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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EXECUTIVE SUMMARY

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

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

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

CONCLUSIONS

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

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

2. There is no *weight of evidence* study, based upon scientifically rigorous *weight of evidence guidelines*, to support the assertion of the EPA Scientific Advisory Board that "LPT is associated with reduced lung function." Thus, it is not clear exactly what scientific criteria the EPA Scientific Advisory Board used to support this statement.

3. The body of literature cited in the DRAFT Quality Review Report to support the assertion that "LPT is associated with reduced lung function" does not provide a definitive, scientifically rigorous basis for making such an assertion. Indeed, one cited publication does not even address the relationship between LPT and lung function and one cited publication is a letter to the editor regarding another cited publication without consideration of the scientifically robust response from the authors.

4. In its DRAFT Quality Review Report, the EPA Scientific Advisory Board did not consider, or even mention, the results of a robust, peer-reviewed Delphi Study that was published as the *American College of Chest Physicians Consensus Statement on the Respiratory Health Effects of Asbestos* in the journal *CHEST* [4] in which there was *strong disagreement* by a panel of 71 experts in the respiratory health effects of asbestos with the statement "pleural plaques alter lung function to a clinically significant degree."

5. In its DRAFT Quality Review Report, the EPA Scientific Advisory Board did not consider, or even mention, the findings of the *Public Health Assessment of the Libby Asbestos Site* that was prepared by the Division of 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

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).

INTRODUCTION

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

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

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

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

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

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

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

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

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

During my review of the DRAFT Quality Review Report, I could find no indication that The Scientific Advisory Board considered the findings of the *Public Health Assessment of the Libby Asbestos Site* that was prepared by the Division of 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

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

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

CRITICAL ASSESSMENT OF THE LITERATURE CITED IN THE SAB REPORT

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

CONCLUSIONS

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

1. There is a large body of conflicting and inconclusive peer-reviewed scientific literature regarding the relationship between asbestos-related localized pleural thickening and lung function. In this regard, there is considerable uncertainty about the scientific validity of any assertion that "LPT is associated with reduced lung function." Further rigorous scientific evaluation is necessary before the EPA Scientific Advisory Board can make this assertion with any acceptable degree of scientific certainty.

2. There is no *weight of evidence* study, based upon scientifically rigorous *weight of evidence guidelines*, to support the assertion of the EPA Scientific Advisory Board that "LPT is associated with reduced lung function." Thus, it is not clear exactly what scientific criteria the EPA Scientific Advisory Board used to support this statement.

3. The body of literature cited in the DRAFT Quality Review Report to support the assertion that "LPT is associated with reduced lung function" does not provide a definitive, scientifically rigorous basis for making such an assertion. Indeed, one cited publication does not even address the relationship between LPT and lung function and one cited publication is a letter to the editor regarding another cited publication without consideration of the scientifically robust response from the authors.

4. In its DRAFT Quality Review Report, the EPA Scientific Advisory Board did not consider, or even mention, the results of a robust, peer-reviewed Delphi Study that was published as the *American College of Chest Physicians Consensus Statement on the Respiratory Health Effects of Asbestos* in the journal *CHEST* [4] in which there was *strong disagreement* by a panel of 71 experts in the respiratory health effects of asbestos with the statement "pleural plaques alter lung function to a clinically significant degree."

5. In its DRAFT Quality Review Report, the EPA Scientific Advisory Board did not consider, or even mention, the findings of the *Public Health Assessment of the Libby Asbestos Site* that was prepared by the Division of 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 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).

NOTES:

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

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

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

REFERENCES

1. Cugell DW, Kamp DW. Asbestos and the pleura. A review. Chest 2004; 125: 1103-1117.

2. Peacock C, Copley SJ, Hansell DM. Asbestos-related benign pleural disease. Clin Radiol 2000; 55:422-432.

3. British Thoracic Society. Pleural Plaques. Information for Health Care Professionals. London: 2011.

4. Banks DE, Shi R, McLarty J, et al. American College of Chest Physicians consensus statement on the respiratory health effects of asbestos: Results of a Delphi study. Chest 2009; 135: 1619-1627.

