Respiratory Diseases and Exposure to Elongated Mineral Particles in Taconite Ore Processing

Final Report

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Abstract

The primary research question addressed in this work is whether long-term on-site exposure to non-asbestiform EMP contributes to the development of mesothelioma and lung cancer observed in the taconite mines. If so, which EMP exposure metric (what size range of the study EMP) is most associated with the mesothelioma cases among taconite worker population.

We reconstructed the historical NIOSH EMP exposures of workers in Minnesota taconite industry from 1955-2010 based on 751 historical and 1285 present-day EMP measurements using two different reconstruction strategies, one based on only historical and present-day EMP data, and the other one further borrowed the time-trend information from the historical dust reconstruction study. Each of the strategies generated a job exposure matrix (JEM) for the NIOSH defined EMP. These two different JEMs (by mine, department and year for NIOSH defined EMP) set the foundation for calculating life-time exposure to NIOSH-EMP for taconite workers in epidemiological studies. The different JEMs also creates research opportunities for investigating how the selection of different exposure reconstruction strategies would affect final risk estimates in epidemiological studies.

A variety of dimensions (lengths and widths) of elongate mineral particles (EMP) have been proposed as being related to health effects such as mesothelioma and lung cancer. The goal of this study was to develop a mathematical approach for deriving numerical conversion factors (CFs) between these exposure metrics. The conversion factor derivation study focused on

creating reasonable conversion factors (CFs) between EMPs of different size ranges based on our understanding on how the overall EMP size would be distributed at different locations in taconite mines. We sent all 1285 achieved EMP samples to an accredited lab for ISO-TEM analysis, obtained size information for 11,190 single EMP, literature-reviewed possible size distribution assumptions and developed a Bayesian model for distribution plot prediction. The comprehensive EMP exposure assessment conducted in this study, particularly the mathematical relationships between the NIOSH EMP and other EMP definitions using the new ISO-TEM results, provides the basis of classification of workers into JEMs based on alternate definitions of EMP for epidemiological studies of mesothelioma, lung cancer, and non-malignant respiratory disease.

This mesothelioma case-control study focused on investigating the association between the long-term exposures to non-asbestiform EMP and the development of mesothelioma observed in the taconite mines. Compared to the 2010 study, case ascertainment was updated using the Minnesota Cancer Surveillance System (MCSS). Secondly, eight different EMP JEMs were used in the study to estimate worker's cumulative exposures to EMP of different size ranges. The result of this study showed an association between mesothelioma and employment duration and possibly NIOSH EMP exposure in taconite mining and processing. This study also found a possible association between mesothelioma and cumulative exposure to Suzuki EMP and cleavage fragments in the Minnesota taconite worker population. This provides epidemiological evidence in support the long-term speculation that short EMP may also be implicated in development of mesothelioma.

Chapter 1. Key Findings, Translation and Impact

Study 1. Reconstructing Historical Exposures to Elongate Mineral Particles (EMPs) in the Taconite Mining Industry for 1955–2010

As part of ongoing epidemiological studies for assessing the association between exposure to dust from taconite operations and the development of respiratory diseases, the goal of this study was to reconstruct the exposures of workers to elongate mineral particle (EMP) in the Minnesota taconite mining industry from 1955-2010.

Historical NIOSH-7400 and equivalent EMP personal exposure data were extracted from two sources: (1) the Mine Safety and Health Administration (MSHA) online database recorded for all inspection results since 1978 with 655 EMP monitoring records from 1978 to 2010 for 13 MSHA Mine IDs associated with this study; and (2) the mining companies' internal monitoring reports contained 96 personal EMP exposure records. NIOSH-7400 EMP personal exposures were measured for workers in different jobs in all active mines in 2010 by obtaining 1285 personal samples. After data treatment, all data were grouped into seven mines and eight departments. Within each mine-department, the yearly EMP mean concentration in f/cc for each year of operation was predicted using two approaches.

The performance of two approaches varied by situation. The assumptions underlying each approach described in this paper have limitations. A linear regression based on limited historical measurements and those made in 2010-2011 (Approach 1) does not yield reasonable and plausible values of the slope. Approach 2 assumes that the EMP and the respirable dust in the same department share the same historical time trend. This approach allowed us to avail of the more reasonable slope estimates from the historical respirable dust data set and yielded more plausible historical exposure estimates for most locations.

This work with two different JEMs provides us with a unique research opportunity to study the potential impact of exposure assessment to epidemiological results. Both JEMs are being used to assess associations between EMP and respiratory disease in epidemiological studies.

Study 2. A Bayesian Approach for Determining the Relationship between Various Elongate Mineral Particles (EMPs) Definitions

A variety of dimensions (lengths and widths) of elongate mineral particles (EMPs) have been proposed as being related to health effects. In this paper, we develop a mathematical approach for deriving numerical conversion factors (CFs) between these EMP exposure metrics and applied it to the Minnesota Taconite Health Worker study which contains 196 different job exposure groups (28 similar exposure groups times 7 taconite mines). This approach comprises four steps: for each group (1) obtain single EMP dimension information using ISO-TEM 10312/13794 analysis; (2) use bivariate lognormal distribution to characterize overall EMP size distribution; (3) use a Bayesian approach to facilitate the formation of the bivariate lognormal distribution; (4) derive conversion factors between any pair of EMP definitions. The final CFs allows the creation of job exposure matrices (JEMs) for alternative EMP metrics using existing EMP exposures already characterized according to the NIOSH-defined EMP exposure metric (length > 5 μm with an aspect ratio ≥ 3.0). The relationships between the NIOSH EMP and other EMP definitions, provide the basis of classification of workers into JEMs based on alternate definitions of EMP for epidemiological studies of mesothelioma, lung cancer, and non-malignant respiratory disease.

Study 3. Mesothelioma Risks and Dimension-based Elongate Mineral Particle (EMP) Definitions in Minnesota Taconite Mining Industry: An update of the Minnesota Mesothelioma Case-Control Study

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 (EMP). As an update of the previous Minnesota mesothelioma study that evaluated the association between mesothelioma, employment and EMP exposures from taconite mining, the goal of this study is to re-evaluate this association for the EMP of multiple types using our updated study cohort and latest EMP job-exposure matrices.
Methods: As of 2015, mesothelioma cases (N=104) were identified through the Minnesota Cancer Surveillance System (MCSS) and death certificates. Four controls of similar age were

selected for each case with 410 controls ultimately eligible for inclusion. Mesothelioma risk specified by EMP definition was evaluated by estimating rate ratios and 95% CIs with conditional logistic regression in relation to duration of taconite industry employment and definition-specified cumulative EMP exposure [(EMP/cc)×years]. Four EMP definitions with different size inclusion criteria were used in this study (NIOSH EMP: Width≥0.25µm, Length>5µm, W/L≥3; Chatfield asbestiform EMP: 0.04 µm ≤W≤1.5 µm, 20≤W/L≤1000; c. Suzuki EMP: W≤0.25 µm, L≤5 µm; d. Chatfield non-asbestiform EMP: W/L<20). Models were adjusted for employment in hematite mining and potential exposure to commercial asbestos products used in the industry.

Results: All mesothelioma cases were male and 72 of the cases had work experience in the taconite industry. Mesothelioma was weakly associated with the number of years employed in the taconite industry (RR = 1.02, 95% CI 1.00 to 1.05). A positive mesothelioma association was consistently observed with cumulative exposure to Suzuki EMP and Chatfield non-asbestiform EMP in models with no latency, a 20-year latency, and a 30-year latency as well as models adjusting for the cumulative NIOSH EMP exposure. These was a weak association between mesothelioma and cumulative NIOSH EMP exposure in taconite mining and processing (RR = 1.11, 95% CI 0.99 to 1.22).

Conclusions: This study re-confirmed the main conclusions in the previous study: there was an association between mesothelioma and employment duration and possibly NIOSH EMP exposure in taconite mining and processing. This study further found an association between mesothelioma and cumulative exposure to Suzuki EMP and Cleavage fragments in Minnesota taconite worker population. The risk of exposure to long and thin fibers was not clear yet given the small samples of such fibers in our study.

Chapter 2. Introduction

Taconite mining in Minnesota and Taconite Workers Health Study (TWHS)

Low-grade taconite ore in Michigan and Minnesota is the primary source of iron for the iron and steel industry in the United States (Hubbell, Heller and Yang, 2001). In 2016, mines in these two states shipped 98% of the usable iron ore products in the US with an estimated value of $3.4 billion (National Minerals Information Center, 2017). Minnesota mines contributes about 76% of the production, and had 4514 employees in 2014 that did not include professional or clerical workers at mines, pelletizing plants, and maintenance shops or research lab workers (U.S. Geological Survey, 2014). Minnesota's taconite mining industry began in the 1950s in northeastern Minnesota along the Mesabi Iron Range after the depletion of hematite reserves (Berndt & Brice, 2008). The mining and processing of the taconite ores include four main steps – mining, crushing, concentrating and pelletizing, that increase the iron content from 15-30% in the ore to as high as 65% in the final product (US EPA, 2012). This process however generates a significant amount of dust that can result in workers' potential exposures to mixtures of respirable dust (containing iron, silica, and other chemicals) and Elongate Mineral Particles (EMP). The respirable dust here refers as the fraction of inhaled airborne particles that can penetrate beyond the terminal bronchioles into the gas-exchange region of the lungs. Its D_{50}, aerodynamic particle diameter corresponding to 50% sampling efficiency, is 4 μm.

Health concerns were initially expressed in the 1970s when increasing number of lung disease cases began to be reported in counties in proximity to where taconite was mined (Axten and Foster, 2008; Wilson *et al.*, 2008). However, follow-up occupational studies demonstrated little evidence of elevated disease rates among workers (Clark *et al.*, 1980; Higgins *et al.*, 1983; Cooper, Wong and Graebner, 1988; Cooper *et al.*, 1992). In 1983, a cohort that included 68,737 individuals who had ever worked in the mining industry in northeastern Minnesota between the 1930s and the end of 1982 was enumerated through the Mineral Resources Health Assessment Program (MRHAP) with the support of the Iron Range Resources and Rehabilitation Board (IRRRB) and the cooperation of the seven mining companies then in operation (MDH, 1985). In 1997, this cohort was matched with cancer information from the Minnesota Cancer Surveillance System (MCSS) and subsequent reports in 2003 and 2007 showed a 2.9-fold increase in the rate of mesothelioma in the iron mining industry workers when compared to the rest of Minnesota (MDH 2003, 2007). These findings challenged conventional understanding since mineralogical data suggest that the ore body involves almost exclusively non-asbestiform EMP (McSwiggen & Morey, 2008; Zanko et al., 2008), that had not been thought to have high potential for disease (Gamble & Gibbs, 2008; Berry & Gibbs, 2008; Mossman, 2008).

Concerns about the potential excess rates of mesothelioma in this cohort led the Minnesota State Legislature in 2008 to fund the Taconite Workers Health Study (TWHS) to evaluate mesothelioma, lung cancer, and non-malignant respiratory disease (University of Minnesota, 2014). Since then, studies on exposure assessment for present-day exposure to respirable dust (RD), respirable silica (RS) and EMP (Hwang *et al.*, 2013, 2014, 2017), mortality (Allen *et al.*, 2014; Mandel, Ramachandran and Alexander, 2016), cancer incidence (Allen et al., 2015), lung cancer case-control (Allen et al., 2015), mesothelioma case-control (Lambert *et al.*, 2016) and pulmonary function tests (Odo *et al.*, 2013) have been reported. These studies report the following broad conclusions: (1) Taconite workers have an increased risk for mesothelioma, lung, laryngeal, stomach, and bladder cancers. (2) Taconite workers may be at increased risk for mortality from lung cancer, mesothelioma, and cardiovascular disease (specifically, hypertensive heart disease and ischemic heart disease). (3) Mesothelioma was associated with the number of years employed in the taconite industry (RR=1.03, 95% CI 1.00 - 1.06), and cumulative EMP exposure (RR=1.10, 95% CI 0.97 –1.24) as defined by the National Institute for Occupational Safety and Health (NIOSH) EMP 7400 method. (4) Lung cancer case-control study suggests that the estimated taconite mining exposures do not increase the risk of developing lung cancer.

New NIOSH-funded study

As part of this research grant, we re-analyzed all 1269 archived EMP personal samples, that were collected in the original TWHS from all six active mines (five in the western and one in the eastern zone of the Mesabi Iron Range), using the more advanced ISO TEM 10312/13794 analytical methods. These methods, compared to the traditional NIOSH 7400/7402 methods can detect EMP with a wider size range and report the length and width information for each of every identified EMP. The new detailed EMP information, in conjunction with existing study cohorts assembled in the original TWHS made the test of the following research hypotheses possible: (1) long-term on-site exposure to non-asbestiform EMP contributes to the development of mesothelioma and lung cancer observed in the taconite mines. (2) the selection of different EMP exposure metrics will impact the disease risk estimated from epidemiological studies.

Beside the new EMP ISO-TEM results, all existing historical industrial hygiene measurements assembled in the original TWHS study were further processed and cleaned. The previous mesothelioma cohort was updated in 2015 based on the Minnesota Cancer Surveillance System (MCSS), and 23 new in-state cases and 1 out of state case were identified.

Asbestos and Elongated Mineral Particles (EMP)

Legislatively, the term “asbestos fiber” refers to a set of six naturally occurring fibrous minerals regulated by the OSHA in 1970s. These minerals include the serpentine mineral - chrysotile, and the five amphibole minerals - actinolite, amosite, anthophyllite, crocidolite, and tremolite (IARC 2012). The definition also specified length and aspect ratios that were derived from measurement reproducibility considerations rather than health relevance. This was the origin of the regulatory definition that a “fiber” should have a length that exceeds 5 μm and an aspect ratio (length: width) that is at least 3:1 (OSHA 1979). Asbestos fibers have been being heavily researched in the past 40 years, and there is general consensus that all types of asbestos cause lung cancer, mesothelioma, cancer of the larynx and ovary, and asbestosis (fibrosis of the lungs) (ICOH, 2013; Collegium Ramazzini, 2016; WHO, 2016).

The term “elongated mineral particles” or EMP, which refer to any mineral particle with a minimum aspect ratio of 3:1 that is of inhalable, thoracic, or respirable size (NIOSH, 2011), is a broader concept. Theoretically, this concept can be further divided into two sub-groups based on mineral habit: asbestiform EMP and non-asbestiform EMP; and the OSHA-specific fibers discussed above belong to the asbestiform EMP. However in practice, traditional analytical methods (Phase Contrast Microscopy (PCM) and Transmission Electron Microscopy (TEM)) cannot explicitly distinguish asbestiform EMP from their non-asbestiform analogues when present in a heterogeneous mixture and it is especially true for amphibole EMP (ISO 1995; ISO 1999; NIOSH 1994). For this reason, some research groups statistically analyzed the potential dimension differences between prepared asbestiform amphibole EMP and non-asbestiform amphibole EMP samples, and proposed dimension-based criteria (Chatfield, 2008; Van Orden *et* *al.*, 2009) in an attempt to solve this differentiation problem. Unfortunately, these criteria might not work well in practice (Harper, 2008; Harper *et al.*, 2008, 2012).

Furthermore, non-asbestiform EMP, based on their origins, can be further divided into naturally occurring EMP and cleavage fragments. Cleavage fragments by definition are the structures that are created via comminution, whether deliberate during crushing or grinding, or incidental in usage (Ilgren, 2004). Although taconite ore itself may not contain many natural occurring EMP, taconite mining processes (e.g. crushing) could create significant numbers of cleavage fragments, that end up creating a dusty non-asbestiform EMP environment.

Because of the difficulty of distinguishing non-asbestiform EMP from other EMP, the relationship between non-asbestiform EMP and adverse health effects is not understood well (NIOSH, 2011). Adverse health effects examined in some epidemiology studies have been linked to non-asbestiform EMP, in gold and talc mining studies, where non-asbestiform EMP exposures also exist. *The NIOSH Roadmap* (NIOSH, 2011) *clearly identifies the taconite miners of northeastern Minnesota as a population that should be studied further with detailed exposure characterization.*

EMP dimensions and health risks

EMP dimension affects penetration and deposition in different regions of the lung. Macrophages cannot remove particles from the lung when the EMP length is longer than the macrophage diameter, and the lung cannot function when the thinner EMP deposit in the deeper alveoli region of the lung (Baron, 2003).

However, the question of how the dimensions of the asbestiform EMP are related to carcinogenic lung disease development has been controversial. Stanton et al. (1981) hypothesized that carcinogenicity of EMP is related to dimension and durability and less with mineral type and ascribed carcinogenicity to EMP with a length > 8 µm and a diameter < 0.25 µm. Subsequently, Lippmann (1988) suggested that lung cancer was associated with associated with asbestos EMP longer than 10 µm with a diameter > 0.15 µm, while mesothelioma was associated with asbestos EMP longer than 5 µm with a diameter < 0.1µm. A series of analyses by Berman et al. (1995, 2003, 2008) consistently suggested that it is likely that length categories with minimum cut points substantially longer than 10 µm contribute most heavily to both asbestos-induced lung cancer and mesothelioma. Loomis et al. (2010, 2012) also found that the occurrence of lung cancer is associated most strongly with exposure to long thin asbestos fibres (5-10 µm long and <0.25 µm in diameter) in workers at asbestos textile mills in North Carolina and South Carolina, USA. A panel of experts convened by ATSDR (Eastern Research Group, 2003) concluded that there is a weight of evidence that asbestos and synthetic vitreous fibers (SVFs) shorter than 5 µm are unlikely to cause cancer in humans.

