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Mesothelioma and other lung disease in taconite miners; the uncertain role of non-asbestiform EMP

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ABSTRACT

The purpose of this paper was to assess the role of non-asbestiform amphibole EMPs in the etiology of mesotheliomas and other lung disease in taconite (iron ore) miners. Increased mesothelioma rates have been described in Minnesota taconite workers since the late 1990s. Currently, over 100 cases have been reported by the Minnesota Department of Health within the complete cohort of miners in Minnesota. Geologic sampling has indicated that only the eastern part of the iron range contains non-asbestiform amphibole elongate mineral particles (EMPs), in close proximity to the ore. This type of EMP has been less studied and also exists in talc and gold mining. A series of investigations into the state's taconite industry have been recently completed. Results from a cohort mortality study indicated an SMR of 2.77 (95% CI = 1.87–3.96) for mesothelioma. In a case-control study, the odds ratio for mesothelioma for high vs. low EMP exposure was 2.25 (5% CI = 1.13–4.5) but EMPs in this study were counted by phase contrast microscopy. Odds ratios were not elevated in mines located in the eastern part of the Mesabi iron range. The overall findings suggest that mesothelioma in taconite miners is related to EMP exposure. Because of the way EMPs were counted, results from these studies cannot allow a firm conclusion about the association between EMP exposure and the reported excess mesothelioma.

1. Introduction

Taconite (iron ore) mining, located in northeastern Minnesota and the upper peninsula of Michigan, has been in existence since the early 1950s. It replaced the mining of more concentrated hematite ore after the latter's depletion after the second world war. The industry has been a major supplier of iron ore to the North American steel manufacturing industry, accounting for around 2/3 of the ore needed. It has also been the predominant employer in northeastern Minnesota and, at its peak, supplied 10–15,000 jobs annually. With enhanced automation and processing, the industry in Minnesota maintains an active work force of 3000–4000 employees.

In the early 1980s, reports of non-malignant lung disease (NMRD) surfaced, causing concern among companies and communities in close proximity to the mining operations. All workers in the industry, along with their work history information, were assembled into a cohort by researchers at the University of Minnesota in 1983. This cohort included those who worked in hematite, taconite and both types of mining (Allen et al., 2014). Also at this time, some companies reported the results of mortality investigations (Cooper et al., 1988, 1992; Higgins et al., 1983). These early studies did not indicate any excess causes of death, although the latency for dust-related conditions at that time was marginal.

Due to ongoing concerns for potential types of lung disease, this cohort was used by the Minnesota Department of Health (MDH), for further investigation. Starting in the late 1990s, MDH linked members in the cohort with the state's cancer surveillance system. This process identified an elevation in the observed to expected ratio for mesothelioma in 1997. This was followed by another updated assessment in 2003 showing an excess of mesothelioma cases in 2006 and 2007 (MDH, 2007). An additional consideration in view of these findings was the fact that the eastern most portion of the Mesabi Iron Range contained non-asbestiform, amphibole elongate mineral particles (EMPs), typically found in close proximity with the iron ore body. An important question arose as to the importance of this EMP in relationship to the excess numbers of mesothelioma cases.

Because of the concerns expressed by communities located on the Mesabi Iron Range, the presence of non-asbestiform EMPs in close proximity with the ore body and the importance of the industry to the state's economy, legislation was passed in 2008, allocating funds to further assess health risks in the taconite industry. This report is a summary of the findings from the series of investigations of the

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industry, known collectively as the Taconite Worker Health Studies (TWHS). Results from these investigations are combined to obtain insights into the role of this exposure with mesothelioma cases and other lung disease in the taconite industry.

2. Methods

With the involvement of the state's legislature, a broader approach was possible in order to address concerns from both the scientific and public health perspectives over a more efficient time frame. Prior to the initialization of any further scientific approaches, study investigators had a series of focus group meetings with employees from all active plants and community representatives. Through this process several key questions were formulated and served as focal points for the scientific work. The following questions were key to the investigations:

1. Is working in the taconite industry associated with mesothelioma and/or other diseases, respiratory and non-respiratory?
2. What factors, particularly exposure to dust from taconite operations, are associated with mesothelioma and/or other respiratory diseases?

