

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

From EPA Libby 2010 SAP (see note 1)						Calculated		
Scenario	Exposure Time (hrs)	Exposure Frequency (days/year)	Target Analytical Sensitivity (f/cc)	note	Draft RfC (f/cc)	Time Weighting Factor, TWF (3)	Required target sensitivity for noncancer Hazard Quotient (HQ) = 1 (4)	Required target sensitivity for 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:

1. 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_SupplementalABS_SAP.pdf
2. 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*
3. 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
5. 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 (5.66×10^7/Volume sampled in Liters)
   Low end assumes $135 per sample including 10 grid openings plus $5 per grid opening thereafter

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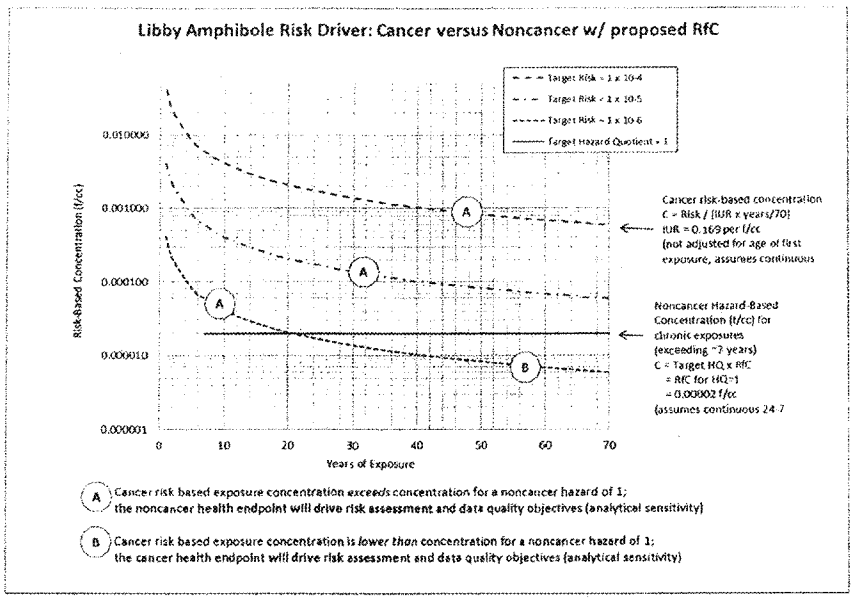
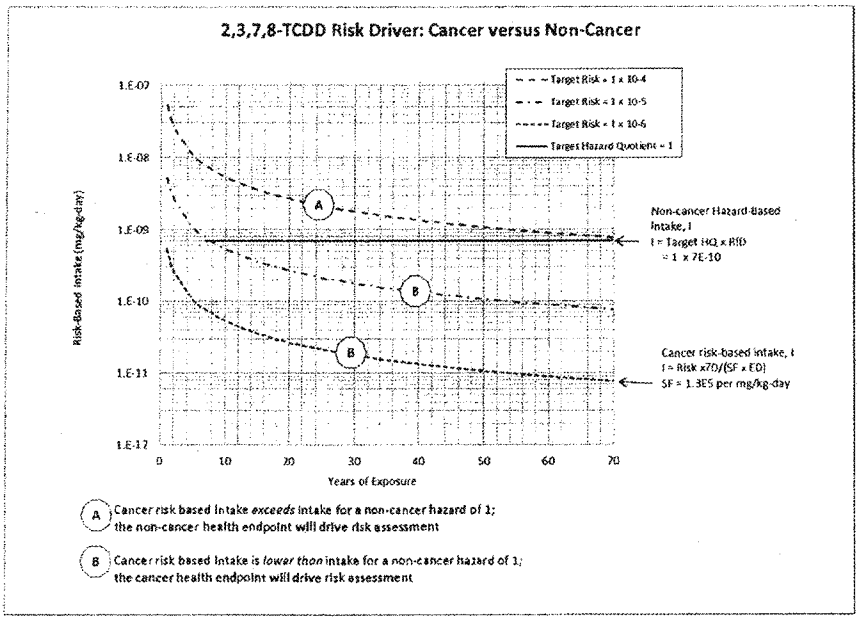