Other researchers have argued against ruling out the effect of short fibers. Dodson et al. (2003) concluded that asbestos EMP of all lengths induce pathological responses and cautioned against ignoring EMP < 5 µm since they constituted the bulk of EMP exposures. Suzuki et al. (2005) concluded that short (≤5 µm), thin EMP (≤0.25 µm) were more strongly associated with malignant mesothelioma through analysis of lung and mesothelial tissues in human patients. Dement et al. (2008) showed using a TEM analysis of chrysotile fibers that all combinations of lengths and widths (lengths ranging from <1.5 µm to > 40 µm and widths ranging from 0.25 - 3.0 µm were highly statistically significant predictors of lung cancer and asbestosis. This reinforced their previous conclusion that since the traditional counting method (NIOSH 7400 PCM and NIOSH 7402 TEM) counts only EMP > 5 µm in length, shorter EMP are not counted, but may contribute substantially to work exposure (Dement *et al.*, 1983). Pott (1987) proposed that for natural fibers and manmade mineral fibers (MMMF), EMP >3 μm in length, <1 μm in width, and >5:1 aspect ratio were carcinogenic.

The above discussion highlights the following – (1) the lack of well-defined studies regarding the health effects of non-asbestiform EMP, and (2) the lack of agreement on the appropriate threshold dimensions of EMP that are health-relevant.

Research objectives

The primary research question addressed in this work is whether long-term on-site exposure to non-asbestiform EMP contributes to the development of mesothelioma and lung cancer observed in the taconite mines. If so, which EMP exposure metric (what size range of the study EMP) is most associated with the mesothelioma cases among taconite worker population. This question could not be well answered in previous TWHS study due to the limitations of the data available at that time.

Specific aim 1

To reconstruct the historical NIOSH EMP exposures of workers in Minnesota taconite industry from 1955-2010 based on 751 historical and 1285 present-day EMP measurements, and some time-trend information learned from specific aim1 using two different reconstruction strategies. The result of this study is two strategy-specific NIOSH-EMP based JEMs. These two JEMs will form the basis for future epidemiological studies.

Specific aim 2

A variety of dimensions (lengths and widths) of elongate mineral particles (EMP) have been proposed as being related to health effects such as mesothelioma and lung cancer. The goal of third study is to develop a mathematical approach for deriving numerical conversion factors (CFs) between these exposure metrics. These CFs will allow us to develop dimensional-specific EMP JEMs based on existing NIOSH-EMP based JEM developed in specific aim 2.

Specific aim 3

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 (EMP). As an update of the 2010 Minnesota mesothelioma study that evaluated the association between mesothelioma, employment and EMP exposures from taconite mining, the goal of this study is to re-evaluate this association for the EMP of different size ranges using the updated study cohort and new dimension-specific EMP JEMs developed in specific aim 3.

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Chapter 3. Reconstructing Historical Exposures to Elongate Mineral Particles (EMPs) in the Taconite Mining Industry for 1955–2010

INTRODUCTION

The Taconite Worker Health Study (TWHS), which was funded by the State of Minnesota in 2008, is the most comprehensive occupational epidemiological investigation into the causes of the excess cases of respiratory diseases (mesothelioma, lung cancer, and non-malignant respiratory disease (NMRD)) among taconite workers in Minnesota [(1)]. Since its inception, a number of studies under the umbrella of this investigation have been published, including occupational exposure assessments [(2–4)], a respiratory health survey [(5)], a cancer incidence study [(6)], retrospective case-control studies [(7,8)], and mortality studies [(8–11)]. The main goal of this paper is to report on the reconstruction of the historical exposures to elongate mineral particle (EMP) from 1955-2010 for different departments in each of the taconite mines.

Since the term "fiber" has been controversial in the context of asbestos [(12)], the National Institute for Occupational Safety and Health (NIOSH) has recently proposed the use of the term "elongate mineral particles" or EMP to refer to mineral particles with a minimum aspect ratio of 3:1 that are of inhalable, thoracic, or respirable size [(13)]. The original Occupational Safety and Health Administration (OSHA) regulation defined asbestos only mineralogically without specifying the habit or asbestiform nature. The definition also specified length and aspect ratios that were derived from measurement reproducibility considerations rather than health relevance. This was the origin of the regulatory definition that a "fiber" should have a length that exceeds 5 μm and an aspect ratio (length: width) that is at least 3:1. However, in many industries including taconite mining and processing, EMPs are created during mechanical processing of the ore (e.g., crushing and fracturing of the mineral) that are referred to as cleavage fragments. These cleavage fragments could meet the regulatory definition of a “fiber” described above, even if they were not asbestiform in habit. NIOSH has explicitly included EMPs from the non-asbestiform analogs of asbestos in its recommended exposure limit (REL). Their rationale for this decision was three-fold (NIOSH, 2011): (1) the epidemiological evidence from studies where worker populations were exposed to non-asbestiform EMPs (New York talc miners and millers, Homestake gold miners, and taconite miners) was considered inconclusive due to inadequate EMP exposure characterization, not accounting for smoking status, poor reliability of death certificate information, and exposures associated with prior employment; (2) animal studies showed differential toxicity of asbestiform and non-asbestiform EMPs with lower effects of exposure to non-asbestiform EMPs and some evidence that EMP dimensions may be predictors of toxicity, (3) current analytical methods used for routine analysis of samples, i.e., the NIOSH 7400 phase contrast microscopy (PCM) and NIOSH 7402 transmission electron microscopy (TEM) methods cannot differentiate between asbestiform and non-asbestiform EMPs when present in a heterogeneous mixture. The term “Elongate mineral particle” or “EMP” used throughout this paper specifically refers to any particles that is longer than 5 μm and has a minimum aspect ratio of 3:1 on the basis of a Phase contrast microscopic (PCM) analysis of an air sample using the National Institute for Occupational Safety and Health (NIOSH) method 7400 or an equivalent method (13). The current NIOSH method 7400 was firstly published in 1989 and is the default method for evaluating the EMP in the US. Prior to this method, some of its equivalent methods had already been existing with the earliest one published around the 1970s [(14)].

Historical EMP exposure reconstruction, especially over a long span of time (1955 to 2010), is challenging. The biggest challenge is that typically industrial hygiene (IH) measurement data are not available for every job for every time point of the study period in the job-exposure matrix

(JEM). Different quantitative strategies have been proposed to overcome the sparse data problem: (1) data pooling: e.g., in the historical tremolite-actinolite exposure reconstruction work for the vermiculite miners and millers between 1930 and 1980 near Libby Montana, Amandus *et al.* (1987) estimated the 8-hr TWA fiber exposure for different jobs in each year of operation of the Libby facility by pooling arithmetic averages of the fiber concentrations from filter samples for years when production processes and dust controls were assumed to be similar; (2) statistical modelling: e.g., in the historical fiber exposure reconstruction work for the chrysotile asbestos textile workers between 1940 and 1975 in Charleston South Carolina, Dement *et al*. (1982) first divided the textile operations into 16 exposure zones according to similarity of processes and exposures, and then applied a linear model to estimate the mean exposure levels over time for each of their exposure zones; (3) hybrid methods: e.g., during the process of reconstructing the historical exposure to Libby vermiculite for the workers between 1972 and 2000, researchers first calculated the natural log-transformed mean for any year with 40 or more sample results, then fitted a smooth curve through these mean values, and finally calculated the yearly fiber exposure levels by exponentiating the value on this curve for each year (17,18).

Based on sparse IH measurements and other information, this paper uses two statistical modeling approaches to reconstruct the historical EMP exposure profiles from 1955 to 2010 for Minnesota taconite miners. The exposure estimates will be used for estimating the life-time cumulative EMP exposure values for taconite workers in epidemiological investigations.

METHODS

TABLE I. Data availability for the seven taconite mines in the study

Taconite Mine	Geological Zone	Year Opened	Status (as of 2010)	Available EMP Measurements by Year

A	Eastern	1955	Active	1973-1976, 1978-1980, 1983-1986, 1990-1993, 1995, 2000, 2001, 2003-2010
B	Western	1974	Active	1985, 1986, 1995, 2000, 2001, 2003, 2007, 2010
C	Western	1964	Active	1978, 1979, 1981-1983, 1985-1990, 1995, 2000, 2001, 2003, 2007, 2010
D	Western	1967	Active	1975-1977, 1987, 2000, 2001, 2003, 2004, 2007, 2010
E	Western	1967	Active	1990, 1991, 1994-1998, 2000, 2001, 2003, 2007, 2010
F	Western	1977	Active	1979, 1981, 1983, 1985, 1986, 1988, 1992, 1999-2001, 2003, 2004, 2007, 2010
G	Eastern	1957	Closed in 2001	1979-1992, 2000, 2001

* Mining Companies: http://www.taconite.org/mining-industry/mines;

Taconite mines and different exposure groups

The TWHS study comprised seven taconite mines within two geological zones (the eastern zone and the western zone) on the Mesabi Iron Range in Minnesota. For confidentiality purposes, all mine names were replaced with a name code that is consistent with previous study publications [2,3]. Mines A and G are located in the eastern zone, and Mines B-F are located in the western zone (Table I). The oldest mine started operating in 1955 and the newest mine in 1977 (19). Six out of these seven mines were still in operation in 2010 when a comprehensive exposure monitoring was conducted [2–4]. The mining processes for all the mines were quite similar, but workers with different tasks were considered to experience different exposures. Hwang *et al.* (2013) grouped all taconite worker job titles into eight exposure departments: Mining, Crushing, Concentrating, Pelletizing, Shop (mobile), Shop (stationary), Janitor, and Office/control room. Given this exposure categorization, the specific aim of this study was to create historical EMP reconstruction for each of these mine-department combinations.

Construction of historical exposure database

Historical EMP measurements included both personal and area samples In this study, which reconstructs exposures for use in epidemiological analysis of worker respiratory health outcomes, only personal historical EMP samples (collected over an 8-hour period) were considered, and all samples were analyzed using the standard phase contrast microscopy (PCM) method as defined by the National Institute for Occupational Safety and Health (NIOSH) (20).

Historical NIOSH-7400 EMP personal exposure data were extracted from two sources: (1) the Mine Safety and Health Administration (MSHA) online database recorded for all inspection results since 1978 with 655 EMP monitoring records from 1978 to 2010 for 13 MSHA Mine IDs associated with this study; and (2) the mining companies' internal monitoring reports contained 96 personal EMP exposure records with the earliest record in 1983. In total, there were only 751 historical EMP personal samples – a small number for the seven mines and eight departments over a 50-year time-span. The apportionment of these samples can be found in Table I and their location distribution is listed in Table II. The data gap is significant for several mines, especially during their early years: for instance, the first EMP measurements for Mine G were made in 1979, ~ 22 years after it started production. Similarly, Mine E, which started operating in 1967, also had no historical EMP measurements until 1990 – 23 years later.

"Year 2010/2011" EMP measurements

As reported in detail in a previous publication [3], a total of 1,285 personal samples from a subset of workers in seven of the eight departments (excluding "Janitor") of each active mine were collected to assess "Year 2010/2011" EMP exposures. This sampling was conducted from January 2010 to May 2011. Mine G, which was closed in 2001, was not covered in this survey.

All these samples were analyzed using the NIOSH 7400 PCM method by an American Industrial Hygiene Association-accredited laboratory (EMSL Analytical Inc., Minneapolis, MN, USA).

Handling data below the limit of detection

Among the 2,036 historical and “Year 2010/2011” measurements, 176 historical measurements and 463 “Year 2010/2011” measurements were either below the limit of detection (LOD) or recorded as zero. All zero values and the values below LOD were replaced with a small positive value (0.001 f/cc), which was approximately one half of the lowest LOD among all study measurements. This substitution method works reasonably well when the percentage of censored data are not too high.

Historical EMP reconstruction strategy

While “Year 2010/2011” measurements enable us to understand the current EMP exposures, historical monitoring data are crucial to estimating how these levels changed over time. However, there were only 751 historical measurements in total in this study that were not uniformly distributed across mine-departments, and 12 locations had no historical data at all (Table II).

To assess exposures in the face of this data sparseness, we used two different approaches. The first one (hereafter referred to as Approach 1) is a regression-based approach. All 2,036 data points were first sorted by mine, and within each mine, a categorical variable for department was created. For each mine, a log-linear regression model was run to obtain a fixed slope estimate (time trend) that is common to all departments (within that mine) and a varying intercept for each department (Eq. 1). The model was also adjusted for ‘present-day’ vs. ‘historical’ measurements to account for systematic differences in sampling strategies between these two sets of measurement data. The sampling strategy for the "Year 2010/2011" exposure assessment was primarily designed to capture a wide range of exposure levels for epidemiological analyses, while the historical measurements were obtained primarily for compliance purposes. Therefore, the linear regression model for each mine included a categorical variable to explain the potential difference in exposure levels by different measurement type. A fixed slope (time trend) model was used so that estimates for departments with fewer monitoring data could borrow strength from departments with more monitoring data. Mine G had no "Year 2010/2011" measurements and its historical data were very sparse as well. Therefore, given their geographical proximity (western zone) and geological similarity (21), we chose to use the data from Mine A as a surrogate to make predictions for Mine G. The Mining department in Mine G and Janitor departments in each of the other mines had no "Year 2010/2011" measurement (shaded gray in Table II). In addition to the seven mines and the eight departments within each mine, an "All 8 departments" department category and an "All 7 mines" mine category were created (see Table II). The results of these two categories would be used to provide exposure estimates for workers with unclear job titles or work histories. The 'All 8 departments' department was modelled using all the data within a mine. The 'All 7 mines' mine was modelled using all the data within the same department across all mines.

It's worth noting that the term $\beta_{9,i}$ in Eq.1 was the predicted time-trend for each mine of this study. Its exponentiation, $i.e., exp(\beta_{9,i})$ (in percentage), reflected the fixed annual mean EMP exposure change in a mine.

$$\log(\hat{Y}_{j,i}) = \beta_{0,i} + \sum_{j=1}^{8} \beta_{j,i} \times Department + \beta_{9,i} \times Year_i + \beta_{10,i} \times Present\_day$$

(Eq. 1)

where $\hat{Y}_{j,i}$ was the predicted EMP mean concentration value (in f/cc) for department j of mine i. $Department$ was a categorical variable that had eight levels corresponding to the eight departments in each mine and $\beta_{j,i}$ (j=1 to 8) were the model coefficients for the eight departments within each mine. The baseline department was the "Mining" department. $Year_i$ was the time variable, from 1955 or later to 2010, depending on the mine. $Present\_day$ was a binary variable with 0 for "Year 2010/2011" measurements and 1 for historical measurements. When we predicted $\hat{Y}_{j,i}$, we set present day variable to '0", i.e, we estimated the log EMP level at a historical time point, if it had been measured the same way as today.

The second approach (Approach 2) used the results from a companion study - Reconstructing Historical Exposures to Respirable Dust (RD) and Respirable Silica (RS) in the Taconite Mining Industry for 1955–2010 (22). These two studies are similar: both are historical exposure reconstructions for the same taconite worker population, and they share the same mine-department combinations with the same reconstruction time period. The only difference between these two studies was the pollutant of interest: one was for EMP exposure, the other was for RS and RD exposure. In the RS-RD study, thanks to the abundant measurements (19,408 respirable dust (RD) measurements and 9,128 respirable silica (RS) measurements), the annual percentage change in RSRD exposure levels over time in each mine-department combination was easier to reconstruct. Since this study to reconstruct EMP exposures has a much sparser data set, we assumed that respirable dust exposure levels and EMP exposure levels for a given mine-department combination have the same annual percentage change over time. For example, a yearly 1% increase/decrease in respirable dust exposure would lead to the same 1% annual change in EMP exposure. The advantage of this assumption was that time-trend slopes from the respirable dust study were more precise given the large number of respirable dust measurements (19,408 respirable dust (RD) measurements and 9,128 respirable silica (RS) measurements) and may better reflect the overall exposure changes over time in the taconite mining industry. EMP exposures, being a subset of the overall dust exposures, might reasonably be assumed to follow the same general time-trends. However, sufficient historical EMP measurement data were not available for us to validate this assumption.

The modelling procedure for Approach 2 was as follows: (1) For each mine-department combination, the mean exposure level at Year 2010 was defined as the log of the geometric mean all "Year 2010/2011" measurements of this location; (2) the mean exposure levels for other years were calculated using Eq. 2; (3) the variance around the mean exposure in each year was assumed to be constant over the entire time period, and was defined as the variance of all "Year 2010/2011" measurements of this location (log($GSD_{i,j,2010}$)).

$$\log(\hat{Y}_{i,j,k}) = \log(GM_{i,j,2010}) - \beta_{i,j,dust} \times (2010 - k)$$

(Eq. 2)

where $\hat{Y}_{i,j,k}$ was the predicted mean exposure level (f/cc) for department *j* of mine *i* in year *k*; $GM_{i,j,2010}$ was the geometric mean (GM) of all "Year 2010/2011" measurements taken in the year 2010 at department *j* of mine *i*; $\beta_{i,j,dust}$ was the estimated annual change for department *j* of mine *i* listed in Table III under the approach 2 subtitle;

Similar to the Approach 1, Mine G was modelled based on the "Year 2010/2011" data in Mine A. The 'All 8 departments' grouping was modelled using all the "Year 2010/2011" data within each mine. The 'All 7 mines' grouping was modelled using all the "Year 2010/2011" data within the same departments across all mines. Janitor departments were modelled using 'All 8 departments' data.

