

ORIGINAL ARTICLE

A case–control study of mesothelioma in Minnesota iron ore (taconite) miners

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ABSTRACT

Objectives An excess of mesothelioma has been observed in iron ore miners in Northeastern Minnesota. Mining and processing of taconite iron ore generate exposures that include elongate mineral particles (EMPs) of amphibole and non-amphibole origin. We conducted a nested case–control study of mesothelioma in a cohort of 68 737 iron ore miners (haematite and taconite ore miners) to evaluate the association between mesothelioma, employment and EMP exposures from taconite mining.

Methods Mesothelioma cases (N=80) were identified through the Minnesota Cancer Surveillance System (MCSS) and death certificates. Four controls of similar age were selected for each case with 315 controls ultimately eligible for inclusion. Mesothelioma risk was evaluated by estimating rate ratios and 95% CIs with conditional logistic regression in relation to duration of taconite industry employment and cumulative EMP exposure [(EMP/cc)×years], defined by the National Institute for Occupational Safety and Health (NIOSH) 7400 method. Models were adjusted for employment in haematite mining and potential exposure to commercial asbestos products used in the industry.

Results All mesothelioma cases were male and 57 of the cases had work experience in the taconite industry. Mesothelioma was associated with the number of years employed in the taconite industry (RR=1.03, 95% CI 1.00 to 1.06) and cumulative EMP exposure (RR=1.10, 95% CI 0.97 to 1.24). No association was observed with employment in haematite mining.

Conclusions These results support an association between mesothelioma and employment duration and possibly EMP exposure in taconite mining and processing. The type of EMP was not determined. The potential role of commercial asbestos cannot be entirely ruled out.

INTRODUCTION

Mining of iron ore along the Mesabi Iron Range in northeastern Minnesota began with haematite ore mining in the late 19th century, and continued in the latter half of the 20th century as taconite ore mining, following the depletion of haematite. Unlike the high-grade haematite, taconite is a lean ore that requires processing to concentrate the iron content, with crushing and separation techniques that break down the taconite rock, producing cleavage fragments and mineral particles of differing sizes. Controversies have existed within the taconite industry regarding exposure and human health.

What this paper adds

- An excess of mesothelioma was previously identified in iron ore miners in Northeastern Minnesota without consideration of occupational exposure.
- Minnesota iron ore miners are exposed to a variety of elongate mineral particles (EMPs), including asbestiform and non-asbestiform types, the latter of which have been incompletely assessed, scientifically.
- In this study mesothelioma risk was associated with employment duration and cumulative exposure to EMPs. The specific type of EMP (asbestiform, non-asbestiform) was not determined.
- Owing to the prolonged latency of this disease, continued follow-up and assessment of this industry is warranted.

Concerns were initially expressed in the 1970s regarding the disposal of taconite waste rock into Lake Superior.¹ In follow-up of this concern, occupational studies were conducted demonstrating little evidence of elevated disease rates among workers.^{2–5} In 2007, the Minnesota Department of Health identified an apparent excess of mesothelioma in taconite miners.⁶ This finding was confirmed in a general cohort mortality analysis, which indicated a 2.9-fold increase in the rate of mesothelioma in the iron mining industry workers when compared to the rest of Minnesota.⁷ While this finding suggested that people working in the iron mining industry were at higher risk for mesothelioma mortality, it did not reveal specifically how work in the taconite industry may be related to this risk, the subject of this paper.

Assessments of workplace mineral exposure and lung disease have been hampered by a confusing terminology that may deal with different measurement techniques and/or different definitions of exposure. As an example, although mesothelioma, a cancer of the mesothelial lining around the lungs or peritoneum, has been strongly linked to asbestos exposure, the term ‘asbestos’ may have different meanings. It may have a commercial connotation, as the six regulated types of asbestos [chrysotile (serpentine) and five types of amphiboles: anthophyllite, tremolite, cummingtonite-grunerite (amosite), riebeckite (crocidolite) and actinolite]



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that have been used in various industrial applications. From a mineralogical view, all types may exhibit the 'asbestiform' habit (morphology), meaning they can be separated in their natural environmental state into hair-like fibres along the longitudinal axis.⁸ The asbestiform type has the highest potential for airborne exposure, due to its natural friability. These types of minerals may also exist naturally in a non-asbestiform habit, with lower exposure potential (non-friability). The term 'fiber' is another ambiguous term, as mineralogical and regulatory definitions of fibre are inconsistent. The mineralogical definition refers to the smallest elongate crystalline unit that can be separated from a bundle or appears to have grown individually in that shape. Polycrystalline aggregates of mineral fibres give rise to a fibrous habit, one specific type of which is referred to as 'asbestiform'. Use of the term 'elongate mineral particle' (EMP) has been employed to clarify some of the confusion around the use of these terms.⁹

