

Mesothelioma Associated With Commercial Use of Vermiculite Containing Libby Amphibole

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Objectives: To describe asbestos-related mortality among manufacturing workers who expanded and processed Libby vermiculite that contained amphibole fiber. **Methods:** Standardized mortality ratio was calculated for 465 white male workers 31 years after last Libby vermiculite exposure. **Results:** Two workers died from mesothelioma, resulting in a significantly increased standardized mortality ratio of 10.5 (95% confidence interval, 1.3 to 38.0). These workers were in the upper 10th percentile of cumulative fiber exposure, that is, 43.80 and 47.23 fiber-years/cm³, respectively. One additional worker with cumulative fiber exposure of 5.73 fiber-years/cm³ developed mesothelioma but is not deceased. There were no other significantly increased standardized mortality ratios. **Conclusions:** Workers expanding and processing Libby vermiculite in a manufacturing setting demonstrated an increased risk for the development of mesothelioma following exposure to the amphibole fiber contained within this vermiculite ore source.

Vermiculite is a naturally occurring mineral that has been widely used in consumer products such as insulation, lawn and garden products, and fireproofing material. While vermiculite itself does not pose a known health hazard, the vermiculite mined from Libby, Montana contained 0.1% to 26% naturally occurring asbestiform minerals,^{1,2} characterized as winchite, richterite, and tremolite.³ From the 1920s to 1990, the Libby mine produced up to 80% of the world's vermiculite supply and shipped it to more than 200 US regional processing facilities.^{4,5}

After the occurrence of a cluster of bloody pleural effusions in workers at an Ohio manufacturing facility expanding Libby ver-

miculite, a 1980 study demonstrated a 2.0% prevalence of localized pleural thickening on chest radiographs.⁶ Localized pleural thickening has historically been associated with commercial asbestos exposure. A 2004 follow-up of this cohort demonstrated a marked increase in the rate of pleural changes (28.6% of participants) 25 years after the last Libby amphibole exposure.⁷ These changes, which were demonstrated in some workers at low lifetime cumulative fiber exposure (CFE) levels, occurred in an exposure-response manner.⁷

Mortality studies of Libby miners and millers with historically high exposure to Libby amphibole have demonstrated significantly increased mortality due to lung cancer, mesothelioma, and nonmalignant respiratory diseases (NMRD) including asbestosis, silicosis, and chronic obstructive pulmonary disease.⁸⁻¹¹ There are indications that malignant and nonmalignant respiratory health risks may not be limited to persons with heavy exposures.^{7,9,12-14} Therefore, the purpose of this analysis was to investigate mortality among workers with relatively low lifetime exposure to asbestiform minerals while processing Libby vermiculite at an Ohio lawn care product manufacturing facility.

METHODS

Study Subjects

Subjects comprised a cohort of 513 workers from an Ohio manufacturing facility who participated in an earlier 1980 pulmonary morbidity study.⁶ Demographic and work history data were obtained from the questionnaires administered in 1980.⁶ Because the original cohort was 97% white and 94% men,⁶ the standardized mortality ratio (SMR) analysis was limited to the 465 white men. This mortality study was approved by the University of Cincinnati institutional review board.

Exposure Assessment

The manufacturing plant began using vermiculite from South Carolina in 1957, and from Libby, Montana in 1959, until 1980.¹⁵ Vermiculite was also obtained from Palabora, South Africa and Louisa County, Virginia starting in 1970 and 1979, respectively.¹⁵ On the basis of industrial hygiene measures that began in 1972, exposure of fiber is defined as particles with a length greater than 5 μ m, a diameter less than 3 μ m, and an aspect ratio of 3:1 or more.⁶ Therefore, CFE is not specific to asbestiform minerals, as it may also include other mineral or nonmineral fibers. For Libby vermiculite, the concentration of asbestiform minerals has been shown to be as high as 26% in ore ready for expansion.¹ Vermiculite from South Carolina, South Africa, and Louisa County, Virginia has also been shown to include asbestiform minerals but at a concentration less than 1%.^{16,17} Self-reported work histories collected in 1980 provided details regarding all jobs held as well as beginning and ending dates to calculate CFE estimates in fiber-year/cm³ (f-yr/cc).^{6,7} Worker smoking history and other commercial asbestos exposure information was also collected. For the analysis reported here, previously used CFE estimates^{6,7} were revised on the basis of additional exposure data obtained in 2010.¹⁵

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Ascertainment of Vital Status

All workers in the cohort were known to be alive in 1980 after the National Death Index (NDI) began compiling data on all US deaths (January 1, 1979). Vital status follow-up from May 1980 to December 2009 was done using the NDI. Vital status through June 30, 2011 was updated using Social Security Administration data through the Internet (RootsWeb.com). All workers were assumed to be alive unless discovered otherwise.

