Libby vermiculite exposure and risk of developing asbestos-related lung and pleural diseases

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Purpose of review
The vermiculite ore formerly mined in Libby, Montana, contains asbestiform amphibole fibers of winchite, richterite, and tremolite asbestos. Because of the public health impact of widespread occupational and nonoccupational exposure to amphiboles in Libby vermiculite, numerous related studies have been published in recent years. Here we review current research related to this issue.

Recent findings
Excess morbidity and mortality classically associated with asbestos exposure have been well documented among persons exposed to Libby vermiculite. Excess morbidity and mortality have likewise been documented among persons with only nonoccupational exposure. A strong exposure–response relationship exists for many malignant and nonmalignant outcomes and the most common outcome, pleural plaques, may occur at low lifetime cumulative exposures.

Summary
The public health situation related to Libby, Montana, has led to huge investments in public health actions and research. The resulting studies have added much to the body of knowledge concerning health effects of exposures to Libby amphibole fibers specifically and asbestos exposure in general.

Keywords
amphibole, asbestos, Libby, respiratory diseases, vermiculite

INTRODUCTION

A vermiculite mine and mill located near Libby, Montana, operated from the early 1920s until 1990. Vermiculite is a naturally occurring laminar aluminum-iron-magnesium silicate. It expands when heated, and has been employed in many applications, such as loose-fill attic insulation, soil additive, and carrier for various chemicals, including herbicides, insecticides, and fertilizers [1]. Vermiculite from other sources is not known to be associated with any substantial adverse health effects [2,3]; however, the vermiculite ore mined in Libby contained elongate mineral particles identified as a mixture of asbestiform amphiboles, including winchite, richterite, and tremolite asbestos [4]. Not only were workers at the mine and mill exposed, but the vermiculite was used in Libby for covering ball fields and outdoor athletic tracks, as loose-fill insulation in buildings, and in gardening activities [5]. This resulted in widespread contamination of the Libby community with asbestos. In addition, the fact that a very large estimated number of homes were insulated with Libby vermiculite represents an ongoing potential hazard. Moreover, Libby vermiculite was shipped throughout the US to more than 200 domestic processing and receiving facilities [6]. Interestingly, the first identification by public health authorities of pulmonary abnormalities associated with Libby vermiculite concerned exposures outside of Libby. Benign pleural effusions were identified among 12 workers in a vermiculite processing plant in Marysville, Ohio, which received most of its vermiculite from Libby [1]. This review will focus on the main nonmalignant and malignant respiratory outcomes associated with exposure to Libby vermiculite, with emphasis on recent findings.

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NONMALIGNANT RESPIRATORY OUTCOMES

The results of several studies have shown excessive mortality attributed to nonmalignant respiratory disease (NMRD) among sub-cohorts of Libby mine and mill workers. In a study commissioned by the mine owners, McDonald et al. [7] found an elevated overall standardized mortality ratio (SMR) of 2.55 for NMRD among mine workers employed for at least 1 year. NMRD mortality was clearly associated with exposure to Libby vermiculite, with SMRs of 3.36 for 10–19 years and 5.30 for more than 20 years since first employment [7]. In another study of Libby mine and mill workers, researchers from the National Institute for Occupational Safety and Health (NIOSH) found a SMR for NMRD of 2.43 [95% confidence interval (CI) 1.48–3.75] [8]. A subsequent expansion and updating of this Libby worker cohort, including all white men who worked in the Libby plant from 1935 to 1981, found a SMR for NMRD of 2.4 (95% CI 2.0–2.9), again demonstrating an obvious correlation with exposure duration: 2.1 for less than 1 year, 2.4 for 1–9.9 years, and 3.6 for more than 10 years [9]. More recently, these results were corroborated by an independent analysis [10[■]]. In addition, McDonald et al. [11] also updated their cohort study to 1998, finding an overall SMR for NMRD of 3.09 (95% CI 2.30–4.06), also associated with cumulative exposure. Finally, Larson et al. [12[■]] updated mortality in the cohort of Libby vermiculite workers through 2006 and, using a multiple cause-of-death approach with an internal comparison, modeled the exposure–response relationship between cumulative exposure to Libby amphibole fiber and select causes of mortality. SMR results for NMRD were similar to previous studies [SMR = 2.4 (95% CI 2.2–2.6)]. Using quartiles of cumulative fiber exposure (CFE) (f/cc-y) in a categorical model, the rate ratios (and 95% CIs) for NMRD were 1.4 (0.9–2.1), 1.8 (1.3–2.7), and 2.5 (1.7–3.6) for 1.4 to below 8.6, 8.6 to below 44.0, and at least 44.0 f/cc-y, respectively [12[■]]. Although most of these studies have a long period of vital status follow-up, important limitations include the potential for exposure misclassification, dependence on death certificate information, and the absence of smoking data.

