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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EXECUTIVE SUMMARY

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

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

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

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

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

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

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

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

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

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

In my opinion, this statement is poorly worded. The two references cited to support this statement (Schwartz et al 1993; Copeley 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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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.

BACKGROUND

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

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

Nonmalignant Pleural Disease

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

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

Benign Asbestos Pleural Effusion (BAPE)

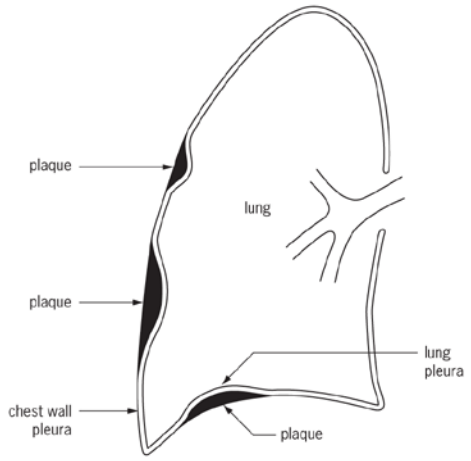
Benign asbestos pleural effusions (BAPE) are thought to be the earliest pleural disorder to occur following asbestosis exposure. [2, 3] Benign pleural effusions were first described in relation to asbestos exposure in the 1960s. [2, 4] Their exact prevalence is unknown, since many cases are subclinical, but one study estimates a prevalence of 3% among 1135 asbestosis-exposed workers. [2, 4, 5] Benign asbestos pleural effusions usually occur within 10 years of exposure [6], but they may develop much later, as well. [3] They are typically hemorrhagic exudates containing mixed cell types and usually do not contain asbestos bodies (so called "ferruginous bodies"). [1, 5] The majority of benign asbestos pleural effusions are unilateral, although bilateral effusions have been reported. [5, 7] Typically, benign asbestos pleural effusions are asymptomatic, but they may be associated with fever and/or pleuritic chest pain. [7] The pleural effusions usually resolve over a few months, but can persist for longer periods or recur after initial resolution. [1, 2] Of importance is the fact that *diffuse pleural thickening* of the *visceral pleura* is commonly seen after resolution of benign asbestosis pleural effusions. [5, 7] 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.

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

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

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

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

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

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

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

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

Rounded Atelectasis

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

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

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

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

Asbestosis Related Lung Fibrosis - Asbestosis

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

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

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

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

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

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

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

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

DEFINITIONS – INTERNATIONAL LABOR (ILO) CLASSIFICATION OF PNEUMOCONIOSES

In 1980, the International Labor Office (ILO) published guidelines for the classification of pleural and parenchymal radiographic findings caused by pneumoconioses. This was entitled *Guidelines for the Use of the ILO International Classification of Radiographs of Pneumoconioses*. These guidelines were intended to facilitate the coding of the posterior-anterior chest radiograph abnormalities of individuals with 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.

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

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

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.

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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*

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

In my opinion, there are potentially significant limitations of this study. This is especially true with regard to *limitations of the data that were available and analyzed by the authors*. Although the methods of data analysis appear to be appropriate, limitations in the data itself introduce considerable uncertainty in the robustness of the above conclusions. Some of the study limitations were appropriately acknowledged and discussed by the authors in the manuscript. I will provide my opinion of potential study limitations in the paragraphs that follows.

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

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

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

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

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

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

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

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

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

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

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

1. The pulmonary function of the screened population as a whole is well within normal limits in all age groups, smoking categories and exposure groups. There was an expected detrimental effect on lung function due to cigarette smoking.

2. In both females and males, and considering smokers and never-smokers, the prevalence of pleural plaques increased with age quartile. As expected, the prevalence of pleural plaques among all age groups was much less in the environmental exposure group (range 0.42–12.74%), as compared with those that worked at the mine (range 20–45.68%), or those who lived with a mine worker (range 1.34–37.67%).

3. With regard to the effect of pleural plaques on FVC in males, there was a small, probably clinically insignificant reduction of < 4.5%. There was no effect attributable to radiographic findings of plaque seen in females.

4. The closing of the old wet and dry mills at the facility appears to be associated with an overall post-1976 reduction in pleural abnormalities in the general population, resulting in prevalence rates < 2% for plaque and < 0.2% for DPT or CAO.

5. DPT is associated with a reduction in FVC, particularly when found to be greater than extent 2 and width a. [1980 ILO Classification]

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

As in the three other recent Libby-related studies reviewed in this report, it is possible that, in some cases, subpleural fat could have been misinterpreted as pleural plaques on the posterior-anterior chest radiographs evaluated in this study. The mean body mass index (BMI) of study subjects was above average in all age groups. The mean BMI of subjects with pleural abnormalities exclusive of diffuse pleural thickening (DPT), costophrenic angle obstruction (CAO) or profusion $\geq$ 1/0 was in the obese range (30.30 +/- 0.24 kg / 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.