Geometric mean (GM) to arithmetic mean (AM) conversion

Both reconstruction approaches were conducted in the log scale, and their model outputs after exponentiation (GMs and geometric standard deviations (GSDs)) were used to calculate the corresponding arithmetic means using Eq. 3.

$$AM = GM \times \exp(\frac{1}{2}\log^2(GSD))$$

(Eq. 3)

Each of the two reconstruction approaches led to the development of a separate EMP job-exposure matrix (JEM) (See Supplementary Materials). Each table contains annual arithmetic mean EMP exposure values (in f/cc) for each possible year-department-mine combination. These two JEMs, when linked to taconite workers' employment histories, allow us to calculate the cumulative exposure (in f/cc-year) for the study population for epidemiological studies.

Data cleaning was performed in SAS 9.3 (SAS Institute, Cary NC). EMP reconstruction was performed in MATLAB R2014b (MATLAB e MathWorks, Inc., Natick, MA).

RESULTS & DISCUSSION

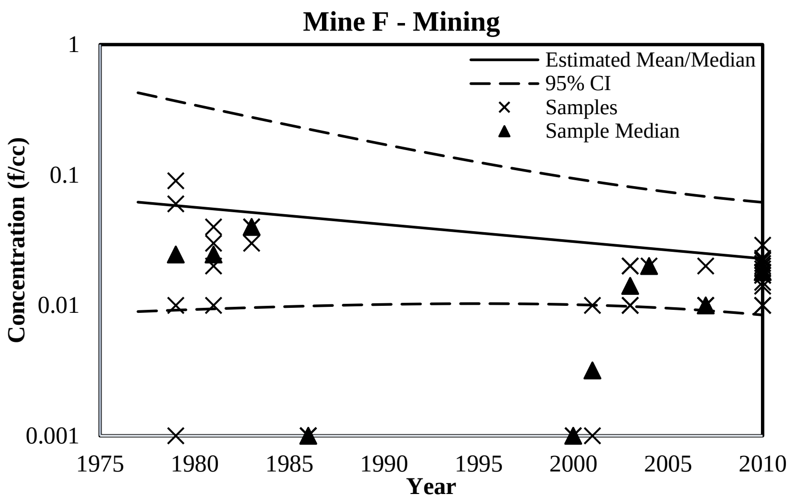
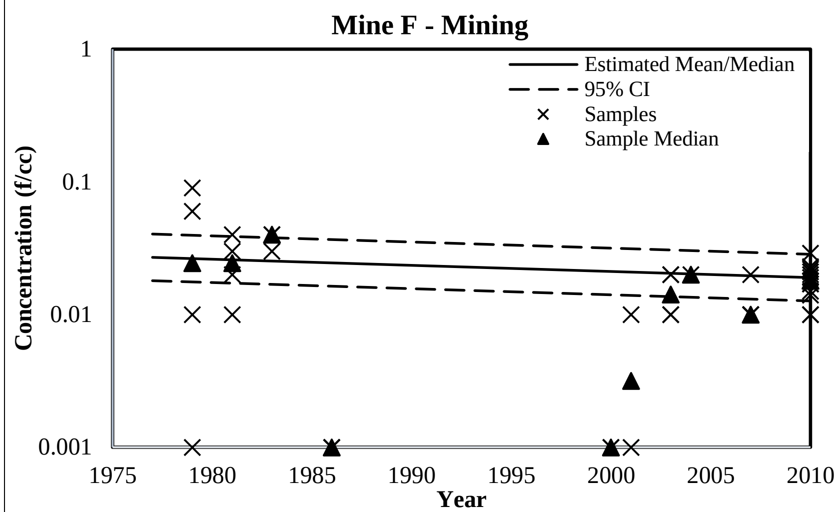
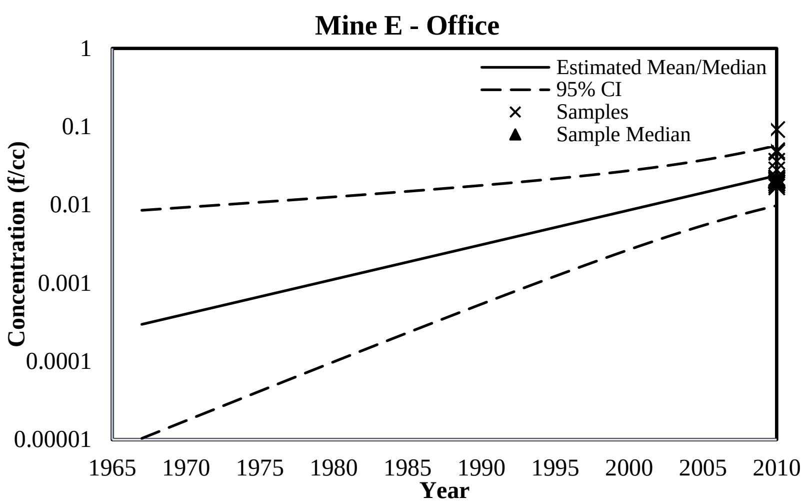
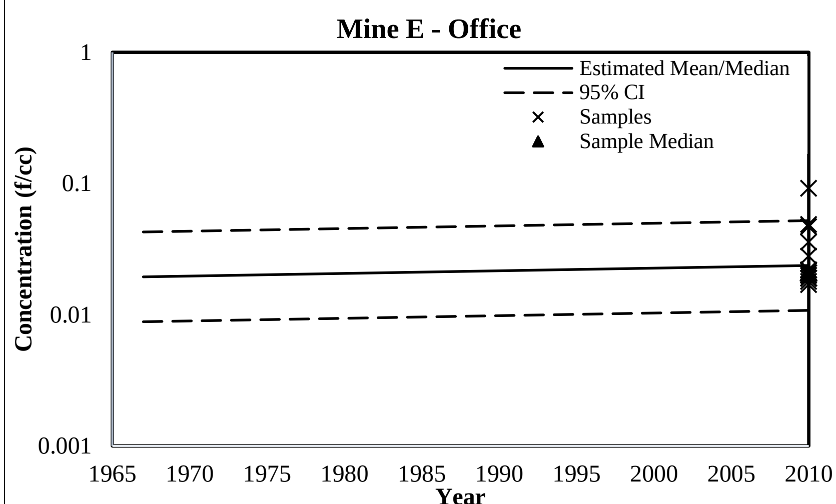
There were a total of 2,036 EMP measurements available across all mines and departments as summarized in Table II. The distribution of these samples, to some extent, reflects overall IH sampling priorities in the taconite industry. Most of IH samples were collected in the four main taconite processes – mining, crushing, concentrating and pelletizing. In contrast, there were no historical data available for all seven Office/control room departments ("Year 2010/2011" measurements did greatly supplement the database for these departments).

Model outputs

Some of the predicted historical EMP exposure values using the two different reconstruction approaches are shown side by side in Figure 1. The three pairs of plots in this figure demonstrate three typical scenarios in the study. The first scenario is when a mine-department location has a fairly good exposure data coverage over its entire time period. Specifically, data are available for the first 10 years and last 10 years in the history of this time. In this scenario, as shown in the two first-row plots, the two approaches provide comparable prediction curves. The predicted EMP exposure slopes by Approach 1 were consistent with the borrowed dust exposure slopes in Approach 2. This result can also be interpreted as the borrowed slope,

TABLE II. Numbers of historical and "Year 2010/2011" EMP measurements for each location

	Mine							
Department	A	B	C	D	E	F	G	All 7 mines
# of historical measurements								
Mining	84	20	21	15	46	31	14	231
Crushing	109	6	36	5	30	35	19	240
Concentrating	13	4	4	4	29	8	3	65
Pelletizing	8	10	3	2	35	5	2	65
Shop (mobile)	54	3	14	5	17	3	1	97
Shop (stationary)	1	0	12	0	0	1	8	22
Office/control room	0	0	0	0	0	0	0	0
Janitor	10	3	4	0	13	1	0	31
All 8 departments	279	46	94	31	170	84	47	751
# of "Year 2010/2011" measurements								
Mining	21	30	24	42	36	11	0	164
Crushing	54	23	36	18	22	11	0	164
Concentrating	32	24	18	24	24	12	0	134
Pelletizing	60	35	57	54	55	29	0	290
Shop (mobile)	42	52	52	30	76	30	0	282
Shop (stationary)	42	24	22	23	30	18	0	159
Office/control room	15	11	12	12	24	18	0	92
Janitor	0	0	0	0	0	0	0	0
All 8 departments	266	199	221	203	267	129	0	1285

	Approach 1	Approach 2
1		
2		

3

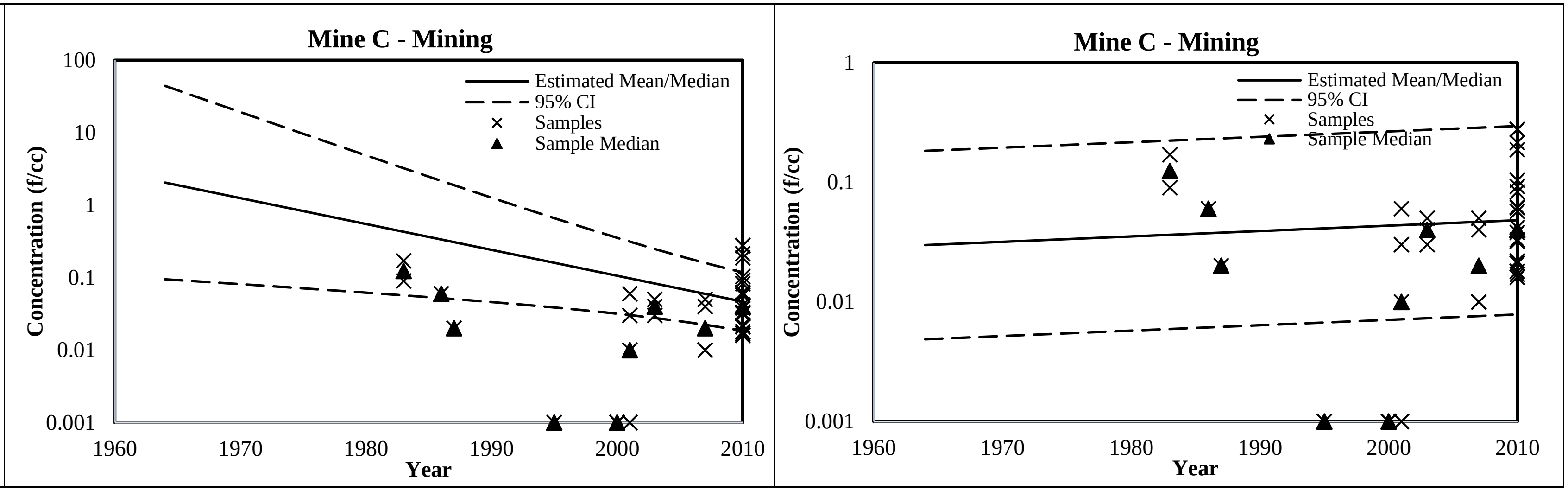


FIGURE 1. Historical EMP exposure reconstruction results for each of three selected mine-department combinations using two approaches

derived from a separate dust reconstruction work, fitted the EMP data in this study well. The second scenario is when a location only had “Year 2010/2011” measurements. In this scenario, as shown in the two second-row plots, Approach 2 is clearly more reasonable than Approach 1 for the following reason: when the historical EMP data were not available for this department, the slope provided by Approach 1 for this department was determined by other departments that also had little EMP historical data. Due to their sparse nature, these data may not adequately reflect the EMP level change in this department. In Approach 2, this slope was determined by the respirable dust measurements for this mine-department. For almost all departments, we have many more historical respirable dust measurements than EMP measurements (19,408 respirable dust (RD) measurements and 9,128 respirable silica (RS) measurements vs. 2,036 EMP measurements). Therefore, the slope used in Approach 2 (that assumes that EMP concentration and RS/RD concentration track each other over time) is more reasonable (and plausible) than the one in Approach 1. The Approach 1’s slope, if it is true, will be against the 3% to 3% slope range that learned from the dust reconstruction study in Minnesota taconite industry. The third scenario is shown in the two third-row plots in Figure 1. Essentially, Approach 1 is a random- intercept model, meaning every department of the same mine shares a common slope but different intercepts. Most times, this assumption should work as each department may have different exposure magnitudes, but their over-time change trend should be in the same direction: all getting better or all getting worse. But sometimes there are exceptions as well as shown in scenario 3. The common slope used in Mine C mining department does not fit the data as good as the one used in Approach 2. Approach 2’s slope, although was derived from historical dust measurements, have a very good fitness than Approach 1.

Predicted annual exposure level change rate by exposure location

Approach 1 made time-trend predictions for the historical exposure change in each mine based on historical and "Year 2010/2011" EMP measurements. The results of these time trends are listed on the last row of Table III. Compared to the time trends in historical respirable dust exposure used in Approach 2 (first 9 rows in Table III), the predicted EMP trends based on limited EMP data tended to be significantly steeper, and some of the annual percent changes seem unrealistic, ranging from -8.2% to 10.2%. Time-trend results from historical respirable dust exposures suggest that the historical exposure change in taconite mining environment should not be excessive, and in most cases, this change should be within -3% to 3% per year.

Predicted arithmetic mean of EMP exposure by exposure location

The arithmetic mean (AM) is a more appropriate exposure metric in creating a job-exposure matrix (JEM) for health studies than the geometric mean (GM) (23–27). The predicted AM range for every mine-department combination are listed in Table IV for Approach 1, and Table V for Approach 2. The full set of predicted AMs can be found in the Supplementary Materials.

For Approach 1, some of the upper bound AM estimates are unrealistically high (e.g., 30.89 f/cc in Mine D). This might be due to several reasons including: some predicted slopes were too steep, no historical data were available for several departments, and there were huge variances in model outputs for some departments. In contrast, predictions from Approach 2 were much more stable. Its overall predicted AM range was 0.01 to 0.23 f/cc. This narrower range suggests that

TABLE III. The annual percent change in historical EMP exposures estimated by Approach 1 and the location-specific annual percent change for historical exposure to airborne dusts used in Approach 2

Mine-Department	A	B	C	D	E	F	G	All 7 mines
				Approach 1				
All 8 departments	-4.5%	2.1%	-8.2%	-1.8%	10.2%	-3.0%	-4.5%	-3.9%
				Approach 2				
Mining	0.4%	-0.1%	1.0%	-1.8%	-0.6%	-1.1%	0.4%	-0.4%
Crushing	-0.1%	-2.5%	2.2%	-3.3%	2.3%	-0.8%	-0.1%	-0.7%
Concentrating	3.2%	1.6%	0.0%	-2.9%	2.2%	-2.7%	3.2%	2.0%
Pelletizing	2.3%	0.9%	0.1%	-1.5%	-0.3%	-2.0%	2.3%	0.2%
Shop (mobile)	-0.4%	-2.1%	-1.4%	-0.3%	-2.5%	-3.0%	-0.4%	-1.0%
Shop (stationary)	1.5%	1.1%	-2.6%	1.2%	0.3%	0.2%	1.5%	-0.2%
Office/control room	0.7%	-1.0%	0.8%	-2.0%	0.5%	-1.8%	0.7%	-0.2%
Janitor	0.7%	-1.0%	0.8%	-2.0%	0.5%	-1.8%	0.7%	-0.2%
All 8 departments	0.7%	-1.0%	0.8%	-2.0%	0.5%	-1.8%	0.7%	-0.2%

TABLE IV. The predicted arithmetic mean (AM) range of historical EMP exposure levels by location (f/cc) –Approach 1

Mine-Department	A		B		C		D		E		F		G		All 7 mines	
	Min	***Max***	***Min***	***Max***	***Min***	***Max***	***Min***	***Max***	***Min***	***Max***	***Min***	***Max***	***Min***	***Max***	***Min***	***Max***
Mining	0.08	2.1	0.02	0.07	0.05	7	0.03	10.89	0	0.04	0.03	0.1	0.13	1.82	0.04	0.41
Crushing	0.13	2.87	0.03	0.07	0.03	3.09	0.02	6.56	0	0.06	0.04	0.15	0.2	2.51	0.06	0.60
Concentrating	0.18	4.17	0.02	0.05	0.05	6.21	0.06	15.22	0	0.07	0.05	0.2	0.28	3.64	0.05	0.47
Pelletizing	0.08	1.81	0.03	0.07	0.03	3.61	0.11	30.89	0	0.06	0.02	0.08	0.12	1.58	0.04	0.45
Shop (mobile)	0.08	1.92	0.03	0.08	0.04	4.2	0.05	14.01	0	0.06	0.03	0.12	0.13	1.67	0.05	0.49