The National Institute for Occupational Safety and Health (NIOSH) defines a recommended exposure limit (REL) for EMPs to include any mineral particle with the defined aspect ratio of 3:1 or more and a length greater than 5 µm. This definition encompasses the regulated minerals chrysotile, amosite, actinolite, anthophyllite, tremolite, and crocidolite, but also includes the non-asbestiform analogues of these minerals, along with amphibole minerals from certain mineral series, and the non-asbestiform cleavage fragments of select serpentine minerals.⁹

The occurrence of mesothelioma has been definitively linked to asbestos exposure.^{10–11} Less is known about the effects of exposure to shorter types of EMPs. Research focused on exposure to non-asbestiform mineral particles has consisted largely of mortality studies within selected mining industries,^{3, 5, 12–15} and has shown little evidence of an association between non-asbestiform amphibole EMP exposure and malignant lung disease. Studies have suggested the development of mesothelioma and lung cancer is most strongly associated with exposure to asbestiform EMPs at least 5–10 µm in length,^{16–18} but particles in a variety of sizes have demonstrated an association with lung and pleural tumours,^{18, 19} including shorter particles, whose length is less than 5 µm.^{20–22} Previous studies of occupational exposure and particle length have focused on asbestiform amphibole EMPs and the serpentine chrysotile EMP.^{17, 18, 23, 24}

EMPs within the taconite industry can vary in mineral type, including non-asbestiform amphiboles and non-amphiboles, and in particle size with particles of NIOSH regulatory length as well as smaller cleavage fragments.^{25–27} This variation is due in part to the location of taconite mine. The mineralogical composition of the Mesabi Iron Range varies along its 122-mile length, and is split into four geological zones.²⁶ All zones have deposits of taconite along with quartz and iron silicates, but the types of EMP encountered vary. The eastern end of the range is Zone 4 where iron-rich amphibole EMPs can be found predominantly as cummingtonite-grunerite.²⁶ The western part of the range, zone 1, comprises approximately two-thirds of the entire Mesabi Iron Range and contains largely non-amphibole EMPs. Zone 2 is considered a transitional zone and contains some amphiboles. There are no mines located in Zone 3.

EMPs in the eastern Mesabi Range have been previously described with the predominant lengths under 5 µm.¹ EMPs in the western Mesabi Range have been described without amphiboles present.²⁷ Cleavage fragment EMP makes up a greater per cent of the western Mesabi Range exposures. These have diameters that, on average, are much larger than those of asbestiform EMPs.²⁸

We performed a nested case–control study to determine if the risk of developing mesothelioma differed by exposure to EMPs generated by the mining and processing of taconite ore.

METHODS

The protocol for this study was reviewed and approved annually by the Human Subjects Committee of the UMN Institutional Review Board.

Study design and population

We conducted a nested case–control study of mesothelioma in a cohort of iron mining workers. This work was one of several studies undertaken as part of the Taconite Workers Health Study, which also included an occupational exposure assessment, mortality analysis and studies of lung cancer and non-malignant lung disease. For specifics on the Taconite Workers Health Study see http://taconiteworkers.umn.edu/news/documents/Taconite_FinalReport_120114.pdf. The University of Minnesota enumerated the study cohort in 1983 as part of the Mineral Resources Health Assessment Program (MRHAP) and included 68 737 individuals identified as employees in the iron ore mining industry in northeastern Minnesota sometime before 1982. The cohort was followed for vital status through 2010 and causes of death were obtained through 2007. Vital status was ascertained using the Social Security Administration, the National Death Index, the Minnesota Department of Health and state death certificates outside of Minnesota. All deaths were coded to the International Classification of Disease (ICD) codes in effect at the time of death.⁷

Selection of cases and controls

All cases and controls were nested within the MRHAP cohort, and had to have clear evidence of employment in the mining industry, based on review of individual work history records. Mesothelioma cases were identified using two sources, the Minnesota Cancer Surveillance System (MCSS) and death certificate records. MCSS has histologically confirmed cancer information dating back to 1988 on cancer cases diagnosed within the state of Minnesota. Linkage of the MRHAP cohort to MCSS identified 63 cases of mesothelioma. Mesothelioma was coded using ICD-O-3 histology codes 9050–9053. Death certificates identified 53 mesothelioma cases using the ICD 10th revision code C45. While MCSS cases were in state only, death certificates identified 17 cases of mesothelioma that occurred in 10 states outside of Minnesota. Both MCSS and death certificate records identified 36 individuals. In total there were 80 mesothelioma cases. Four controls were selected for each case using an incidence density sampling approach. For each case, controls were selected from risk sets of cohort members of similar age (years of birth ± 2 years) and who were alive and without a diagnosis of mesothelioma on the date of diagnosis or death of the case. Five controls were eliminated from the study due to lack of evidence of employment in mining, giving 315 controls and a total study population of 395 miners.