Because no single study could address both of these questions, the following designs were developed:

3. Exposure assessment

A key initial study involved a comprehensive exposure assessment, the results of which could be integrated into other designs (Hwang et al., 2013, 2014). This assessment was done in two steps. The first step involved the prospective monitoring of all key job functions in all six active mining facilities. Sampling strategies were established to monitor for EMP, respirable silica and respirable dust without silica during the 2010–11 period. Initially, research staff and company industrial hygienists reviewed all jobs in mining and processing and determined 28 unique job functions that existed within all of the six active mines. Each of these 28 functions was referred to a similar exposure group (SEG). For the sampling of EMPs, defined as any inhalable mineral particle with a minimum aspect ratio of 3:1, In order to best represent the number of plants by location (east-west), two workers per SEG were selected for personal sampling during three different shifts for plants in the eastern most part of the iron range (one plant). For the five plants in the western part of the iron range, eight workers per SEG were sampled, with each worker sampled on three different shifts. Area monitoring for EMP was conducted using a Micro Orifice Uniform Deposit Impactor (MOUDI) size-fractionating sampler. For 20% of the samples, EMP on stages of the MOUDI were characterized as to whether they were asbestiform or non-asbestiform. MOUDI samples are taken from size-specific orifices (stages) and represent actual EMP dimensions within 13 different stages. The EMPS were also counted with the NIOSH 7400 method (PCM) (NIOSH, 2003) and sized using an indirect transfer transmission electron microscope (ISO 13794) method.

The second step in the exposure assessment was to reconstruct a job-exposure matrix from existing EMP sampling data. This involved data that the plants collected over the years as well as measurements from the Mining Safety and Health Administration (MSHA), that existed from the mid-1970s forward. The exposure reconstruction also utilized a regression approach that was able to estimate SEG exposures by year, formed from the onsite and existing company/MSHA measurements. This allowed for the creation of a job-exposure matrix (JEM) that extended from the beginning of the taconite industry in Minnesota (approximately mid-1950s) until 2011. Very few historical monitoring data existed prior to the early 1970s.

Industrial hygiene samples obtained in the more current, onsite monitoring by researchers were referred to a laboratory that was certified in the counting and characterizing of EMP. EMP counts for the epidemiologic investigations were made according to the NIOSH 7400 method, using phase contrast microscopy and assessing all EMP greater than 5 μm with a 3:1 or greater aspect ratio.

In several of the subsequent epidemiologic investigations, the JEM was combined with work history information to obtain a cumulative EMP exposure estimate. This was expressed as (EMP/cm^3)-years of exposure.

4. Cohort mortality

To address concerns about occupational exposures resulting in both respiratory and non-respiratory disease, a cohort mortality study was conducted (Allen et al., 2014). To better capture work in the taconite industry, and not the earlier hematite industry, a birth date of 1920 was used as a requirement for worker inclusion in this study. Another requirement was that at least one year of employment in the industry was necessary to be included in the cohort, which covered the years 1960 through 2010. A total of 31,067 workers met these criteria and contributed over 1 million person-years. For all of those individuals, vital status was determined and for the identified 9094 deaths, death certificates were obtained (1157 individuals did not have a vital status determined and were assumed to be alive; there were 144 individuals for whom a death certificate was not found). From the certificate, causes of death were obtained using certified nosologists. Deaths were assessed using a standardized mortality ratio (SMR) and 95% confidence intervals, based on the observed number of cohort deaths within a disease category compared to the age, sex and disease-specific expected numbers of death in the general population of Minnesota. Exposure data were not used for this investigation but the large size of the cohort allowed for the easier detection of elevated cancer rates.

5. Cancer incidence

A standardized incidence ratio (SIR) analysis was undertaken for the cohort to determine cancer morbidity using the Minnesota Cancer Surveillance System (MCSS) (Allen et al., 2015a, 2015b). This cohort was enumerated in 1983 and included some 68,000 individuals. Because MCSS began in 1988, cohort members alive as of this date were included (40,720 individuals). This added to the mortality analysis as it also included individuals who were living with their illness. A total of 5700 cancers were included in this investigation and included 51 mesotheliomas and 973 lung cancers, including four major subcategories of lung cancer. Exposure data were not used for this investigation. Standardized incidence ratios and 95% confidence intervals were determined, adjusting for age, gender, calendar period and out-of-state migration. This study had the advantage of identifying cancers that may not result in death.