Shop (stationary)	0.08	1.82	0.02	0.06	0.04	3.69	0.03	9.14	0	0.04	0.02	0.09	0.12	1.58	0.04	0.41
Office/control room	0.02	0.5	0.02	0.06	0.03	3.17	0.02	7.42	0	0.03	0.03	0.12	0.03	0.44	0.02	0.23
Janitor	0.08	1.82	0.02	0.03	0.03	1.93	0.05	3.32	0	0.05	0.03	0.09	0.13	1.61	0.04	0.45
All 8 departments	0.08	1.82	0.02	0.03	0.03	1.93	0.05	3.32	0.00	0.05	0.03	0.09	0.13	1.61	0.04	0.45

TABLE V. The predicted arithmetic mean (AM) range of historical EMP exposure levels by location (f/cc) – Approach 2

Mine-Department	A		B		C		D		E		F		G		All 7 mines	
	Min	***Max***	***Min***	***Max***	***Min***	***Max***	***Min***	***Max***	***Min***	***Max***	***Min***	***Max***	***Min***	***Max***	***Min***	***Max***
Mining	0.07	0.08	0.02	0.02	0.05	0.07	0.04	0.08	0.03	0.04	0.02	0.03	0.07	0.08	0.04	0.05
Crushing	0.21	0.22	0.03	0.07	0.01	0.03	0.03	0.13	0.03	0.08	0.04	0.05	0.22	0.22	0.09	0.13
Concentrating	0.04	0.2	0.01	0.02	0.05	0.05	0.07	0.23	0.02	0.05	0.04	0.1	0.04	0.15	0.03	0.08
Pelletizing	0.03	0.09	0.03	0.04	0.04	0.04	0.12	0.23	0.13	0.15	0.02	0.05	0.03	0.07	0.07	0.08
Shop (mobile)	0.16	0.2	0.04	0.08	0.05	0.1	0.06	0.07	0.07	0.22	0.03	0.08	0.16	0.2	0.06	0.11
Shop (stationary)	0.05	0.11	0.02	0.03	0.03	0.09	0.02	0.03	0.05	0.05	0.02	0.02	0.05	0.09	0.05	0.05
Office/control room	0.01	0.02	0.02	0.03	0.01	0.02	0.02	0.05	0.02	0.03	0.03	0.05	0.01	0.02	0.02	0.03
Janitor	0.09	0.14	0.03	0.04	0.03	0.04	0.06	0.15	0.06	0.07	0.03	0.05	0.09	0.13	0.06	0.07
All 8 departments	0.09	0.14	0.03	0.04	0.03	0.04	0.06	0.15	0.06	0.07	0.03	0.05	0.09	0.13	0.06	0.07

borrowing time-trend information from the dust exposure study greatly reduced the uncertainties in prediction. Given the sparseness of the historical EMP measurements, the predictions of Approach 2 (that relies solely on "Year 2010/2011" EMP data and a borrowed slope) seem more plausible than Approach 1 in reconstructing the historical EMP exposure profiles in this study.

Historical exposure reconstruction relying on limited information is always challenging, and the assumptions underlying each approach have limitations. A linear regression based on limited historical data (Approach 1) does not yield reasonable and plausible values of the slope. Approach 2 assumes that the EMP and the respirable dust in the same department share the same historical time trend. While this approach allowed us to avail of the more reasonable slope estimates from the historical respirable dust data set and yielded more plausible historical exposure estimates for most locations, the assumption is hard to validate. Such a validation would require both EMP and respirable dust data to be available for each year of the study time period for each mine-department combination.

The results presented here were used for several epidemiological analyses [5, 6, 7, 8] and reviews by others [28, 29]. These epidemiological analyses used the reconstruction of exposures presented here for non-asbestiform EMP (a number of previous studies have shown that there are no asbestiform EMP in the ore body [3, 30, 31]) as well as exposures to commercial asbestos reported previously [6, 7, 8]. This work is the first time EMP exposures have been reconstructed using information of other exposures in the same mine-department and shows the feasibility of this approach when data are very sparse.

CONCLUSIONS

Historical exposure reconstruction often relies upon limited information and is a challenging but important component of epidemiological investigations. In this study, we conducted a comprehensive reconstruction for the historical EMP exposures of all study mine-department combinations using two different reconstruction approaches. The reconstruction approaches resulted in two distinct EMP estimates for each mine, department, and year. Each approach has advantages and disadvantages, but overall, the approach that incorporated borrowed time-trend information from a companion study might provide more plausible exposure estimates. However, both JEMs can be used to assess associations with EMP and respiratory disease in future epidemiological studies to assess the effect of these assumptions.

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Chapter 4. A Bayesian Approach for Determining the Relationship between Various Elongate Mineral Particles (EMPs) Definitions

Introduction

Since the term "fiber" has been controversial in the context of asbestos (1), the National Institute of Occupational Safety and Health (NIOSH) has proposed the use of the term "elongate mineral particles" or EMPs to refer to any mineral particle with a minimum aspect ratio of 3:1 that is of inhalable, thoracic, or respirable size (2). In the US, the current standard analytical method for measuring EMP is *the NIOSH Manual of Analytical Methods (NMAM) 7400: Asbestos and Other Fibers by Phase Contrast Microscopy (PCM)* with its latest update in 2019 (3). EMP can be asbestiform or non-asbestiform, and although the chemical composition of asbestiform and non-asbestiform EMP can be the same, they differ in their "habit" or morphology (4). The original Occupational Safety and Health Administration (OSHA) regulation defined asbestos only mineralogically without specifying the habit or asbestiform nature. The definition also specified length and aspect ratios that were derived based on measurement reproducibility considerations rather than health relevance (5). This was the origin of the regulatory definition that a "fiber" should have a length that exceeds 5 μm and an aspect ratio (length: width) that is at least 3:1. However, in many industries including taconite mining and processing, EMPs are created during mechanical processing of the ore (e.g., crushing and fracturing of the mineral) that are referred to as cleavage fragments. These cleavage fragments could meet the regulatory definition of a "fiber" described above, even if they were not naturally occurring and asbestiform in habit.

Non-asbestiform EMPs are mineralogically no different from asbestiform EMPs (Berndt & Brice, 2008), but are morphologically different, with needle-like (acicular) or prismatic crystalline habits (2,6). NIOSH has explicitly included EMPs from the non-asbestiform analogs of asbestos in its recommended exposure limit (REL). Their rationale for this decision was three-fold (2): (a) the epidemiological evidence from studies where worker populations were exposed to non-asbestiform EMPs (New York talc miners and millers, Homestake gold miners, and taconite miners) was considered inconclusive due to inadequate EMP exposure characterization, not accounting for smoking status, poor reliability of death certificate information, and exposures associated with prior employment; (b) animal studies showed differential toxicity of asbestiform and non-asbestiform EMP with lower effects of exposure to non-asbestiform EMP and some evidence that EMP dimensions may be predictors of toxicity, (c) current analytical methods used for routine analysis of samples, i.e., the NIOSH 7400 phase contrast microscopy (PCM) and NIOSH 7402 transmission electron microscopy (TEM) methods cannot differentiate between asbestiform and non-asbestiform EMP when present in a heterogeneous mixture. This NIOSH definition, regardless of existing criticism targeting its absence of biological evidence (7,8) and PCM's inadequacy for differentiating asbestiform from non-asbestiform (9), has become the most commonly used definition of EMP to the extent that other size of EMP are routinely not considered during analysis.

The primary goal of the Minnesota Taconite Work Health Study (TWHS) (10) was to evaluate whether the elevated mesothelioma rate reported among taconite mining workers in the Mesabi Iron Range in northeastern Minnesota can be attributed to their long-term exposure to the workplace non-asbestiform EMPs. A comprehensive EMP exposure assessment was carried out by collecting all available historical EMP sampling results from different sources (all based on the NIOSH 7400 definition), obtaining more than 1200 new EMP personal samples and analyzing them using the NIOSH 7400 method (11–13). A mesothelioma case-control study found that mesothelioma was probably associated with cumulative NIOSH 7400 EMP exposure (RR=1.10, 95% CI = 0.97-1.24) (14).

Over the years, there have been several EMP definitions proposed based on alternative size ranges (1,2,23–25,15–22). Dodson et al. (2003) concluded that asbestos EMPs of all lengths induce pathological responses and cautioned against ignoring EMP < 5 μm since they constituted the bulk of EMP exposures. Suzuki et al. (2005) concluded that short (≤5 μm), thin EMP (≤0.25 μm) were more strongly associated with malignant mesothelioma through analysis of lung and mesothelial tissues in human patients. In contrast, Chatfield (2008) suggested that thin (0.04 μm ≤width≤0.25 μm) and long (20≤aspect ratio≤1000) EMPs are more dangerous. Dement et al. (2008) showed using a TEM analysis of chrysotile fibers that all combinations of lengths and widths (lengths ranging from <1.5 μm to > 40 μm and widths ranging from 0.25 - 3.0 μm were highly statistically significant predictors of lung cancer and asbestosis. This reinforced their previous conclusion that since the traditional counting method (NIOSH 7400 PCM and NIOSH 7402 TEM) counts only EMPs > 5 μm in length, shorter EMPs are not counted but may contribute substantially to work exposure (Dement et al., 1983). Pott(1987)proposed that for natural fibers and man-made mineral fibers (MMMF), EMPs >3 μm in length, <1 μm in width, and >5:1 aspect ratio were carcinogenic.

A re-analysis of the 1267 filter samples collected during the TWHS to obtain the sizes of all EMP presents a unique opportunity to more definitively address the various competing hypotheses regarding the health effects of different EMP dimensions. The objectives of this study are twofold. First, we propose a new approach for deriving numerical relationships between several EMP dimension-specific definitions. Second, this approach will be applied to the taconite EMP data so as to derive a set of numerical conversion factors for each Mine-SEG unit of the Minnesota Taconite Worker Health Study. These factors will allow the creation of JEMs for alterative EMP metrics from our existing NIOSH-EMP JEM for future epidemiologic analysis.

Methods

The TWHS comprises seven taconite mines, coded as Mine A through Mine G in the paper, of which one (Mine G) was inactive in 2010 when onsite exposure assessments were conducted. By geological location, Mine A is in the eastern range ("Zone 4") of the Mesabi Iron Range and the remaining six mines are in the western range ("Zone 1" and "Zone 2"). Existing mineralogical evidence (27,28) shows that Zone 4 contains largely amphibole EMPs (ie. cummingtonite-grunerite) whereas non-amphibole EMPs dominate in Zone 1. Zone 2 is considered a transitional zone and contains both amphiboles and non-amphiboles. Hwang et al (2013) grouped all taconite workers job titles into 28 similar exposure groups (SEG) and collected EMP personal samples in all six active mines (Table I). Of the 28 SEGs, 27 SEGs were monitored. The Janitor SEG was not monitored because all janitors in the current taconite mining industry were independent contractors and not employed by the mining companies.

The detailed sampling procedures used to collect EMP samples are described elsewhere (11,13). In brief, personal samples were collected on the Iron Range from January 2010 to May 2011. Two workers per SEG were selected for personal EMP sampling in the eastern zone and each worker was sampled during three different shifts. In the western zone, approximately eight workers per SEG were chosen, with each worker being sampled on three different shifts. The average sampling time was 6 hours, and EMPs were collected using a mixed cellulose ester membrane filter, 25 mm in diameter with 0.8 μm pores. The filter was placed in a polycarbonate membrane cassette with a conductive extension cowl of 50 mm. Prior to this study, all personal samples had been analyzed using the NIOSH 7400 PCM method.

TABLE I. EMP samples used in this paper by mine

Zone	Mine	# of Personal EMP Samples
Eastern	Mine A	253
Western	Mine B	198
	Mine C	216
	Mine D	200
	Mine E	270
	Mine F	130
Total		1267

STEP 1: Obtain single EMP dimension information using ISO-TEM analysis

In this study, all 1267 archived personal samples were analyzed using the ISO 10312 or 13794 TEM methods in an AIHA-accredited laboratory (EMSL Analytical, Inc). Specifically, each personal sample was first screened by the ISO 10312 TEM method with 15 grid openings. If a particular filter was overloaded, then it would be re-analyzed using the ISO 13794 method but with 10 grid openings. The total filter area needed for this ISO-TEM analysis was about ¼ of the original complete filter (complete filter area: 490 mm^2). Under a high-resolution TEM microscope (~20,000X magnification), the lengths and widths of all eligible EMP (width (W) ≥ 0.01 μm, length (L) ≥ 0.3 μm, aspect ratio, AR = L/W ≥3) were measured and reported. The new method allowed us to observe a much wider range of EMP compared to the traditional NIOSH PCM method. Moreover, this ISO-TEM method can also provide chemical composition and crystal structure information for each EMP.

The ISO-TEM methods classified EMP's structures into four primary categories and multiple sub-categories: Fiber, Bundle, Cluster and Matrix. While it is possible that EMPs with different structures might play different roles in disease development, there is no consensus on how to quantify this difference. In this study, we ignore differences between different types of structures.

STEP 2: Use bivariate lognormal distribution to characterize overall EMP size distribution

EMP size distributions can be simply described by a bivariate lognormal distribution, in which EMP lengths and widths individually follows a univariate lognormal distribution (29–33). The shape of a bivariate lognormal distribution is shown in Figure I.

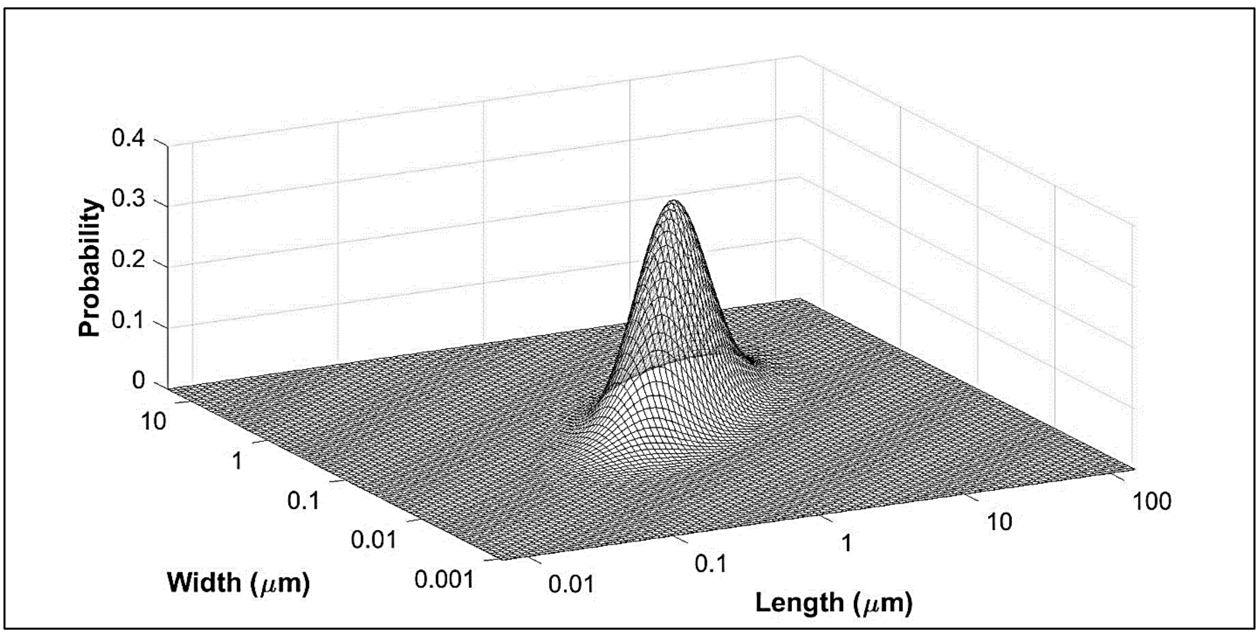

FIGURE I. A bivariate lognormal distribution density plot example

Mathematically, a bivariate lognormal distribution can be described by five parameters ($\mu_L, \mu_W, \sigma_L, \sigma_W, \rho$), and its probability density function is expressed as follows:

$$f(l,w)=\frac{1}{2\pi\sigma_L\sigma_W\sqrt{1-\rho^2}}\exp\left[-\frac{(\frac{\ln l-\mu_L}{\sigma_L})^2+(\frac{\ln w-\mu_W}{\sigma_W})^2-2\rho(\frac{\ln l-\mu_L}{\sigma_L})(\frac{\ln w-\mu_W}{\sigma_W})}{2(1-\rho^2)}\right], \quad (1)$$

where $\mu_L, \mu_W, \sigma_L, \sigma_W$ are the means and standard deviations of the natural logarithms of L and W, respectively; and ρ is the correlation between *ln* L and *ln* W. An important property of this distribution is that its marginal distributions are lognormal as well. In other words, *ln* L and *ln* W individually follow a normal distribution (Eq. 2).

$$\ln L \sim N(\mu_L, \sigma_L^2);\ \ln W \sim N(\mu_W, \sigma_W^2) \quad (2)$$

Equivalently, we can get the geometric mean (GM) and the geometric standard deviation (GSD) of L and W using Eq. 3.

$$GM(L)=e^{\mu_L},\ GM(W)=e^{\mu_W},\ GSD(L)=e^{\sigma_L},\ GSD(W)=e^{\sigma_W} \quad (3)$$

STEP 3: Use a Bayesian approach to facilitate the formation of the bivariate lognormal distribution

Our aim is to estimate the distribution of fiber lengths and widths in each mine-SEG combination. Although this study sampled a larger number of EMPs than previous studies, after we separated them by their sampling location, data were not evenly distributed across the SEGs. For example, as shown in Table IV, Mine A-Crusher maintenance had 844 EMP while no EMPs were found among Mine C-Carpenter. To address this sparsity and provide reasonable estimates for all mine-SEG combination, we fitted a flexible hierarchical model to the EMP data in order to represent the nested structure of the data. This hierarchical model estimated SEG and mine specific length and widths from the individual EMP dimensional information. The SEG and mine specific dimensions were assumed to be exchangeable within a given mine and a second stage of the hierarchical model allowed EMP length and width information to be borrowed between

SEGs in the same mine. For example, EMPs in the crusher operator SEG in one mine were estimated as a weighted average of the crusher operator EMPs and the other SEG specific EMP dimensions in that mine (34). We did not assume there was exchangeability between mines because, based on geological information, EMP characteristics could vary substantially by mine location. The Bayesian model is shown in Eqs. 4-8.