Exposure assessment

The details of the exposure assessment have been described elsewhere.²⁵ Briefly, a database of mining job titles was created that sorted jobs by similar tasks and processes, referred to as similar exposure groups (SEGs). Job titles were collected from the Mining Safety and Health Administration (MSHA), a 1986 University of Minnesota study by Sheehy and McJilton,²⁹ and the internal industrial hygiene databases of three current taconite companies. In collaboration with company industrial

hygienists, job information was used to create 28 SEGs. Historical exposure data were collected from MSHA and taconite mining companies. Using all sources, historical data on EMPs were available for the period 1977 to 2009.

Historical samples were available from 1977 to 2010. A total of 682 EMP measurements were available from seven mining facilities. The samples occurred predominantly between 1977 and 1988 and between 1999 and 2010 in approximately equal amounts by year in those intervals. The industry was economically less active during the 1988–1999 interval. Except for one facility that closed in 2001, the remaining six facilities had 1280 on-site measurements taken by study investigators from 2010 to 2011.

From 2010 to 2011, measurements of personal and area exposure levels were taken by study investigators at all six active taconite mines. Personal sampling was conducted for each SEG in existence at each mine, with volunteer miners wearing a personal air-sampling pump. Two workers per SEG were selected for personal EMP sampling in Zone 4, and each worker was sampled during three different shifts. In Zone 1, approximately eight workers per SEG were chosen, with each worker sampled on three different shifts. Mineral exposures in Zone 2 were determined to be most similar to Zone 4, therefore Zone 4 exposures were used for Zone 2 SEGs as there was no active mine in Zone 2 for sampling. All personal EMP samples were analysed using the NIOSH 7400 phase contrast microscopy (PCM) method which counts EMPs with a length $> 5 \mu\text{m}$ and an aspect ratio ≥ 3 . Because PCM may miss thin fibres below $0.25 \mu\text{m}$, 20% of the personal samples had dimensions measured with a transmission electron microscopy (TEM) method (NIOSH 7402). Amphibole EMPs were identified with energy dispersive X-ray analysis and crystalline structure by selected area electron diffraction. EMPs were further differentiated as asbestiform or non-asbestiform using TEM.

Personal sampling data were combined with historical personal exposure data for the years 1977–2009, obtained from the MSHA and three of the six currently operating taconite mines. The combined exposure data served as the basis for a time-varying linear regression model that imputed EMP yearly cumulative exposure averages for each of the 28 SEGs within each of seven different mines for the period of 1955–2010.

EMP exposures encountered in taconite mining have been addressed elsewhere.^{25 30} In brief, three main exposures were measured, crystalline silica, EMPs and respirable dust containing iron particulates) Of the EMPs measured by the NIOSH 7400 approach, most were found to be within exposure guidelines (see online supplements 1 and 2). Amphibole EMPs were restricted to the eastern most Mesabi Range and were substantially lower than measured total EMPs. No asbestiform amphibole EMPs were found in any of the onsite samples.

Area measurements using a cascade impactor were obtained at locations corresponding to the various SEGs. These were analysed using ISO-TEM method 13794 that allows the determination of wider range of dimensions of the EMPs including shorter ones. With the use of these area samples, EMPs could be counted by multiple definitions. It was found that the EMP counts according to the different definitions were highly correlated and alternate exposure definitions were not used for this study.³⁰

Work history and exposure matrix

Work history information for cases and controls, including all job titles and dates, was abstracted from available mining company work records through 1982, the time the cohort was

enumerated. Mining job titles were standardised and mapped to an SEG. Departmental information was used to assign SEGs when the job title did not provide enough information. Additional SEGs were created for jobs where some idea of job task was possible that categorised jobs into departmental level classifications. Missing or vague job titles were assigned to an 'Unknown' SEG. Exposure values for department level SEGs were based on the average of other SEGs in that department. Exposures for the Unknown SEG at each mine were an average of all SEGs at that mine.

Some members of the MRHAP cohort worked in the earlier haematite industry. Haematite does not require the processing and concentrating techniques of taconite and does not have the same exposures. Therefore haematite and taconite work histories were separated. Historical data on mining operations and yearly taconite production totals were used to determine a taconite start date for each company. Jobs held before the taconite start dates were assigned to a haematite SEG. The exposure value for the haematite SEG was zero as no data were available on exposures within haematite operations.

Exposure data matrices were created to calculate the cumulative EMP exposure value for each individual. Each SEG had a daily EMP concentration that differed depending on the company and year of employment. The concentration for an SEG was multiplied by the length of time spent working in the SEG, and the values for all SEGs summed to give the cumulative EMP exposure for a worker. Cumulative exposures were measured by $(\text{EMP}/\text{cc}) \times \text{years}$, a metric based on time and intensity of exposure.

Commercial asbestos was used in the processing operations buildings as well as in some of the processes and was an important potential confounder. No quantitative data exist on commercial asbestos exposure in these operations so a qualitative scale was established to estimate exposures by job title. The study team and taconite company industrial hygienists estimated the probability and frequency of exposure to commercial asbestos within each SEG, and assigned a commercial asbestos score of low, medium or high based on these estimates. Several metrics were evaluated, and the number of years worked in an SEG with a high commercial asbestos score was ultimately used as a metric to control for the potential effects of asbestos exposure.