A few studies have specifically evaluated the mortality from asbestosis among persons exposed to Libby vermiculite. Sullivan [9] reported 22 deaths from asbestosis (expected = 0.13 deaths) among 1672 Libby vermiculite workers during 1960–2001, for a SMR of 165.8 (95% CI 103.9–251.1); this study revealed a striking association of asbestosis mortality with levels of cumulative exposure and duration of exposure. A recent update [12[■]] of that cohort also demonstrated an elevated SMR for asbestosis of 142.8 (95% CI 111.1–180.8) and a rate ratio of 11.8 (95% CI 4.9–28.7) in the highest exposure group (44.0 f/cc-y).

A study [13[■]] of Libby residents who were 18 years of age or less when the vermiculite mine closed in 1990 identified self-reported respiratory symptoms that were associated with several vermiculite exposure pathways. Prevalences of several of these, including cough (10.8%), shortness of breath (14.5%), and coughing up bloody phlegm (5.9%), were higher than expected based on comparison with national population rates from the 2001 to 2002 National Health and Nutrition Examination Survey (NHANES), controlling for sex, age, smoking status, and family smoking status.

RADIOGRAPHIC PLEURAL ABNORMALITIES

The most common pleural abnormalities associated with asbestos exposure are localized pleural thickening (pleural plaques) and diffuse pleural thickening, either of which can be accompanied by pleural calcification [14]. These are also commonly found among persons with occupational and nonoccupational exposure to Libby vermiculite. Most epidemiological studies use the International Labour Office (ILO) International Classification of Radiographs of Pneumoconioses [15] to determine the presence and location of pleural abnormalities in asbestos-exposed populations.

In an early radiographic survey conducted by NIOSH researchers [16], the prevalence of any pleural abnormality (pleural plaque or diffuse pleural thickening of the chest wall, diaphragm, or other site, excluding costophrenic angle obliteration) was 15.2% among 184 active Libby mine workers, with a statistically significant association with CFE. The prevalence of pleural abnormalities of the chest wall was 13.0%. In another study of the Libby mining operation, McDonald et al. [17] found a comparable

prevalence of 15.9% pleural abnormalities of the chest wall among 164 active miners; the corresponding prevalence among 80 former mine workers was 52.5%.

As part of the federal response to the widespread asbestos contamination in Libby, the Agency for Toxic Substances and Disease Registry (ATSDR) offered health screenings for the population. A total of 6668 persons participated in radiographic screening during 2000–2001. An exposure–response relationship was evident between exposure pathways and the prevalence of pleural abnormalities, which was 51% among former mine workers, 23% among household contacts of former workers, and 14% among other Libby residents [5]. In another round of screenings conducted in 2003–2007, with the participation of 2954 persons, the prevalence of pleural abnormalities was similar: 53, 24, and 16%, respectively, for the previously mentioned exposure categories (Helgerson S, personal communication).

A follow-up study [18] re-evaluated the chest radiographic status of the original 1980 Marysville worker cohort [1] 25 years after their last exposure to Libby vermiculite. The prevalence of pleural changes among the 280 participants was 28.7%. A significant trend of increasing prevalence of localized pleural changes with increasing cumulative exposure was observed among Marysville workers. Further, prevalence of pleural abnormalities was associated with very low lifetime cumulative exposures, even among persons with less than 1 f/cc-y [18].