For each individual EMP k in the SEG j and the Mine i, we assumed its length L_{ijk} and its width W_{ijk} follow a bivariate lognormal distribution;

$$\left(\ln L_{ijk}, \ln W_{ijk}\right)^T \sim Bivariate\ N\left(\left(\alpha_{L,ij}, \alpha_{W,ij}\right)^T, \begin{pmatrix} \sigma_{L,i}^2 & \sigma_{LW,i} \\ \sigma_{LW,i} & \sigma_{W,i}^2 \end{pmatrix}\right); \quad (4)$$

Where $\alpha_{L,ij}$ and $\alpha_{W,ij}$ are the ith mine and jth SEG specific mean fiber ln-length and ln-width, respectively. We further assumed that those mine and seg-specific means are normally distributed about common mine-specific mean lengths, $\mu_{L,i}$, and widths, $\mu_{W,i}$. Non-informative priors are placed on each of these mine-specific dimensions.

$$\alpha_{L,ij} \sim N\left(\mu_{L,i}, \tau_L^2\right);\ \alpha_{W,i,j} \sim N\left(\mu_{W,i}, \tau_W^2\right); \quad (5)$$

$$\mu_{L,i} \sim N(0,1000); \mu_{W,i} \sim N(0,1000); \quad (6)$$

$$\tau_L^2 \sim Inverse\ Gamma(.1,.1);\ \tau_W^2 \sim Inverse\ Gamma(.1,.1); \quad (7)$$

Within each mine i, all SEGs uses the same variance-covariance matrix $\begin{pmatrix} \sigma_{L,i}^2 & \sigma_{LW,i} \\ \sigma_{LW,i} & \sigma_{W,i}^2 \end{pmatrix}$. This matrix follows an inverse Wishart distribution;

$$\begin{pmatrix} \sigma_{L,i}^2 & \sigma_{LW,i} \\ \sigma_{LW,i} & \sigma_{W,i}^2 \end{pmatrix} \sim Inverse\ Wishart\left(\begin{pmatrix} 1 & 0 \\ 0 & 1 \end{pmatrix}, 2\right); \quad (8)$$

STEP 4: EMP size-based definitions

TABLE II. EMP definitions considered in this study

#	EMP definitions	Width (μm)	Length (μm)	Aspect Ratio (AR)
1	ISO-TEM EMP (1995, 1999)	≥0.01*	≥0.3**	≥3***

2	NIOSH EMP (1994)	≥0.25****	>5	≥3
3	Chatfield asbestiform EMP (2008)	0.04-1.5	NA	20-1000
4	Suzuki EMP (2005)	≤0.25	≤5	NA
5	Chatfield non-asbestiform EMP or cleavage fragments (2008)	NA	NA	<20

* the minimum reported diameter in our study.
** the minimum reported length in our study. The method default value was 0.5 μm.
*** the actual AR used in our study. The method default AR was 5:1.
******** EMP less than approximately 0.25 μm in diameter will not be detected by PCM

The five EMP definitions considered in this study are listed in Table II. The (1) ISO-TEM EMP has the widest size range and can help us to see a nearly complete picture of the total EMP population; (2) the NIOSH EMP and (3) the Chatfield asbestiform EMP refer to long and thin fibers; (4) the Suzuki EMP refer to short fibers; (5) the Chatfield non-asbestiform EMP (referred to as cleavage fragments in Hwang et al., 2014) are created by mechanical processes in mining, and should be less biologically potent than the naturally occurring fibers (6,35,36).

Figure II shows the regions of the hypothetical overall EMP bivariate lognormal distribution that correspond to each definition (non-gridded area). The volume under each region is proportional to the number of EMP according to that particular EMP definition.

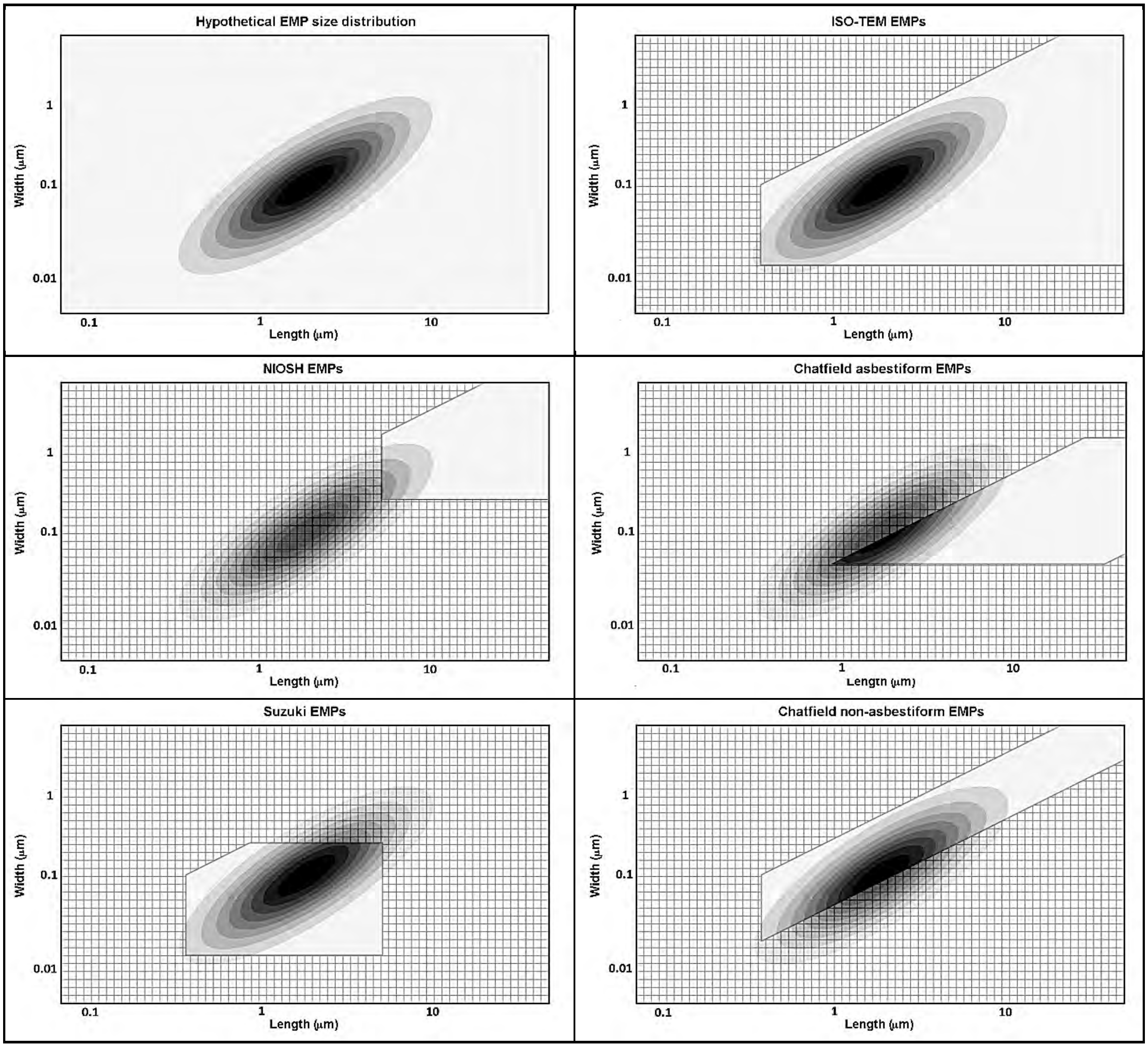

FIGURE II. Specific area within the overall EMP size distribution corresponding to each EMP definition

STEP 5: Deriving conversion factors between any two EMP definitions

The final mine- and SEG-specific conversion factor between any two EMP definitions is the ratio of the proportion of the density under the area of the fitted bivariate distribution for the definitions in STEP 4. For example, if for a given mine/SEG combination, 3% of the EMP density falls under the NIOSH EMP area, and 60% of the total population falls under the Suzuki EMP area, then the conversion factor between the NIOSH EMP and the Suzuki EMP is 1:20.

Thus, if a sample NIOSH 7400 result is 1 EMP/cc for example, then the corresponding Suzuki EMP concentration will be 20 EMP/cc.

Software used

In this study, the EMP length and width ISO-TEM result was stored and sorted using SAS statistical software (version 9.4, SAS Institute, Cary, North Carolina, United States). The Bayesian modelling in STEP 3 was implemented in R with the Bayesian Graphical Models using MCMC 'rjags' package (R version 3.4.1, rjags version 4-6). STEP 4 and 5 were implemented in MATLAB (MATLAB version R2014b, the MathWorks, Inc., Natick, Massachusetts, United States).

Results & discussion

Measured EMP by SEG

The ISO-TEM analysis of the 1,267 EMP personal samples resulted in a total of 11,147 eligible ISO-TEM EMPs by mine and SEG as listed in Table IV. Of the 162 mine-SEG combinations (6 mines by 27 SEGs), 37 combinations (23%) had fewer than 4 measured EMPs. For these combinations, we did not carry out Bayesian updating, and instead used the mine-level priors for the parameter estimates listed in Table II as the final model output. The combination with the most available measurement data is the SEG *Crusher maintenance* of the Mine A mine with 844 EMPs. This high number is due to an above-average 6 personal samples, in addition to a higher general exposure level in this SEG, so for the same 6-hr long sampling period, more EMPs are expected to be collected and analyzed.

Conversion factors from NIOSH 7400 to alternative EMP metrics

The goal of this study was to derive numerical conversion factors between various EMP definitions that will allow us to create alternative JEMs based on EMP metrics other than the NIOSH-EMP JEM for future epidemiologic analyses. Three tables (see Table IV-VI) of conversion factors were derived for converting from the NIOSH EMP to Chatfield asbestiform EMP, the Suzuki EMP, and the Chatfield non-asbestiform, respectively.

The median [IQR] of the conversion factors to "Chatfield asbestiform EMP", "Suzuki EMP", and "Chatfield non-asbestiform EMP" from the "NIOSH EMP" were 0.37 [0.16-0.74], 10.85 [6.13-13.19], and 15.13[10.28-18.12] respectively. The interpretation of these values is that if we observed 100 NIOSH EMP using PCM on a filter, there would have been, on average, around 37 Chatfield asbestiform EMP, 1085 Suzuki EMPs and 1513 Chatfield non-asbestiform EMPs existing on that filter as well. In other words, NIOSH 7400 method reports a small portion of total EMPs collected on a sampling filter. The majority of taconite EMPs are short Suzuki EMPs and Chatfield non-asbestiform EMPs (cleavage fragments). NIOSH EMPs are a very small fraction of the overall EMP population, and the long and thin Chatfield asbestiform EMPs are even rarer than the NIOSH EMP in taconite mines.

TABLE IV. The numerical conversion factors (NIOSH to Chatfield asbestiform)

Mine/SEG	Mine A	Mine B	Mine C	Mine D	Mine E	Mine F
Auto mechanic	0.03	0.73	2.31	0.82	0.34	0.93
Balling drum operator	0.03	0.74	0.24	1.85	0.40	0.47
Basin operator	0.05	0.93	0.21	0.26	0.09	0.84
Boiler technician	0.05	0.74	0.16	0.56	0.46	0.84
Carpenter	0.05	0.64	0.27	0.32	0.10	0.84
Concentrator maintenance	0.11	1.63	0.09	1.06	0.34	0.53
Concentrator operator	0.05	1.72	0.40	0.66	0.13	0.66
Control room operator	0.16	0.40	0.25	0.57	0.24	1.20
Crusher maintenance	0.02	0.77	0.28	0.45	0.06	0.40
Crusher operator	0.03	0.15	0.09	0.18	0.10	0.90
Dock man	0.30	1.90	0.29	0.80	0.09	0.63
Electrician	0.03	0.52	0.19	1.34	0.12	0.44
Furnace operator	0.03	0.74	0.42	1.55	0.54	0.55
Lab analyst	0.05	1.35	0.51	0.76	0.24	1.81
Lubricate technician	0.03	0.74	0.34	0.57	0.21	1.19
Maintenance technician	0.04	0.29	0.20	0.58	0.41	0.94
Mining operator 1	0.02	0.96	0.11	0.34	0.31	1.43
Mining operator 2	0.03	0.53	0.11	0.35	0.05	0.57
Office staff	0.09	1.71	0.27	0.09	0.21	0.84
Operating technician	0.06	0.74	0.26	0.56	0.21	0.83
Pelletizing maintenance	0.08	0.83	0.18	0.45	0.16	1.31
Pelletizing operator	0.07	0.64	0.28	1.32	0.17	1.04
Pipefitter/Plumber	0.05	0.74	0.34	0.56	0.64	0.84
Rail road	0.05	0.74	0.27	0.56	0.21	0.84
Repairman	0.05	1.88	0.27	0.57	0.33	2.23
Supervisor	0.02	0.30	0.67	0.16	0.39	0.70
Warehouse technician	0.04	0.23	0.25	0.56	0.20	0.68

TABLE V. The numerical conversion factors (NIOSH to Suzuki)

Mine/SEG	Mine A	Mine B	Mine C	Mine D	Mine E	Mine F
Auto mechanic	0.93	14.14	9.99	9.03	7.01	16.29
Balling drum operator	3.26	12.79	16.25	10.92	10.08	21.54
Basin operator	1.99	13.37	6.31	10.11	5.36	12.64
Boiler technician	1.98	12.88	10.10	10.83	28.34	12.63
Carpenter	1.99	7.31	11.63	6.51	5.66	12.60
Concentrator maintenance	2.68	18.75	20.12	9.39	7.53	8.84
Concentrator operator	1.76	25.75	12.35	10.14	3.70	5.18
Control room operator	2.92	6.81	12.72	12.31	14.86	13.07
Crusher maintenance	1.30	13.05	27.46	13.20	3.61	3.01
Crusher operator	1.37	4.69	4.16	10.70	5.03	13.19
Dock man	4.93	11.17	15.64	10.60	6.12	10.52
Electrician	2.10	7.68	3.87	12.08	4.76	10.12
Furnace operator	3.46	12.84	40.03	15.79	7.82	20.91
Lab analyst	2.28	23.91	11.99	15.04	7.45	14.21
Lubricate technician	1.26	12.82	18.88	10.85	8.52	11.11
Maintenance technician	1.66	9.11	5.85	8.23	12.11	13.42
Mining operator 1	1.23	21.84	8.47	16.68	11.24	15.63
Mining operator 2	1.41	8.26	6.13	10.42	9.31	14.40
Office staff	2.11	20.34	11.65	10.61	13.12	12.64
Operating technician	3.03	12.84	17.08	10.84	8.55	12.61
Pelletizing maintenance	2.47	13.96	18.53	8.40	7.19	16.90
Pelletizing operator	4.11	12.33	22.78	10.92	15.64	28.50
Pipefitter/Plumber	1.99	12.84	6.75	10.84	14.43	12.63
Rail road	1.52	12.81	11.64	10.85	8.55	12.62
Repairman	1.99	19.43	11.65	10.83	11.29	20.37
Supervisor	1.57	18.37	12.14	12.14	14.27	9.81
Warehouse technician	1.01	13.44	11.85	10.87	7.52	15.37

TABLE VI. The numerical conversion factors (NIOSH to Chatfield non-asbestiform)

Mine/SEG	Mine A	Mine B	Mine C	Mine D	Mine E	Mine F
Auto mechanic	3.42	18.58	9.56	11.66	10.61	22.04
Balling drum operator	7.87	16.84	23.10	11.23	14.31	31.62
Basin operator	5.28	16.87	10.35	15.55	10.13	17.67
Boiler technician	5.28	16.95	15.94	14.82	36.24	17.66
Carpenter	5.29	10.28	17.00	10.33	10.38	17.64
Concentrator maintenance	5.84	21.06	30.34	11.39	11.33	13.94
Concentrator operator	4.80	28.73	17.10	13.56	7.17	8.18
Control room operator	5.87	10.55	18.54	16.64	21.46	16.90
Crusher maintenance	4.49	17.05	36.44	18.34	7.74	5.84
Crusher operator	4.47	8.97	8.29	17.01	9.48	18.16
Dock man	8.08	11.75	21.87	13.63	11.22	15.78
Electrician	5.72	11.24	7.11	13.79	8.84	16.26
Furnace operator	8.25	16.92	50.00	17.45	10.84	30.17
Lab analyst	5.76	27.84	16.13	19.17	11.76	16.46
Lubricate technician	4.10	16.89	25.53	14.84	13.42	14.44
Maintenance technician	4.74	14.31	9.84	11.48	16.79	18.32
Mining operator 1	4.37	26.89	14.28	23.47	16.27	19.34
Mining operator 2	4.51	11.95	11.02	15.39	16.60	21.33
Office staff	5.07	22.63	17.02	18.10	19.47	17.71
Operating technician	6.90	16.91	23.94	14.83	13.46	17.69
Pelletizing maintenance	5.74	17.97	26.55	12.20	11.99	21.33
Pelletizing operator	8.52	16.66	30.78	12.51	23.22	36.89
Pipefitter/Plumber	5.29	16.91	10.27	14.83	18.56	17.67
Rail road	4.43	16.87	16.99	14.86	13.44	17.67
Repairman	5.28	21.13	17.01	14.81	16.24	22.59
Supervisor	4.90	26.47	15.66	19.22	19.63	14.49
Warehouse technician	3.56	20.68	17.40	14.87	12.17	22.06

The comparison between lab results and model predictions for each EMP definition

Like any statistical approach, this Bayesian hierarchical model relies on several important assumptions: the bivariate lognormal distribution can well describe the overall EMP size distribution for each mine-SEG combination, and a common variance/covariance structure across all SEGs in a mine. To examine the soundness of our approach, we compared the actual and the predicted definition-specific EMP counts across all study mine-SEG combination. In other words, we were comparing what we saw from our sample to what we derived from the population we built based on our sample. Take Mine A - Auto mechanic as an example. Table III suggests that there are 55 single EMPs found in this location. Among these 55 EMPs, if we screen them by each study EMP definition, there are 14 NIOSH EMPs, 11 Suzuki EMPs, 3 Chatfield asbestiform EMPs and 52 Chatfield non-asbestiform EMPs. The above numbers are the actual counts we observed from our sample. Alternatively, we can predict these numbers based on our proposed conversion factor-based approach. We form a bivariate lognormal distribution to characterize the overall size distribution of the EMPs from this location, and we calculate conversion factors. In this particular case, if there were 55 ISO-TEM EMPs, we would expect to see 15.9 NIOSH EMPs, 14.8 Suzuki EMPs, 0.55 Chatfield asbestiform EMPs and 54.4 Chatfield non-asbestiform EMPs. under this over size distribution. The complete actual counts vs. predicted counts comparison are demonstrated in four bubble plots of Figure III. The size of a bubble represents the actual total ISO-TEM EMP count found in that mine-SEG combination (also listed in Table III).

