Review

A Review of Mortality Associated With Elongate Mineral Particle (EMP) Exposure in Occupational Epidemiology Studies of Gold, Talc, and Taconite Mining

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Background *Mining of gold, taconite, and talc may involve exposure to elongate mineral particles (EMP). The involved EMPs are typically non-asbestiform, include dimensions that regulatory definitions exclude, and have been less studied.*
Methods *A review of the literature was undertaken for this exposure and occupational epidemiological studies that occur in gold, talc, and taconite mining.*
Results *Quantitative EMP exposure information in these industries is incomplete. However, there are consistent findings of pneumoconiosis in each of these types of mining. A recent case-control study suggests a possible association between this exposure and mesothelioma. Lung cancer is inconsistently reported in these industries and is an unlikely outcome of non-asbestiform EMP exposure. There is evidence of cardiovascular mortality excess across all of these types of mining.*
Conclusions *Non-malignant respiratory disease and cardiovascular mortality have been consistently increased in these industries. Further investigation, including additional insights for the role of non-asbestiform EMP, is warranted.* Am. J. Ind. Med. 59:1047–1060, 2016. © 2016 Wiley Periodicals, Inc.

KEY WORDS: mining; epidemiology; exposure assessment; taconite mining; gold mining; talc mining; non-asbestiform; elongate mineral particle

BACKGROUND

Non-asbestiform elongate mineral particle (EMP) exposures are encountered in several types of mining. Concerns about these exposures have surfaced from time to time, partly due to the chemical similarity to asbestiform EMP, which have well-established risks for cancer along with interstitial and pleural lung disease. The physical characteristics of these fibers are distinct from asbestiform types, despite similar chemistries. Exposures to non-asbestiform EMP are possible in some gold, talc, and taconite mining operations. Some of these industries may have a combination of non-asbestiform and asbestiform EMP exposure.

Assessment of non-asbestiform EMP exposures and disease has been hampered by a confusing terminology that may deal with different meanings, measurement techniques and/or different definitions of exposure [Lambert et al., 2015]. For example, the term "asbestos" may have different connotations. It may have a commercial implication related to the six regulated types of asbestos. These include

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chrysotile/serpentine, and five amphiboles (anthophyllite, tremolite, cummingtonite-grunerite/amosite, riebeckite/crocidolite, and actinolite). All may be used in various industrial applications. From a mineralogical view, all of these types may exhibit an "asbestiform" habit, in that they can form hair-like fibers that cleave along the longitudinal axis and have a high potential to separate naturally [Gunter et al., 2007] (Fig. 1). The asbestiform habit has the highest potential for lung exposure and disease because of this characteristic. All regulated types may also exist in a non-asbestiform habit where fibers do not split along the longitudinal axis, with lower exposure, and disease potential.

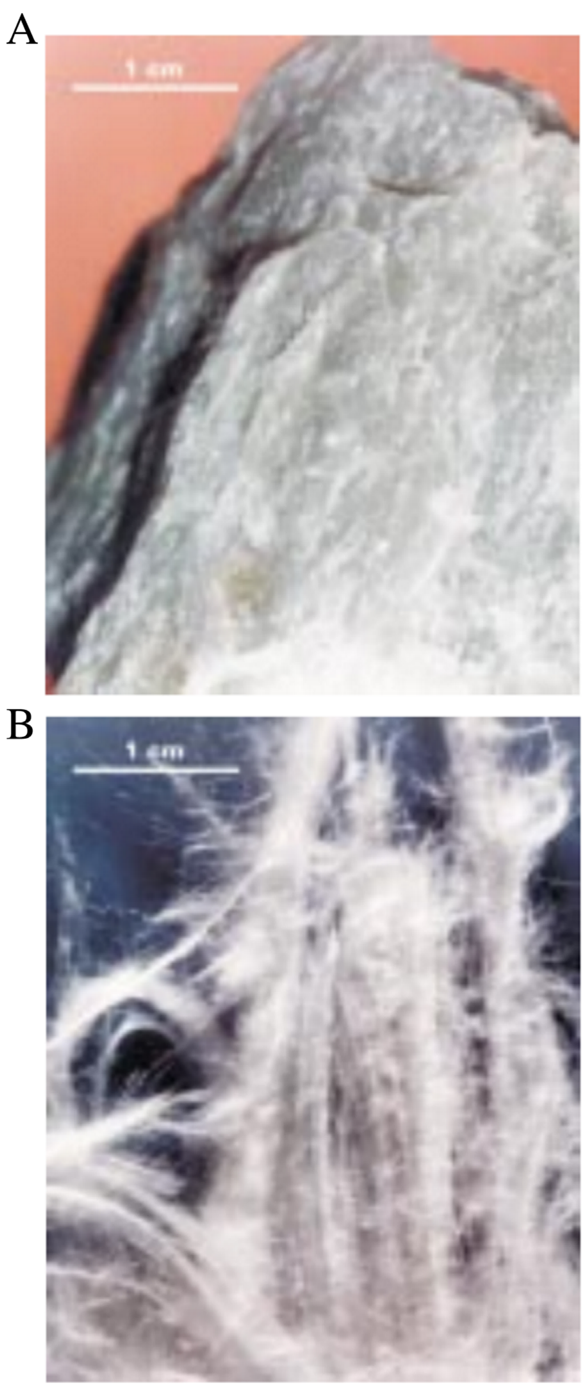

FIGURE 1. Tremolite in non-asbestiform (**A**) and asbestiform (**B**) habits. U.S. Geological Survey; "Some Facts About Asbestos"; FS-012-01; March, 2001; Photographs by Garrett Hyde from U.S. Bureau of Mines Information Circular 8751, 1977.

There is a well-established, causal relationship between asbestiform EMPs and mesothelioma, lung cancer and non-malignant respiratory disease (NMRD) [IARC, 1987; ATSDR, 2001; IOM, 2006]. This is likely influenced by fiber dimension, chemical composition, surface reactivity, and persistence [Lippmann, 1990; IOM, 2006]. Asbestiform EMP are typically longer and narrower and may exhibit aspect ratios of 40:1 or greater (Fig. 2). Alternatively, non-asbestiform EMP dimensions, including cleavage fragments, are shorter and wider (Fig. 2). These size characteristics are thought to influence how the body's defense mechanisms eliminate these minerals with longer and narrower EMP being more problematic [ATSDR, 2001].