Analysis

Descriptive analyses compared cases and controls by demographic and occupational factors. The effect of employment duration in taconite mining and cumulative exposure to EMPs on mesothelioma risk was estimated using conditional logistic regression to account for the person-time matching of cases and controls within risk sets. Cumulative exposure was determined from the SEG specific exposure estimates based on the models using current and historical measurements; a secondary analysis utilised current measurements alone. Risk estimates were expressed as estimated rate ratios and 95% CIs. In addition to the main effect variables, final models included terms for the number of years employed in haematite mining and number of years spent working in SEGs with a high commercial asbestos score. Employment and $(\text{EMP}/\text{cc}) \times \text{years}$ models based on the NIOSH 7400 counting method were run with no latency and with a 20-year latency. All analyses were conducted with SAS V9.2.

RESULTS

Characteristics of cases and controls

A total of 80 cases and 315 controls were included in the study (table 1). All were pleural types. Fifty-seven cases and 184

Table 1 Characteristics of all cases and controls in study population, and cases and controls who worked in taconite

All workers	Cases N (%)	Controls
Total	80	315
Female	0 (0.0)	17 (5.4)
Male	80 (100.0)	298 (94.6)
Type of ore mining		
Haematite only	23 (28.7)	131 (41.6)
Taconite and haematite	25 (31.3)	81 (25.7)
Taconite only	32 (40.0)	103 (32.7)
Years of employment (years)	Mean (SD)	Mean (SD)
Taconite employment	7.7 (9.6)	5.5 (8.4)
Haematite employment (years)	2.8 (6.2)	3.1 (5.9)
Total employment	10.6 (11.6)	8.6 (10.9)
Taconite workers	Cases N (%)	Controls N (%)
Total	57	184
Female	0 (0.0)	9 (4.9)
Male	57 (100.0)	175 (95.1)
Geological zone-ever worked*		
Zone 1	18 (31.6)	74 (40.2)
Zone 2	31 (54.4)	58 (31.5)
Zone 4	12 (21.1)	66 (35.9)
Years of employment	Mean (SD)	Mean (SD)
Total employment	13.7 (11.8)	13.3 (12.0)
Taconite employment	10.9 (9.7)	9.4 (9.3)
Hematite employment	2.9 (6.3)	4.0 (7.0)
Employment by geological zone (years)		
Zone 1	3.5 (6.7)	3.1 (5.6)
Zone 2	5.7 (9.1)	2.5 (6.8)
Zone 4	1.6 (5.9)	3.7 (8.1)
NIOSH 7400 (EMP/cc)×years	Mean (SD)	Mean (SD)
Total (EMP/cc)×years	2.2 (1.2)	1.7 (0.4)
(EMP/cc)×years by geological zone		
Zone 1	0.5 (1.2)	0.1 (0.4)
Zone 2	1.4 (2.1)	0.5 (1.5)
Zone 4	0.4 (1.4)	1.0 (2.3)
Employment in SEGs with high commercial asbestos† (years)	1.6 (3.8)	0.8 (2.8)

*Cases and controls may have worked in multiple zones.

†SEGs with a high asbestos score are crusher maintenance, furnace operator, electrician, carpenter, auto mechanic, pipefitter/plumber, and lubricate technician. EMP, elongate mineral particles; NIOSH, National Institute for Occupational Safety and Health; SEGs, similar exposure groups.

controls worked at some point in the taconite industry, with 23 cases and 131 controls working exclusively in the haematite industry. All cases and 95% of controls were male. Between two and five cases occurred within MCSS annually from 1988 to 2010. The mean length of haematite employment was similar for cases and controls but the mean length of taconite employment was greater in cases. Zone 2 had the greatest number of mesothelioma cases. Mean cumulative exposure to NIOSH 7400 EMPs and mean years spent in SEGs with a high commercial asbestos score were greater for cases.

Taconite employment duration

The risk of mesothelioma was associated with the number of years of employment in the taconite mining industry (RR=1.03,

95% CI 1.00 to 1.06) (table 2). Models dividing workers into categories based on the median and tertiles of length of employment of controls, suggested an association between employment length and mesothelioma risk. All risk estimates were adjusted for age (matched on birth year) and years of employment in haematite operations. The risk of mesothelioma was increased with duration of employment in both Zone 1 and Zone 2, but was not associated with employment duration in Zone 4. Models that incorporated a 20-year lagged exposure had similar results. Excluding female controls did not alter the results.