Libby Amphibole Risk Driver: Cancer versus Noncancer w/ proposed RfC
Target Risk = 1 x 10-4
Target Risk = 1 x 10-5
Target Risk = 1 x 10-6
Target Hazard Quotient = 1
Risk-Based Concentration (f/cc)
0.010000
0.001000
0.000100
0.000010
0.000001
0
10
20
30
40
50
60
70
Years of Exposure
A
B
Cancer risk-based concentration
C = Risk / [IUR x years/70]
IUR = 0.169 per f/cc
(not adjusted for age of first exposure, assumes continuous
Noncancer Hazard-Based Concentration (f/cc) for chronic exposures (exceeding ~7 years)
C = Target HQ x RfC
= RfC for HQ=1
= 0.00802 f/cc
(assumes continuous 24-7
A Cancer risk based exposure concentration exceeds concentration for a noncancer hazard of 1; the noncancer health endpoint will drive risk assessment and data quality objectives (analytical sensitivity)
B Cancer risk based exposure concentration is lower than concentration for a noncancer hazard of 1; the cancer health endpoint will drive risk assessment and data quality objectives (analytical sensitivity)


2,3,7,8-TCDD Risk Driver: Cancer versus Non-Cancer
Target Risk = 1 x 10-4
Target Risk = 1 x 10-5
Target Risk = 1 x 10-6
Target Hazard Quotient = 1
Risk-Based Intake (mg/kg-day)
1.E-07
1.E-08
1.E-09
1.E-10
1.E-11
1.E-12
0
10
20
30
40
50
60
70
Years of Exposure
A
B
Non-cancer Hazard-Based Intake, I
I = Target HQ x RfD
= 1 x 7E-10
Cancer risk-based intake, I
I = Risk x70/(SF x ED)
SF = 1.3E5 per mg/kg-day
A Cancer risk based intake exceeds intake for a non-cancer hazard of 1; the non-cancer health endpoint will drive risk assessment
B Cancer risk based intake is lower than intake for a non-cancer hazard of 1; the cancer health endpoint will drive risk assessment

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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.

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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.

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"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 at 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." 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.

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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 and 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.

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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

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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] The 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.

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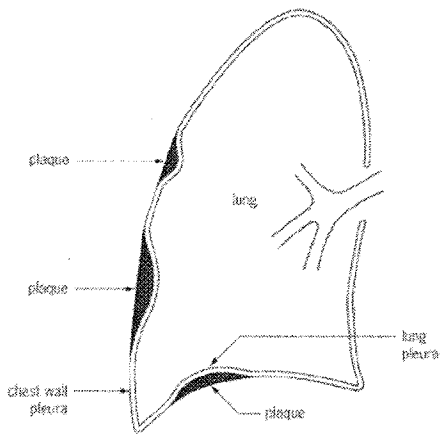
Pleural Plaques (Localized Pleural Thickening)

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 predominence 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

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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 "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]

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

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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]

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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]

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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]

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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 pneumonconioses 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.

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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), costophenic 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

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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 plural 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

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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 at 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 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.

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

I was retained by Exponent to review the EPA draft assessment and provide comments to the EPA and the SAB; I understand that the work was funded by W R Grace.

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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:10.10.1136/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*

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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.

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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 $\geq$ 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

spirometery; 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 care 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.

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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.

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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]

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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 $\geq$ 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.

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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]

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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 / m^2). 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 / m^2). 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 / m^2). 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 BM1 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 sine 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 PLEUAL 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

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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

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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 Heath 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

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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 Heath 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).

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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.

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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

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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 Heath 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