Existing reports suggest that non-asbestiform minerals are less pathogenic [Gamble and Gibbs, 2008; Gibbs and Berry, 2008; Mossman, 2008; Wilson et al., 2008]. Non-asbestiform amphibole EMPs have been studied in different settings that include mortality studies of the Homestake gold miners [Gillam et al., 1976; McDonald et al., 1978; Steenland and Brown, 1995a,b], taconite miners [Higgins et al., 1983; Cooper et al., 1988, 1992; Allen et al., 2014] and talc workers [Selevan and Dement, 1979; Wergeland et al., 1990; Honda et al., 2002; Wild et al., 2002; Coggiola et al., 2003].

Relevant exposures to EMPs in mining may occur from a natural component of the ore (non-asbestiform EMP) or from commercial grade asbestos (asbestiform EMP), which has been used historically in many mining facilities as an insulator and other applications. While the mineral dust is a complex mixture, the relevant exposure for this review is to non-asbestiform amphibole EMPs. This exposure may include cleavage fragments (CFs), which are produced as a result of mechanical fracturing of the mineral by crushing or grinding. In most cases CFs are produced by breaking of crystals in preferred directions, related to their crystalline structures. But this is not always the case, as some minerals do not break along cleavage planes (e.g., quartz). It may be difficult to distinguish between amphibole asbestos and amphibole CF using standard methods, because their dimensional attributes may overlap [Harper et al., 2012]. NIOSH, OSHA, and the EPA includes CFs in their fiber counting methods.

Iron ore (taconite) mining operations within the United States takes place in northeastern Minnesota and western Michigan. It consists of open pit (above ground) mining of the ore, which contains 15–30% iron and is in the same setting as naturally occurring cummingtonite and grunerite EMP in a non-asbestiform habit. The major processing steps

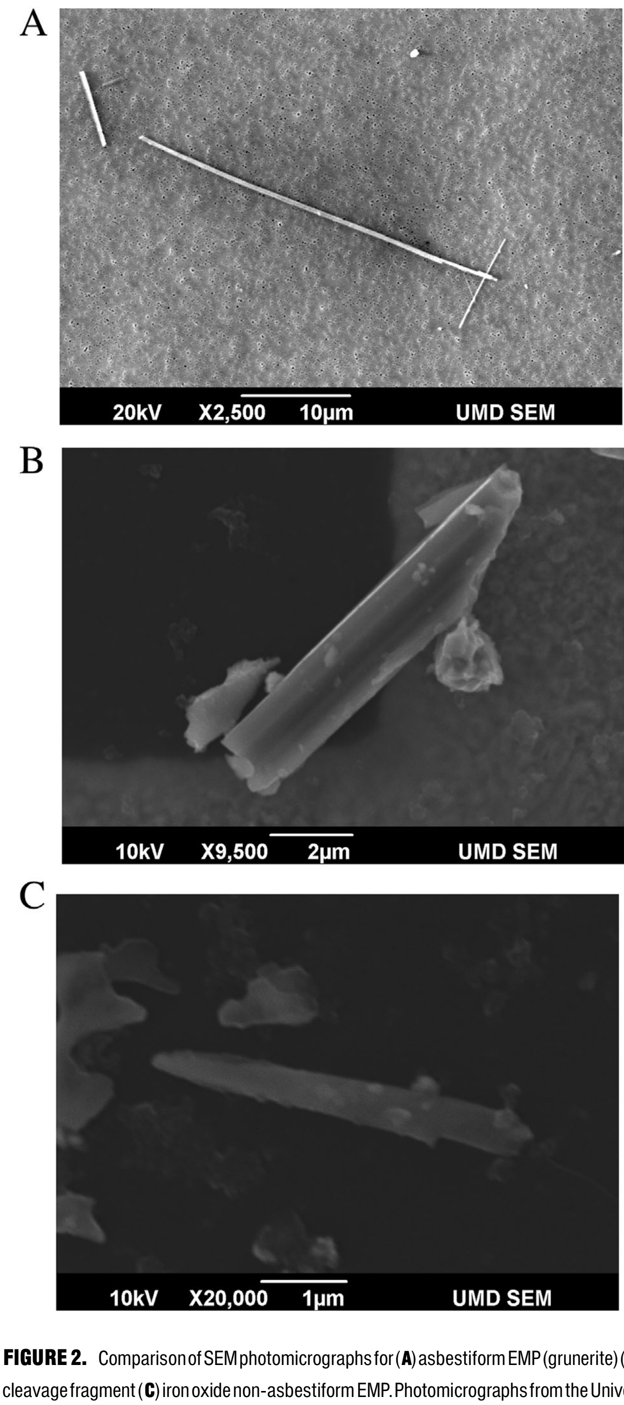

FIGURE 2. Comparison of SEM photomicrographs for (**A**) asbestiform EMP (grunerite) (**B**) cleavage fragment (**C**) iron oxide non-asbestiform EMP. Photomicrographs from the University of Minnesota Natural Resources Research Institute (NRRI) Minerals-Metallurgy-Mining Initiative (M3), unpublished data.

include mining, crushing, magnetic separation, concentrating, and pelletizing.

Concerns were initially expressed in the 1970s regarding the disposal of taconite waste rock, which contained EMPs, into Lake Superior and ultimately into the city of Duluth, Minnesota's drinking water [Levy et al., 1976]. In follow-up of this, occupational studies were conducted without evidence of disease excess [Higgins et al., 1983; Cooper et al., 1988, 1992]. In 2007, the Minnesota Department of Health identified an apparent excess of mesothelioma in a cohort of taconite miners [MDH Report, 2007], using the state's cancer registry to identify cases. This issue was further investigated in a series of "Taconite Worker Health Studies," discussed below.

South Dakota is a site of gold mining where non-asbestiform EMP exposure, also of the cummingtonite-grunerite series, may occur. An initial investigation of workers in this industry suggested an excess of lung cancer that triggered additional studies [Gillam et al., 1976], and follow-up investigations [McDonald et al., 1978; Steenland and Brown, 1995a]. Talc mining has been studied in multiple sites within the United States and Europe. EMP exposure in this mining typically involves tremolite and anthophyllite, although other mineral series may be encountered.