TABLE III. Summary of the reported EMP counts collected by personal samples

Mine/SEG	Mine A	Mine B	Mine C	Mine D	Mine E	Mine F	Total
Auto mechanic	55	60	9	7	16	13	160
Balling drum operator	226	0	55	57	78	36	452
Basin operator	0	20	30	2	11	0	63
Boiler technician	0	0	22	0	48	0	70
Carpenter	0	21	0	9	29	0	59
Concentrator maintenance	435	175	28	50	77	38	803
Concentrator operator	497	312	111	34	71	9	1034
Control room operator	147	5	23	1	16	13	205
Crusher maintenance	844	135	162	46	51	16	1254
Crusher operator	723	79	101	26	35	120	1084
Dock man	68	8	61	21	17	9	184
Electrician	434	43	67	12	105	12	673
Furnace operator	149	0	118	29	13	13	322
Lab analyst	833	108	40	28	1	17	1027
Lubricate technician	174	0	347	0	0	36	557
Maintenance technician	32	40	26	1	8	23	130
Mining operator 1	167	39	14	45	15	101	381
Mining operator 2	255	92	15	113	29	8	512
Office staff	5	43	0	5	9	0	62
Operating technician	99	0	124	0	0	0	223
Pelletizing maintenance	90	27	91	27	8	17	260
Pelletizing operator	241	17	33	63	44	97	495
Pipefitter/Plumber	0	0	70	0	44	0	114
Rail road	121	0	0	0	0	0	121
Repairman	0	117	0	0	54	29	200
Supervisor	554	7	6	5	71	3	646
Warehouse technician	16	19	4	0	4	13	56
Total	6165	1367	1557	581	854	623	11147

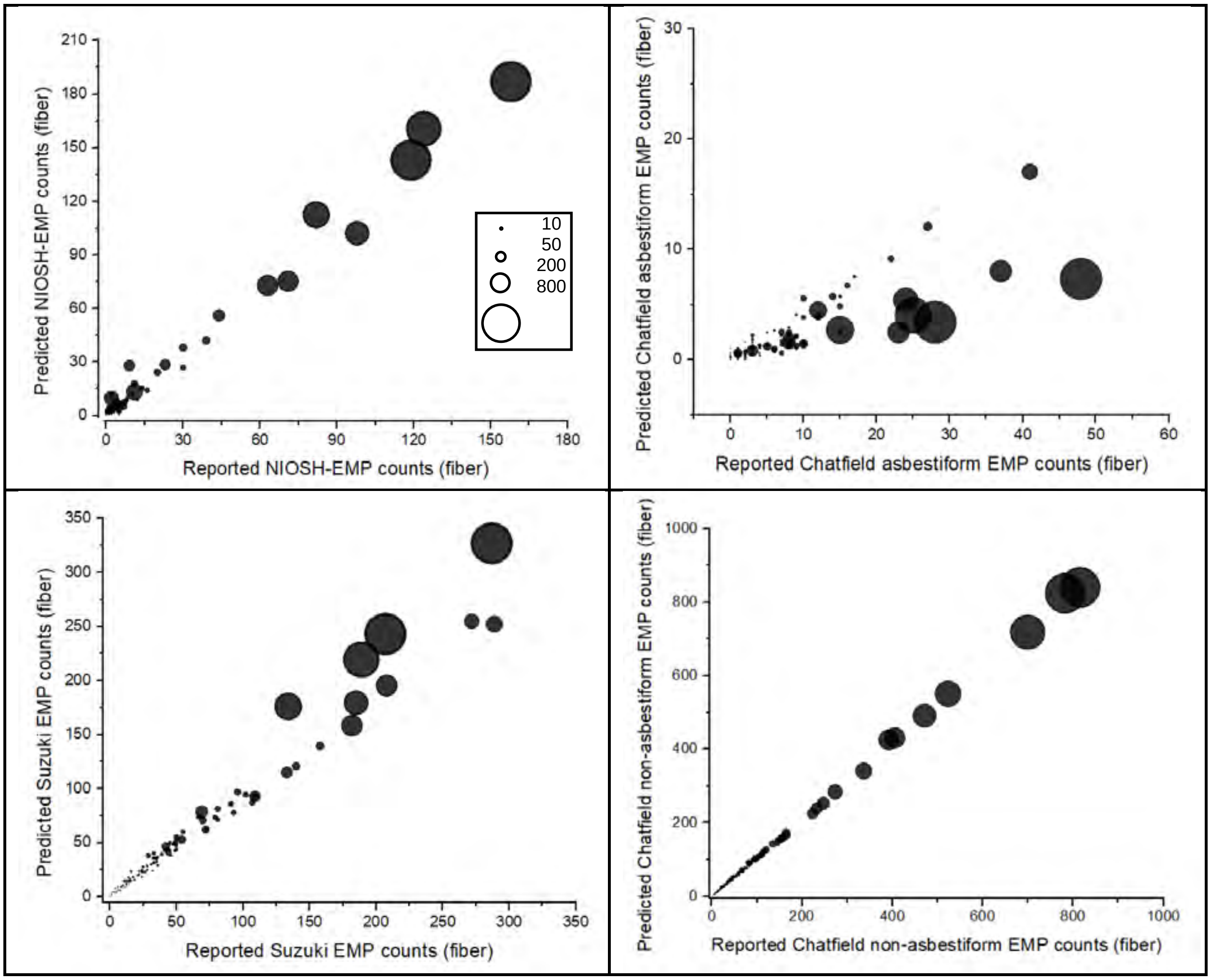

FIGURE III. Actual and predicted definition-specific EMP counts given the total actual ISO-TEM EMP counts reported in each mine/SEG combination

For NIOSH 7400, Suzuki EMP, and Chatfield non-asbestiform EMP cases, plots show some linearity indicating the predicted and actual values are highly consistent. We did not see a strong linear line in the Chatfield asbestiform EMP plot. One possible reason could be this type of EMP is much rarer in the taconite mines than the other three EMP types, so too little information was available to form a prefect bivariate lognormal distribution for Chatfield asbestiform EMP. From Figure III, we can also see that most of Taconite mine related EMPs are neither the traditional regulated NIOSH fibers (median 7% with IQR 4%-11%) nor the long Chatfield asbestiform

EMP (median 3% with IQR 1%-5%), but rather a majority of the EMP collected in the taconite mines are the short Suzuki EMP and/or the Chatfield non-asbestiform EMP.

Improvements from the previous study

A previous study conducted by Hwang et al. (2014) had developed conversion factors, but had several drawbacks: (1) it had small EMP samples: size information was obtained for only 2,791 single EMP from the ISO-TEM analysis of 92 area samples; (2) it was not probability-based method, and the conversion factors were derived based on actual sample results, and many locations had zero EMP count. As a result, the derived conversion factors had a high correlation between the NIOSH EMP JEM and other developed JEMs. Lambert *et al.* in 2015 reported that the JEMs, which were developed using the previous conversion factors, were highly correlated. One motivation of conducing this study was to improve upon the study by Hwang et al. (2014). This study addresses the above limitations by developing a model-based Bayesian approach. It creates probability density plots for each location based on a bivariate lognormal distribution for 11,190 EMPs. The new conversion factors vary by location and are mildly correlated (Pearson correlation $R^2 = 0.4 – 0.6$), reflecting the natural association between these EMP definitions.

Conclusion

The Bayesian approach applied to the parameters of the bivariate lognormal distribution allows us to create an overall EMP size distribution for each of the mine-SEG combinations using EMP dimensional information. This method provides more robust estimates compared to estimates based on limited personal measurements. The mathematical relationships between the NIOSH EMP and other EMP definitions using the new ISO-TEM results provide the basis of classification of workers into JEMs based on alternate definitions of EMP for epidemiologic studies of mesothelioma, lung cancer, and non-malignant respiratory disease. This approach is generalizable for any future research that study EMP size distribution.

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Chapter 4. Mesothelioma Risks and Dimension-based Elongate Mineral Particle (EMP) Definitions in Minnesota Taconite Mining Industry: An update of the Minnesota Mesothelioma Case-Control Study

INTRODUCTION

Iron ore mining on the Mesabi Iron Range in Minnesota has produced a substantial portion of the iron for the US steel industry for more than a century. High grade iron ore, hematite, was depleted in the middle of the 20th Century and the industry moved toward mining and processing a lower grade ore, taconite, to be shipped to US steel mills. Potential health concerns related to taconite mining and processing date to the 1970s. (Berndt and Brice, 2008). To address these concerns, and particularly concerns about mesothelioma risk, a large study of the industry, the Taconite Worker Health Study (TWHS), was initiated in 2008 funded by the state of Minnesota. This study explored the association between the mesothelioma risks and working in the taconite industry and occupational exposures to the elongate mineral particles (EMP). The original study results were published in 2016 (Lambert *et al.*, 2016) and shown that 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 elongate mineral particle (EMP) exposure (RR=1.10, 95% CI 0.97 to – 1.24). The EMP in this study was defined by the National Institute for Occupational Safety and Health (NIOSH) EMP 7400 counting rules that only counted long fibers (length >5 μm, length/width ratio≥3) (hereafter referred as "NIOSH EMP"). After the 2016 study, the team, in the past few years, continued to improve study quality through multiple updates, and new research questions, such as whether EMP of other dimensions have the same potency as the NIOSH EMP in causing the mesothelioma, or how the dimensions of EMP are related to mesothelioma development in taconite mining worker population, would like to be answered this time.

In the literature, the question of how the dimensions of the EMP are related to carcinogenic lung disease development has been controversial. Stanton et al. (1981) hypothesized that carcinogenicity of EMP is related to dimension and durability and less with mineral type and ascribed carcinogenicity to EMP with a length > 8 μm and a diameter < 0.25 μm. Subsequently, Lippmann (1988) suggested that lung cancer was associated with associated with asbestos EMP longer than 10 μm with a diameter > 0.15 μm, while mesothelioma was associated with asbestos EMP longer than 5 μm with a diameter < 0.1μm. A series analyses by Berman et al. (1995, 2003, 2008) consistently suggested that it is likely that length categories with minimum cut points substantially longer than 10 μm contribute most heavily to both asbestos-induced lung cancer and mesothelioma. Loomis et al. (2010, 2012) also found that the occurrence of lung cancer is associated most strongly with exposure to long thin asbestos fibers (5-10 μm long and <0.25 μm in diameter) in workers at asbestos textile mills in North Carolina and South Carolina, USA. Chatfield (2008) suggested that thin (0.04 μm ≤width≤0.25 μm) and long (20≤aspect ratio≤1000) EMP are more dangerous. A panel of experts convened by ATSDR (Eastern Research Group, 2003) concluded that there is a weight of evidence that asbestos and synthetic vitreous fibers (SVFs) shorter than 5 μm are unlikely to cause cancer in humans.

Other researchers however have argued against ruling out the effect of short fibers. Dodson et al. (2003) concluded that asbestos EMP of all lengths induce pathological responses and cautioned against ignoring EMP < 5 μm since they constituted the bulk of EMP exposures. Suzuki et al. (2005) concluded that short (≤5 μm), thin EMP (≤0.25 μm) were more strongly associated with malignant mesothelioma through analysis of lung and mesothelial tissues in human patients. Dement et al. (2008) showed using a TEM analysis of chrysotile fibers that all combinations of lengths and widths (lengths ranging from <1.5 μm to > 40 μm and widths ranging from 0.25 - 3.0 μm were highly statistically significant predictors of lung cancer and asbestosis. This reinforced their previous conclusion that since the traditional counting method (NIOSH 7400 PCM and NIOSH 7402 TEM) counts only EMP > 5 μm in length, shorter EMP are not counted, but may contribute substantially to work exposure (Dement *et al.*, 1983). Pott (1987) proposed that for natural fibers and manmade mineral fibers (MMMF), EMP >3 μm in length, <1 μm in width, and >5:1 aspect ratio were carcinogenic.

To answer the above question as well as to update the previous findings, we have been improving the previous case-control study through multiple updates: (1) 24 additional cases were identified by the Minnesota Cancer Surveillance System (MCSS) from 2010 to 2015; (2) Historical EMP exposures were reconstructed using multiple methods; (3) multiple EMP job-exposure matrices (JEMs) based on different EMP definitions were created.

We expect that, by using this updated study cohort and some newly-developed exposure information, we can better understand how the dimensions of EMP are related to the mesothelioma development in Minnesota taconite worker population, and provide some new evidence to the “long fiber vs. short fiber” debate mentioned above.

METHODS

Study design and population

We conducted a nested case-control study of mesothelioma in a cohort of iron mining workers. The study cohort is a subset of the overall Minnesota iron worker cohort - Mineral Resources Health Assessment Program (MRHAP). This MRHAP cohort was enumerated by the University of Minnesota in 1983 with the support of the Iron Range Resources and Rehabilitation Board (IRRRB) and the cooperation of the seven mining companies then in operation, and included 68737 individuals identified in employee records from the mining industry in northeastern Minnesota between the 1930s and the end of 1982. It includes workers who were employed in both the hematite and taconite industry. The MRHAP 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, and 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. The new study is an expansion of the 2015 study by adding new 24 cases.

Selection of cases and controls

Cases of mesothelioma were identified through the Minnesota Cancer Surveillance System (MCSS) and/or death certificates for out of state cases. In addition to the original 80 mesothelioma cases, 24 additional cases were identified (23 through MCSS and one outside of Minnesota). Mesothelioma in MCSS was coded using ICD-O-3 histology codes 9050–9053 and death certificates had ICD 10th Revision code C45. Four controls 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. 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. Finally, the new study population is constituted of 104 cases and 410 controls.

Exposure assessment

The detailed exposure assessment for taconite mining workers can be found elsewhere (Hwang *et al.*, 2013). In brief, there were seven taconite mines that are associated with this study: Arcelor Mittal, Hibbtac, Keetac, Minntac and Utac in Zone 1, LTV in Zone 2 and Northshore in Zone 4 of the Mesabi Iron Range. As of 2010, when the comprehensive onsite investigation was conducted by the TWHS study, six of these seven mines were still in operation and LTV mine was closed in 2001. The mining process for each mine was similar, but workers with different tasks may experience different exposure situations. Hwang *et al.* (2013) grouped all taconite worker job titles into 28 similar exposure groups (SEG) within eight departments: Mining [Basin operator, Mining operator 1, Mining operator 2, Rail road] Crushing [Crusher maintenance, Crusher operator, Operating technician], Concentrating [Concentrator maintenance, Concentrator operator], Pelletizing [Balling drum operator, Dock man, Furnace operator, Pelletizing maintenance, Pelletizing operator], Shop (mobile) [Boiler technician, Carpenter, Electrician, Lubricate technician, Maintenance technician, Pipefitter/Plumber, Repairman, Supervisor], Shop (stationary) [Auto mechanic, Lab analyst, Warehouse technician] Janitor [Janitor] and Office/control room [Control room operator, Office staff]. The onsite exposure monitoring was conducted from January 2010 to May 2011 for nearly all SEGs (except Janitor) of all six active mines. Two workers per SEG were selected for personal EMP sampling in the eastern zone and each worker was sampled during three different shifts. In the western zone, approximately eight workers per SEG were chosen, with each worker being sampled on three different shifts. The averaged sampling time was 6 hours, and EMP were collected using a mixed cellulose ester membrane filter, 25 mm in diameter with 0.8 μm pores. The filter was placed in a polycarbonate membrane cassette with a conductive extension cowl of 50 mm. Finally, 1185 present-day personal EMP samples were collected and analyzed using the NIOSH 7400 PCM method.

