Vermiculite Worker Mortality: Estimated Effects of Occupational Exposure to Libby Amphibole

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Objective: To examine the relationship between cumulative fiber exposure (CFE) and mortality in a retrospective cohort study of vermiculite workers exposed to Libby amphibole (n = 1862). **Methods:** Extended Cox regression was used to estimate the hazards associated with CFE as a time-dependent covariate of multiple-cause mortality. **Results:** The Cox models for mesothelioma, asbestosis, lung cancer, and non-malignant respiratory disease were significant with rate ratios that increased monotonically with CFE. The model for deaths due to cardiovascular disease was also significant (rate ratio for CFE ≥44.0 f/cc-y vs <1.4 f/cc-y was 1.5; 95% confidence interval = 1.1 to 2.0). **Conclusions:** By using a within-cohort comparison, the results demonstrate a clear exposure-response relationship between CFE and mortality from asbestos-related causes. The finding of an association between CFE and cardiovascular mortality suggests persons exposed to Libby amphibole should be monitored for this outcome.

Libby, Montana was the site of a vermiculite mining and processing operation from the 1920s to 1990. Although vermiculite causes no known adverse health effects, Libby vermiculite is contaminated with a mixture of amphibole fibers. These amphiboles have been collectively called tremolite by the community, popular press, and in some scientific literature[1] but Libby vermiculite also contains actinolite[2] and unregulated asbestos-like fibers, including winchite and richterite.[1,3] The only chemical difference between these amphiboles is their iron content; this mineralogic difference is somewhat arbitrary and may have no biological significance.[2] Regardless, the raw vermiculite ore mined in Libby contained up to 26% amphibole fibers by mass.[4] Libby is thought have produced 80% of the world's supply of vermiculite during the 20th century.[5]

Because many of its years of operation predated significant regulation of occupational asbestos exposure, the amphibole exposures at the Libby vermiculite operation were quite high, especially before engineering controls were put in place in the late 1960s and early 1970s. The resulting health effects of working at the Libby vermiculite operation have been well documented, demonstrating excesses of asbestos-related morbidity and mortality.[6–8]

An excess of asbestos-related mortality among Libby vermiculite workers is not surprising given their occupational amphibole exposures. In this study, we use mortality data on the entire vermiculite worker cohort updated through the end of 2006. Our objective was to conduct an exposure-response study to obtain estimates of the hazard of asbestos-related mortality associated with cumulative asbestos exposure.

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MATERIALS AND METHODS

Study Cohort

The Agency for Toxic Substances and Disease Registry (ATSDR) reconstructed the vermiculite worker cohort (n = 1862; Table 1) from company records as part of its public health response to the situation in Libby. Data obtained from company documents included name, date of birth, Social Security Number, and complete work history. ATSDR then actively attempted to locate and interview members of the cohort for its Tremolite Asbestos Registry, a database comprising Libby vermiculite workers and their household contacts as well as persons who lived, worked, or played in Libby for at least 6 months before the mine closed at the end of 1990. In addition, decedents were identified using the National Death Index (NDI), Social Security Death Index, and LexisNexis databases.

Exposure Estimates

In the early 1980s, research teams from McGill University and the National Institute for Occupational Safety and Health (NIOSH) separately published results of mortality studies of subcohorts of Libby vermiculite workers.[7,8] This required estimating cumulative fiber exposures (CFE) for each worker. By using the same data, both research teams separately performed this estimation. Historical air sampling data were used to estimate the 8-hour time-weighted average (TWA) fiber exposure for all areas of the vermiculite operation for various time periods in the company's history. The proportion of each day spent at each location was calculated for each job title, and an 8-hour TWA exposure was estimated for each job at a given time. CFE for each job that a worker held was estimated by weighting the 8-hour TWA exposure for a given job held by the worker by length of time (in years) spent at that job. Finally, lifetime CFE for each worker was obtained by summing the CFE for each job that worker held. CFE has the unit fibers/cubic centimeter-year (f/cc-y) and is analogous to cigarette pack-years. A thorough description of how each research team estimated CFE for the Libby worker vermiculite worker cohort is available elsewhere.[8,9] The methods used by each team to estimate exposures differed only slightly, and their respective mortality studies obtained similar results.[7,8]

We obtained the NIOSH exposure estimates for each job title and applied them to the work history obtained for each worker, expanding on the exposure estimates by including exposures that occurred between the early 1980s through 1993 (when demolition of the facilities was completed). By using the work histories, which included each worker's job title and dates of employment at that job, we calculated CFE for each worker in the same manner as the McGill and NIOSH research teams did in the early 1980s. The McGill and NIOSH studies[7,8] used lifetime CFE that a given worker experienced through his/her last day of employment. For this analysis, in addition to total CFE, we also took into account the timing of exposure, allowing the use of CFE as a time-dependent covariate of mortality.