The purpose of this review is to assess the collective exposure and occupational epidemiology literature to obtain perspectives on potential risks of working in the setting where non-asbestiform EMP exposures may be encountered, namely within taconite, gold, and talc mining. Silica exposures, commonly encountered in these types of mining and others, have also been addressed.

METHODS

A literature search was developed to capture relevant occupational mining exposure assessment and mining epidemiology studies from the peer-reviewed literature in order to summarize the current state of knowledge about health issues involving non-asbestiform amphibole EMPs. Only studies of cohorts where exposure to EMP involved a formal occupational exposure assessment were selected. Some studies also included an exposure assessment for silica but the primary exposure of interest was to EMP. The search was undertaken primarily within PubMed of the National Library of Medicine, included research papers with original data and excluded editorials, case reports, and commentaries. Search terms included individual and/or combinations of the following: mining type (gold, taconite talc) in combination with mineral fiber, non-asbestiform elongate mineral particle, cleavage fragment, silica, non-malignant lung disease (NMRD), pneumoconiosis, asbestosis, respiratory cancer, lung cancer, mesothelioma, epidemiology, exposure assessment. In addition, searches were made of publically available doctoral theses, NIOSH mining publications (available at www.cdc.gov) and recent taconite reports (available at www.taconiteworkers.umn.edu). Title and abstract information was initially used to select papers of relevance. All selected papers were checked for additional references that may not have been captured initially by electronic literature searches.

For cohorts with multiple updates, the most recent was included in this review unless the methodology changed.

Papers were categorized by study type, size, exposure assessment data, key outcomes, control of key confounding variables and potential for bias, with information tabulated accordingly. Efforts were made to present summary information within study types that had more robust risk estimates (cohort, case-control studies), although cross-sectional studies were also used. Because of greater uncertainty in risk estimation, proportionate mortality/morbidity ratio (PMR) studies were not included. Common criteria in the assessment of epidemiologic investigations were used to provide additional context [U.S. Surgeon General Report on Smoking, 1964; Hill, 1965]. These included the strength of association, consistency, temporality, and exposure-response.

RESULTS

There were 14 mortality, three cross-sectional morbidity, four case-control, and eight exposure assessment studies identified in occupational settings where non-asbestiform EMP exposure could occur (Tables I–III). These studies occurred within the Homestake gold mines of South Dakota, the taconite mining facilities in northeastern Minnesota, and in talc workers in different settings in the United States and Europe. In addition to non-asbestiform amphiboles, crystalline silica exposure was a component of the dust exposure in many of these settings as was respirable dust, although not necessarily quantified in a formal exposure assessment. There were six different occupational cohorts studied with potential non-asbestiform exposure within the talc industry. These involved different exposures to EMPs that consisted of tremolite and anthophyllite or actinolite. The gold and taconite workers are felt to have predominantly cummingtonite-grunerite exposure [Gamble and Gibbs, 2008]. These three industries may also have had small amounts of fibrous amphiboles in connection with the ore body. In taconite, for example, fibrous amphiboles were felt to represent less than 1% of the amphiboles present [Ross et al., 2008]. No asbestiform EMPs were identified in the current occupational setting of taconite mining [Hwang, 2013; Hwang et al., 2013]. In talc mining, fibrous tremolite, and anthophyllite has been described [Dement and Zumwalde, 1978].

Formal exposure assessment studies have been done in taconite, gold, and talc mining settings (Table I). Gold mining exposure estimates were made in two studies (Table I). Personal samples were collected from 448 miners during an entire work shift over a 2-week period [Zumwalde et al., 1981]. Mean exposures to silica, radon daughters, arsenic, and asbestos fibers were within OSHA standards for most job classes at that time. In the Gillam study, fiber concentrations were estimated at 0.25 fibers/cm^3 for fibers over 5 μm. A comparison of fiber size and concentration with Homestake and Silver Bay mines (Minnesota's Iron Range) revealed comparable results. Average mean concentrations and ranges were 4.8 fiber/cm^3 in South Dakota versus 4.7 fibers/cm^3 in Minnesota, with ranges of 0.7–11.8 and 0.5–11.0, respectively. In Homestake samples, 6% were longer than 5 μm, compared to 5–10% in Minnesota samples.

Sheehy and McJilton [1987] assessed exposures in the earlier part of the taconite industry (1957–1983) but EMP data were not reported. Exposures to silica containing dusts in the mining, crushing and concentrating jobs exceeded the NIOSH REL and OSHA PEL guidelines in some of the plants in the concentrator area.

Studies by Hwang [2013] and Hwang et al. [2013, 2014] were completed in connection with the most recent epidemiological investigations [Allen et al., 2015a; Lambert et al., 2015]. This was the only exposure assessment where estimates were made for EMP, silica, and respirable dust, all generated from iron ore (taconite) operations. These studies included a comprehensive, onsite measurement of exposure categories coupled with an assessment of historical measurements to EMP and silica. For 20% of the total samples taken, EMP concentrations were measured by phase contrast microscopy (NIOSH 7400 method), transmission electron microscopy (NIOSH 7402), EDXA, and ISO 13794. Exposures for total EMPs were generally below the NIOSH REL in these assessments except for a few sites where some jobs were over the REL, which NIOSH intends to be used for asbestiform fibers and their non-asbestiform analogs.

Hwang specifically measured amphibole EMPs. These were found in the eastern-most portion of the Minnesota's iron range and were not identified in the west. Onsite measures of silica revealed more excursions over the time-weighted average (TWA) than other exposures.

Different EMP definitions, based on dimensions, were highly correlated, limiting the ability to understand associated health endpoints with specific EMP size [Hwang et al., 2014]. Through the use of TEM, it was found that the most prevalent EMP size in taconite operations was 1–3 μm in length and 0.2–0.5 μm in diameter [Hwang et al., 2014]. Respirable silica (RS) and respirable dust (RD) exposures were also measured at all six active mines with the use of NIOSH 7500 and NIOSH 600 methods, respectively [Hwang et al., 2013].

