

# **Libby Amphibole Asbestos Science Advisory Board**

## **Panel Comments**

### **1. Introduction**

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

The Revised ILO 2000 Guidelines state the following at page7:

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

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

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

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

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

### 3. Tremolite asbestos compared to LAA

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

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

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

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

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

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

#### 4. In vitro comparison studies

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

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

The SAB should recommend to EPA the following:

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

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# Attachment 1

## Professional Background

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

## Attachment 2

### References Cited

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