Historical NIOSH-7400 EMP personal exposure data were extracted from two sources (See Chapter 3): (1) the Mine Safety and Health Administration (MSHA) online database records for all inspection results since 1978 with 655 EMP monitoring records from 1978 to 2010 under 13 MSHA Mine IDs associated with this study; and (2) the mining companies' internal monitoring reports contain 96 personal EMP exposure records with the earliest record in 1983. In total, there were 751 historical EMP personal samples.

The detailed historical EMP reconstruction process based on above present-day and historical EMP measurements were described in detail elsewhere (Lambert et al. 2015, Chapter 3). In brief, historical NIOSH EMP exposures were reconstructed using three different reconstruction strategies.

The first reconstruction strategy (hereafter referred as "Strategy1") was the one used in the 2016 paper. All historical and present-day NIOSH 7400 personal EMP sample data were grouped by mine, and within each mine, a categorical variable was created to further assign these data into 28 SEGs. All data were log-transformed for subsequent modelling. For each mine, an intercept-varying regression model was used to fit these time-series data in estimating the mean exposure level at each year point over the entire mine history for each of all 28 SEGs. Different SEGs within the same mine shared the same regression slope but a different intercept. After this modeling, model outputs – geometric mean exposure values (GMs) were used to form a NIOSH EMP job-exposure matrix (JEM) for epidemiological studies.

The second strategy (hereafter referred as "Strategy2") was a variation of the first strategy. All the monitoring data this time was grouped at department level. We hope, by doing this aggregation/ reducing the location number, more data would be available at each location for prediction and more precise prediction can be made for the study. But we also understand this aggregation to the department level may generate more exposure misclassification compared to Stategy1. Similar to Stategy1, all data were log-transformed first and was applied to an intercept-varying regression model in each mine-department combination. The model outputs – GMs were, in this strategy, converted to their corresponding arithmetic means (AMs) as AMs were suggested(Seixas, Robins and Moulton, 1988; Rappaport, 1991; Crump, 1998) to be a better metric for in creating a job-exposure matrix (JEM) for future health studies. We formed the second NIOSH EMP JEM using these AMs.

The third strategy (hereafter referred as "Strategy3") did not use any of the historical monitoring data, but instead used the time-trend information from the historical dust reconstruction work in Chapter 2. This strategy assumed that dust exposures and EMP exposures in the same mine-department combination are correlated with each other and shared the same time-trend. The advantage of this assumption is that time-trend slopes from the dust study are very accurate given the large number of dust measurements (19,408 respirable dust (RD) measurements and 9,128 respirable silica (RS) measurements) used for modelling, and reflected the overall exposure changes over time in the taconite mining industry. The reconstruction model was conducted in the natural logarithmic scale. The modelling procedure is as follows: (1) For each mine-department combination, the mean exposure level at Year 2010 was given by the log of the geometric mean all present-day measurements of this location; (2) the mean exposure level in other year points was calculated based on Year 2010 value and the slope value; (3) the variance around the mean exposure in each year was fixed over the entire time period, and was given by the variance of all present-day measurements of this location. Similar to the second strategy, the model outputs – GMs were converted to their corresponding AMs, we formed the third NIOSH EMP JEM using these AMs.

The next step was to create JEMs based on alternative EMP definitions from the NIOSH EMP JEMs using the conversion factors (CFs) derived in another study (Chapter 3). Table 1 listed the EMP definitions of our interest. These selected definitions, to some extent, can be very representative: (1) the NIOSH EMP, defined by NIOSH, is by far the most frequent exposure metric used in exposure assessment and health studies; (2) the Chatfield asbestiform EMP refers to long and thin fibers; (3) the Suzuki EMP refers to short fibers; (4) the Chatfield non-asbestiform EMP (referred to as cleavage fragments in Hwang et al., 2014) are created by the mechanical processes in mining, and should be less biologically potent than the naturally occurring fibers (Ilgren, 2004; Gamble and Gibbs, 2008; Harper et al., 2008).

TABLE 1 Selected EMP definitions

#	**EMP definitions**	**Width (μm)**	**Length (μm)**	**Aspect Ratio (AR)**
1	NIOSH EMP (1994)	NA	>5	≥3
2	Chatfield asbestiform EMP (2008)	0.04-1.5	NA	20-1000
3	Suzuki EMP (2005)	≤0.25	≤5	NA
4	Chatfield non-asbestiform EMP (2008)/ Cleavage fragments	NA	NA	<20

The entire CF derivation process can be briefly summarized as five steps: (1) Obtain single EMP dimension information using ISO-TEM analysis (identifies EMP with width >0.01 μm, length > 0.3 μm, aspect ratio ≥ 3.0); (2) Use bivariate lognormal distribution to characterize overall EMP size distribution; (3) Use Bayesian approach to facilitate the formation of the bivariate lognormal distribution; (4) apply each of EMP definitions to the overall distribution plot; (5) Deriving conversion factors between any two EMP definitions. After these five steps, for each mine-department, we got three CFs (‘NIOSH EMP’ to ‘Chatfield asbestiform EMP’, ‘NIOSH EMP’ to ‘Suzuki EMP’ and ‘NIOSH EMP’ to ‘Chatfield non-asbestiform EMP’).

In summary, we first created three NIOSH-EMP JEMs using three different reconstruction strategies (‘Strategy1’, ‘Strategy2’ and ‘Strategy3’). For each NIOSH-EMP JEM, we then used the CFs to create three additional JEMs (one ‘Chatfield asbestiform EMP’ JEM, one ‘Suzuki EMP’ JEM and one ‘Chatfield non-asbestiform EMP’). A total of 12 different EMP JEMs were created this time.

Work history and cumulative EMP exposure calculation

Work history information for cases and controls, including all job titles and dates, was abstracted from available mining company work records through the end of 1982, the time the MRHAP cohort was enumerated. All job titles were standardized into 28 SEGs of 8 departments. Some study subjects worked in the earlier hematite industry. Hematite as a “direct shipping ore” does not require the processing and concentrating techniques of taconite and does not have the same EMP exposures. Therefore, hematite and taconite work histories were separated. The exposure value for the hematite SEG was set as zero as no data were available on exposures within hematite operations. For each study subject, we estimated his cumulative exposure values based on each of the 12 JEMs developed. These values include: three cumulative 'NIOSH EMP' exposures ('Strategy1', 'Strategy2', 'Strategy3'), three cumulative "Chatfield asbestiform EMP" exposures ('Strategy1', 'Strategy2', 'Strategy3'), three cumulative "Suzuki EMP" exposures ('Strategy1', 'Strategy2', 'Strategy3') and three cumulative "Chatfield non-asbestiform EMP" exposures ('Strategy1', 'Strategy2', 'Strategy3'). A cumulative exposure was calculated as the sum of the products of time/location-specific exposure concentrations and the time each individual spent in each exposure category. The unit of cumulative exposure is (EMP/cc)×years, which reflects both the duration and the intensity of exposure. Commercial asbestos was likely 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 each of the multiple (EMP/cc)× years exposure metrics on mesothelioma risk was estimated using conditional logistic regression to account for the person-time matching of cases and controls within risk sets. 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 hematite mining and number of years spent working in SEGs with a high commercial asbestos score. Employment and (EMP/cc)× years models were run without lag, with a 20-year lag and with a 30-year lag. All analyses were conducted with SAS V.9.4.

RESULTS

Characteristics of cases and controls

A total of 104 cases and 410 controls were included in the study (Table 2). All cases and 94% of controls were males. Compared to the control population, higher percentage in the case population were taconite related workers. The duration of hematite employment was similar for cases and controls, but cases had a longer mean taconite-years. The cumulative exposure values of all kind for cases were almost always higher than the values for controls. The cumulative exposure values based on Strategy1 were similar those based on Strategy3. Strategy2 tends to provide higher exposure values for both cases and controls compared with other two versions. Mean years spent in SEGs with a high commercial asbestos score were greater for cases.

TABLE 2 Characteristics of all cases and controls in study population, and cases and controls who worked in taconite

All workers	**Cases N (%)**	**Controls N (%)**
Total	104	410
Female	0 (0.0)	23 (5.6)
Male	104 (100.0)	387 (94.4)
Type of ore mining		
Hematite only	33 (31.7)	174 (42.4)
Hematite and Taconite	28 (27.0)	96 (23.4)
Taconite only	43 (41.3)	140 (34.2)
Years of employment (years)†	**Mean (Min, Max)**	**Mean (Min, Max)**
Taconite employment	7.1 (0.0, 27.6)	5.2 (0.0, 36.3)
Hematite employment	2.6 (0.0, 27.7)	2.7 (0.0, 27.7)
Total employment	9.7 (0.0, 35.2)	7.9 (0.0, 37.3)
Taconite workers	**Cases N (%)**	**Controls N (%)**
Total	71	236
Female	0 (0.0)	12 (5.0)
Male	71 (100.0)	224 (95.0)
Geological zone-ever worked*		
Zone 1	24 (32.0)	93 (37.5)
Zone 2	37 (49.3)	69 (27.8)
Zone 4	14 (18.7)	86 (34.7)
Years of employment (years)	**Mean (Min, Max)**	**Mean (Min, Max)**
Taconite employment	10.4 (0.0, 27.6)	9.0 (0.0, 36.3)
Hematite employment	2.8 (0.0, 22.3)	3.4 (0.0, 27.7)
Total employment	13.2 (0.0, 35.2)	12.3 (0.0, 37.3)
Employment by geological zone		
Zone 1	3.3 (0, 17.2)	3.0 (0, 17.5)
Zone 2	5.1 (0, 26.0)	2.4 (0, 26.0)
Zone 4	2.0 (0, 27.6)	3.6 (0, 36.3)
Cumulative exposure (EMP/cc) ×years_Strategy1	**Mean (Min, Max)**	**Mean (Min, Max)**
NIOSH 7400 EMP	2.1 (0.0, 8.3)	1.6 (0.0, 11.3)
Chatfield asbestiform EMP	1.1 (0.0, 11.4)	0.7 (0, 13.4)
Suzuki EMP	19.4 (0.0, 148.3)	12.3 (0.0, 169.7)
Chatfield non-asbestiform EMP	27.4 (0.0, 166.3)	18.1 (0.0, 187.2)

NIOSH 7400 (EMP/cc) ×years_Strategy1 by geological zone		
Zone 1	0.4 (0, 5.3)	0.1 (0, 4.2)
Zone 2	1.2 (0, 7.4)	0.5 (0, 6.9)
Zone 4	0.5 (0, 8.3)	1.0 (0, 11.3)
Cumulative exposure (EMP/cc) ×years_Strategy2	**Mean (Min, Max)**	**Mean (Min, Max)**
NIOSH 7400 EMP	10.7 (0.0, 62.1)	8.9 (0.0, 79.1)
Chatfield asbestiform EMP	4.4 (0.0, 38.6)	3.5 (0, 82.3)
Suzuki EMP	110.3 (0.0, 933.2)	88.8 (0.0, 1966.8)
Chatfield non-asbestiform EMP	161.0 (0.0, 1331.9)	133.0 (0.0, 2504.1)
NIOSH 7400 (EMP/cc) ×years_Strategy2 by geological zone		
Zone 1	3.7 (0, 62.1)	3.0 (0, 17.5)
Zone 2	5.2 (0, 27.8)	2.4 (0, 26.0)
Zone 4	1.8 (0, 25.6)	3.6 (0, 36.3)
Cumulative exposure (EMP/cc) ×years_Strategy3	**Mean (Min, Max)**	**Mean (Min, Max)**
NIOSH 7400 EMP	1.1 (0, 4.7)	0.9 (0, 5.4)
Chatfield asbestiform EMP	0.9 (0, 16.8)	0.9 (0, 32.1)
Suzuki EMP	15.9 (0, 163.2)	14.1 (0, 311.9)
Chatfield non-asbestiform EMP	20.5 (0, 148.6)	17.5 (0, 284.2)
NIOSH 7400 (EMP/cc) ×years_Strategy3 by geological zone		
Zone 1	0.3 (0, 2.9)	0.3 (0, 2.7)
Zone 2	0.6 (0, 4.7)	0.2 (0, 4.8)
Zone 4	0.2 (0, 4.7)	0.4 (0, 5.4)
Employment in SEGs with high commercial asbestos **(years)	1.2 (0, 16.4)	0.6 (0, 22.0)

†Employment records were only available till the end of 1982.
*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.

Taconite employment duration

Table 3 showed that the risk of mesothelioma was associated with the number of years of employment in the taconite mining industry (RR = 1.02, 95% CI 1.00 to 1.05). This is consistent with what we found previously. Model dividing workers into categories based on the median and tertiles of length of employment of cases, suggested an association between employment length in taconite mines and mesothelioma risk. All risk estimates were adjusted for age and years of employment in hematite operations. The zone-specific risk estimates were also consistent with the previous study. The mesothelioma risk was increased with duration of employment in both Zone 1 and Zone 2, but not associated with duration of employment in Zone 4.

TABLE 3 Overall and zone specific rate ratio estimates for mesothelioma by years of employment in taconite

	Cases	**Controls**	**Rate Ratio†**	**95% CI**
Taconite years*	104	410	1.02	1.00 to 1.05
Hematite years**	104	410	0.99	0.94 to 1.04
High vs. Low taconite employment‡				
< 7.70 and >0 year	36	128	1	
≥ 7.70 years	35	108	1.04	0.58 to 1.86
0 year (hematite-only workers)	33	174	0.62	0.35 to 1.11
Taconite years employment tertiles§				
< 3.90 years	24	100	1	
≥ 3.90 to <13.39 years	23	65	1.56	0.78 to 3.13
≥13.39 years	24	71	1.24	0.63 to 2.46
0 year (hematite-only workers)	33	174	0.73	0.39 to 1.36
Exposure by geological zone***				
Zone 1 taconite years	104	410	1.05	0.99 to 1.11
Zone 2 taconite years	104	410	1.05	1.02 to 1.08
Zone 4 taconite years	104	410	0.98	0.94 to 1.02

†adjusted for age, employment in hematite, and potential for commercial asbestos exposure.
* include entire study population, taconite-year equals to 0 for the hematite only workers.
** include entire study population, hematite-year equals to 0 for the taconite only workers.
‡High group represents workers with employment duration greater than the taconite case median duration.
§Based on the lower, middle and upper third of the taconite case employment duration distribution.
***include entire study population, zone-specific year equals to 0 for those who never worked in this zone.
(EMP/CC)×years of exposure

Three versions of cumulative NIOSH EMP exposure values were calculated, and the mesothelioma risks under each of these three versions were estimated respectively (Table 4). One unit increase in cumulative NIOSH EMP exposure values, regardless of which EMP reconstruction method used, were weakly associated with the risk of mesothelioma (‘Strategy1’: RR=1.10, 95% CI 0.99 to 1.22; ‘Strategy2’: RR=1.01, 95% CI 1.00 to 1.03; ‘Strategy3’: RR=1.20, 95% CI 0.99 to 1.46). Model dividing workers into categories based on the median and tertiles of cumulative exposure values of cases, suggested an association between cumulative NIOSH EMP exposure and mesothelioma risk, still regardless of which exposure reconstruction method used. Mesothelioma risk among the workers in the highest exposure category were higher than those in the lowest exposure categories. All risk estimates were adjusted for age and years of employment in hematite operations. The Zone-specific risks were in the same fashion with what we found in above *Taconite employment duration* section. Workers in Zone 2 shows a very strong exposure-response association for all three EMP reconstruction methods, but we did not found this association in Zone 4. Zone 1’s results varied depending on which EMP reconstruction method used. Results based on ‘Strategy1’ and ‘Strategy3’ exposure estimations showed a significant positive association (‘Strategy1’: RR=1.87, 95% CI 1.20 to 2.93; ‘Strategy3’: RR=1.77, 95% CI 1.04 to 3.03), but results got attenuated after we switched to use ‘Strategy2’ exposure estimations. As mentioned in the method section, ‘Strategy2’ and ‘Strategy1’ were very similar in the mathematical models they used, their main difference were how the raw data aggregated. By aggregated data from a SEG level to a higher department level, the prediction accuracy may increase, but we in the same time may introduced more misclassification in exposure into the epidemiological analysis as well. These introduced misclassifications caused the attenuation in the final risk estimates.