Several factors may affect the accurate detection of pleural abnormalities. One concern with using conventional radiographs to identify asbestos-related diseases is their apparent lack of sensitivity and specificity for detecting these lesions. Using high-resolution computed tomography (HRCT) of the chest, Muravov *et al.* [19] found pleural abnormalities in 28% of 353 Libby residents whose radiographs had been found to be 'indeterminate' based on classifications by three B Readers, indicating standard chest radiography may not be the optimal method for detecting subtle pleural abnormalities. However, an important limitation of that study was the lack of HRCTs of people with totally negative or totally positive chest radiographs, which may have restricted its conclusions. Screening the Libby population has also shown that pleural fat can be mistaken for pleural plaque on chest radiographs [20]. Among participants of the screening program in Libby, 32% were obese; hence there is a need to control for the potential confounding effect of body mass index in analyses relating to pleural thickening in asbestos-exposed populations [5]. Another issue is the latency between initial exposure to asbestos and

detection of associated pleural abnormalities in chest radiographs. By conducting a study that used retrospective analysis of a series of chest radiographs of Libby vermiculite workers, Larson *et al.* [21■] recently demonstrated that this period may be shorter than usually reported for asbestos-exposed workers (i.e. 20 years for pleural plaques [14]). The median latency for detecting localized pleural thickening was 8.6 years, ranging from 1.4 to 14.7 years. For diffuse pleural thickening, the median (range) latency from hire date was 27 years (10.7–29.8 years). Clinicians should be aware that latencies for plaque may be shorter than has been reported previously for asbestos-exposed workers, and that plaque can occur in pediatric patients.

Recent findings from a large community-based cohort study in Libby [22] demonstrated a statistically significant association between localized pleural thickening and restrictive spirometry. In addition, among patients with restrictive spirometry, the odds of functional impairment increased with extent of localized pleural thickening.

RADIOGRAPHIC PARENCHYMAL ABNORMALITIES

Asbestosis is the interstitial pneumonitis and fibrosis caused by inhalation of asbestos fibers; its prevalence is influenced by duration and intensity of exposure [14]. The radiographic presentation of asbestosis is usually of small irregular parenchymal opacities in the lower lobes bilaterally. Most epidemiological studies use the International Labour Office (ILO) International Classification of Radiographs of Pneumoconioses [15] to determine the presence and extent (profusion) of parenchymal abnormalities in asbestos-exposed populations.

The first studies to describe the prevalence of parenchymal abnormalities in Libby vermiculite workers found it to range from 10 to 18% and to be strongly associated with CFE [16,17]. Peipins *et al.* [5] reported that the overall prevalence of parenchymal abnormalities among 6668 individuals screened by ATSDR in 2000–2001 was 0.8% and varied among different exposure groups: 3.8% for former mine workers, 1.2% for household contacts, and 0.5% for other residents. These prevalences were somewhat higher among participants of the second ATSDR screening activity (13.3, 2.5, and 4%, respectively), possibly due to differences in radiographic reading methods, such as the number of B Readers used (Helgerson S, personal communication). Of the 280 Marysville workers followed up 25 years after their last exposure to Libby vermiculite, eight (2.9%) had parenchymal abnormalities consistent with asbestosis [18]. The mean CFE for these eight was

significantly greater than that for Marysville workers with normal radiographs and also significantly greater than that for Marysville workers with pleural abnormalities only.

Among asbestos-related diseases, radiographic parenchymal abnormalities are generally more strongly associated with lung function defects, specifically restrictive pattern, than are radiographic pleural abnormalities. As expected, in a recent analysis of 6475 screening participants [22], we found that restrictive spirometry was strongly associated with parenchymal abnormalities [odds ratio (OR) 2.9; 95% CI 1.4–6.0], after controlling for age, sex, smoking status, and body mass index.

MALIGNANT DISEASES

According to the International Agency for Research on Cancer (IARC), all forms of asbestos are carcinogenic to humans. In addition, mineral substances (e.g. talc or vermiculite) that contain asbestos should also be regarded as carcinogenic to humans. The most common malignancies associated with asbestos exposure are lung cancer and malignant mesothelioma of the pleura, peritoneum, and other sites. More recently, IARC deemed that cancers of the larynx and ovary were also caused by asbestos exposure, and there was limited evidence for associations between asbestos exposure and cancers of the colorectum, pharynx, and stomach [23].