Death certificates for deceased workers were obtained according to US and state requirements and regulations for studies involving human subjects. Underlying cause of death was determined by death certificates as coded by a single nosologist according to International Classification of Disease (ICD), 9th and 10th Revisions (ICD-9 and ICD-10),^{18,19} or by NDI Plus (for two deaths for which obtaining death certificates was difficult). The analysis focused on malignancies, including lung cancer and mesothelioma, which have been associated with occupational asbestos exposure. In addition, cancer of the digestive tract was examined. Nonmalignant respiratory diseases were analyzed as separate categories including asbestosis, silicosis, other pneumoconiosis, chronic obstructive pulmonary disease, and other respiratory diseases (including interstitial pulmonary disease with fibrosis).

Before 1999, a unique ICD code for mesothelioma did not exist. Starting in 1999, a unique ICD-10 code (C45) was established for mesothelioma. Therefore, analyses for mesothelioma were based on deaths from 1999 to June 30, 2011, using ICD-10 C45. For deaths from 1980 to 1999, "possible mesothelioma" was categorized for ICD codes including cancer of other respiratory sites, cancer of pleura, and cancer of other and unspecified sites.²⁰

Data Management and Analysis

Questionnaire data (1980) were double entered into SAS PROC FSEDIT and stored as SAS data sets. All death certificate data were double-entered into a Microsoft 2007 ACCESS database and compared using SAS PROC COMPARE. A random 10% of the data was verified with hardcopy records after identified data entry errors were rectified. For white men, Life Table Analysis System (LTAS, Net Version 3.0),²¹ developed by the National Institute for Occupational Safety and Health,^{22–25} was used to determine expected deaths, SMRs, and 95% confidence intervals (CIs). Standardized mortality ratios adjusted for age and calendar year were calculated to determine whether workers experienced a greater mortality from specific causes than was expected on the basis of the US population. For causes of death with larger numbers (all cancers; cancer of trachea, bronchus, or lung; cancer of digestive system and peritoneum), SMRs and standardized rate ratios (SRRs) were calculated using tertiles of the CFE distribution among the 465 workers. For nonwhite and female workers, limited sample size did not allow for SMR analysis stratified by race or gender, and results were described.

RESULTS

Of the 465 white men from the original cohort, 136 were deceased as of June 30, 2011. Demographic and exposure characteristics for selected causes of deaths are shown in Table 1. Among the 136 deceased, 16 (11.8%) died of lung cancer and 2 (1.5%) died of mesothelioma. The mean exposure duration as of 1980 was longer for those who died of lung cancer (16.4 years) and mesothelioma (19.0 years) than all workers (11.0 years). Similarly, mean CFE was higher for deaths due to lung cancer (15.34 f-yr/ee) and mesothelioma (45.51) than for all workers (9.00).

Table 2 shows SMR results. The SMR for mesothelioma based on two deaths that occurred after 1998 was significantly increased at 10.5 (95% CI, 1.3 to 38.0). There were no deaths due to cancer of pleura, peritoneum, or pericardium. There were also no deaths due to silicosis or other pneumoconiosis. The two deaths in the NMRD category "other respiratory diseases" were specifically "interstitial

pulmonary diseases with fibrosis" (J84.1). The 13 cancers of the digestive system and peritoneum consisted of the following: 3 of esophagus (C15.9), 4 of pancreas (C25.9), and 6 of intestine (C18.9).

For causes of death with larger numbers (all cancers; cancer of trachea, bronchus, or lung; cancer of digestive system and peritoneum), SRRs and SMRs were calculated using tertiles of the CFE distribution among the 465 workers (Table 3). There were no significant SRRs or SMRs for these diagnoses. Although not significant, SRRs increased with increasing CFE category for cancer of digestive system and peritoneum.

Of the original cohort of 513 workers, 16 were nonwhite men and 32 were women. The 16 nonwhite men had an average CFE of 2.50 (SD, 7.48) f-yr/ee. Of those 16 nonwhites, 4 were deceased by June 30, 2011. Among the 12 living nonwhite workers, average age as of June 30, 2011, was 59.9 (SD, 6.5) years. Causes of death among the four deceased nonwhite workers were cancer of the intestine (C18.9), cerebrovascular disease (I61.9), ischemic heart disease (I21.9), and pneumonia (J18.9). The worker who died of cancer of the intestine (C18.9) was hired in 1977, was 61 years old at death (2002), and had a CFE level of 2.75 f-yr/ee.