6. Mesothelioma case-control

This case-control study originated from within the above cohort (nested design) where the cohort was expanded without including a date of birth cutoff (so all identified cases could be assessed) (Lambert et al., 2016). This study is the only quantitative assessment of exposures in the industry and, again, involved all mining sites within the Minnesota industry. Cases were obtained by matching social security numbers from members of the cohort with MCSS, a histologically-based registry, and through the identification of mesothelioma on death certificates for individuals in the cohort who died out of state. Despite the fact that mesothelioma ICD coding was not available until 1999, because MCSS is a tissue-based registry, cases were available prior to that date. Even so, cases identified were likely to have been under ascertained. Four controls were selected from the remaining cohort for each case, using an incidence density sampling protocol, matched on age and without evidence of mesothelioma at the time of the case diagnosis, or death. There were 80 cases, all in men, and 315 controls in this investigation. Rate ratios and 95% confidence intervals were determined for mesothelioma. Covariates included employment in hematite and taconite (years), majority geographic zone worked in (east, west, intermediate), SEGs where commercial asbestos exposure was likely (yes, no) and included an estimation of cumulative EMP exposure [(EMP/cm^3)-years] for cases and controls. Smoking data were not available for this investigation but smoking has not been found to be related to mesothelioma in prior investigations.

7. Lung cancer case-control

Because of the known relationship of asbestiform EMP and lung cancer, a separate case-control study was conducted for this endpoint. This case-control study also originated from the above cohort (nested design) (Allen et al., 2015a, 2015b) and is the only study in the taconite industry that has utilized a quantitative exposure assessment. Cases were identified through vital records and MCSS data from 1988 to 2010. For each case, two age-matched controls alive and lung cancer free at the time of case diagnosis were selected using an incidence density sampling approach. Controls were selected by age, within five years of each case. There were 1706 cases and 3381 controls in this analysis. Odds ratios and 95% confidence intervals were determined. Covariates included gender, work time in hematite and taconite mining (years), cumulative silica exposure [(mg/m^3)-years], SEGs where commercial asbestos exposure was likely (yes, no), majority geographic zone worked in (east, west, intermediate) and an estimation of cumulative exposure [(EMP/cm^3)-years] for cases and controls. Lung cancer subtypes were also assessed in this manner. The absence of smoking data was a limitation of this study but the large number of cases allowed for analysis by histologic type.

8. Respiratory health survey

In order to characterize EMP exposures in taconite mining and processing, to determine their relative impact on lung fibrosis and to assess their impact on common lung conditions, a cross-sectional screening of current and former workers and their spouses was conducted in 2010–11 (Report, 2014). The presence of fibrosis reflected the possibility of additional lung disease, including malignancy (ATSDR, 2001). Spouses were included to address the issue of potential exposure from "take home" exposures. The screening included a detailed work, smoking and medical history obtained by self-administered questionnaire along with chest x-ray, screening spirometry and a blood draw. A random sample of 3310 workers was determined from across the iron range and invited to participate in the survey. X-rays were interpreted by a consensus of two B-readers, with a third to arbitrate discrepancies. International Labor Organization (ILO, 2000) criteria were used to define pleural and parenchymal abnormalities. Parenchymal abnormalities were defined as small opacities of profusion (ILO category 1/0 or above) and pleural abnormalities defined as any finding consistent with Pneumoconiosis. Pleural and parenchymal abnormalities were assessed for their association with cumulative EMP exposure by Poisson regression. Covariates included age, BMI, gender, smoking status (current, former, never), work time in hematite and taconite mining (years), work in non-taconite jobs where asbestos exposure likely (yes, no), taconite SEGs where commercial asbestos exposure was likely (yes, no) and cumulative EMP exposure [EMP/cm^3)-years]. Although cross-sectional in design, EMP exposure was determined as a cumulative exposure, utilizing the NIOSH 7400 counting method, and B-readings were done by a consensus of two independent readers.

A review was previously undertaken by one of the authors to capture other mining studies where non-asbestiform amphibole EMP exposure occurred (Mandel et al., 2016). Only studies where exposure to EMPs involved a formal exposure assessment were used. The search was undertaken within PubMed of the National Library of Medicine and included search terms, individually or in combination, as follows: gold, talc, taconite mining; non-asbestiform elongate mineral particle, cleavage fragment, pneumoconiosis, asbestosis, respiratory cancer, mesothelioma, epidemiology and exposure assessment. Other publications were included such as NIOSH mining publications (available at https://www.cdc.gov/niosh/az/a.html) and doctoral theses. All publications were checked for additional references not located on the primary search. This information is presented in the following results section.