Talc mining exposures were also assessed [Selevan and Dement, 1979; Oestenstad et al., 2002]. In the former study, baseline surveys were made in 1991. These were combined with a categorical rating system made by experts to obtain an estimated job area concentration for each work location by time period forming a job-exposure matrix. Estimated exposures ranged from 0.1 to 1.7 mg/m^3. Baseline survey cumulative exposures ranged from 0.1 to 2.67 mg/m^3 with a mean cumulative exposure of 0.47 mg/m^3 (SD = 0.49). Selevan analyzed both airborne and bulk samples. No

TABLE I. Exposure Assessment Studies Involving Non-Asbestiform Amphiboles

Author	Type	Publication date	Key outcomes	Exposure type	Exposure details	Exposure measurement
Taconite mining						
Sheehy	Assessment of 16,000 dust samples from taconite mining facilities 1957–1975	1986	Gradual reduction in dust levels for some, but not all, jobs	Silica characterized for five jobs in four plants	For all jobs, the highest respirable mass concentration exceeded NIOSH REL and PEL	Respirable mass[c] Crusher laborer-0.56 Crusher op-0.3
Hwang	Collection of current 1,280 current and assessment of 682 historical exposures to EMPs. EMP $\Rightarrow 5\ \mu m$ length with aspect ratio $>$3:1	2013	Most jobs had EMP measures below exposure guideline; NIOSH REL[b]; Nearly all jobs had amphibole EMP below NIOSH REL	Non-asbestiform cummingtonite, grunerite Actinolite, hornblende; 28 similarly exposed jobs characterized in six active mines	Non-asbestiform amphibole EMP found in eastern Mesabi Range. No amphiboles found in western Mesabi Range; Jobs with highest EMP exposures: electrician, crusher maintenance, crusher operator	Total EMP[d] Electrician-0.309 Crusher maint-0.194 Crusher op-0.193 Amphibole EMP[d] Electrician-0.063 Crusher maint-0.026 Crusher op-0.03
Hwang[a]	Assessed current exposure to crystalline silica and respirable dust in active taconite mining	2013	Most jobs had respirable dust measures below OSHA PEL; Some jobs had silica measures over OSHA PEL	Silica and respirable dust; 28 similarly exposed jobs characterized in six active mines	Little variability among all six mines for silica and respirable dust	Respirable: Dust[e] / Silica[e] Concentrator maintenance 0.25 / 0.16 Concentrator operator 0.93 / 0.009 Pelletizing op 0.51 / LOD Crusher maint 0.28 / 0.032 Crusher op 0.22 / 0.061
Hwang	Comparison of four different definitions for EMP by size	2014	All four EMP size definitions highly correlated	Non-asbestiform cummingtonite, grunerite; actinolite, hornblende; total and amphibole EMP concentration and dimensions determined for six active mines	Non-asbestiform amphibole EMP found in eastern Mesabi Range. No amphiboles found in western Mesabi Range; Most frequent EMP dimension was 1–3 μ in length	% total EMP 1–3 μm in length Concentrator 59% Pelletizing 53% Maintenance 40% Laboratory 61%
Gold mining						
Gillam	Characterization of dust in breathing zone	1976		Non-asbestiform cummingtonite, grunerite; 60–70% grunerite, 1–2% cummingtonite,	Major mineral components are quartz, cummingtonite-grunerite, sulfides including arsenopyrites	Average fiber concentration by PCM = 0.25 fibers/cm^3; 94% of fibers $<5\ \mu m$; Silica average breathing zone concentration $= 1.7 \times 10^6$ particles/cubic foot
Zumwalde	NIOSH industrial hygiene report; Personal samples collected from 448	1981	"Exposures to silica, radon daughters, arsenic and asbestos	Non-asbestiform cummingtonite, grunerite	Midget impinge samples used to sample 170 workers; underground mining	Mean = 4.8 fibers/cm^3 Range = 0.7–11.8 fibers/cm (6% $> 5\ \mu m$)

(*Continued*)

TABLE I. (*Continued*)

Author	Type	Publication date	Key outcomes	Exposure type	Exposure details	Exposure measurement
	miners during entire shift over 2-week period		fibers are within OSHA standards for most job classifications."			
Talc mining						
Selevan (VT)	General assessment of airborne dust	1979	Air and bulk samples free of asbestos. Silica content low.	Non-asbestiform talc	Five companies from three geographic areas included; dust samples and talc bulk samples from all companies showed similar composition; No asbestos detected	Historical samples suggest past exposure levels to far exceed present OSHA standard of 20 mppcf; All levels of free silica in bulk samples <0.25%
Oestenstad (NY)	1,322 historical exposure measurements collected; 422 fiber counts	2002		Non-asbestiform talc (anthophyllite)	Baseline measurements were correlated with historical data and used to calculate relative ranking of exposures in jobs. Respirable talc dust used as the basis of cumulative exposure estimates rather than dust count	Baseline respirable dust exposures[e] ranged from 0.01–2.67 mg/m^3; arithmeticmean = 0.47 mg/m^3, Standard Deviation = 0.49.

[a]Report available at: www.taconiteworkers.umn.edu.
[b]The NIOSH REL is intended for regulated asbestiform EMP and for their non-asbestiform analogs [NIOSH, 2011].
[c]Units in mg/m^3.
[d]Units in fibers/cm^3.
[e]TLV for non-asbestiform talc = 2 mg/m^3.

asbestos was detected in any of the samples analyzed by either X-ray diffraction or electron microscopy.

Mortality studies that involved exposures to cummingtonite and grunerite as the exposure of interest are listed in Table II. These occurred in two industries, the Homestake gold mine in South Dakota and the iron ore (taconite) industry of northeastern Minnesota. There have been four mortality studies of gold miners identified with potential exposure to cummingtonite and grunerite (Table II). The initial investigation [Gillam et al., 1976] followed miners from 1960 through 1973 and indicated an elevation in respiratory cancer (SMR = 3.7, $P < 0.01$). This study had incomplete follow-up of the entire cohort. This finding was not replicated in subsequent analyses of the same cohort where the entire cohort was accounted for [McDonald et al., 1978; Steenland and Brown, 1995a]. The Steenland study is the most recent and has the largest cohort size. It reports an SMR for lung cancer of 1.13 (95%CI = 0.94–1.36). Both of these studies did suggest an increased risk for pneumoconiosis. The silica-specific investigation by Steenland and Brown [1995b] demonstrated increasing mortality risk from silicosis with increasing exposure.