Outcomes of Interest

The NDI was used to determine vital status of each worker. By using NDI data, we attempted to obtain death certificates for decedents and ultimately acquired certificates for 762 (80%) of the

TABLE 1. Characteristics of the Libby Vermiculite Worker Cohort (25th to 75th Percentile)

Cohort	*n* (%)	Median Cumulative Fiber Exposure (Fiber/cc-yr)	Median Year of Hire	Median Age at Hire	Median Length of Employment (yr)
Living	726 (39)	3.0 (0.5–11.0)	1970 (1962–1975)	23.6 (20.4–28.5)	1.2 (0.2–4.5)
Deceased	952 (51)	8.6 (1.4–44.0)	1949 (1946–1960)	32.3 (24.9–42.2)	0.9 (0.1–4.9)
Not located	184 (10)	1.7 (0.2–4.4)	1953 (1946–1973)	27.4 (22.4–40.6)	0.2 (0.0–0.6)
Entire cohort	1862 (100)	4.3 (0.8–22.5)	1958 (1947–1971)	27.4 (22.1–36.7)	0.8 (0.1–4.1)

TABLE 2. SMR and 95% CI for Selected, Multiple Causes of Death in the Libby Vermiculite Worker Cohort (n = 1862)

Multiple Cause of Death	Observed	Expected	SMR (95% CI)
All causes (multiple)	2247	1768.7	1.3 (1.2–1.3)
Mesothelioma*	19	0.2	94.8 (57.0–148.0)
Malignant neoplasms of the bronchus or lung†	104	64.6	1.6 (1.3–2.0)
All non-malignant respiratory diseases‡	425	179.0	2.4 (2.2–2.6)
Asbestosis§	69	0.5	142.8 (111.1–180.8)
COPD‖	152	68.0	2.2 (1.9–2.6)
Silicosis¶	4	0.3	15.3 (4.2–39.4)
Other respiratory diseases#	120	42.6	2.8 (2.3–3.4)
Heart diseases**	552	592.6	0.9 (0.9–1.0)
Ischemic heart disease††	247	341.8	0.7 (0.6–0.8)
Other heart diseases‡‡	120	81.3	1.5 (1.2–1.8)
Diseases of the circulatory system§§	258	186.2	1.4 (1.2–1.6)
Hypertension without heart disease‖‖	42	25.0	1.7 (1.2–2.4)
Diseases of arteries, veins, or lymphatic vessels¶¶	136	81.6	1.7 (1.4–2.0)
Malignant neoplasms of digestive organs and peritoneum##	39	48.3	0.8 (0.6–1.1)

*ICD-10: C45.
†ICD-9: 162; ICD-10: C33–C34.
‡ICD-9: 470–478, 494–495, 504, 506–519; ICD-10: J30–J33, J34.1–J34.8, J35–J39, J47, J66–J95, J98–J99, R09.1.
§ICD-9: 501; ICD-10: J61.
‖ICD-9: 490–492, 496; ICD-10: J40–J44.
¶ICD-9: 502; ICD-10: J62.
#ICD-9: 470–478, 494–495, 504, 506–519; ICD-10: J30–J33, J34.1–J34.8, J35–J39, J47, J66–J95, J98–J99, R09.1.
**ICD-9: 390–398, 402, 404, 410–414, 429.2, 424, 425, 426–427, 420–423, 428, 429.0–429.1, 429.3–429.9; ICD-10: I00–I09, I11, I13, I20–I22, I24–I25, I51.3, I51.6, I34–I38, I42, I52.8, I44–I49, R00.1, R00.8, I30–I33, I40, I50, I51.0–I51.2, I51.4–I51.5, I51.7–I51.9, I52.0–I52.1, I97.0–I97.1, I97.8–I97.9.
††ICD-9: 410–414, 429.2; ICD-10: I20–I22, I24–I25, I51.3, I51.6.
‡‡ICD-9: 420–423, 428, 429.0–429.1, 429.3–429.9; ICD-10: I30–I33, I40, I50, I51.0–I51.2, I51.4–I51.5, I51.7–I51.9, I52.0–I52.1, I97.0–I97.1, I97.8–I97.9.
§§ICD-9: 430–438, 401, 403, 405, 415–417, 440–459. ICD-10: G45.0–G45.2, G45.4–G45.9, I60–I69, I10, I12, I26–I28, I70–I87, I89–I95, I97.2, I99, M30–M31, R58.
‖‖ICD-9: 401, 403, 405; ICD–10: I10, I12.
¶¶ICD-9: 415–417, 440–459; ICD-10: I26–I28, I70–I87, I89–I95, I97.2, I99, M30–M31, R58.
##ICD-9: 150–159; ICD–10: C15–C26, C48.