TABLE 4 Mesothelioma risk estimates for cumulative EMP* exposure as a continuous, categorical and geological zone specific

Cumulative NIOSH EMP exposure_Strategy1	Cases	Controls	Rate Ratio†	95% CI
1 unit increase in (EMP/cc)×year*	104	410	1.10	0.99 to 1.22
High vs. Low‡				
Low:>0 to < 1.1 (EMP/cc) ×years	35	160	1	
High:≥ 1.1 (EMP/cc) ×years	36	76	2.10	1.13 to 3.87
Hematite-only workers: 0 (EMP/cc) ×years	33	174	0.85	0.48 to 1.53
Cumulative exposure tertiles§				
Low:>0 to < 0.3 (EMP/cc) ×years	23	118	1	
Medium: ≥0.3 to <2.1 (EMP/cc) ×years	24	58	2.07	1.07 to 4.00
High: ≥2.1 (EMP/cc) ×years	24	60	1.78	0.86 to 3.69
Hematite-only workers: 0 (EMP/cc) ×years	33	174	0.92	0.48 to 1.75
Exposure by geological zone**				
Zone 1 (EMP/cc)×years	104	410	1.87	1.20 to 2.93
Zone 2 (EMP/cc)×years	104	410	1.30	1.12 to 1.50
Zone 4 (EMP/cc)×years	104	410	0.95	0.80 to 1.11
Cumulative NIOSH EMP exposure_Strategy2	**Cases**	**Controls**	**Rate Ratio†**	**95% CI**
1 unit increase in (EMP/cc)×year	104	410	1.01	1.00 to 1.03
High vs. Low				
Low:>0 to < 4.3 (EMP/cc) ×years	35	140	1	
High:≥ 4.3 (EMP/cc) ×years	36	96	1.37	0.77 to 2.42
Hematite-only workers: 0 (EMP/cc) ×years	33	174	0.72	0.40 to 1.29
Cumulative exposure tertiles				
Low:>0 to < 1.3 (EMP/cc) ×years	24	114	1	
Medium: ≥1.3 to <17.0 (EMP/cc) ×years	23	65	1.68	0.85 to 3.31
High: ≥17.0 (EMP/cc) ×years	24	57	1.75	0.88 to 3.51
Hematite-only workers: 0 (EMP/cc) ×years	33	174	0.87	0.46 to 1.64
Exposure by geological zone				
Zone 1 (EMP/cc)×years	104	410	1.01	0.98 to 1.03
Zone 2 (EMP/cc)×years	104	410	1.06	1.02 to 1.09
Zone 4 (EMP/cc)×years	104	410	0.97	0.93 to 1.02

Cumulative NIOSH EMP exposure_Strategy3	**Cases**	**Controls**	**Rate Ratio†**	**95% CI**
1 unit increase in (EMP/cc)×year	104	410	1.20	0.99 to 1.46
High vs. Low				
Low:>0 to < 0.8 (EMP/cc) ×years	36	148	1	
High:≥ 0.8 (EMP/cc) ×years	35	88	1.51	0.85 to 2.69
Hematite-only workers: 0 (EMP/cc) ×years	33	174	0.73	0.41 to 1.29
Cumulative exposure tertiles				
Low:>0 to < 0.3 (EMP/cc) ×years	23	109	1	
Medium: ≥0.3 to <2.1 (EMP/cc) ×years	24	65	1.76	0.91 to 3.42
High: ≥2.1 (EMP/cc) ×years	24	62	1.66	0.83 to 3.32
Hematite-only workers: 0 (EMP/cc) ×years	33	174	0.84	0.45 to 1.56
Exposure by geological zone				
Zone 1 (EMP/cc)×years	104	410	1.77	1.04 to 3.03
Zone 2 (EMP/cc)×years	104	410	1.52	1.15 to 1.99
Zone 4 (EMP/cc)×years	104	410	0.85	0.61 to 1.20

†adjusted for age, employment in hematite, and potential for commercial asbestos exposure.
* include entire study population, the cumulative EMP exposure equals to 0 for the hematite only workers.
‡High group represents workers with cumulative exposure greater than the case median exposure.
§Based on the lower, middle and upper third of the case exposure distribution.
**include entire study population, zone-specific cumulative EMP exposure equals to 0 for those who never worked in this zone.

Different EMP definitions

For each EMP reconstruction method, we developed 4 different JEMs based on different EMP definitions. We evaluated the mesothelioma risk under each of these definitions to determine which definition or which size range of EMP has the strongest association with the mesothelioma in our taconite worker population. Although the results varied a little bit by EMP reconstruction method used, Table 5 shown that cumulative exposures to the Suzuki EMP and the Chatfield non-asbestiform EMP were significantly associated with mesothelioma in the Minnesota taconite worker population. Cumulative exposures to the NIOSH EMP and the Chatfield asbestiform EMP were not significantly associated with the risk of mesothelioma. This findings, for the first time, provided some evidences to support the ideas that the 'short fibers', 'non-asbestiform' EMP and Cleavage fragments created by taconite mining process, may contribute to the development of the mesothelioma found among taconite worker population in Minnesota. Traditionally, these fibers, compared to the long and thin fibers, have not been regulated and have been thought to be safe.

TABLE 5 The mesothelioma risk estimates under different EMP definitions

#		Previous study population (80 cases + 314 controls)	Updated study population (104 cases + 410 controls)
1	NIOSH (EMP/cc)×years_Strategy1	1.11 (0.98, 1.26)	1.10 (0.99, 1.22)
	Chatfield asbestiform (EMP/cc)×years_Strategy1	1.10 (0.98, 1.24)	1.09 (0.97, 1.22)
	Suzuki (EMP/cc)×years_Strategy1	1.01 (1.00, 1.02)	**1.01 (1.00, 1.02)**
	Chatfield non-asbestiform (EMP/cc)×years_Strategy1	1.01 (1.00, 1.02)	**1.01 (1.00, 1.02)**
2	NIOSH (EMP/cc)×years_Strategy2	1.01 (0.99, 1.03)	**1.01 (1.00, 1.03)**
	Chatfield asbestiform (EMP/cc)×years_Strategy2	1.02 (0.99, 1.04)	1.01 (0.99, 1.04)
	Suzuki (EMP/cc)×years_Strategy2	1.00 (1.00, 1.00)	**1.00 (1.00, 1.00)**
	Chatfield non-asbestiform (EMP/cc)×years_Strategy2	1.00 (1.00, 1.00)	**1.00 (1.00, 1.00)**
3	NIOSH (EMP/cc)×years_Strategy3	1.20 (0.96, 1.50)	1.20 (0.99, 1.46)
	Chatfield asbestiform (EMP/cc)×years_Strategy3	1.01 (0.93, 1.10)	1.02 (0.94, 1.10)
	Suzuki (EMP/cc)×years_Strategy3	1.00 (1.00, 1.01)	**1.00 (1.00, 1.01)**
	Chatfield non-asbestiform (EMP/cc)×years_Strategy3	1.00 (1.00, 1.01)	**1.01 (1.00, 1.01)**

All adjusted for age, hematite years, commercial asbestos.
Single EMP exposure term was used in each model
Model with two cumulative EMP exposure terms

To further verify what we found above regarding the risk of Suzuki EMP and the Cleavage fragments, in this section, we would like to estimate their risks after adjusting for the NIOSH EMP. We were aware of mild correlations between the NIOSH EMP and either of these two EMP among study population (Pearson Correlation Coefficients (R) between cumulative exposure to NIOSH EMP and cumulative exposure to Suzuki EMP was 0.46, R =0.6 between NIOSH EMP and Chatfield non-asbestiform EMP). The results (Table 6) strength our above findings that the risk of mesothelioma was significantly associated with the cumulative exposure to Suzuki EMP as well as the cumulative exposure to Chatfield non-asbestiform EMP after adjust for cumulative exposure to NIOSH EMP.

TABLE 6 The mesothelioma risk estimates after including two (EMP/cc)×years exposure metrics

#	Primary exposure	Adjusted for	Updated study population (104 cases + 410 controls)
1	NIOSH (EMP/cc)×years_Strategy1	Chatfield asbestiform (EMP/cc)×years_Strategy1	1.07 (0.95, 1.22)
	NIOSH (EMP/cc)×years_Strategy1	Suzuki (EMP/cc)×years_Strategy1	1.04 (0.90, 1.20)
	NIOSH (EMP/cc)×years_Strategy1	Chatfield non-asbestiform (EMP/cc)×years_Strategy1	1.00 (0.85, 1.19)
2	Chatfield asbestiform (EMP/cc)×years_Strategy1	NIOSH (EMP/cc)×years_Strategy1	1.05 (0.92, 1.20)
3	Suzuki (EMP/cc)×years_Strategy1	NIOSH (EMP/cc)×years_Strategy1	**1.01 (1.00, 1.02)**
4	Chatfield non-asbestiform (EMP/cc)×years_Strategy1	NIOSH (EMP/cc)×years_Strategy1	**1.01 (1.00, 1.02)**

All further adjusted for age, hematite years and commercial asbestos.

Lagged model

Besides models without lag, we also ran the models with a 20-year lagged exposure and a 30-year lagged exposure. Similar to what we found in the regular model, both lagged models found that the risk of mesothelioma was associated with the cumulative exposure to Suzuki EMP as well as the cumulative exposure to Chatfield non-asbestiform EMP. However, the risk of mesothelioma was no longer associated with the number of years of employment in the taconite mining industry in these lag models. It's also worth noting that cumulative exposure to Chatfield asbestiform EMP in the 30-year lag model was also associated with the risk of mesothelioma. We did not see this association in the regular models. In Minnesota taconite mines, as shown in Table 2, long and thin fibers such as Chatfield asbestiform EMP were very rare. Their small numbers in our personal samples made us hard to estimate its present-day concentrations, let alone its historical values. So more research is needed to further test this association in the future.

TABLE 7 The mesothelioma risk estimates from lag-effect models

#	Exposure metric used in the model	Time lag	Updated study population (104 cases + 410 controls)
1	Taconite years	20 years	1.02 (0.99, 1.05)
	NIOSH (EMP/cc)×years_Strategy1		1.10 (0.98, 1.23)
	Chatfield asbestiform (EMP/cc)×years_Strategy1		1.11 (0.99, 1.25)
	Suzuki (EMP/cc)×years_Strategy1		**1.01 (1.00, 1.02)**
	Chatfield non-asbestiform (EMP/cc)×years_Strategy1		**1.01 (1.00, 1.02)**
2	Taconite years	30 years	1.02 (0.97, 1.07)
	NIOSH (EMP/cc)×years_Strategy1		1.13 (0.98, 1.29)
	Chatfield asbestiform (EMP/cc)×years_Strategy1		**1.20 (1.02, 1.41)**
	Suzuki (EMP/cc)×years_Strategy1		**1.02 (1.00, 1.03)**
	Chatfield non-asbestiform (EMP/cc)×years_Strategy1		**1.01 (1.00, 1.02)**

All adjusted for age, hematite years, commercial asbestos.
Single EMP exposure term in each model

DISCUSSION

In this paper, historical EMP exposures were reconstructed using three different strategies ('Strategy1', 'Strategy2' and 'Strategy3'). As a result, a worker's cumulative exposures to, the same NIOSH EMP for example, estimated based on these different reconstructions were also different. We estimated the disease risk under each of these different cumulative exposures, and their results are not exactly the same (see Table 4). Take the risk values in the "1 unit increase in (EMP/cc)×year" rows in Table 4 as an example. For Strategy 1, its estimated risk is 1.10 with 95% CI of 0.99 to 1.22. the result for Strategy 2, however, is 1.01 with 95% CI of 1.00 to 1.03. For these two different results, we attempt to explain it by the difference in these two reconstruction strategies themselves. First, in Table 2, we found that these two strategies produced very different cumulative exposure values. For Strategy 1, its mean cumulative NIOSH EMP exposure in the case group is 2.1 f/cc×year, while this value jump to 10.7 f/cc×year for Strategy 2. Meanwhile, these two strategies conducted their EMP reconstructions at different data level: the SEG level for Strategy 1 and the department level for Strategy 2. Another difference between them is their different exposure metric selected: Strategy 2 uses AMs while Strategy 1 uses GMs. For health study, in theory, AM could be a better exposure metric than its GM as suggested by several researchers (Seixas, Robins and Moulton, 1988; Rappaport, 1991; Crump, 1998). During the GM to AM conversion process, however, the variances (GSDs) associated with the mean exposures (GMs) will be added to AMs to be calculated. In this study, the variances could be huge for the locations where had no/little EMP monitoring data. The calculated AMs, in these locations, could become very high or low – far beyond a reasonable EMP exposure range. Because of both the GM to AM conversion and data aggregation to the department level mentioned above, we believe, Strategy 2 will bring more exposure misclassification than Strategy 1 to our epidemiological analysis. The attenuated results for Strategy 2 in Table 4 support our viewpoints.

The mesothelioma risk for Strategy 3 is 1.20 with 95% CI of 0.99 to 1.46, which is similar with or even better than Strategy 1's result. Its point estimate is further away from the null, and it has a wider CIs. This may suggest that Strategy 3, compared to Strategy 1, reduces the exposure misclassification to some extent in the study.

One improvement of this study, compared to the previous study, is that we estimated taconite workers' cumulative exposures to different sized EMP listed in Table 1 thanks to the conversion factors described in Chapter 4. These cumulative exposure values were mildly to strongly (see Table 7) correlated with each other among taconite worker population due to, we believe, the natural link between these EMP definitions. For example, in nature, the short fiber - Suzuki EMP, approximately, a complement to the long and thin fiber – Chatfield asbestiform EMP. It is also, approximately, quite similar to Chatfield non-asbestiform EMP as both of them focus on short EMP. Because of these high correlations, the results, in Table 5, for Suzuki EMP are almost identical to the Chatfield non-asbestiform EMP's results. This suggests that perhaps we could have deleted one, either Suzuki EMP or Chatfield non-asbestiform EMP, in the study. But it's worth noticing that the NIOSH EMP is not highly correlated with any of other three EMP. This makes the adjustment in Table 6 meaningful. We saw results changed before and after adjusting a second exposure term.

TABLE 8 Pearson Correlation Coefficients between different cumulative EMP exposures (CE)

	CE_NIOSH EMP	CE_Chatfield asbestiform EMP	CE_Suzuki EMP	CE_Chatfield non-asbestiform EMP
CE_NIOSH EMP	1.00	0.30(<.0001)	0.46(<.0001)	0.60(<.0001)
CE_Chatfield asbestiform EMP	0.30(<.0001)	1.00	0.95(<.0001)	0.88(<.0001)
CE_Suzuki EMP	0.46(<.0001)	0.95(<.0001)	1.00	0.98(<.0001)
CE_Chatfield non-asbestiform EMP	0.60(<.0001)	0.88(<.0001)	0.98(<.0001)	1.00

CE refers to cumulative exposure

Table 5 compared the risk estimates using the previous study population vs. updated study population. General speaking, they are consistent with each other. For example, for the same exposure information (NIOSH (EMP/cc)×years_Strategy1), the risk in the previous study population is 1.11 with 95% CI of 0.98 to 1.26. The same risk in the updated study population was 1.10 with 95% CI of 0.99 to 1.22. Their mean estimates are comparable, but by using the updated study population with more cases and controls, the new 95% CIs became narrower with less variances compared to the previous one. This changes illustrates the improvement of this study.

Limitations

In this study, we did not update the vital status of the entire MRHAP cohort through the agencies (ie. NDI) as we did previously. All new mesothelioma cases were in state cases which were identified through MCSS system in Minnesota. Therefore, it is possible that we missed some out-of-state cases this time. Among the 80 old cases, 17 cases were diagnosed out of Minnesota. Given this ratio, we may miss about 6 out-of- state cases. Another potential issue of not updating vital status is that maybe some new controls who were alive by 2010 may had been dead afterwards. For example, a case who was dead in 2013 may matched with a control who may have been dead in 2012. But this will have little effects on our final results as all study population by this time point have been retired and their exposure information would not be changing anymore.

Exposure reconstruction in this investigation was based on all available work history information. This information was available through the end of 1982. It's very likely that some study subjects were still working after this cutting point. If it is the case, then the life-time exposure values estimated for these subjects could be lower than their real received exposures. To partially address this study defect, besides models with no latency, we also ran models with a 20-year latency as well as with a 30-year latency. By doing that (the date of diagnosis – 20 or 30 years), nearly all study subjects would have a complete exposure history. Meanwhile, we found that results from the lag models are consistent with those from the regular models.

The LTV mine is a puzzle compared to all other six mines in the taconite study. We had no present-day measurements and very little historical measurements for this mine. It was also the only mine in Zone 2 of the Mesabi Iron Range. In the meantime, nearly 50% of the mesothelioma cases were found in this mine. The zone-specific mesothelioma risks in Table 4 for zone 2 are all significant regardless of which reconstruction strategy used. For this mine, more research and information collected are needed.

CONCLUSION

This study re-confirmed the main conclusions in the previous study: there was an association between mesothelioma and employment duration and possibly NIOSH EMP exposure in taconite mining and processing. This study further found an association between mesothelioma and cumulative exposure to Suzuki EMP and Cleavage fragments in Minnesota taconite worker population. The risk of long-term exposure to long and thin fibers was not clear yet given the small samples of such fibers in our study.

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1. Yuan Shao, Jooyeon Hwang, Bruce H. Alexander, Jeffrey H. Mandel, Richard F. MacLehose, Gurumurthy Ramachandran, Reconstructing Historical Exposures to Elongate Mineral Particles (EMPs) in the Taconite Mining Industry for 1955–2010. In review, *Journal of Occupational and Environmental Hygiene*, 2019.
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