Several of the taconite studies were done over 20 years ago and may not have had a long enough latency to show elevated mortality rates. The study by Allen et al. [2014] was the largest. It included all workers throughout the entire industry and also had the longest latency. Findings of interest included respiratory cancer (SMR = 1.16, 95%CI = 1.09–1.24), mesothelioma (SMR = 2.77, 95%CI = 1.87–3.96), and hypertensive heart disease (SMR = 1.81, 95%CI = 1.39–2.33).

Mortality studies in talc workers have been performed in the United States and Europe (Table III). The amphibole exposure in these settings is predominantly non-fibrous tremolite and anthophyllite. Six cohort mortality studies have been done in this exposure setting. These cohorts yielded relatively small studies ranging in size from 193 to 1974

TABLE II. Mortality Studies Involving Potential Exposure to Non-Asbestiform Amphibole[a] (Cummingtonite-Grunerite)

Author	Type	Publication date	Sample size	Exposure assessment approach	Key outcomes	Control for confounding	Potential issues
Taconite mining							
Higgins	Mortality	1983	9065 (5751 >1 year	By length of employment	All-cause SMR = 0.87; Respiratory cancer = 0.84	Yes-by proxy	Use of proxy responders; small n
Cooper	Mortality	1988	3444	By job category and length of employment	All-cause SMR = 0.88; Respiratory cancer = 0.59	No	No control for smoking; small n
Cooper	Mortality	1992	3431	By job category and length of employment	All-cause SMR = 0.91; Respiratory cancer = 0.97	No	No control for smoking; Small n
Allen	Mortality	2014	31,067	By length of employment	All-cause SMR = 1.04; Respiratory cancer = 1.16, 95%CI = 1.09–1.24; Mesothelioma SMR = 2.77 (1.87–3.96); Hypertensive heart disease SMR = 1.81 (1.39–2.33)	No	No control for smoking or quantitative workplace exposure
Gold mining							
Gillam	Cohort mortality; Homestake gold miners; Long-term male workers (>5 yr)	1976	440	Dust characterization performed without formal exposure assessment	Respiratory cancer SMR = 3.7[b] 5–19 years SMR = 5.3[c] >20 years SMR = 3.2[b] NMRD SMR = 3.2[c,d]	No	Smoking not controlled; Completeness of cohort not determined
McDonald	Cohort mortality; Homestake gold miners; Long-term male workers	1978	1321	Dust exposure categories used	Respiratory cancer high exposure SMR = 1.2[e]; Pneumoconiosis Relative Risk = 19.9[f] in highest exposure group	No	Smoking not controlled; Cohort completely determined
Steenland	Cohort Mortality; Homestake gold miners	1995	3328	Dust exposure categories used	Lung cancer SMR = 1.13 (0.94–1.36); Silicosis SMR = 2.61 (2.11–3.2)	No	Smoking not controlled; three of 115 lung cancer deaths with silicosis on death certificate

(*Continued*)

TABLE II. (*Continued*)

Author	Type	Publication date	Sample size	Exposure assessment approach	Key outcomes	Control for confounding	Potential issues
Steenland	Cohort Mortality for silicosis only; Homestake gold miners	1995	3330	Cumulative silica exposure determined	Increasing mortality risk from silicosis by increasing exposure (mg/m^3)-years	Controlled for age and calendar time	Conversion of dust counts to gravimetric measurements

[a]Non-asbestiform amphibole found within the ore body.
[b]Significant at $P < 0.01$
[c]Observed to expected comparison of two highest exposure groups to whole cohort as a reference.
[d]"NMRD" stands for non-malignant respiratory disease.
[e]High or very high exposure categories.
[f]Defined as ratios of SMR for two highest exposure groups versus two lowest.

individuals. Only the Honda talc investigation, with 27% mortality, revealed an excess of lung cancer (SMR = 2.32, 95%CI = 1.57–3.29). The risk for lung cancer did not increase with increasing cumulative exposure. In those with the highest tertile of cumulative exposure, the relative risk was 0.5, 95%CI = 0.2–1.3). In view of these findings and in consideration of other factors, the investigators suggested that the elevated SMR for lung cancer "is unlikely to be related to respirable talc ore dust per se."

Mortality studies within the talc industry have a uniform finding of excess death from non-malignant respiratory disease (NMRD) (Table III). NMRD consists of all lung disease except neoplastic disease and would include pneumoconiosis and infection as well as chronic lung disease from other causes (smoking), as detected on chest X-ray or spirometry. Generally, mortality is not an ideal measurement for NMRD because of its chronic nature and the possibility for individuals to die from other causes. Because of the multiple diseases within the category of NMRD, there is uncertainty about what this category specifically represents along with the potential for disease misclassification. Despite this, the NMRD SMRs were statistically significant in four of

TABLE III. Occupational Cohort Mortality Studies of Non-Asbestiform Amphibole Exposures in Talc Mining (Anthophyllite, Tremolite)

Author	Publication date	Main exposure	Sample size	Lung cancer SMR and 95%CI	NMRD S MR and 95%CI	Control for smoking
Selevan (Vermont)	1979	Non-asbestiform talc; Magnesite; Chlorite; Dolomite	392	1.63 (0.6–3.54) Mine: 4.35[b] Mill: 1.02	2.99[c] Miner: 1.6 Miller: 4.1	No
Wergeland (Norway)	1990	Non-asbestiform tremolite, anthophyllite; Low quartz content	389	0.92(0.34–2.01)	0.28(0.06–0.8)	Yes upon follow-up
Honda[a] (New York)	2002	Non-asbestiform tremolite, anthophyllite	782 (1960–1989) (27% mortality)	2.32 (1.57–3.29)[e] Mine: 3.94 (2.33–6.22) Mill: 1.28 (0.51–2.63)	2.21 (1.47–3.2)	No
Wild (France)	2002	Non-asbestiform talc/chlorite	1070	1.23 (0.76–1.89)	5.56 (1.12–16.2)	Yes
Wild (Austria)	2002	Non-asbestiform talc/chlorite/quartz/dolomite/mica	542	1.06 (0.43–2.19)	0.27 (0.01–1.52)	Yes
Coggiola[d] (Italy)	2003	Non-asbestiform talc	1974 (men)	0.94 (0.68–1.26)	Miners: 3.05 (2.49–3.69): Millers: 1.03 (0.65–1.57)	No