952 deceased workers. Using the death certificates, immediate and underlying causes of death were coded by a certified nosologist using the International Classification of Disease, 9th Revision (ICD-9). If mesothelioma was listed on the death certificate, it was coded C45, the ICD-10 code for mesothelioma. For workers for whom we were unable to obtain a death certificate, we relied on NDI coded causes of death (n = 102; NDI data is coded ICD-9 for the years 1979–1999 and ICD-10 for 2000–2006). We were able to ascertain vital status but not cause of death for 88 workers. ICD codes servings as case definitions for comparisons with a national population were NIOSH major and minor disease categories and are listed in the footnotes for Table 2. For internal-comparison models, we created dichotomous variables for several outcomes of interest: deaths from mesothelioma, asbestosis, lung cancer, non-malignant respiratory disease (NMRD) excluding pneumoconiosis, cancer of the digestive system, and cardiovascular disease. The footnotes in Table 3 show the ICD codes functioning as case definitions for the exposure-response models. ICD codes used to define cardiovascular disease were the same as those used in a recent study of the association between particulate matter and hospitalization from cardiovascular outcomes.[10] If a subject had more than one of these causes of death, each was used to fit separate Cox models. Considering multiple causes of death in this fashion rather than just the underlying cause of death has been shown to have minimal impact on risk estimates while increasing statistical precision.[11]

Analysis

Each subject not identified as deceased was censored at the date of last follow-up. The date of last follow-up for subjects not known to be deceased during the ATSDR locating activity was assumed to be December 31, 2006, the date ending the period of available NDI data. Workers that were not located were censored at the date they stopped working at the Libby vermiculite operation.

To describe mortality with an external comparison, we used the NIOSH freeware program Life Table Analysis System (LTAS.NET, Version 2)[12] to calculate multiple-cause standardized mortality ratios (SMR) and 95% confidence intervals (CI) for the outcomes of interest. Footnotes in Table 2 show the ICD codes used for NIOSH major and minor causes of death that most closely approximate the outcomes of interest for this study. Multiple cause death rates for the U.S. 1960–2002 were used for the reference; consequently deaths occurring outside of this period were excluded from the SMR calculations.

We conducted internal exposure-response analyses using Cox regression for select causes of death using the PHREG procedure in SAS Version 9.[13] The extended Cox model with time-dependent covariates models the log of the hazard ratio as a linear combination of predictors and allows for the introduction of CFE over time as it was experienced in the cohort. For each model, CFE, calculated for each 12-month period since date of birth (rendering date of birth as the origin of time), was examined as a time-dependent covariate of mortality. Each model was fitted using lags of 0 to 20 years in 5-year increments. The results from fitted models were used to estimate hazard (rate) ratios for each quartile of CFE experienced by all decedents.