The 32 female workers had an average CFE of 0.98 (SD, 2.36) f-yr/ee. Of these, 7 were deceased by June 30, 2011. Among the 25 living women, average age as of June 30, 2011 was 61.1 (SD, 10.6) years. Causes of death among the seven deceased women were cancer of the intestine (C18.9), other respiratory cancer (C38.9), disease of the circulatory system (I71.3), leukemia (C92.0), pneumonia (J18.9), dementia (F03), and ischemic heart disease (I25.1). The female worker who died of cancer of the intestine (C18.9) was hired in 1974, was 82 years old at death, and had a CFE level of 0.10 f-yr/ee. The female worker who died of other respiratory cancer (C38.9) was hired in 1969, was 66 years old at death, and had a CFE level of 6.93 f-yr/ee.

DISCUSSION

This study found a significantly elevated SMR for mesothelioma. The two mesothelioma deaths were in the top-tenth CFE percentile, specifically 43.80 and 47.23 f-yr/ee. There were no significantly elevated SMRs for other malignant or NMRDs, consistent with asbestos exposure. One reason for nonelevated asbestos-related malignant and NMRD SMRs may be due to relatively low fiber exposure (CFE mean, 9.0; median, 0.63; range, 0.0 to 106.31 f-yr/ee). Previous studies of Libby vermiculite miners and millers with higher CFE levels have shown significantly increased mortality due to lung cancer, mesothelioma, and NMRD.^{8–11} In a 1987 study of 575 Libby mine workers with an average exposure of 200 f-yr/ee, SMRs for lung cancer and NMRD was 2.2 (95% CI, 1.4 to 3.4) and 2.4 (95% CI, 1.5 to 3.8), respectively.⁸ In a 2004 study of 406 Libby mine workers, SMRs for respiratory cancer and NMRD was 2.4 (95% CI, 1.7 to 3.2) and 3.1 (95% CI, 2.3 to 4.1), respectively.¹⁰

In a 2007 study of 1672 Libby vermiculite mine workers with a median fiber exposure of 8.7 f-yr/ee (ranging from 0 to >250 f-yr/ee), SMRs were as follows: lung cancer, 1.7 (95% CI, 1.4 to 2.1); mesothelioma, 15.1 (95% CI, 1.8 to 54.4); NMRD, 2.4 (95% CI, 2.0 to 2.9); asbestosis, 165.8 (95% CI, 103.9 to 251.1); and chronic obstructive pulmonary disease, 2.4 (95% CI, 2.0 to 2.9).⁹ Other studies of Libby vermiculite mine workers have shown decreased SMRs for cancer of the digestive system and peritoneum: 0.7 (95% CI, 0.3 to 1.6)⁸ and 0.8 (95% CI 0.6 to 1.1).¹¹ In the current analysis, cancer of the digestive system and peritoneum demonstrated increased SRRs with increasing CFE categories. These SRRs were not statistically significant, and this finding should be interpreted with caution because of small sample size.

Several other studies of higher CFE levels among the Libby mine worker cohort showed an exposure-response relationship of increased mortality with increasing CFE categories.^{8–11} Nevertheless, only one study⁹ calculated SMRs for workers with

TABLE 1. Demographic and Exposure Characteristics of White Male Workers (N = 465): Deaths From 1980 to June 30, 2011

Characteristic	All Workers	All Deaths	Lung Cancer*	Mesothelioma†
No. workers	465	136	16	2
Mean age in 1980 (range)	37.8 (19.2–66.1)	49.1 (21.0–66.1)	51.3 (39.7–63.3)	53.9 (45.6–62.1)
Mean year of birth	1942	1931	1929	1926
Mean year of hire	1969	1964	1964	1961
Mean age at first exposure (range)	26.8 (15.3–54.2)	33.5 (18.0–53.2)	34.9 (18.0–51.8)	35.1 (30.9–39.3)
Mean year of death	‡	2001	2001	2006
Mean age at death (range)	‡	70.4 (29.1–92.4)	72.6 (60.0–85.5)	80.7 (75.1–86.2)
Mean time in years (SD) and (range) from first exposure to date of death§	‡	36.9 (10.6) (2.0–54.0)	37.7 (9.8) (18.6–52.1)	45.6 (1.9) (44.3–46.9)
Mean exposure duration§ in years (range)	11.0 (0.3–23.7)	15.6 (0.8–23.7)	16.4 (2.0–23.4)	19.0 (15.0–23.0)
Mean CFE§ (fiber-years/cm³) (SD) and (range)	9.00 (20.84) (<0.01–106.31)	16.76 (28.44) 0.02–106.29	15.34 (30.35) 0.03–106.29	45.51 (2.43) (43.8–47.23)
Pack-years 1980 (SD) and (range) (ex- and current smokers)	17.8 (16.5) (0.3–96.0)	29.0 (19.2) (0.5–96.0)	43.2 (16.2) (28.0–74.0)	20.5 (12.02) (12.0–29.0)
Smoke ever 1980, % (n)	64.1 (298)	71.3 (97)	93.8 (15)	100 (2)
Smoke status 1980, % (n)				
Never	35.9 (167)	28.7 (39)	6.3 (1)	0
Ex	25.6 (119)	31.6 (43)	18.8 (3)	100 (2)
Current	38.5 (179)	39.7 (54)	75.0 (12)	0