(EMP/cc)×years of exposure

Higher exposure to EMPs, as defined by the NIOSH 7400 method, was associated with increased risk of mesothelioma. Each additional (EMP/cc)×year of exposure was associated with an elevated but non-significant risk of mesothelioma (RR=1.10, 95% CI 0.97 to 1.24) (table 3). When cumulative exposure was divided into high and low categories based on the median cumulative exposure of the controls, the rate of mesothelioma was about 2.25 times greater for workers in the highest exposure category relative to those in the lowest (95% CI 1.13 to 4.50). Use of tertiles resulted in an increased rate ratio in the highest exposure category. As with duration of employment, the associations with (EMP/cc)×year varied across zones in a similar fashion, being elevated in Zone 1 and Zone 2 but not in Zone 4. The effect estimates for (EMP/cc)×year were adjusted for years in haematite mining and years of employment with high probability of exposure to commercial asbestos. Using other classifications of commercial asbestos exposure (ever/never) did not substantially change the estimates, nor did use of a 20-year lag, excluding female controls or using only current exposure data to estimate historical exposures.

Table 2 Overall and zone specific rate ratio estimates for mesothelioma by years of employment in taconite

	Cases	Controls	RR*	95% CI
Taconite years	57	184	1.03	1.00 to 1.06
Haematite years†	48	212	0.99	0.94 to 1.04
High vs low employment‡				
<6.74 years	26	92	1.00	
≥6.74 years	31	92	1.23	0.67 to 2.28
Haematite only	23	131	0.59	0.30 to 1.14
Years employment tertiles§				
<1.65 years (REF)	13	61	1.00	
≥1.65<12.91 years	23	61	1.90	0.86 to 4.20
≥12.91 years	21	62	1.62	0.73 to 3.58
Haematite only	23	131	0.78	0.36 to 1.72
Employment by geological zone¶				
Zone 1 taconite years	18	74	1.05	1.00 to 1.11
Zone 2 taconite years	31	58	1.06	1.02 to 1.09
Zone 4 taconite years	12	66	0.97	0.92 to 1.03

*Rate ratio; adjusted for age, and years of employment in haematite.

†Years in haematite include those employed in haematite only and in both taconite and haematite.

‡High group represents workers with employment duration greater than the control median duration.

§Based on lower, middle, and upper third of control employment duration distribution.

¶Results adjusted for age, employment in haematite, and employment in other zones. Cases and controls may have worked in more than one zone. REF, referent comparison group.

Table 3 Mesothelioma risk estimates (RR) for cumulative EMP* exposure as a continuous, categorical and geological zone specific

Exposure	Cases	Controls	RR†	95% CI
(EMP/cc)×years	57	184	1.10	0.97 to 1.24
High vs low‡				
Low: <0.40 (EMP/cc)×years	17	92	1.00	
High: ≥0.40 (EMP/cc)×years	40	92	2.25	1.13 to 4.50
Cumulative exposure tertiles§				
0 to <0.16 (EMP/cc)×years (REF)	15	61	1.00	
≥0.16 to <1.15 (EMP/cc)×years	11	62	0.69	0.28 to 1.68
≥1.15 (EMP/cc)×years	31	61	1.97	0.89 to 4.32
Exposure by geological zone¶				
Zone 1 (EMP/cc)×years	18	74	1.96	1.15 to 3.34
Zone 2 (EMP/cc)×years	31	58	1.31	1.12 to 1.54
Zone 3 (EMP/cc)×years	12	66	0.88	0.71 to 1.09

*Measured by NIOSH 7400 method (NIOSH EMP definition: >5 µm length, aspect ratio ≥3).

†Results adjusted for age, employment in haematite, and potential for commercial asbestos exposure.

‡High group represents workers with cumulative exposure greater than the control median exposure.

§Based on the lower, middle and upper third of the control exposure distribution.

¶Results adjusted for age, employment in haematite, potential for commercial asbestos and exposures in other zones. Cases and controls may have worked in more than one zone.

EMP, elongate mineral particles; NIOSH, National Institute for Occupational Safety and Health.

DISCUSSION

This study attempted to understand mesothelioma risk associated with EMP exposure in taconite miners. An association was observed between duration of employment in taconite operations and risk of mesothelioma. There was also some evidence of an increased risk of mesothelioma with increasing exposure to EMPs, as defined by the NIOSH 7400 method. This definition does not distinguish amphibole from non-amphibole or asbestiform from non-asbestiform EMPs.⁹ Although an association exists, the increase in risk was not associated with exposure in the portion of the Mesabi Range where non-asbestiform amphibole (80% cummingtonite–grunerite; 20% tremolite–actinolite) is encountered.¹ Also, the facility with the highest rate of mesothelioma is no longer in operation and exposure estimates for that site were not determined. The association we observed is intriguing as current understanding of cancer risk based on fibre length and composition, suggests that exposure to non-asbestiform, shorter EMPs would not entirely explain the EMP-mesothelioma association found in this study.^{1 17–19} Naturally, these findings must be interpreted with consideration of limitations and strengths of the study.

There are a number of strengths in this study. The exposure assessment is the first quantitative approach to be incorporated into an epidemiological study. On site exposures were systematically obtained for all SEGs in all active mines. The potential impact from non-taconite mining exposures (haematite) was controlled in the analysis. The study population was large enough to enable the examination of a rare disease like mesothelioma. Although smoking information was not available for analysis, mesothelioma is not known to be associated with cigarette smoking.