To complement and corroborate the Cox regression, we also fit a Poisson model for each cause of death having a significant Cox model. To do this, we used the SAS macro %Stratify[14] to calculate person-time for risk sets stratified by CFE (quartiles experienced by all

TABLE 3. Characteristics of Workers With Each Modeled Cause of Death and of the Censored Population, Expressed as Medians (25th–75th Percentile)

Cause of Death	*n*	Cumulative Fiber Exposure (Fiber/cc-yr)	Year of Hire	Years Between Hire and Death or Censoring	Age at Hire	Length of Employment (yr)
Mesothelioma*	19	50.0 (27.3–230.2)	1953 (1947–1962)	35.4 (31.7–41.6)	26.9 (24.0–31.0)	7.8 (2.7–16.0)
Asbestosis†	69	39.0 (14.6–283.2)	1953 (1947–1962)	40.5 (30.6–46.7)	31.8 (25.4–37.6)	10.4 (1.2–19.5)
Lung cancer‡	98	23.1 (2.6–84.1)	1951 (1947–1963)	33.0 (23.6–42.0)	31.6 (25.4–38.0)	2.4 (0.2–13.1)
NMRD§	203	12.7 (2.1–58.9)	1949 (1946–1960)	36.6 (28.4–46.4)	32.1 (25.4–39.7)	1.28 (0.1–6.3)
Digestive system cancer‖	31	28.2 (3.8–194.3)	1949 (1946–1953)	37.4(25.8–41.9)	29.2 (25.0–40.5)	2.1 (0.2–12.7)
Cardiovascular disease¶	443	10.6 (1.6–48.0)	1948 (1945–1956)	34.6 (24.9–45.0)	34.8 (26.5–44.7)	0.7 (0.1–4.5)
Censored population	910	2.4 (0.4–9.0)	1969 (1957–1974)	29.6 (21.7–38.3)	24.2 (20.7–29.7)	0.8 (0.2–3.5)

*As listed on death certificate or coded C45 (ICD-10).
†ICD-9: 501; ICD-10: J61.
‡ICD-9: 162.2–162.9; ICD-10: C34.
§ICD-9: 490–496, 510–519; ICD-10: J40–J47, J80–J98.
‖ICD-9: 150–159; ICD-10: C15–C26.
¶ICD-9: 410–414, 426–438, 440–448; ICD-10: I25, I70–I79.
Cause of death categories are neither exhaustive nor mutually exclusive.

TABLE 4. Cox Models for Select Causes of Death With No and 20-yr Lags

Outcome	Lag	Parameter Estimate	Standard Error	*P*	% Increase in Hazard
Mesothelioma	0	0.0007493	0.0005377	0.1634	0.1
	20	0.00137	0.0005535	0.0134	0.1
Asbestosis	0	0.00136	0.0001959	<0.0001	0.1
	20	0.00162	0.0002383	<0.0001	0.1
Lung cancer	0	0.0007133	0.0002505	0.0044	0.1
	20	0.00106	0.00031	0.0006	0.1
NMRD	0	0.0006205	0.0001885	0.0015	0.1
	20	0.0007514	0.000243	0.0028	0.1
Digestive system cancer	0	0.0006975	0.0004532	0.1238	0.1
	20	0.0008043	0.0006248	0.198	0.1
Cardiovascular disease	0	0.0005581	0.0001379	<0.0001	0.1
	20	0.0005258	0.0001939	0.0067	0.1

The percent increase in hazard is with a 1 f/cc-y increase in cumulative fiber exposure.

decedents) and age (age, <60, 60 to 64, 65 to 69, and ≥70). We then fitted Poisson models using the GENMOD procedure in SAS.[13]

RESULTS

Of the 1862 vermiculite workers identified by ATSDR, 1667 (90% of the cohort) were located, of which 952 (51% of the cohort) were identified as being deceased. Table 1 compares characteristics of living, deceased and not-located workers. Decedents had the greatest median exposure and longest length of employment and as a group were hired at an older age and earlier in the vermiculite operation's history. Workers lost to follow-up, like decedents, tended to have been hired at earlier in the vermiculite operation's history. However, they also had lower CFE and shorter employment durations than living workers.

Comparison With U.S. Population

Table 2 shows SMR results for causes of death of interest. Deaths from all, multiple causes were significantly elevated as were deaths from mesothelioma, asbestosis, malignant neoplasms of the bronchus or lung, all non-malignant respiratory diseases combined, and diseases of the circulatory system. Significantly elevated minor categories of NMRD were asbestosis, chronic obstructive pulmonary disease, silicosis, and other respiratory diseases. Although Libby workers were not significantly different from the national population in terms of all heart diseases combined, the SMR for ischemic heart disease was significantly depressed and the category "other heart diseases" (ie, pericarditis, endocarditis, heart failure, and ill-defined descriptions and complications of heart disease) was significantly elevated. The SMR for diseases of the circulatory system was also significantly elevated, as were the minor categories hypertension without heart disease and diseases of arteries, veins, and lymphatic vessels. The SMR for neoplasms of the digestive organs and peritoneum was not elevated.