All epidemiological studies that have assessed the association between exposure to the Libby vermiculite and cancers of the respiratory tract have found a strong relationship. Using the US white male population as comparison, Amandus and Wheeler [8] described a SMR of 2.23 (95% CI 1.36–3.45) for respiratory cancers, and McDonald et al. [7] found a corresponding SMR of 2.45. Both studies observed statistically significant associations with CFE and time since first exposure. When Montana controls were used instead of national US rates, the SMR increased to 3.03 in the latter study [7]. An update of that cohort to 1999, which doubled the number of respiratory cancers in the analysis, found a SMR of 2.40 (95% CI 1.74–3.22) [11]. Similarly, Sullivan [9] found 89 cases of cancer of the trachea, bronchus, or lung, for a SMR of 1.7 (95% CI 1.4–2.1); in addition, two deaths from mesothelioma (in 1999–2001) and four deaths from cancer of the pleura were identified, for SMRs of 15.1 (95% CI 1.8–54.4) and 23.3 (95% CI 6.3–59.5), respectively. Both cumulative exposure and exposure duration were statistically significant predictors of lung cancer mortality in that study. A shortcoming of these mortality studies is that the analyses have not been formally controlled for cigarette smoking.

A case series of malignant mesothelioma associated with environmental exposure in Libby described a total of 11 patients (10 pleural, 1 peritoneal) diagnosed in 1995–2006. No occupational exposure was reported in 9 of these 11 patients; many had vermiculite insulation in their homes, lived in the vicinity of vermiculite processing facilities, or were household contacts of workers [24].

As mentioned earlier, Libby vermiculite was shipped to many processing facilities across the US. In an attempt to estimate the burden of asbestos-related disease in these areas, Horton et al. [25] identified 262 sites in 40 states that processed Libby vermiculite. According to death certificates, SMRs for cancer of the pleura and peritoneum were elevated in Portland, OR; Utica, NY; Hamilton Township, NY; Jersey City, NJ; Newark, NJ; Tampa, FL; and Milwaukee, WI. In addition, standardized incidence ratios, calculated using cancer registry data, were elevated in Jersey City, NJ; Kearny, NJ; Camden, NJ; Kenosha, WI; Portland, OR; Jefferson Parish, LA; and six pooled sites in IL [25]. Although this ecological study cannot directly link exposure to Libby vermiculite with asbestos-related disease, it suggests a need for additional studies in these areas.

More recently, Larson et al. [12▪] demonstrated SMRs for lung cancer among the Libby vermiculite worker cohort to be 1.6 (95% CI 1.3–2.0). Exposure–response analysis of that updated cohort showed that rate ratios for lung cancer increased monotonically with increasing CFE, becoming statistically significant for the fourth quartile: with a CFE at least 44 f/cc-y the rate ratios were 3.2 (95% CI 1.8–5.3) [12▪]. Bias analysis suggested that cigarette smoking had minimal impact on the exposure–response relationships in this study.

CONCLUSION

Strong evidence exists to support the association between exposure to asbestiform amphibole fibers in Libby vermiculite and the occurrence of asbestos-related diseases, especially nonmalignant pleural abnormalities, lung cancer, and malignant mesothelioma (Table 1). The studies presented here may share limitations common in other epidemiological studies: some of them lack appropriate comparison populations, whereas others are limited in their ability to control for the potential influence of confounders such as cigarette smoking. Nevertheless, the evidence for causation of disease from Libby amphibole exposure includes several factors: similarity and consistency of results among studies; monotonically increasing exposure–response pattern across studies; and temporal association

Table 1. Summary of key findings on respiratory outcomes associated with Libby amphibole exposure