9. Results

9.1. Exposure assessment

Results from the exposure assessment have been described and include 1298 personal samples (Hwang et al., 2013, 2014) where counts were done according to the NIOSH 7400 method. In brief, measurement of current (onsite) EMPs revealed that, for multiple SEGs in the six active mines, mean exposure levels (in particles per cc) for total EMPs were higher than the NIOSH Recommended Exposure Limit (REL). (The NIOSH REL is intended to be used for regulated asbestiform EMPs and their non-asbestiform analogs.) The EMP classification does not necessarily refer to regulated EMP since the NIOSH 7400 method can't differentiate asbestiform and non-asbestiform EMPs (NIOSH, 2003). Using TEM analysis (NIOSH 7402), amphiboles were also assessed. Concentrations were well-controlled across all mines, approximately a magnitude lower than the total EMP measurement. Amphibole EMPs were only found in the facility within the eastern most portion of the Mesabi Iron Range. Using area samples, the highest concentrations were found for EMP that were 1–3 μm in length and 0.2–0.5 μm in width (Hwang et al., 2014).

10. Cohort mortality

Table 1 lists the observed, expected, SMR and 95% confidence interval for selected diseases in the cohort mortality study. Of interest is the fact that mesothelioma and lung cancer SMRs were statistically significantly higher than expected. This elevation occurred across all three zones of the iron range, without an association found for duration of employment. This is the first time these findings were described since early epidemiologic studies of mortality did not reveal elevated SMRs. Also of interest, and somewhat unusual for working populations, was the finding of an increased SMR for heart disease, specifically ischemic heart disease.

11. Cancer incidence

Results of the cancer incidence investigation confirmed the findings for mesothelioma (SIR = 2.4 (95% CI = 1.8–3.2) and lung cancer (SIR = 1.3 (95% CI = 1.2–1.4). In addition, cancers of the larynx and stomach were elevated and statistically significant (SIR = 1.4 (95% CI = 1.1–1.7), SIR = 1.4 (95% CI = 1.1–1.6), respectively. The SIRs for lung cancer were determined by histological subtype. All subtypes,

Table 1
Selected SMRs for Minnesota taconite workers with greater than one year of work.

Disease	Observed	Expected	SMR[a]	95% CI
All cancers	2710	2609.86	1.04	1.0–1.08
Respiratory cancer	981	846.74	1.16	1.09–1.23
Trachea/lung/Bronchus	949	815.67	1.16	1.09–1.24
Mesothelioma	30	10.82	2.77	1.87–3.96
Heart disease	2676	2435,81	1.10	1.06–1.14
Hypertensive heart disease	62	34.17	1.81	1.39–2.33
Ischemic heart disease	2185	1964.93	1.11	1.07–1.16
COPD	363	369.8	0.98	0.88–1.09

[a] Adjusted for age, calendar period and sex.

Table 2
Findings from mesothelioma case-control study in taconite miners.

Variable classification	Rate ratio[a]	95% CI
Years worked in taconite industry (unit)	1.03	1.0–1.06
Years worked in hematite industry (unit)	0.99	0.94–1.04
Years of work in taconite over median (6.74 years)	1.23	0.67–2.28
(EMP/cm^3)-years (unit)	1.10	0.97–1.24
Cumulative EMP exposure > median	2.25	1.13–4.50

[a] Results adjusted for age, employment in hematite and potential for commercial asbestos exposure.

including adenocarcinoma, squamous cell, small cell and non-specific lung cancer were statistically significantly elevated, with SIRs ranging from 1.3 to 1.6. Smoking data were not available for this investigation.

12. Mesothelioma case-control

Results from the mesothelioma study focused on years of employment within the taconite industry and by estimates of cumulative exposure to EMPs within taconite industry SEGS, using the NIOSH 7400 counting method (Table 2) (Lambert et al., 2016). Results indicated a 3% increase in risk for mesothelioma for each year of work within the taconite industry.

No risk was identified for working in the hematite industry. The unit rate ratio for cumulative EMP exposure was 1.10 (95% CI = 0.97–1.24). This indicated a 10% increase in the risk for each increase in (fiber/cm^3)-year or, as an example, over 10 years if the cumulative EMP was 0.1 fiber/cm^3. For those workers with a cumulative EMP exposure over the median, the risk for mesothelioma was approximately two-fold. Analysis of rate ratios by location of employment indicated an elevated and statistically significant finding for working in the western and intermediate parts of the Mesabi Iron Range (western RR = 1.05 (95% CI = 1.0–1.11; intermediate RR = 1.06 (95% CI = 1.02–1.09). For those miners who worked in the portion of the iron range where non-asbestiform amphibole EMPs were in close proximity to the ore body (eastern most part of the Mesabi Range), the RR was not elevated (RR = 0.88 (95% CI = 0.71–1.09).