[a]Previous studies of this cohort included Brown and Wagoner [1978]; Stille and Tabershaw [1982]; Lamm et al. [1988]; Brown et al. [1990].
[b]$P < 0.05$.
[c]$P < 0.01$.
[d]Previous studies of this cohort included Rubino, 1976.
[e]Relative risk for lung cancer in longest employed group was 1.9 (95%CI = 0.4–8.1).

TABLE IV. Cross-Sectional Occupational Morbidity Studies of Non-Asbestiform Amphibole Exposures in Taconite Mining (Cummingtonite-Grunerite)

Author	Publication date	Sample size	Exposure assessment	Key outcomes	Control of smoking	Potential issues
Clark	1979	249	No	CxR findings consistent with silicosis in three of 249	No	Selection bias
Odo	2013	1084 (current and former workers)	No	Spirometric restriction[a]/mixed disease in 7.4%; Obstruction in 16.8%	No	Selection bias; No control for workplace exposure; Response bias
Odo	2016	1089 (current and former workers)	Yes	5.4% of workers with CxR evidence of parenchymal abnormality; 16.7% of workers with pleural abnnormality	Yes	Selection bias; No control for workplace exposure; Response bias

[a]Restrictive pattern on PFT defined as Forced Vital Capacity less than the lower 5% of the distribution; Covariates included in this model were silica measured in (mg/m^3)-years, age (5-year categories), body mass index (continuous variable), smoking (current, former, none), potential for prior asbestos exposure (high, low).

the six cohorts where non-asbestiform amphibole exposures occur. Two studies showed lower SMRs than expected [Wergeland et al., 1990; Wild et al., 2002]. These occurred in smaller cohorts without the availability of more detailed exposure information.

Cross-sectional studies of non-asbestiform amphibole exposure involved taconite workers (Table IV). The initial investigation of taconite workers occurred in 1979 and consisted of chest X-ray evaluations of 249 non-randomly selected workers. Three workers were described with findings consistent with “early silicosis.” Pulmonary function studies and chest X-rays were assessed in the more recent studies and demonstrated parenchymal abnormalities in 5% and pleural abnormalities in 16% [Odo et al., 2013; Odo, 2016]. Pleural findings occurred more often when duration of employment was over 35 years (RR = 1.84, 95%CI = 1.11–3.07).

Nested case-control studies have been done within the talc and taconite industries, corresponding to findings on cohort mortality studies (Table V). In the former, a nested case-control study was done for lung cancer in the New York talc industry [Gamble, 1993]. This was to address previous lung cancer mortality findings [Lamm et al., 1988; Stille and Tabershaw, 1992] and in NIOSH Health Hazard Evaluations. This included 22 cases and 66 controls. When stratified by smoking status, lung cancer risk decreased with increasing talc exposure.

An additional nested case-control study was done for lung cancer and NMRD in French and Austrian Talc workers [Wild et al., 2002]. Odds ratios for lung cancer did not increase with increasing cumulative exposure to talc. Cumulative exposure to talc was associated with increasing ORs for NMRD.

Lung cancer was assessed within the iron ore (taconite) industry by a case-control study [Allen et al., 2015a]. An excess of lung cancer was present in the preceding mortality investigation (SMR = 1.16, 95%CI = 1.09–1.16) [Allen et al., 2014]. There were 1,706 cases and 3,381 controls included in the case-control study. The unit OR for duration of employment was 1.0 (95%CI = 0.96–1.01). The unit OR for cumulative exposure to EMP was 0.94 (95%CI = 0.89–1.01). The EMP exposure metric was based on the NIOSH 7400 method, with fibers counted if they were over 5 μm in length and had a 3:1 or greater aspect ratio. Jobs were assessed for potential exposure in a blinded fashion, using a job-exposure matrix. This matrix consisted of data from onsite exposure measurements by study investigators and by the use of historical measurement data from companies and from the Mining Safety and Health Administration. [Hwang, 2013; Hwang et al., 2013]. Smoking information was not available for this study.

A nested case-control study was also done in the taconite industry to explore an increased SMR for mesothelioma [Lambert et al., 2015], with 80 cases and 315 controls. The SMR for mesothelioma in this population was 2.77 (95%CI = 1.87–3.96). The same job-exposure matrix was used in this effort as in the lung caner study [Allen et al., 2015a]. The number of years employed in the taconite industry was associated with mesothelioma risk (RR = 1.03, 95%CI = 1.0–1.06) and the cumulative EMP exposure was associated with mesothelioma, albeit imprecisely (RR = 1.10, 95%CI = 0.97–1.24). The study attempted to control for potential exposure to commercial asbestos by expert judgment ratings of job categories. Smoking was not controlled for but, unlike lung cancer, has not been shown to be a risk factor for mesothelioma.