There are also study limitations. The primary EMP exposure in this investigation used the NIOSH 7400 definition, which identifies the EMP as over 5 µm in length with a 3:1 or greater aspect ratio. The most frequent EMP measured in the onsite assessment was between 1–3 µm in length and 0.2–0.5 µm in

width.³⁰ An attempt was made to assess the risk with smaller EMP definitions, including cleavage fragments. The correlation coefficients between EMP definitions ranged from 0.6 to 0.96 and because of this, we were not able to estimate the independent effects of each EMP definition.

The NIOSH REL is 0.1 fibre (EMP) per cubic centimeter of air measured as a time-weighted average, although the 7400 method is not able to distinguish amphibole from non-amphibole EMP or asbestiform from non-asbestiform EMP. In the taconite industry relevant exposures to EMPs could be generated from a natural component of the ore or from commercial grade asbestos, which was used historically in various parts of the processing facilities as an insulator.

Exposure reconstruction in this investigation was based on all available work history information. The work history data were obtained from seven different companies. The level of specificity varied by company. Work histories with less information about jobs could not be classified into the most specific SEG for the exposure reconstruction. The less specific jobs were assigned to an SEG at the department or mine level, which used an exposure estimate based on all the SEGs in that department. This exposure misclassification was possible for cases and controls, but the ultimate direction of residual bias is unknown. When developing exposure estimates for each SEG, the exposure reconstruction used all available historical data and the more comprehensive onsite measurement data collected for the Taconite Worker Health Study. Historical data were sparse in the early years of operation, thus potentially introducing exposure misclassification. Additional models were fit based only on the onsite measurement data to classify exposures for the SEGs. These two approaches to determine cumulative exposure did not yield appreciably different results.

Multiple data sources were used to identify mesothelioma cases in the cohort, thus we believe we identified essentially all Minnesota cases occurring from 1988 onward. It is possible, however, that cases were missed in cohort members living outside of Minnesota and dying prior to 1999, the date when mesothelioma could be systematically identified on death certificates with a newly created mesothelioma code in ICD-10. We estimate the effect would be small as a majority of the MCSS cases were identified after 1997. Only 17 cases of mesothelioma had been identified within the MCSS by 1997 and a majority (70%) of the decedents in the mortality analysis cohort had a Minnesota death certificate.

Of the total 80 cases, 23 occurred in workers who only worked in the haematite mining industry and another 25 had at least some work in haematite. We observed no association between employment in haematite and mesothelioma risk in this population. Haematite ore was depleted following the heavy demand for steel during World War II. It was a high-grade ore that required minimal processing, and presumably would have resulted in lower exposures. Detailed exposure information for that industry was not available for this study. Haematite mining occurred in the western Mesabi Range, where non-asbestiform amphibole exposures have not been described.

Many of the mining facilities were constructed during the 1950s and 1960s, when commercial asbestos was widely used in construction and industrial applications. There is anecdotal information to suggest that some processes in taconite mining had direct exposure to commercial asbestos. However, there is insufficient evidence to determine if the use of taconite in this industry varied across the geological zones. As no records were available to quantitatively characterise exposure to commercial asbestos in our SEGs, we relied on expert judgment to

qualitatively estimate exposure. Statistical analyses of EMP exposures controlled for commercial asbestos exposure based on the number of years worked in an SEG with high a probability of asbestos exposure. SEGs with high commercial asbestos scores included crusher maintenance, furnace operator, electrician, carpenter, pipe fitter/plumber, lubricate technician and auto mechanic. The potential confounding effect of exposure to commercial asbestos was modelled using other classifications of commercial asbestos exposure, for example, ever worked in exposed SEG, ever worked in SEG with high exposure. These different classifications of commercial asbestos variables resulted in nearly identical risk estimates. These classifications likely did not represent all variability in past asbestos exposure in this population. It is possible that exposure to commercial asbestos exposure in the taconite industry could account for the association observed.

Mesothelioma risk estimates from employment duration reflect the risk from all exposures in the taconite industry including non-asbestiform amphibole EMPs, commercial asbestos, respirable dust, and respirable silica, and correspond to a unit average of 3% increase in risk with each additional year of employment in taconite mining. The risk of mesothelioma from EMP exposure is measured in (EMP/cc)×years, where an additional (EMP/cc)×year of exposure corresponds to an estimated 10% increase in mesothelioma risk. Workers with exposure above the median cumulative EMP level had approximately twice the rate of mesothelioma when compared to workers with an exposure below the median level. This analysis lends support to the hypothesis that workers with a higher cumulative exposure to EMPs had a higher rate of mesothelioma.

We examined whether exposures differed by location on the Iron Range, comparing cumulative exposure levels for workers in each of the geological regions, known as Zones 1, 2, and 4. When the NIOSH EMP definition was used in the zone-specific analyses, there was evidence of increased risks within Zones 1 and 2, but not Zone 4. This pattern was not consistent with the estimated levels of EMP exposure, which were lowest in zone 1 for cases and controls.²⁵ The incongruity of this finding could suggest the impact of uncontrolled confounding factors and points to the need for further study of zone-specific exposures.