*ICD-10 C33–34.

†ICD-10 C45

‡These numbers are not applicable to “all workers” because only 136 of the 465 all workers were deceased. See “all deaths” column for data regarding 136 deaths.

§Cumulative fiber exposure estimates begin in 1957. The manufacturing plant began using vermiculite from South Carolina in 1957 and from Libby, Montana, in 1959. For those workers hired before 1957, exposure began in 1957. For those workers hired after 1957, exposure began at the date of hire. Exposure duration is the year exposure began up to 1980.

TABLE 2. Standardized Mortality Ratios for Selected Cancers and Diseases Among White Male Workers (N = 465) by Underlying Cause of Death (From 1980 to June 30, 2011)

Cause of Death	ICD-9 Codes	ICD-10 Codes	Obs Deaths	US Exp Deaths	US SMR ^a (95% CI)
All causes			136	182.1	0.8 (0.6–0.9)*
All cancers	140–239, 273.1, 273.3	C00–C99	46	48.9	0.9 (0.7–1.3)
Cancer of trachea, bronchus, or lung	162	C33–34	16	16.9	0.9 (0.5–1.5)
Mesothelioma ^b	^b	C45	2	0.2	10.5 (1.3–38.0)**
Nonmalignant respiratory disease ^c					
Asbestosis	501	J61	1	0.1	15.4 (0.4–85.9)
Chronic obstructive pulmonary disease	490–492, 496	J40–J44	8	8.4	1.0 (0.4–1.9)
Other respiratory diseases ^d	470–478, 494–95, 504, 506–519	J30–J33, J34.1–J34.8, J35–J39, J47, J66–J95, J98–J99	2 ^d	2.4	0.8 (0.1–3.0)
Cancer of the digestive system and peritoneum ^e	150–159	C15–C26, C48	13	11.8	1.1 (0.6–1.9)

*P < 0.01; **P < 0.05.

^aComparison of SMR for deaths in the US population of same age category, race, and sex during the same calendar year.^bSMRs for mesothelioma include only deaths from 1999 to June 30, 2011. There is no ICD-9 code for mesothelioma. In 1999, a unique ICD-10 code was assigned to mesothelioma. There were no “possible mesothelioma” deaths before 1999 (ICD-9): cancer of other respiratory sites (160, 164–165); cancer of pleura (163); or cancer of other and unspecified sites (187, 194–199).^cThere were no deaths due to silicosis (J62) or other pneumoconiosis (J60, J63–J64).^dThe 2 deaths in the category “other respiratory diseases” were specifically “interstitial pulmonary diseases with fibrosis (J84.1).”^eThere were no deaths due to cancer of the peritoneum.

SMR indicates standardized mortality ratio; CI, confidence interval.

TABLE 3. Standardized Rate Ratios and Standardized Mortality Ratios Among Workers (N = 465) by Underlying Cause of Death (From 1980 to June 30, 2011) Based on Tertiles of the Cumulative Fiber Distribution*

Cause of Death	Cumulative Exposure Category* (fiber-years/cm ³)	Person-years	Obs	Exp	SRR (95% CI)	SMR (95% CI)
All cancers	0.00–0.31	5,342	5	7.5	(reference)	0.7 (0.2–1.6)
	>0.31–1.40	6,300	21	19.4	1.1 (0.3–4.1)	1.1 (0.7–1.7)
	>1.40–106.31	6,436	20	21.9	1.1 (0.3–4.0)	0.9 (0.6–1.4)
Cancer of trachea, bronchus, or lung	0.00–0.31	5,342	2	2.4	(reference)	0.8 (0.1–3.0)
	>0.31–1.40	6,300	7	6.8	1.0 (0.2–4.9)	1.0 (0.4–2.1)
	>1.40–106.31	6,436	7	7.7	0.9 (0.2–4.6)	0.9 (0.4–1.9)
Cancer of digestive system and peritoneum	0.00–0.31	5,342	2	1.9	(reference)	1.1 (0.1–3.8)
	>0.31–1.40	6,300	6	4.7	3.4 (0.7–17.6)	1.3 (0.5–2.8)
	>1.40–106.31	6,436	5	5.2	4.2 (0.8–23.7)	1.0 (0.3–2.2)

Comparison of SMR for deaths in the US population of same age category, race, and sex during the same calendar time period.