DISCUSSION

Studies of workers with exposure to non-asbestiform amphiboles have taken place intermittently over the last five decades, predominantly in the form of mortality. Much of the concern surrounding this exposure is related to the

TABLE V. Occupational Case-Control Studies Involving Non-Asbestiform Amphibole Exposure

Author	Type	Publication date	Sample size	Exposure assessment	Odds Ratio and (95% Confidence Interval)	Key outcomes	Control of smoking	Potential issues
Gamble [1993]	Nested lung cancer NY Talc	1993	22 cases 66 controls	Yes	Lung cancer **OR = 0.7 (0.25–1.08)**, (high exposure group)	Lung cancer not related to occupational exposure	Yes-by question-naire	Potential misclassification in non-talc exposures and smoking; Short-term workers influence lung cancer risk
Wild et al. [2002]	Nested lung cancer and NMRD French and Austrian talc	2002	Lung cancer: 30 cases 88 (controls); NMRD 40 cases 115 controls	Yes	Lung cancer[a] **OR = 1.23 (0.76–1.89)** NMRD OR = 5.56 (1.12–16.2), (French cohort)	Lung cancer not related to talc; NMRD risk increased with increasing talc exposure	Yes	Relatively low power; Exposure-response with NMRD
Allen et al. [2014]	Nested lung cancer MN Taconite	2014	1706 cases 3381 controls	Yes	Lung cancer **OR = 0.82 (0.57–1.19)**	Lung cancer not associated with workplace exposure	No; Smoking estimated from parallel study	Commercial asbestos exposure concentration not available
Lambert et al. [2015]	Nested mesothel-ioma MN Taconite	2015	80 cases 315 controls	Yes	Mesothelio-ma **OR = 1.93 (1.15–3.34)**, (high vs. low EMP exposure groups)	Mesothelio-ma related to duration of employment; possible role of EMP	No	Commercial asbestos exposure concentration not available; EMP counted with phase contrast microscopy

Bold values indicates OR = odds ratio with 95% confidence interval included in parentheses.

pathogenicity of asbestiform amphiboles, which have demonstrated consistent associations with lung cancer, mesothelioma, and non-malignant respiratory disease (NMRD). Mortality studies predominate the non-asbestiform amphibole literature (Tables II and III). In most of the mortality investigations, job exposures were considered without personalized exposure measurements to EMP. These studies may lack accuracy and precision in the determination of risk. Many of the non-asbestiform amphibole studies involve relatively small numbers of workers, did not control for potential confounding variables including smoking and did not account for co-exposures to silica and respirable dust.

Some non-asbestiform EMP exposures may be accompanied by asbestiform EMPs. In the setting of iron ore (taconite) mining, asbestiform EMP is felt to be less than 1% of the total rock mass of the eastern Mesabi Iron Range [Wilson et al., 2008], but exposures to silica and respirable dust also occur. In European talc mining, contamination by asbestiform EMPs has not been detected [Wild et al., 2002] but has been detected in New York talc [Dement and Zumwalde, 1978]. In some studies, respirable dust concentrations, rather than counts were used as the basis of cumulative exposure [Oestenstad et al., 2002]. Still others describe a mixed exposure of talc and silica [Coggiola et al., 2003].

Cleavage fragments (CF) form as the ore body is crushed in mining and processing. A review of CFs has suggested they present less toxicity due to their chemical and physical properties [ATSDR, 2001]. Although asbestiform amphiboles have crystalline structures that grow along unidirectional planes, CFs have crystalline structures that grow in multiple planes. Breakage occurs along these planes and does not result in fiber formation. Asbestiform amphiboles generally form fibers that are long and thin. Although CFs may have lengths beyond 5 μm, when this happens the CF's thickness also increases, making them less biologically relevant [ATSDR, 2001].

Despite the above, some consistent disease findings in worker studies have been reported. The most consistent finding in epidemiological investigations within these mining industries is NMRD. Although this category contains pneumoconiosis, it also contains chronic lung disease and infection and introduces the possibility of disease misclassification. Whether NMRD is included on death certificates of individuals dying from other causes is another limitation of these mortality studies. In these studies, if listing NMRD on the death certificates of workers in these industries occurred more frequently than in the general population, SMRs could be biased upwards. Despite this potential problem, NMRD still occurred more frequently within the highest exposure categories in several studies. It occurred in excess in studies of all three types of mining, in U.S. and European settings. The etiology of NMRD in these settings has been incompletely assessed, partly due to the likelihood of additional, unmeasured exposures, including silica and respirable dust.

There is evidence of increasing NMRD risk with increasing silica exposure in studies where non-asbestiform EMP exposures also occurred [Steenland and Brown, 1995a] or increasing talc dust [Honda et al., 2002; Wild et al., 2002]. Some studies demonstrated an increased risk associated with work earlier in the industry [Steenland and Brown, 1995b; Honda et al., 2002]. One study included quantitative exposure estimates to EMP, silica, and respirable dust and was included in a morbidity assessment [Odo, 2016]. There was a specific association described with EMP exposure and pleural abnormalities in this investigation. Of interest is the fact that this occurred in a subset of the same cohort that also revealed an excess of mesothelioma [Lambert et al., 2015]. In the Honda study, although the SMR for NMRD was elevated in the highest exposure grouping, (SMR = 2.48 (95%CI = 1.19–4.56) the relative risk (RR) showed a modest, and imprecise increase (RR = 1.6, 95%CI = 0.4–5.9), likely a reflection of the relatively small number of subjects (n = 782). Work in taconite was not associated with increased mortality from respiratory disease (SMR = 0.94, 95%CI = 0.86–1.02) [Allen et al., 2014]. The association of NMRD with work in these collective mining industries was the most consistent finding.

Another finding described in several of these investigations was an apparent excess of cardiovascular disease. Gold miners have increased mortality from diseases of the heart where the relative risk in "high" exposure settings was 1.3 versus 1.1 in "low exposure" settings [McDonald et al., 1978]. This same cohort was updated in 1995 and demonstrated an SMR for circulatory disease of 1.19 (95%CI = 1.02–1.38) [Steenland and Brown, 1995a]. Talc workers had a non-significantly elevated SMR for cardiovascular disease (SMR = 1.11, 95%CI = 0.67–1.73) [Honda et al., 2002]. In an Italian cohort of talc workers, the SMR for cardiovascular disease was decreased (SMR = 0.77, 95%CI = 0.62–0.95) [Coggiola et al., 2003]. Taconite workers had increased mortality from "heart disease" (SMR = 1.10, 95%CI = 1.06–1.14) [Allen et al., 2014]. This same study demonstrated elevated SMRs for hypertensive heart disease (SMR = 1.81, 95%CI = 1.39–2.22) and ischemic heart disease (SMR = 1.11, 95%CI = 1.07–1.16). Allen's investigation included over 30,000 workers throughout the entire industry in Minnesota.