13. Lung cancer case-control

Odds ratios for lung cancer by employment duration or cumulative EMP, using the NIOSH 7400 counting method, did not suggest an association to this exposure (Allen et al., 2015a, 2015b). The unit OR for years of work in the taconite industry was 0.99 (9%% CI = 0.96–1.01). None of the seven major departments, which were comprised of multiple SEGs, had elevated ORs. Evaluation of lung cancer risk by EMP quartile of exposure did not reveal a statistically significant association. No lung cancer subtypes were associated with cumulative EMP exposure.

14. Cross-sectional survey of current and former workers and spouses

Of the 3310 workers eligible, 1322 (40%) participated. Of those, 134 did not participate in the testing, resulting in 1188 participants. Of the participants, 60% of those eligible workers living within one hour of the testing facility participated. The average age of the participants was 60 years. Of the participants, 12% were current and 50% former smokers. Male participants made up 91% of the study group. Consensus B-readings suggested that 5.3% of participants had evidence of parenchymal disease, most were 1/0 or 1/1 categories; 16.7% had evidence of pleural disease by consensus, with 97% as pleural plaques, 47% bilateral and 8.8% with calcifications.

Table 3 lists variables associated with pleural and parenchymal abnormalities in the participants of the cross-sectional survey. Unit prevalence rate ratios did not reach significance for either pleural or parenchymal disease. Associations of pleural/parenchymal abnormalities and years worked in the taconite industry revealed elevated, but not statistically significant findings in any quartile. When assessing the association of pleural disease and EMP quartiles, quartiles 2 and 3 had significant while quartile 4 did not (Table 3). Spouses had parenchymal chest x-ray findings in less than 1% of participants and pleural abnormalities in 4.3%.

Table 3
Findings from cross-sectional survey of current and former taconite miners.

Exposure category	Prevalence ratio (PR)[a]	95% CI
Parenchymal disease		
Years worked in taconite industry (unit)	1.01	0.98–1.03
(EMP/cm^3)-years (unit)	0.98	0.91–1.06
Pleural disease		
Years worked in taconite industry (unit)	1.01	0.99–1.02
EMP/cm^3)-years (unit)	1.02	0.98–1.05
Cumulative EMP	1.0 (ref)	
Quartile 1	1.53	–
Quartile 2	1.63	1.07–2.17
Quartile 3	1.25	1.14–2.32
Quartile 4		0.86–1.82

[a] Results adjusted for age, BMI, hematite years, gender, smoking, non-taconite work where asbestos exposure likely, SEGs in taconite where commercial asbestos likely.

The review of studies where asbestiform amphibole EMP exposure occurred included the following industries: taconite mining (4 studies), Homestake gold mining (2 studies), talc mining (2 studies). Within these same industries, there were 14 mortality studies identified, four in taconite and gold and six in talc mining. Within this review, death from cardiovascular disease and from non-malignant respiratory disease were identified in several studies. Aside from the taconite mining industry, only one other study identified the presence of mesothelioma where two cases were found (Honda et al., 2002). Both were felt to be related to asbestiform fiber exposure prior to work in the talc industry. Lung cancer was elevated in the gold mining industry but was not statistically significant and control for smoking was not done. Talc studies did not reveal an excess of lung cancer.

15. Discussion

The collective studies within the TWHS represent a comprehensive assessment of the industry and allow for further insights into the health risks of taconite mining. (See www.taconiteworkers.umn.edu for full report.) Based on current exposure assessment, EMPs appear to be well-managed in all active facilities. However, historical EMP exposure has greater uncertainty, especially due to the fact that the industry began prior to the regulatory era in the United States. This, coupled with the fact that commercial asbestos was typically widely used in all taconite processing facilities, makes it difficult to accurately define the risks associated with asbestiform EMPs.

Some important perspectives have been established with these investigations. First, based on mortality, both mesothelioma and lung cancer SMRs are clearly elevated. This SMR has the advantage of representing all individuals born after 1920 who worked within all mining sites of the Minnesota industry. It is only industry-wide study and demonstrated these diseases occurring at higher rates than expected.