There is a well-established, causal relationship between mesothelioma and asbestiform EMPs,^{31–32} likely related to fibre dimension, chemical composition, surface reactivity and persistence.^{16–31–32} The most common EMP within the onsite samples is 1–3 µm in length.³⁰ It is a non-asbestiform type and is exclusive to the eastern end of the Range. Estimates suggest 1% or less of the ore body contains asbestiform EMP.³³ Although controversies exist around the health effects of non-asbestiform exposure, existing reports suggest that these minerals are less pathogenic.^{1–34–36} The non-asbestiform variety has not had clearly established mesothelioma or lung cancer risk associated with exposure in studies of Homestake gold miners and New York talc workers.^{12–15–35–39}

Investigations of non-asbestiform amphibole exposures in gold miners and talc workers, have demonstrated associations with non-malignant respiratory disease, but not cancer.³⁵ Homestake gold miners have exposures to cummingtonite–grunerite mineral, similar to taconite miners. Talc workers are the other main group with non-asbestiform amphibole exposure. Talc is associated most commonly with tremolite and anthophyllite exposure. In some circumstances (Libby tremolite), the presence of asbestiform amphiboles has been described but exposures in the talc industry are felt to be non-asbestiform.¹³

In these occupational settings, the average fibre length is less than 5 µm and fibres over 5 µm are a relatively small per cent of the total exposure.¹³ To date, the finding of excess mesothelioma in taconite workers is unique among studies of non-asbestiform amphiboles.

In summary, our results suggest an association between employment duration in taconite mining and the risk of mesothelioma. There is also some evidence of an association between mesothelioma and cumulative EMP exposure as measured by the NIOSH 7400 method, although findings do not correspond to the location within the Mesabi Range where amphiboles are found. The lack of understanding of exposure to commercial asbestos also limits further insight into the association of non-asbestiform EMP exposure and mesothelioma in taconite miners.

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REFERENCES

- 1 Wilson R, McConnell EE, Ross M, *et al*. Risk assessment due to environmental exposures to fibrous particulates associated with taconite ore. *Regul Toxicol Pharmacol* 2008;52(Suppl 1):23–45.
- 2 Cooper WC, Wong O, Graebner R. Mortality of workers in two Minnesota taconite mining and milling operations. *J Occup Med* 1988;30:506–11.
- 3 Cooper WC, Wong O, Trent LS, *et al*. An updated study of taconite miners and millers exposed to silica and non-asbestiform amphiboles. *J Occup Med* 1992;34:1173–80.
- 4 Clark TC, Harrington VA, Asta J, *et al*. Respiratory effects of exposure to dust in taconite mining and processing. *Am Rev Respir Dis* 1980;121:959–66.
- 5 Higgins IT, Glassman JH, Oh MS, *et al*. Mortality of Reserve Mining Company employees in relation to taconite dust exposure. *Am J Epidemiol* 1983;118:710–19.
- 6 Minnesota Department of Health. Mesothelioma in Northeastern Minnesota and Two Occupational Cohorts: 2007 Update. <http://www.health.state.mn.us/divs/hpcd/cdee/mcss/documents/nemeso1207.pdf>
- 7 Allen EM, Alexander BH, MacLehose RF, *et al*. Mortality experience among Minnesota taconite mining industry workers. *Occup Environ Med* 2014;71:744–9.
- 8 Gunter ME, Belluso E, Mottana A. Amphiboles: environmental and health concerns. *Rev Mineral Geochem* 2007;67:453–516.
- 9 National Institute for Occupational Safety and Health. (2011). Asbestos fibers and other elongate mineral particles: State of the science and roadmap for research, Current intelligence bulletin 62, DHHS(NIOSH) Publication No. 2011–159. Intelligence. Cincinnati, OH.
- 10 Roggli VL, Pratt PC, Brody AR. Asbestos fiber type in malignant mesothelioma: an analytical scanning electron microscopic study of 94 cases. *Am J Ind Med* 1993;23:605–14.
- 11 Robinson BW, Musk AW, Lake RA. Malignant Mesothelioma. *Lancet* 2005;366:397–408.
- 12 Brown DP, Sanderson W, Fine LJ. NIOSH Health Hazard Evaluation Report: R.T. Vanderbilt Company, Gouverneur, New York. HETA 90–390-2065, MHETA 86-012-2065. <http://www.cdc.gov/niosh/hhe/reports/pdfs/1990-0390-2065.pdf>
- 13 Gamble JF, Gibbs GW. An evaluation of the risks of lung cancer and mesothelioma from exposure to amphibole cleavage fragments. *Regul Toxicol Pharmacol* 2008;52 (Suppl 1):S154–86.
- 14 Brown DP, Kaplan SD, Zumwalde RD, *et al*. Retrospective cohort mortality study of underground gold mine workers. In: Goldsmith D, Winn D, Shy C, eds. *Silica, silicosis, and lung cancer*. New York: Praeger, 1986:335–50.