The cardiovascular findings are not exposure-specific but are potentially work-related. Investigations from the air pollution literature have suggested associations with heart disease and particulate matter (PM), especially particulate matter (PM 2.5) [Pope et al., 2009]. Although EMP exposures 1–3 μm in length are the most prevalent [Hwang et al., 2014], the exposure measurement in this investigation was not done on all samples and results by size of EMP were highly correlated. Lifestyle factors could also have been involved in the Allen study findings. Cardiovascular disease in non-asbestiform amphibole mining remains an important area of investigation.

Respiratory cancer risk has been reported as increased in gold miners (SMR = 3.7; $P < 0.01$) [Gillam et al., 1976]. Follow-up assessments of the same cohort were done with complete cohort enumeration [McDonald et al., 1978; Steenland and Brown, 1995b]. These investigations demonstrated increased, but statistically non-significant, respiratory cancer SMRs (Table II). The largest cohort mortality investigation was in the taconite industry [Allen et al., 2014] and also revealed an increased risk for respiratory cancer (SMR = 1.16, 95%CI = 1.09–0.123). Within the respiratory cancer grouping, lung cancer had the largest risk (SMR = 1.16, 95%CI = 1.09–1.24). None of these studies controlled for smoking.

Lung cancer was further assessed in three nested case-control studies [Gamble, 1993; Wild et al., 2002; Allen et al., 2015a] The Allen study was the largest with 1706 cases and 3381 controls. This investigation used an accompanying, detailed exposure assessment to determine associations with cumulative exposures to EMPs and silica [Hwang, 2013; Hwang et al., 2013, 2014]. Neither exposure type was significantly associated with lung cancer. For EMP exposure to non-asbestiform amphiboles, the odds ratio was 0.94 (95%CI = 0.89–1.01). For cumulative silica exposure, the odds ratio (OR) was 1.22 (95%CI = 0.81–1.83). Cumulative EMP and silica exposures also assessed subtypes of lung cancer. The subtypes included squamous cell, adenocarcinoma, small-cell, and non-specified. None of the subtypes demonstrated significantly increased ORs by EMP or silica exposures. Neither Gamble nor Wild demonstrated increasing lung cancer risk with increasing exposure.

The taconite investigations included an assessment of cancer incidence [Allen et al., 2015b]. Standardized Incidence Ratios (SIRs) were determined for major cancer categories, including lung and mesothelioma. This was conducted in conjunction with the Minnesota Cancer Surveillance System, in existence since 1988, and which has a capture rate in excess of 98% for all cancers occurring in the state, with the exception of skin cancer. After adjustments for age, gender, calendar period, and out-of-state migration, the following SIRs were reported: mesothelioma SIR = 2.4 (95%CI = 1.8–3.2, Lung SIR = 1.3 (95%CI = 1.2–1.3), larynx SIR = 1.4 (95%CI = 1.1–1.7), stomach SIR = 1.4 (95%CI = 1.1–1.6), bladder SIR = 1.1 (95%CI = 1.0–1.2). A probabilistic bias analysis to account for confounding by smoking, attenuated these associations, but did not eliminate the association with lung cancer (SIR = 1.1, 95%CI = 1.0–1.3).

The only investigation involving mesothelioma and a detailed exposure assessment in the non-asbestiform amphibole literature was done within the taconite industry [Lambert et al., 2015]. There have been mesothelioma cases included in some studies where non-asbestiform amphibole exposures were possible in the talc industry [Honda et al., 2002]. The two cases in this study were felt to be unrelated to exposure encountered in the talc industry. In one case, the latency was around 11 years, unusually short for mesothelioma. In another, the individual briefly worked in the talc industry and shortly after starting, developed a mesothelioma. This individual also had potential commercial asbestos exposure in a different work setting.

Mesothelioma occurrence in the taconite industry of Minnesota has been noted since 2003 [Brunner et al., 2008]. Both cohort mortality and cancer incidence studies indicated a 2.5–3-fold higher rate of mesothelioma than expected [Allen et al., 2014, 2015b]. A nested case-control study of 80 cases and 315 controls demonstrated an association with mesothelioma and time worked in the taconite industry [Lambert et al., 2015]. Cumulative exposure to EMP, defined by the NIOSH 7400 phase contrast method, was also related to mesothelioma. The unit rate ratio for duration of employment was 1.03 (95%CI = 1.0–1.06), or an increased mortality of 3% per year worked. The unit rate ratio for cumulative EMP exposure was 1.10 (95%CI = 0.97–1.24) or a 10% increase for each (EMP/cc)-year exposure. Those who worked in jobs above the mean cumulative EMP exposure had twice the risk for mesothelioma as those below the mean exposure.

Although the association with EMP and mesothelioma in this study was possible, there were remaining uncertainties. Most importantly, the location of workers where the rate ratio was highest (western most Mesabi Range) was not where EMP amphibole exposures occurred. The method of counting EMP in the Lambert study was by phase contrast microscopy, where differentiating asbestiform and non-asbestiform EMP can not be done. Given the lack of cancer findings in other studies of non-asbestiform amphibole exposure, and that no association was observed in the region of the Mesabi Range where non-asbestiform amphibole minerals are most common, it seems unlikely that non-asbestiform amphibole exposure would account for the total mesothelioma risk demonstrated in this study.

CONCLUSIONS

Occupational studies where non-asbestiform EMPs occur have demonstrated an increased risk for several diseases, most consistently NMRD. This risk appeared to be higher in these industries prior to the regulatory era and occurred in gold, taconite, and talc mining. In studies where exposure assessments were more rigorous, lung cancer was not associated with this exposure. Case-control studies revealed odds ratios that were near null and did not change with increasing exposure. Increased risk for mesothelioma occurred in a recent taconite case-control investigation. Although mesothelioma was related to duration of work time and possibly cumulative EMP exposure, there were uncertainties as to the type of EMP exposure. There was a suggestion of cardiovascular disease excess in several of these studies. Whether this indicated disease related to particle size or whether lifestyle risk factors were involved is an important and unresolved issue.

AUTHORS' CONTRIBUTIONS

JHM, BHA, and GR were involved in various aspects of the design, acquisition, interpretation and review of this work.

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The authors declare no conflict of interest.

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Steven Markowitz declares that he has no competing or conflicts of interest in the review and publication decision regarding this article.

DISCLAIMER

None.

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