Exposure-Response Analyses

Table 3 compares direct and indirect measures of exposure for the causes of death to which we fitted extended Cox models. Workers with asbestosis and mesothelioma had a much greater median lifetime CFE (50.0 and 39.0 f/cc-y for asbestosis and mesothelioma, respectively, compared with 2.3 f/cc-y for censored workers) and median length of employment (7.8 and 10.4 years for asbestosis and mesothelioma, respectively, compared with 0.8 years for the censored population). The numbers of deaths differ from those enumerated in Table 2 because of the exclusion of deaths that occurred outside of the comparison rates year range in for SMR calculation and slightly different case definitions than we used for the internal comparisons.

Table 4 shows Cox models for select causes of death with no and 20-year lags. The models for asbestosis, lung cancer, NMRD, and cardiovascular disease were all significant at both lags. Mesothelioma was not significant ($\alpha = 0.05$) with 0, 5, and 10 year lags but was significant with lags of 15 years (data not shown) and greater. The parameter estimates for all significant models were <0.01, indicating <1% increase in the hazard of mortality, accounting for the timing and intensity of exposure, for each additional f/cc-y of exposure. The parameters and variances were minimally altered by lagging for all outcomes except mesothelioma. The model for digestive system cancer was not significant.

Table 5 presents rate ratios (RRs) by quartiles of CFE for all decedents to illustrate the effects of increasing cumulative exposure on results from the statistically significant Cox models. The RRs increase monotonically with increasing CFE for mesothelioma, asbestosis, lung cancer, and NMRD. However, the RRs did not become statistically significant until the fourth quartile for mesothelioma and lung cancer and the third quartile for asbestosis and

TABLE 5. Estimated RR and 95% CI for the Effect of Cumulative Fiber Exposure (20 yr lag), Presented by Quartiles of Exposure Experienced by All Decedents

Cause of Death	Cumulative Exposure Level (f/cc-y)	*n*	RR (95% CI)
Mesothelioma	<1.4	1	1.0
	1.4 to <8.6	2	1.9 (0.3–13.6)
	8.6 to <44.0	5	4.5 (0.8–24.6)
	≥44.0	11	17.1 (3.7–78.1)
	Model *P*-value		0.01
Asbestosis	<1.4	4	1.0
	1.4 to <8.6	8	2.8 (1.0–7.6)
	8.6 to <44.0	25	8.0 (3.2–19.5)
	≥44.0	32	11.8 (4.9–28.7)
	Model *P*-value		<0.0001
Lung cancer	<1.4	19	1.0
	1.4 to <8.6	20	1.1 (0.6–2.1)
	8.6 to <44.0	21	1.7 (1.0–3.0)
	≥44.0	38	3.2 (1.8–5.3)
	Model *P*-value		0.0006
NMRD	<1.4	43	1.0
	1.4 to <8.6	46	1.4 (0.9–2.1)
	8.6 to <44.0	56	1.8 (1.3–2.7)
	≥44.0	58	2.5 (1.7–3.6)
	Model *P*-value		0.0028
Cardiovascular disease	<1.4	97	1.0
	1.4 to <8.6	125	1.3 (1.0–1.6)
	8.6 to <44.0	107	1.3 (1.0–1.6)
	≥44.0	114	1.5 (1.1–2.0)
	Model *P*-value		0.0067

NMRD. Mesothelioma and asbestosis had the greatest RRs for the ≥44.0 f/cc-yr quartile (17.1 and 11.8, respectively). For deaths due to cardiovascular disease, no monotonic trend was detected and only the RR for the ≥44.0 f/cc-yr quartile was significant (1.5; 95% CI = 1.1 to 2.0). The Poisson model results (not shown) for each cause of death were similar to those of the Cox models.