5. Agency for Toxic Substances and Disease Registry, Division of Health Assessment and Consultation. Public Health Assessment: Libby Asbestos Site, Libby County, Montana (EPA Facility ID MT0009083840). Atlanta: 2010.

6. Copely SJ, Wells AU, Rubens MB, et al. Functional consequences of pleural disease evaluated with chest radiography and CT. Radiology 2001; 220: 237-243.

7. Lilis R, Miller A, Godbold E, et al. Pulmonary function and pleural fibrosis: quantitative relationships with an integrative index of pleural abnormalities. Am J Ind Med 1991; 20: 145-161.

8. Paris C, Thierry S, Brochard P, et al. Pleural plaques and asbestos: dose-and- time response relationships based on HRCT data. Eur Respir J 2009; 34: 72-79.

9. Clin B, Paris C, Ameille J, et al. Do asbestosis-related pleural plaques on HRCT scans cause restrictive impairment in the absence of pulmonary fibrosis? Thorax 2011; 66: 985-991.

10. American Thoracic Society. Diagnosis and initial management of nonmalignant diseases related to asbestos. Am J Respir Crit Care Med 2004; 170: 691-715.

11. Ohlson CG, Rydman T, Sundell L, et al. Decreased lung function in long-term asbestos cement workers; a cross-sectional study. Am J Ind Med 1884; 5: 359-366.

12. Ohlson CG, Bodin L, Rydman T, Hogstedt C. Ventilatory decrements in former asbestos cement workers: a four year follow-up. Br J Ind Med 1985; 42: 612-616.

13. Jarvholm B, Sanden A. Pleural plaques and respiratory function. Am J Ind Med 1986; 10: 419-426.

14. Hjortsberg U, Orbaek P, Arborelius M, et al. Railroad workers with pleural plaques: I. spirometric and nitrogen washout investigation on smoking and nonsmoking asbestos-exposed workers. Am J Ind Med 1988; 14: 635-641.

15. Oliver LC, Eisen EA, Greene R, Sprince NL. Asbestos-related pleural plaques and lung function. Am J Ind Med 1988; 14: 649-656.

16. Bourbeau J, Ernst P, Chrome J, et al. The relationship between respiratory impairment and asbestos-related pleural abnormality in an active work force. Am Rev Respir Dis 1990; 142: 837-842.

17. Schwartz DA, Fuortes LJ, Galvin JR, et al. Asbestosis-induced pleural fibrosis and impaired lung function. Am Rev Respir Dis 1990; 141: 321-326.

18. Miller A, Lilis R, Godbold J, et al. Relationship of pulmonary function to radiographic interstitial fibrosis in 2,611 long-term asbestos insulators. Am Rev Respir Dis 1992; 145: 263-270.

19. Van Cleemput J, DeRaeve H, Verschakelen JA, et al. Surface of localized pleural plaques quantitated by computed tomogrraphy scanning – no relation with cumulative asbestos exposure and no effect on lung function. Am J Respir Crit Care Med 2001; 163: 705-710.

20. Miller A. Pleural plaques and lung function [Letter to the Editor]. Am J Respir Crit Care Med 2002; 165: 305-306.

21. Whitehouse AC. Asbestos-related pleural disease due to tremolite associated with progressive loss of lung function: serial observations in 123 miners, family members, and residents of Libby, Montana. Am J Ind Med 2004; 46: 219-225.

22. Sichletidis L, Chloros D, Chatzidimitriou N, et al. Diachronic study of pleural plaques in rural population with environmental exposure to asbestos. Am J Ind Med 2006; 49: 643-641.

23. Wilken D, Garrido MV, Manuwald U, Baur X. Lung function in asbestos-exposed workers, a systematic review and meta-analysis. J Occupat Med and Tox 2011; 6: 21.

24. Weed DL. Weight of evidence; a review of concept and methods. Risk Anal 2005; 25: 1545-1557.

25. Linkov I. Weight of evidence: what is the state of science? [Letter to the Editor]. Risk Anal 2006; 26: 573-575.

26. Linkov I, Loney D, Cormier S, et al. Weight-of-evidence evaluation in environmental assessment; review of qualitative and quantitative approaches. Sci Tot Environ 2009; 407: 5199-5205.