Second, the mesothelioma case-control study provides some evidence to suggest that the mesothelioma excess is associated with cumulative exposure to EMPs. A two-fold, statistically significant excess in the rate ratio occurred in those individuals with exposures above the median exposure level of the cumulative exposure distribution. However, the EMPs used in this association were counted by the NIOSH 7400 method (NIOSH, 2001). This approach only counts those EMPs greater than 5 μm in length, with an aspect ratio of 3:1 or greater. It does not separate asbestiform from non-asbestiform EMPs and findings must be interpreted with this in mind. However, looking at associations for mines in the eastern portion of the Mesabi Range, where non-asbestiform amphibole exposures occur, did not reveal higher rate ratios compared to plants in the western portion.

It has been estimated that asbestiform EMPs comprise less than 1% of the amphibole EMPs within the Mesabi Range (Ross et al., 2008). Based on assessments of current EMP exposures in taconite operations, the predominant EMP is in the range of 1–3 μm in length, with EMPs sparsely present at lengths greater than 5 μm (Hwang et al., 2014). It also is less likely that EMPs under 5 μm would be related to mesothelioma, based on a series of toxicity studies of asbestiform EMP, cleavage fragments and non-asbestiform amphibole EMPs in animal studies. Shorter EMP exposures (less than 5 μm) resulted in demonstrably less than toxicity/tumor formation compared to EMPs over 5 μm based on individual reports (Mossman, 2008; Davis et al., 1986; Moalli et al., 1987; Lemaire et al., 1985) and extensive reviews of this topic (Berman et al., 1995; Berman, 2008; ATSDR, 2001).

Additional perspectives on the pathogenicity of non-asbestiform amphibole EMPs in taconite mining may be obtained from two other investigations within the TWHS. The lung cancer case-control study assessed the association with EMP exposure. No statistically significant relationship was demonstrated. Although asbestiform EMP have a clear association with lung cancer (McDonald, 1996), the association with non-asbestiform EMPs has been lacking in other settings including the Homestake gold and talc industries (Honda et al., 2002; Steenland and Brown, 1995; McDonald, 1978; Gillam et al., 1976; Selevan and Dement, 1979; Wergeland et al., 1990; Wild et al., 2002; Coggiola et al., 2003). Asbestiform EMP exposure also appears to be related to lung cancer and mesothelioma differently, the former occurring more commonly in those with underlying lung fibrosis (ATSDR, 2001). Although the situation in the TWHS is consistent with asbestiform EMP exposure, the lack of quantitative information on non-asbestiform amphibole EMP and on commercial asbestos exposure makes it difficult to determine specific associations.

The screening of current and former taconite miners also suggests a less fibrogenic exposure. Around 5% of participants had evidence of parenchymal lung disease in this assessment. Due to the response rate of 36%, there is a question about how representative the participants are. However, an evaluation of cumulative EMP exposure in participants and non-participants suggests that participants may actually have had higher cumulative exposure (Perlman et al., 2018). Workers with heavy asbestiform EMP exposure in other settings have demonstrated higher amounts of parenchymal abnormalities, with prevalence rates in the range of 25–35% (Kilburn, 2008).

Interestingly, the association with pleural abnormalities in taconite workers was related to cumulative exposure in quartiles two and three of the EMP distribution. The EMPs were counted with the NIOSH 7400 method, like the association of cumulative EMP exposure and mesothelioma, and asbestiform vs. non-asbestiform EMPs can't be differentiated.

The original questions that directed the TWHS were answered, although incompletely. The diseases associated with working in this industry included mesothelioma, lung cancer, heart disease, a mild-moderate degree of lung fibrosis and pleural abnormalities. In terms of the mesothelioma excess, associated factors were duration of employment (3% per year worked) and cumulative exposure to EMPs (10% increase for each unit EMP-year worked), measured by the NIOSH 7400 method. This latter finding could be interpreted as the combination of 10 years employment at an exposure concentration of 0.1 EMP or 1 year at 1 EMP. Pleural abnormalities also were related to this exposure. Parenchymal disease and lung cancer were not associated with EMPs over 5 μm in length. Cardio-vascular mortality was not investigated further.