DISCUSSION

We 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 Libby amphibole fiber exposure and select causes of mortality. With the exception of digestive system cancers, the results from these models show a small, statistically significant increase in the hazard of death with each additional unit of exposure (ie, 1 f/cc-y). At CFE levels experienced by decedents in this cohort, the exposure-response relationship for mesothelioma and asbestosis is striking and the peak magnitude of the associations of lung cancer and non-malignant respiratory disease are moderate to strong (Table 5). We also modeled deaths from digestive system cancer and cardiovascular disease due their association with asbestos exposure in some studies and biologic plausibility, respectively. Although the Cox model for digestive system cancer was not significant, the model for cardiovascular disease shows a significantly increased hazard for each f/cc-y similar in magnitude as causes of death traditionally associated with asbestos exposure (Table 4).

Several studies have shown an association between particulate matter and hospital admissions for cardiovascular disease.[10,15] The mechanism through which particulate matter affects the cardiovascular system is poorly understood but may involve oxidative stress, impairment of antioxidant defenses, or disturbances of the cardiac autonomic nervous system.[16,17] Recent investigations have shown associations between occupational exposure to silica and ischemic heart disease mortality[18,19] and other inorganic dusts and ischemic heart and cerebrovascular disease.[17] The hypothetical mechanism of action linking inhaled particles to ischemic heart disease involves low-grade inflammation of the pulmonary system resulting in increased coaguability of the blood and consequent adverse cardiovascular outcomes.[17,18] A recent mortality analysis of textile workers exposed primarily to chrysotile found excess deaths from diseases of the heart and other circulatory disease[20] whereas another study found inhaled chrysotile exacerbated atherosclerotic lesions in mice.[21] Given this information, it seem reasonable to conjecture that inhalation of asbestos may similarly trigger cardiovascular disease. Consequently, our finding of an association between exposure to Libby amphibole and multiple-cause cardiovascular mortality appears biologically plausible. The SMR results for cardiovascular diseases varied in magnitude; consideration should be given to conducting a study of cardiovascular disease incidence among survivors of this cohort, with emphasis on the outcomes that had significantly elevated SMRs.

In previous mortality studies of this cohort, investigating teams have conducted external comparisons with U.S. and/or state death rates.[7,8,22,23] Particularly germane to our analysis is the recent NIOSH mortality study of male workers hired between 1935 and 1981 and followed up through 2001.[23] Despite our use of multiple underlying causes of death through 2002 and inclusion of female workers, the SMRs found here are similar to those reported by Sullivan for asbestosis, lung cancer, NMRD, and deaths from all causes using the underlying cause of death.[23] In addition, Sullivan[23] also found an excess of circulatory disease involving arteries, veins, and lymphatic vessels. Similar to a result found by Amandus and Wheeler[7] for Libby workers with CFE <50 f/cc-y, we also found significant reduction in the SMR for ischemic heart disease (Table 2). The Cox model results show the risk for mesothelioma, asbestosis, lung cancer, NMRD, and cardiovascular disease each increases by about 0.4% at the median CFE—4.3 f/cc-y—experienced by the entire cohort. This is comparable to the risk estimated by Amandus and Wheeler[7] for lung cancer in an unrestricted linear model (0.6% increase per f/cc-y) but is about 10-fold greater than the risks estimated by McDonald et al[22] for lung cancer and NMRD.

Overall, the exposure-response relationships shown in Table 5 make sense in the context of studies of the health effects of other fiber types.[24] Although presenting risk by categories of exposure is an important, initial analytical step that allows one to examine non-linearity in the exposure-response relationship, this method assumes homogeneous risk within each exposure category which may not necessarily be true. Further, the choice of cut-points may be arbitrary and result in obscuring important areas of the exposure-response curve as well as misclassification.[25,26] The use of spline functions overcome these limitations,[25,26] and we are currently exploring their application to the Cox model results to more closely examine the exposure-response curve, especially at the lower end of the exposure spectrum.

The major limitations of this study include potential exposure misclassification, reliance on death certificate information, and lack of smoking data. Because we relied on the NIOSH exposure estimates, the same limitations noted by the original NIOSH investigators apply to this study. When the exposure estimates were originally developed, many judgments were made to make use of

the available air sampling data. These data were collected over a long period by the vermiculite operation and by state and federal agencies. Relatively few samples were taken before 1969 and none before 1956. Before 1967, many samples were collected using a midget impinger, whereas later samples were collected with a membrane filter. A conversion factor was used to convert the average respirable dust content of the impinger results to fiber exposure. Finally, most sampling results were from area samples from which the 8-hour TWA had to be estimated.[9] It should be noted that the exposure levels estimated by the NIOSH and McGill University teams may have systematically underestimated actual dust levels at the Libby vermiculite operation.[27] It follows that as exposure increased, there would have been greater variation in the CFE estimate. Given this, the effect of underestimates of exposure would be more pronounced among highly exposed workers and would bias hazard estimates toward the null.[28]