Outcome studied	Study population	Population size	Study period	Key findings	Reference
NMRD mortality	Libby vermiculite workers	406	Before 1963–1983	SMR 2.55*	[7]
		575	Before 1970–1981	SMR 2.43 (95% CI 1.48–3.75)	[8]
		1672	1960–2001	SMR 2.4 (95% CI 2.0–2.9)	[9]
		1662	1935–1981	SMR 2.29 (95% CI 1.89–2.74)	[10▪]
		406	Before 1963–1999	SMR 3.09 (95% CI 2.30–4.06)	[11]
		1862	1941–2006	SMR 2.4 (95% CI 2.2–2.6)	[12▪]
Respiratory symptoms	ATSDR screening participants**	1003	2000–2001	Higher prevalence compared to NHANES: cough (10.8%); shortness of breath (14.5%); bloody phlegm (5.9%)	[13▪]
Pleural abnormalities	Libby vermiculite workers	184	1975–1982	Prevalence associated with cumulative exposure; 13.0% of active miners had pleural abnormalities on chest wall	[16]
		244	1983	Prevalence associated with cumulative exposure; 15.9% of active miners and 52.5% of former miners had pleural abnormalities on chest wall	[17]
		84	1955–2004	Latency for localized pleural thickening may be shorter than previously reported; plaque may occur in pediatric patients	[21▪]
	ATSDR screening participants	6668	2000–2001	Prevalence 51% among former vermiculite workers; 23% among household contacts; 14% among other residents	[5]
		6668	2000–2001	Odds of restrictive spirometry elevated among those with plaque [OR 1.39 (95% CI 1.09–1.76)] and associated with plaque extent	[22]
		353	2001	Radiographs may not be optimal to detect subtle pleural abnormalities	[19]
	Marysville vermiculite workers	501	1980	Prevalence of pleural effusion 2.4%	[1]
		280	2004–2005	Prevalence 28.7%; localized pleural thickening associated with lifetime cumulative exposures <1 f/cc-y	[18]
Radiographic parenchymal abnormalities	Libby vermiculite workers	184	1975–1982	Prevalence 10%	[16]
		244	1983	Prevalence 18%	[17]
	ATSDR screening participants	6668	2000–2001	Prevalence 3.8% among former vermiculite workers; 1.2% among household contacts; 0.5% among other residents	[5]
		6668	2000–2001	Odds of restrictive spirometry 3.9 (95% CI 1.7–9.0)	[22]
	Marysville vermiculite workers	280	2004–2005	Prevalence 2.9%	[18]

Table 1 (Continued)

Outcome studied	Study population	Population size	Study period	Key findings	Reference
Asbestosis mortality	Libby vermiculite workers	1672	1960–2001	SMR 165.8 (95% CI 103.9–251.1)	[9]
		1862	1941–2006	SMR 142.8 (95% CI 111.1–180.8)	[12■]
Lung cancer mortality	Libby vermiculite workers	575	Before 1970–1981	SMR 223.2 (95% CI 136.3–344.7)	[8]
		406	Before 1963–1983	SMR 3.03 for respiratory cancer	[7]
		406	Before 1963–1999	SMR 2.40 (95% CI 1.74–3.22) for respiratory cancer	[11]
		1672	1960–2001	SMR 1.7 (95% CI 1.4–2.1)	[9]
		1662	1935–1981	SMR 1.65 (95% CI 1.33–2.01)	[10■]
		1862	1941–2006	SMR 1.6 (95% CI 1.3–2.0)	[12■]
Mesothelioma mortality	Libby vermiculite workers	1672	1960–2001	SMR 15.1 (95% CI 1.8–54.4)	[9]

ATSDR, Agency for Toxic Substances and Disease Registry; CI, confidence interval; NHANES, National Health and Nutrition Examination Survey; NMRD, nonmalignant respiratory diseases; OR, odds ratio; SMR, standardized mortality ratio.
*95% CIs not presented in article.
**Restricted to participants who were 18 years of age or less when mine closed.

between start and duration of exposure and disease onset.

The widespread asbestos contamination in Libby has prompted an unprecedented public health response, with large-scale – and still ongoing – health screening supported by ATSDR, and the recent declaration of a public health emergency by the Environmental Protection Agency [26].

REFERENCES AND RECOMMENDED READING

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