To summarize the mesothelioma findings and related factual information, taconite workers in Minnesota have an established risk for mesothelioma related to cumulative EMP exposure. Because of the type of counting method (NIOSH 7400), the type of EMP (asbestiform or non-asbestiform) accounting for this association has not been determined with certainty. It is also uncertain as to whether the EMPs over 5 μm in length are the best metric in this situation, given that the predominant EMP exposure is to minerals 1–3 μm in length. As stated above, there are studies suggesting non-asbestiform EMPs are less pathogenic than asbestiform EMP and that shorter EMPs, that predominantly occur in the taconite industry, are also less pathogenic, compared to those EMP over 5 μm in length. There is a lack of evidence of excess mesothelioma in industries where analogous exposures occur (Homestake gold mining, talc mining). There is a lack of an association with this exposure and lung cancer findings from the case-control study in taconite workers. The low prevalence of parenchymal disease in current and former workers suggests less pathogenicity associated with this exposure. However, because of the lack of quantitative data on non-asbestiform amphibole EMP, there remains uncertainty surrounding the role of this exposure and the association with mesothelioma. There is additional uncertainty created by the lack of quantitative data involving historical exposure to asbestiform EMPs from commercial asbestos use.

16. Conclusion

Taconite workers have an increased rate of mesothelioma that is associated with cumulative exposure to EMPs. Uncertainty exists regarding the type of EMP (asbestiform or non-asbestiform) responsible for this association because of the use of phase contrast microscopy for counting EMPs. Other diseases in taconite workers, including lung cancer and parenchymal fibrosis were not associated with this exposure.

Conflict of interest statement

The data for this paper were the result of several projects that were funded by the State of Minnesota. The opinions expressed in the manuscript belong to the authors and do not reflect the State of Minnesota. No other third party financial support was used for this paper or for the original research that was used to generate this paper. JHM has received funding from the U.S. Sand and Gravel Association for an unrelated feasibility project. Other resources that were used in the same topic matter, but which did not influence opinions in this paper, were obtained by a separate federal grant (NIOSH RO1 OH010418). JHM has presented data from the submitted paper at the Monticello Conference, October 2017. There are no patents or other copyrights planned for the submitted work.

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References

Agency for Toxic Substances and Disease Registry (ATSDR), 2001. Toxicologcal Profile for Asbestos. U.S. Department of Health and Human Services. Public Health Service. ATSDR.
Allen, E.M., Alexander, B.H., MacLehose, R.F., Ramachandran, G., Mandel, J.H., 2014. Mortality experience among Minnesota taconite mining industry workers. Occup. Environ. Med. 71 (11), 744–749.
Allen, E.M., Alexander, B.H., MacLehose, R.F., Nelson, H.H., Ryan, A.D., Ramachandran, G., Mandel, J.H., 2015a. A case-control study of lung cancer in taconite miners of Minnesota. Occup. Environ. Med. 72 (9), 633–639.
Allen, E.M., Alexander, B.H., MacLehose, R.F., Nelson, H.H., Ramachandran, G., Mandel, J.H., 2015b. Cancer incidence among Minnesota taconite mining industry workers. Ann. Epidemiol. 72 (9), 633–639.