Determination of the cause of death is also a major limitation. Known deaths in the cohort took place over an extended period from 1941 through 2006. During this period, knowledge of pneumoconiosis increased greatly and case definitions evolved. Thus, earlier causes of deaths are potentially more likely to have been misdiagnosed; consequently our evaluations of the hazards associated with asbestos exposure may be underestimated. In addition, we were unable to locate 10% of the worker cohort and consequently censored them at the date they ceased to work at the vermiculite operation. The impact of omitting their contribution of person-time and deaths is unknown.

We were unable to obtain the cause of death for 114 (13%) of the 876 deceased workers. As a group, these workers had a lower median CFE estimate (3.1 f/cc-y vs 8.7 for the other decedents) and a shorter median length of employment (0.3 years vs 0.9 for the other decedents). Because of lower median exposures and shorter median tenures, the hazards estimated for the lower exposure groupings might have been greater had we been able to include the causes of death for this subgroup. Sullivan[23] points out that the dustiest jobs were given to new workers who may have only endured for a short period of employment. The impact of such short-term yet high intensity exposure should not be taken for granted; one case study documented fatal asbestosis after only two summers of employment involving shoveling Libby vermiculite.[29]

Finally, smoking status was an unmeasured confounder for much of this cohort. Because smoking and asbestos exposure are both associated with several outcomes (ie, lung cancer, NMRD, and cardiovascular disease), the results from our exposure-response analysis may be attributable in part to differential smoking habits among exposed and unexposed workers (eg, the prevalence of smoking may have been greater among workers with higher CFE). Evidence of excess smoking among vermiculite workers compared with the general population can be seen in the elevated SMR for chronic obstructive pulmonary disease (Table 2). To estimate its impact on the exposure-response relationship, we used probabilistic bias analysis[30] to model the error from unmeasured smoking. In these models, we defined exposure as ≥8.6 f/cc-y, the median CFE among decedents, and made informed assumptions about the possible proportion of current and ex-smokers among exposed and unexposed workers. Based on smoking data available for 336 workers who participated in screening conducted by ATSDR in Libby in 2000/2001,[6] we assumed that in the entire cohort, the proportion of smokers ranged 50% to 66% among the unexposed and 66% to 85% among the exposed. By using published ranges of the risks of lung cancer, NMRD and cardiovascular disease associated with smoking,[31–33] we used a Monte Carlo-approach in which we randomly sampled from distributions based on these parameters 10,000 times to obtain an RR adjusted for smoking. After adjustment, the RR for lung cancer was reduced from 2.4 to 2.0. The resulting bias factor ($RR_{unadjusted}/RR_{adjusted}$) of 1.3 is similar to those reported for the contribution of smoking to the exposure-response relationship noted in other occupational cohorts,[34] validating our selection of the proportions of smokers among exposed and unexposed workers. Further, the $RR_{adjusted}$ for lung cancer indicates that workers with higher exposures were also more likely to have been smokers. This may be related to a secular trend between exposures, which were generally higher earlier in history of the vermiculite operation, and a period when smoking was more prevalent in the United States. The modeled results were similar for NMRD (RR_{unadj} = 2.1, RR_{adj} = 1.8, bias factor = 1.2) and cardiovascular disease (RR_{unadj} = 1.6, RR_{adj} = 1.5, bias factor = 1.1). These adjusted results show only a modest decrease toward the null for lung cancer and NMRD and a minimal change for cardiovascular disease. Further, the unadjusted exposure-response relationships shown in Table 5 are clear and imply that smoking would have to be strongly associated with CFE to have a large confounding effect. These bias analysis results suggest smoking had minimal impact on the exposure-response relationships in this study.

In conclusion, we were able to model the exposure-response relationship between Libby amphibole and selected causes of death. The relationships are striking for causes of death traditionally associated with asbestos. We also found a significant relationship for death from cardiovascular disease, indicating persons exposed to Libby amphibole should be monitored for this outcome.

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