*Categories based on tertiles of the cumulative fiber distribution among white men (N = 465) followed in this cohort (fiber-years/cm³).

SMR indicates standardized mortality ratio; SRR, standardized rate ratio; CI, confidence interval.

lower CFE estimates. Among workers with less than 4.5 f-yr/cc, lung cancer SMR was elevated at 1.5 (95% CI, 0.9 to 2.3).⁹ Among workers with 4.5 to 22.9 f-yr/cc, lung cancer SMR was significantly elevated at 1.6 (95% CI, 1.1 to 2.5).⁹ Among workers with less than 4.5 f-yr/cc and 4.5 to 19.9 f-yr/cc, NMRD SMR was significantly elevated at 1.8 (95% CI, 1.1 to 2.8) and 2.0 (95% CI, 1.3 to 3.0), respectively.⁹

A recent case series also reported mesothelioma due to occupational exposure or potential environmental exposure or both to Libby vermiculite ore.¹⁴ Of 15 mesothelioma cases, 4 were reported for Libby mine workers and the remaining 11 reported potential nonoccupational exposures: 9 from environmental exposure and 2 from home contamination by family employed at the mine/mill facility. On the basis of interviews with patients or next of kin, latencies ranged from 13 to 67 years from first known potential exposure to Libby vermiculite.

In the formal SMR analysis, there were two deaths due to mesothelioma. One worker began employment at the facility in 1943, was first exposed to vermiculite in 1957, and had a CFE level of 47.23 f-yr/cc. He died in 2004 at the age of 86 years, 47 years after his initial exposure. In 1980, he had reported no known commercial asbestos exposure. He worked in multiple work areas including maintenance, warehousing, and production areas using vermiculite. The second death was reported for a worker who began employment at the facility in 1965 and had a CFE level of 43.80 f-yr/cc. He died in 2009 at the age of 75 years, 44 years after his initial exposure. He worked in areas using vermiculite and reported no known commercial asbestos exposure.

Through continued follow-up of this cohort, it is known that another worker had a diagnosis of mesothelioma in 2010 at the age of 66 years. He began employment in 1966 and had a CFE level of 5.73 f-yr/cc. In 1980, he reported no known commercial asbestos exposure. This worker is not deceased but the case has been described here to offer a glimpse at the future possibility of mortality among this cohort.

This cohort offered a unique perspective because of its relatively low cumulative exposure to Libby vermiculite compared with most studies that involve more heavily exposed Libby mining and milling workers. An ample latency period had occurred, with a mean of 44 (range, 31 to 54) years since initial exposure to vermiculite. In addition, industrial hygiene records, worker job histories, and respiratory health histories were available to recreate CFE estimates and historical smoking status.

The number of deaths in this cohort was relatively low, reducing the power to detect mortality potentially related to Libby vermiculite exposure. Another limitation was the potential misclassification of exposure estimates as derived from previous historic industrial hygiene records available. This analysis, however, used updated CFE estimates based on additional quantitative and qualitative exposure information obtained in 2010.¹⁵ The SMR for all causes of death (0.8; 95% CI, 0.6 to 0.9) was significantly lower in our analyses than in the national population, suggesting a healthy worker effect. Furthermore, SMRs by CFE exposure should be interpreted with caution. Limitations of this approach include possible different person-year distributions by exposure category due to differences in worker ages (older workers have higher fiber exposure). Standardized rate ratios do not have this limitation. Finally, among the original cohort of 513 workers, 16 were nonwhite men and 32 women. The limited sample size of these groups did not allow for SMR analysis stratified by race or gender.

In conclusion, the results of this study demonstrate an increased risk of malignant mesothelioma mortality in a worker population involved with expanding and using Libby vermiculite as a carrier for lawn care products. Further follow-up of this aging cohort will provide additional data and statistical power to determine potential association between relatively low CFE in workers exposed to Libby vermiculite that contained amphibole fiber and malignant and NMRDs.

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