Berman, D.W., Crump, K.S., Chatfield, E.J., Davis, J.M.G., Jones, A.D., 1995. The sizes, shapes, and mineralogy of asbestos structures that induce lung tumors or mesothelioma in AF/HAN rats following inhalation. Risk Anal. 15 (2), 181–195.
Coggiola, M., Bosio, D., Pira, E., Piolatto, P.G., LaVecchia, C., Negri, E., Michelazzi, M., Bacaloni, A., 2003. An update of a mortality study of talc miners and millers in Italy. Am. J. Ind. Med. 44, 63–69.
Cooper, W.C., Wong, O., Graebner, R., 1988. Mortality of workers in two Minnesota taconite mining and milling operations. J. Occup. Med. 30 (6), 506–511.
Cooper, W.C., Wong, O., Trent, L.S., Harris, F., 1992. An updated study of taconite miners and millers exposed to silica and non-asbestiform amphiboles. J. Occup. Med. 34 (12), 1173–1180.
Davis, J.M.G., Addison, J., Bolton, R.E., Donaldson, K., Jones, A.D., Smith, T., 1986. The pathogenicity of long versus short fibre samples of amosite asbestos administered to rats by inhalation and intraperitoneal injection. Br. J. Exp. Pathol. 67 (3), 415–430.
Gillam, J.D., Dement, J.M., Lemen, R.A., Wagoner, J.K., Archer, V.E., Blejer, H.P., 1976. Mortality patterns among hard rock gold miners exposed to an asbestiform mineral. Ann. N. Y. Acad. Sci. 271, 336–344.
Higgins, I.T., Glassman, J.H., Oh, M.S., Cornell, R.G., 1983. Mortality of reserve mining company employees in relation to taconite dust exposure. Am. J. Epidemiol. 118, 710–719.
Honda, Y., Beall, C., Delzell, E., Oestenstad, K., Brill, I., Matthews, R., 2002. Mortality among workers at a talc mining and milling facility. Ann. Occup. Hyg. 46, 575–585.
Hwang, J., Ramachandran, G., Alexander, B.H., Mandel, J.H., 2013. A comprehensive assessment of exposures to elongate mineral particles (EMP) in the taconite mining industry. Ann. Occup. Hyg. 57 (8), 966–978.
Hwang, J., Ramachandran, G., Raynor, P.C., Alexander, B.H., Mandel, J.H., 2014. The relationship between various exposure metrics for elongate mineral particles (EMP) in the taconite mining and processing industry. J. Occup. Environ. Hyg. 11 (9), 613–624.
ILO Guidelines for the use of the International Labor Organization International Classification of Radiographs of Pneumoconioses, 2000. Occupational Safety and Health Series No. 22. Geneva International Labor Office, Geneva, Switzerland.
Kilburn, K., 2008. Chapter 23, Asbestos and Other Fibers. In: Wallace, R.B., Kohatsu, N., Last, J.M. (Eds.), Public Health and Preventive Medicine, 15th edn. McGraw Hill Publishers, New York, NY.
Lambert, C., Alexander, B.H., Ramachandran, G., MacLehose, R., Nelson, H.H., Ryan, A., Mandel, J.H., 2016. A case-control study of mesothelioma in Minnesota iron ore (taconite) miners. Occup. Environ. Med. 73 (2), 103–109.
Lemaire, I., Nadeau, D., Dunnigan, J., Masse, S., 1985. An assessment of the fibrogenic potential of very short 4T30 chrysotile by intratracheal instillation in rats. Environ. Res. 36 (2), 314–326.
Mandel, J.H., Alexander, B.H., Ramachandran, G., 2016. A review of mortality associated with elongate mineral particle (EMP) exposure in occupational epidemiology studies of gold, talc, and taconite mining. AJIM 59, 1047–1060.
Minnesota Department of Health, 2007. Mesothelioma in Northeastern Minnesota and Two Occupational Cohorts. Update. Available at: http://www.health.state.mn.us/divs/hpcd/cdee/mcss/documents/nemeso1207.pdf.
Moalli, P.A., MacDonald, J.L., Goodglick, L.A., Kane, A.B., 1987. Acute injury and regeneration of the mesothelium in response to asbestos fibres. Am. J. Pathol. 128 (3), 426–445.
Mossman, B.T., 2008. Assessment of the pathogenic potential of asbestiform vs. non-asbestiform particulates (cleavage fragments) in in vitro (cell or organ culture) models and bioassays. Regul. Toxicol. Pharmacol. 52 (1 suppl), 200–203.
NIOSH, 2003. NIOSH Manual of Analytical Methods: Asbestos and Other Fibers by PCM 7400. Available at. http://www.cdc.gov/niosh/docs/2003-154/pdfs/7400.pdf.
Perlman, D., Mandel, J.H., Odo, N.U., Ryan, A., Lambert, C., MacLehose, R.F., Ramachandran, G., Alexander, B.H., 2018. Pleural abnormalities and exposure to elongate mineral particles in Minnesota iron ore (taconite) workers. AJIM 1–9 Epub ahead of pring.
Report to the Minnesota Legislature, 2014. Available at: www.taconiteworkers.umn.edu.
Ross, M., Nolan, R.P., Nord, G.L., 2008. The search for asbestos within the Peter Mitchell taconite iron ore mine, near Babbitt, Minnesota. Regul. Toxicol. Pharmacol. 52 (1 suppl) (43–40).
Selevan, S.G., Dement, J.M., 1979. Mortality patterns among miners and millers of non-asbestiform talc: preliminary report. J. Environ. Pathol. Toxicol. 2, 273–284.
Steenland, K., Brown, D., 1995. 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. 27, 217–229.
Wergeland, E., Andersen, A., Baerhelm, A., 1990. Mortality in talc-exposed workers. Am. J. Ind. Med. 17, 505–551.
Wild, P., Leodolter, K., Refregier, M., Schmidt, H., Zedek, T., Haidinger, G., 2002. A cohort mortality and nested case-control study of French and Austrian talc workers. Occup. Environ. Med. 59, 98–105.