- 15 Steenland K, Brown D. Mortality study of gold miners exposed to silica and non-asbestiform amphibole minerals: an update with 14 more years of follow-up. *Am J Ind Med* 1995;27:217–29.
- 16 Lippmann M. Asbestos exposure indices. *Environ Res* 1988;46:86–106.
- 17 Berman DW, Crump KS. A meta-analysis of asbestos-related cancer risk that addresses fiber size and mineral type. *Crit Rev Toxicol* 2008;38(Suppl 1):49–73.
- 18 Loomis D, Dement JM, Elliott L, et al. Increased lung cancer mortality among chrysotile asbestos textile workers is more strongly associated with exposure to long thin fibres. *Occup Environ Med* 2012;69:564–8.
- 19 Stanton MF, Layard M, Tegeris A, et al. Relation of particle dimension to carcinogenicity in amphibole asbestoses and other fibrous minerals. *J Natl Cancer Inst* 1981;67:965–75.
- 20 Suzuki Y, Yuen SR. Asbestos fibers contributing to the induction of human malignant mesothelioma. *Ann N Y Acad Sci* 2002;982:160–76.
- 21 Dodson RF, Atkinson MA, Levin JL. Asbestos fiber length as related to potential pathogenicity: a critical review. *Am J Ind Med* 2003;44:291–7.
- 22 Adib G, Labrèche F, De Guire L, et al. Short, fine and WHO asbestos fibers in the lungs of Quebec workers with an asbestos-related disease. *Am J Ind Med* 2013;56:1001–14.
- 23 Loomis D, Dement J, Richardson D, et al. Asbestos fibre dimensions and lung cancer mortality among workers exposed to chrysotile. *Occup Environ Med* 2010;67:580–4.
- 24 Stayner L, Kuempel E, Gilbert S, et al. An epidemiological study of the role of chrysotile asbestos fibre dimensions in determining respiratory disease risk in exposed workers. *Occup Environ Med* 2008;65:613–19.
- 25 Hwang J, Ramachandran G, Raynor PC, et al. Comprehensive assessment of exposures to elongate mineral particles in the taconite mining industry. *Ann Occup Hyg* 2013;57:966–78.
- 26 McSwiggen PL, Morey GB. Overview of the mineralogy of the Biwabik Iron Formation, Mesabi Iron Range, northern Minnesota. *Regul Toxicol Pharmacol* 2008;52(Suppl 1):S11–25.
- 27 Zanko LM, Niles HB, Oreskovich JA. Mineralogical and microscopic evaluation of coarse taconite tailings from Minnesota taconite operations. *Regul Toxicol Pharmacol* 2008;52(Suppl 1):S51–65.
- 28 Ilgren EB. The biology of cleavage fragments: a brief synthesis and analysis of current knowledge. *Indoor Built Environ* 2004;13:343–56.
- 29 Sheehy JW, McJilton CE. Development of a model to aid in reconstruction of historical silica dust exposures in the taconite industry. *Am Ind Hyg Assoc J* 1987;48:914–8.
- 30 Hwang J, Ramachandran G, Raynor PC, et al. The relationship between various exposure metrics for elongate mineral particles (EMP) in the taconite mining and processing industry. *J Occup Environ Hyg* 2014;11:613–24.
- 31 Institute of Medicine of the National Academies. Background information on asbestos. In: Asbestos: Selected cancers committee on asbestos: Selected health effects 49–61. 2006.
- 32 Agency for Toxic Substances and Disease Registry (ATSDR). Toxicological Profile for Asbestos. ATSDR; Centers for Disease Control. 2001.
- 33 Ross M, Nolan RP, Nord GL. The search for asbestos within the Peter Mitchell taconite iron ore mine, near Babbitt, Minnesota. *Regul Toxicol Pharmacol* 2008;52(Suppl 1):S43–40.
- 34 Mossman BT. Assessment of the pathogenic potential of asbestiform vs. nonasbestiform particulates (cleavage fragments) in *in vitro* (cell or organ culture) models and bioassays. *Regul Toxicol Pharmacol* 2008;52(Suppl 1):S200–3.
- 35 Honda Y, Beall C, Delzell E, et al. Mortality among workers at a talc mining and milling facility. *Ann Occup Hyg* 2002;46:575–85.
- 36 Coggiola M, Bosio D, Pira E, et al. An update of a mortality study of talc miners and millers in Italy. *Am J Ind Med* 2003;44:63–9.
- 37 Gamble JF. A nested case control study of lung cancer among New York talc workers. *Int Arch Occup Environ Health* 1993;64:449–56.
- 38 Finkelstein MM. Malignant mesothelioma incidence among talc miners and millers in New York State. *Am J Ind Med* 2012;55:863–8.
- 39 Nolan RP, Gamble JF, Gibbs GW. Letter to the Editor on Commentary: Malignant Mesothelioma Incidence among talc miners and millers in New York state by MM Finkelstein.